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Charles R. Thomas, Jr.
Editors

Oncologic Emergency Medicine

Principles and Practice

Springer

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Associate Editors:
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This book is dedicated to my wife, Courtenay Carmody, and my two sons, Samuel and Benjamin, whose love and support bring great joy to my life and purpose to my work.

In memory of my mother, Mary Kate Todd, who left us much too early.

–KHT

To my supportive wife, Muriel Elleen; our wonderful two children, Julian Franklin and Aurielle Marie; our parents; and siblings for their love and support of my career path.

In memory of my mother, Ruth Marie Wilson Thomas, who fought gallantly in the war against cancer and whose prayers have blessed me over the past five decades.

–CRT

Foreword

If you or members of your healthcare team ever have questions about the best, most current evaluation and management plans for patients with just about any oncologic emergency, *Oncologic Emergency Medicine: Principles and Practice* is your answer. This text is written with the clinical provider continuum in mind, so important in modernized oncology practice. We are privileged to write this foreword to such a needed resource. Oncologic Emergency Medicine is an important and rapidly evolving area of clinical collaboration among groups of providers who desire together to take the very best care of their shared patients. No longer should those with cancer enter the emergency department without some certainty about what will likely transpire and that they will receive care that is closely coordinated between emergency care providers and the oncology team.

One overarching theme in this first comprehensive text dedicated to the best, personalized, patient centric clinical care is enhanced communications. We believe the best and most effective clinical care is derived from establishing communication standards prior to any emergency department (ED) encounter. This may include pre-ED communication (EHR, email, texting, phone calls, etc.), appropriate time frames for responses, appropriate physical space, coordinated evaluation plans, and transparent communications among various members of the emergency oncology team to achieve optimal results. The complexities of personalized oncology care require advance preparation, mutual goal setting among the patient and family, as well as the emergency and oncology clinical teams.

This text is written by distinguished experts from a large, multidisciplinary pool and is focused on the cancer survivor, from incipient diagnosis through therapy and its complications, including appropriate measures to control pain and distress, involving attention to superior palliative care. The publication of this text is critically timed given the very recent engagement of the National Cancer Institute (NCI) in moving forward with descriptive studies of cancer patients presenting to US emergency departments. Specifically, the NCI is sponsoring the creation of the Comprehensive ONCologic Emergencies Research Network (CONCERN), a research consortium to begin to address important research needs among emergency department patients with cancer (http://epi.grants.cancer.gov/Consortia/single/concern.html).

This text should be on the bookshelf (or on the wireless network, compact disk, MP3, or all) of all who provide cutting-edge diagnosis and management to those with oncologic emergencies. The editors and authors are communicating a message of hope to those with cancer by supporting the development of personalized oncologic emergency care for each human, based upon their needs, and applying the latest knowledge to optimize care for individual patients, their disease, and their unique circumstances. Of the more than 136 million encounters and growing in US emergency departments, larger proportions are likely to present with

an oncologic emergency. Excellent communications among multiple disciplines are essential to optimal care for those with cancer. This foundational text represents a critical addition to this conversation.

Columbus, OH, USA

Richard M. Goldberg
Thomas E. Terndrup

Preface

It is with great excitement that we present the first edition of *Oncologic Emergency Medicine: Principles and Practice*. Against the backdrop of rising numbers of cancer patients and survivors as the US population ages and a forecast shortage of cancer care providers, this book is designed to serve as the first authoritative, single-source clinical reference on oncologic emergencies. This comprehensive text was specifically designed to address the complexities of understanding and managing cancer emergencies with an emphasis on increasing communication and collaboration between emergency physicians and the multiple providers who participate in caring for those with cancer.

The contributors include a broad spectrum of experts in emergency medicine, surgical and medical oncology, hematology, diagnostic and interventional radiology, palliative care, psychiatry, critical care, dermatology, ophthalmology, clinical pharmacy, addiction psychology, and health services research (including epidemiology, outcome disparities, health economics, and bioethics).

Emergency departments account for approximately one-half of all hospital admissions, and this proportion is likely higher for those with cancer. While the largest portion of the book focuses on a number of clinical oncologic emergencies and their varied presentations to the emergency department, this text offers the opportunity to address more broadly and systematically the vantage point of emergency physicians who work in a critical hub of patient care: the emergency department. Emergency department visits resulting from disease progression as well as toxicities of anticancer treatments serve as a patient-oriented metric of cancer care quality. This text emphasizes the critical importance of emergency department care within a comprehensive cancer treatment system. The principles of care will be similar whether the emergency department is in a dedicated clinical cancer care facility or a matrix care structure. The methods of executing best practices may differ based on the structure of the cancer care system; however, the vast majority of emergency care for those with cancer is similar across emergency department settings, whether in academic or community settings.

The text is structured to cover four fundamental areas of emergency care:

Part I is centered on systems and contextual issues surrounding the emergency department. We discuss existing models of emergency department care, the evolving role of quality measures for oncologic emergency medicine, ethics of care, rapid healthcare learning systems, and the important roles of emergency department social workers and patient navigators.

Part II, capably edited by Steven Bernstein, considers the role of emergency medicine in primary and secondary cancer prevention, including smoking cessation, cervical cancer prevention and detection, ionizing radiation exposure, as well as a discussion of radio terrorism.

Part III will seem perhaps the most familiar to readers and includes considerations of a variety of oncologic emergencies, organized by organ systems, cancer type, and treatment-related toxicities. We appreciate the work of our associate editor, Jim Yeung, in editing this section.

Part IV, edited with the assistance of Tammie Quest, examines important issues related to the end of life care, including the role of palliative surgery, the management of symptoms in those with advanced cancer, approaches to opioid analgesic use (and misuse), as well as the

significance of emergency department use at the end of life as an indicator of cancer care quality. The section ends with an analysis of how to build palliative care capacity within our discipline.

The editors and associate editors are extremely proud of this first edition of *Oncologic Emergency Medicine: Principles and Practice*, and we wish to thank all of the contributors who have given of their time, insight, and experience to create a truly unique text which will serve as a valuable resource for practitioners, researchers, policy makers, trainees, payors, and administrators, as we care for those with urgent cancer needs.

Mendoza, Argentina — Knox H. Todd
Portland, OR, USA — Charles R. Thomas Jr.

Acknowledgments

The authors would like to thank all of the contributors, without whose hard work and dedicated expertise such a project would be frankly impossible. The quality of their scholarly efforts speaks for themselves; nonetheless, we thank all our coauthors for their commitment to cancer patients and oncologic research.

Additional thanks go to Ms. Jennifer Schneider and Ms. Shelley Reinhardt of Springer, whose efforts to bring this book to completion required significant time and effort and whose assistance has made the finished product a better (and more enjoyable) project than the editors could have conceived. We are grateful to Mr. Ron Jaworsky whose initial efforts to get this project off the ground are appreciated.

Special thanks are extended to Ms. Lyn Atkin and Ms. Bridgett Sparkman, our in-house editorial assistants, who were indispensable in maintaining regular contact with the myriad of contributors and meticulously routing the manuscripts to and from multiple editorial levels. Their herculean efforts cannot be overstated.

Finally, we wish to thank our patients, mentors, and colleagues, who are all integral contributors in the effort to further understand the complexities and stark realities involving the diagnosis and management of oncologic emergencies.

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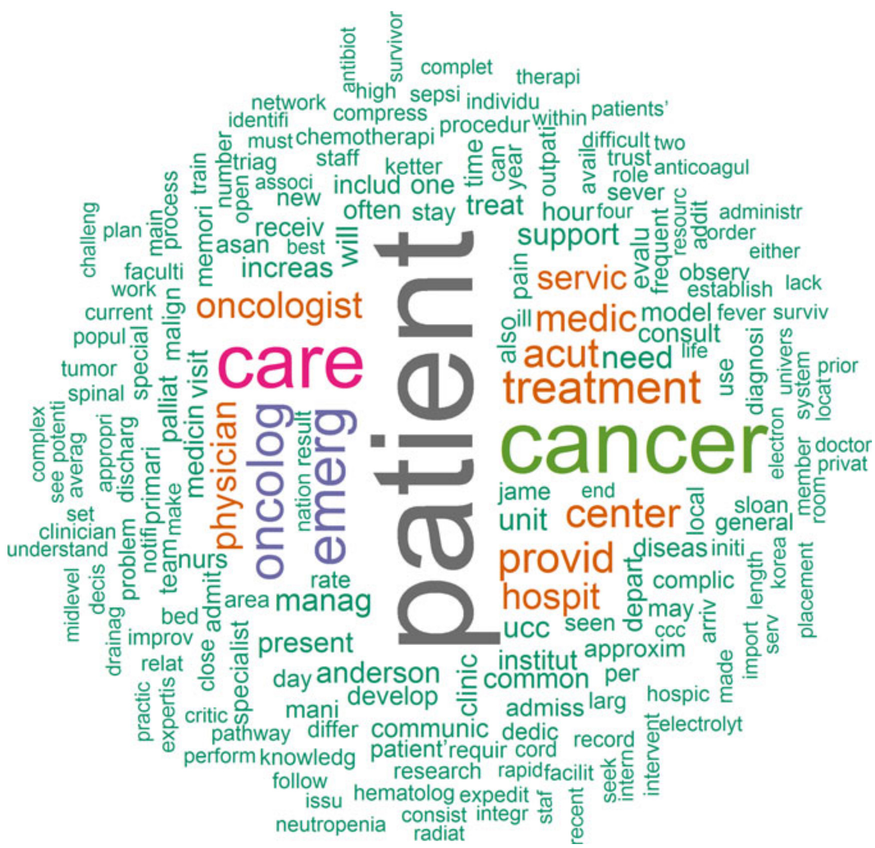
Part I

Systems and Contextual Issues

Models of Care for Cancer Emergencies

Terry W. Rice, Adam Klotz, Helen L. Neville-Webbe,
Shin Ahn, and Eric J. Adkins



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Introduction/Background

Both the emergency medicine community and the oncology community recognize that cancer patients need specialized emergency care and are better served by professionals who are knowledgeable about their unique needs. Patients often relate stories of being told in their local emergency department (ED) to go to their cancer center for further treatment after emergent conditions have been excluded. Conversely, oncologists rarely have access to emergency departments with specific oncology expertise. Patients express the concern that emergency physicians in the community are not completely comfortable caring for complex oncology patients and lack of knowledge of their disease and treatment. Knowing of patients' prior experiences in these settings, oncologists are often hesitant to recommend to their patients in emergency departments with limited oncologic expertise.

Many oncologists who work in large centers are requesting urgent and emergent after-hours services by personnel who are trained in handling oncologic emergencies. With overcrowding and prolonged waits for treatment that characterize many of our nation's EDs, those with cancer and complex care needs, including immunocompromise, intractable pain, and end-of-life care, may best be served in regionalized emergency departments specializing in oncology care.

The numbers of cancer patients and survivors among the general population are increasing. The life expectancy of cancer patients has increased significantly in the last six decades. Comparative survival data from the MD Anderson Cancer Registry (the University of Texas MD Anderson Cancer Center, Houston), which was started in 1944, demonstrate a marked improvement in survival rates for most malignancies. Examples include breast cancer, the 10-year overall survival rate having increased from 25 % in 1944 to 76.5 % in 1995 for patients treated at MD Anderson. For prostate cancer, the most common malignancy in men, the 10-year survival rate increased from 8.5 % in 1944 to 82.5 % in 1995. Acute myeloid leukemia was simply fatal in 1944, with a median survival from diagnosis of 8 weeks and a 99 % mortality rate at 12 months, by 2004, the long-term survival rate had increased to over 25 %. Remission rates in acute myeloid leukemia patients under age 60 years have reached 65 % [1]. Thus, there are many cancer survivors seeking medical care in primary care offices and EDs around the country.

Several other factors have increased the population of oncology patients and survivors seeking acute care. In the last few years, more oncology patients have been receiving treatment as outpatients. Leukemia and stem cell transplant patients spend less time in the hospital and often receive the majority of their chemotherapy in outpatient treatment centers. These patients are no longer universally admitted to the hospital for neutropenia if there is no evidence of infection. Instead, they make frequent trips to the hospital for treatment and laboratory evaluations. Often, patients arrange temporary housing in the area of the oncology treatment center. This practice has also increased the need for unscheduled acute care. Furthermore, cancer patients and survivors have a combination of medical problems that may or may not be related to their cancer history and a wide range of potential residual medical issues related to their prior disease and/or treatments. Meanwhile, oncology care is becoming increasingly specialized. Oncology practice is focusing on emerging treatments and targeted therapies. As more treatment options become available, more expertise is needed in each oncologic subspecialty. Along with the increasing treatment options, there are more potential side effects and treatments available for the supportive care of these patients.

Cancer patients not only suffer from complex medical problems related to their disease and therapy but also are particularly vulnerable emotionally. Patients suffering from a life-threatening illness often have stronger bonds with their medical providers that may be associated with higher expectations for care and an increased sensitivity to their care providers' words or actions; conversations can take on a greater meaning and become more emotionally charged than under normal circumstances [2]. Caring for patients with advanced cancer is stressful for clinicians, and discussing bad news often evokes strong emotional feelings. Not all physicians are formally trained for this difficult communication task. End-of-life talks are time-consuming and stressful in any environment, but this is compounded in the ED, where the cancer patient's needs must compete with the treatment demands of other patients. Unfortunately, evaluation in the ED often reveals progression of the underlying malignancy and may raise the topic of transition to palliative care. Most emergency physicians feel ill-equipped to have this discussion due to the brief nature of their relationship with the patient and lack of depth of understanding of the patient's disease, its progression, and possible therapeutic options. At the same time, the patient, faced with new knowledge about disease progression manifested by the symptomatology that has resulted in the emergency visit, may have multiple questions and a high level of anxiety. At this time, the patient is at high risk for feelings of abandonment [2], especially if the emergency physician is unable to answer questions or provide adequate reassurance that the patient's primary oncologist will be available to them in a timely fashion. Nursing staff may also be unprepared to care for patients who are actively dying and lack the skills to manage end-of-life symptoms.

Despite these needs, there are very few acute care facilities dedicated entirely to the care of cancer patients. MD Anderson and Memorial Sloan Kettering Cancer Center (New York) have such centers. Other institutions with a large percentage of oncology patients are developing resources to provide the specialized care these patients need and to mitigate the difficulties these patients can present to a busy ED. Some institutions are opening fully integrated cancer units within their EDs. They are examining ways to quickly recognize acutely ill oncology patients so that high-risk

patients are treated expeditiously [3], while maintaining an appropriate triage system so that other patients do not perceive oncology patients as receiving preferential treatment.

In this chapter, we describe several models for providing care for oncology patients in the emergency setting. The models range from EDs at large, dedicated cancer centers (MD Anderson and Memorial Sloan Kettering); to a cancer-dedicated emergency department alongside a general emergency department, with some shared resources (Asan Medical Center, Seoul, Korea); to a distributed model in which an oncology service provides support at general acute care facilities, often rural (Merseyside and Cheshire Cancer Network, England). We also describe a fully integrated oncology ED that is under development (the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute ("The James"), Columbus, Ohio) to illustrate some of the pivotal issues of institutions embarking on this endeavor.

Common issues that are considered essential to all of these models include:

- Recognition and expeditious treatment of oncologic emergencies such as neutropenic fever, spinal cord compression, tumor lysis syndrome, and pulmonary embolism
- Appropriate management of pain for patients who are not opioid naïve
- Management of frequently needed procedures such as thoracentesis and paracentesis
- Early recognition and proper management of patients who have Do Not Resuscitate (DNR) orders or are near the end of life
- Knowledgeable management of complications of cancer treatment
- Proper communication regarding disease progression with the patient and oncologist
- Adequate support from end-of-life services such as palliative care and hospice
- Consistent and reliable method of communication with the patients' oncologists
- Support for patients who are new to the institution and attracted by the cancer ED designation

Different models for providing emergency care to cancer patients are derived from the variable needs and characteristics of each practice, such as the prevalence of cancer types, the physical and administrative organization of the local oncology services, and the resources available.

MD Anderson Cancer Center

The Emergency Center at MD Anderson Cancer Center is dedicated exclusively to the care of cancer patients. It is located in the main hospital building and is designated a level III ED by the Joint Commission and the Centers for Medicare and Medicaid Services. Ninety-eight percent of patients treated in MD Anderson's ED have cancer or a cancer history. The ED has a large role in the inpatient services provided at MD Anderson. Thirty-nine percent of hospital admissions come through the ED [4].

However, MD Anderson did not open its doors with an ED in place. The ED developed gradually as a response to the needs for acute care for the large number of outpatients being treated at MD Anderson. Initially, urgent and emergent services were provided in an open ward. No doctors were assigned to the area, and when a patient requiring emergent care arrived, the patient's physician was notified and sent to the ward to evaluate the patient. This situation was not optimal for acutely ill patients or for patients scheduled in the clinic, and the lack of individual patient rooms made it difficult to maintain patients' privacy and confidentiality [5]. The system was also disruptive for oncologists, who already had full clinical schedules. Eventually, full-time physician coverage was established, initially provided by the Department of General Internal Medicine. In 1986, the ED was formally opened. Initially, it had 23 private rooms and provided care to approximately 14,000 patients per year. In 2007, the emergency center moved to its current expanded location. In 2011, MD Anderson established an academic Department of Emergency Medicine, the first such department dedicated entirely to oncologic emergency medical care, education, and research. The MD Anderson ED currently has 45 private rooms, a six-chair unit, and a two-chair triage bay. The ED is equipped with two resuscitation rooms in which critical care is provided to patients with high acuity that arrive from the clinics, walk-in or arrive by ambulance. The ED now sees over 24,000 patient visits annually. All of the patients have cancer or are cancer survivors, except for an occasional family member of a patient or an employee.

The ED is staffed with full-time faculty members, the majority of whom are board certified in internal medicine or emergency medicine. Some faculty members are board certified in surgery, pediatrics, or infectious disease, or palliative medicine. The physicians are faculty at the University of Texas and have similar academic obligations for research, administration, and teaching as other MD Anderson faculty members. The Department of Emergency Medicine recently initiated an oncologic emergency medicine fellowship, now in its third year. Mid-level providers are utilized in the ED but provide a relatively small portion of the care.

The department's 19 faculty members provide round-the-clock coverage. Coverage ranges from two to six physicians with an additional mid-level provider at the busiest times. The ED employs approximately 75 registered nurses with a nurse-to-patient ratio of approximately 1 to 3.

Care and treatment decisions are made by the ED faculty. However, the oncologists do provide a call schedule, and there is frequent communication on an as-needed basis between the

ED physicians and primary oncologists. Oncologists do not routinely round in the ED unless they have admitted patients who are boarding there. The electronic medical record provides the full access to the patient's medical record. Oncologists can notify the ED staff of a patient's pending arrival with the addition of important clinical information by entering a note in the medical record. After patients are seen, a note is generated by the ED physicians notifying the primary oncologist that the patient was seen. If consultation is warranted, the oncologist is contacted by phone.

The average ED length of stay is just over 6 h for a non-admitted patient and over 9 h for an admitted patient. The ED admits 51 % of the patients presenting for treatment. Approximately 30 % of unique patients have hematologic tumors (leukemia or lymphoma) or have received stem cell transplantation, comprising 50.3 % of all patient visits [4]; the remainder have solid tumors.

Of all the patients visiting the ED in 2010, hematologic patients averaged 2.2 visits per patient, and solid-tumor patients averaged 1.8. Of these patients, 12 % had four visits or more, with a range of 1–31 visits per patient. Most patients were receiving multiple medications and presented with several complaints. The complexity of their illness and frequent requirements for intravenous fluids, antibiotics, electrolytes, and blood products resulted in a prolonged length of stay compared to other EDs. The high level of acuity is reflected in the 10.9 % mortality rate associated with admission of these patients [4]. The mortality rate is higher for patients with hematologic tumors (13.6 %) than for patients with solid tumors (9.8 %).

Patients are presented to the oncologic ED with a multitude of different complaints. At MD Anderson, the most common chief complaint is fever, present in 23 % of patients. This is closely followed by abdominal pain, generalized pain, shortness of breath, nausea and vomiting, weakness and fatigue, back pain, chest pain, bleeding, cough, and diarrhea.

Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering has an Urgent Care Center (UCC), dedicated solely to the care of oncology patients. The number of patient encounters per year in the UCC has steadily increased from 14,800 in 2000 to 21,800 in 2013. Although the UCC receives Memorial patients who arrive from the community via ambulance, general 911 calls from the community are not brought to Memorial. The physical size of the unit has grown over time. Originally an eight-bed unit with and adjunct clinic space, the UCC now consists of 19 telemetry beds and 4 transfusion chairs. Turnover of these beds occurs more than four times per day.

The driving forces behind this growth are an increase in the number of patients receiving treatment at Memorial Sloan Kettering and the continued transition of oncologic care away from the inpatient setting. As cancer treatment paradigms change, the UCC is key to the institution's ability to provide acute evaluation and management to an increasingly large and complicated outpatient population. The recent addition of a freestanding same-day surgical center and the continued expansion of the outpatient bone marrow transplantation program are examples of the trend toward outpatient treatment of cancer patients.

The clinical staff consists of 13 full-time board-certified internal medicine physicians, some of whom have completed subspecialty training in palliative care, anesthesia/critical care, and infectious disease. UCC physicians are considered academic faculty who are responsible for teaching medical students and residents from Weill Cornell Medical College as well as participating in clinical research.

Patients treated in the UCC reflect the spectrum of disease seen at Memorial. Most patients have solid tumors (72 %) and are evaluated for acute complications of their disease and treatment. The most common chief complaints include dyspnea (17 %), fever (14 %), pain (11 %), nausea (10 %), and fluid/electrolyte disturbances (9 %). The average length of stay in the UCC is 4 h, and slightly more than half of the patients seen in the UCC will require admission to the hospital. Occasionally, patients with advanced disease who have been treated at other institutions or individuals with a suspected but unconfirmed cancer diagnosis seek to transfer their care by visiting the UCC. Emergent problems are acutely managed; however, referral for expedited outpatient evaluation is the preferred pathway, as the UCC is not intended to be the first point of contact for a new patient.

The UCC has attempted to integrate successful models of care from emergency medicine as volume and throughput have increased. A modified Emergency Severity Index tool is used for triage. Patients are assigned a score of 1–5 based on the need for a lifesaving intervention, the presence of a high-risk situation, the number of resources a patient will require, and predefined vital signs. Specific triaging emphases that reflect the unit's focus on oncology include with the rapid identification any of the following conditions: recent bone marrow transplantation, febrile neutropenia, and potential spinal cord compression. During peak hours, a UCC physician assists the triage nurse, a model that has been associated with faster throughput and improved patient outcomes in non-cancer EDs [6].

As many patients are referred internally by treating oncologists and surgeons, an electronic "UCC Notification Order" allows these individuals to communicate the most likely diagnosis, the need for admission, and which tests and consultants will expedite care.

Oncology patients have an inherent risk for developing sepsis. An institutionally derived algorithm is used to screen all

electronically documented vital signs for sepsis. When potentially significant abnormalities are identified, an alert is triggered, prompting a clinician to assess the patient for the possibility of sepsis. This process is time sensitive and requires the clinician to either document a reason for exclusion (dehydration, arrhythmia, end-of-life/palliative care, etc.) or acknowledge the alert and initiate the sepsis management protocol within 30 min.

Patients who arrive critically ill and in need of an immediate intervention such as endotracheal intubation, cardiopulmonary resuscitation, or initiation of vasopressor support are frequent challenges in cancer EDs. At Memorial Sloan Kettering, the primary oncologist has often already established and documented the goals of care in the electronic medical record. If the patient has previously consented to a DNR order, this information is displayed in the header at the top of the screen, next to the patient's name and medical record number. This order must be confirmed and renewed with each hospitalization, as per New York State law. For critically ill patients without previously established advanced directives, the UCC clinician will rapidly determine the goals of care with the patient, healthcare proxy, and primary physician at MSK. For individuals who decline life-sustaining interventions, the UCC clinician will enter a DNR order and initiate palliative care. Pre-existing order sets for narcotic analgesia and a palliative care consultant facilitate care. A medical ethics consultation service is available 24 h a day for encounters in which the goals of care are difficult to establish.

A Fast-Track Pathway is used for patients with a low Emergency Severity Index (ESI) score. One of the most common diagnoses in this group is a new, suspected, or incidentally identified thromboembolic disease. If anticoagulation is indicated, the patient is often discharged on rivaroxaban with close follow-up in the Anticoagulation Management Clinic.

In July 2013, the UCC opened an observation unit, intended for patients who were unsuitable for discharge but had an expected duration of care lasting less than 24 h. Although the observation unit is physically located in the hospital, this nine-bed unit is considered an outpatient service and is staffed by UCC physicians and mid-level providers. During the first 6 months of the program, roughly 10 % of UCC visits ($n = 1013$) resulted in patient placement in the observation unit. The proportion of admissions to the hospital from the UCC with a length of stay less than 24 h dropped significantly after observation unit implementation (2.4–1.1 %). The most common reasons for observation unit placement are fluid and electrolyte disorders (14 %), pain control (14 %), dyspnea (13 %), and fever (9 %). Interventions for patients in the observation unit include placement or revision of drainage catheters (pleural, biliary, genitourinary tract, abscess); endoscopy and transfusion in patients with hemodynamically stable gastrointestinal bleeding; correction of uncomplicated electrolyte derangements; administration of intravenous (IV), antiemetics, IV antibiotics (for treatment of cellulitis, pneumonia, and uncomplicated febrile neutropenia), or IV analgesia; and the management of severe constipation. Approximately one third of patients placed in the observation unit require admission to the hospital for ongoing care. Extending the observation period to 48 h may decrease this number.

Approximately 15 patients a week are seen in the UCC for elective palliative paracentesis, which is performed by the UCC clinical staff. Drainage of symptomatic pleural effusions is performed in the observation unit by pulmonary medicine. Patients with low-risk febrile neutropenia are either discharged or placed in the observation unit for 24 h.

When possible, management decisions are made with input from a patient's primary oncologist or surgeon, who is notified automatically by e-mail during check-in and discharge. While these individuals may be off-site, they are able to review all relevant clinical data, including lab findings, chart notes, and radiology and telemetry results. An electronic status board, visible on all computer terminals within the institution and on overhead monitors in the UCC, facilitates a quick grasp of key metrics related to an individual patient and overall throughput at any given time. This tool facilitates communication about arrival and waiting times, who are treating or covering UCC staff, pending diagnostic tests and consultants, disposition (admitted/discharged/observed), and bed status.

Asan Medical Center

The Asan Medical Center in Seoul, Korea, opened a Cancer ED in 2010. Asan is a 2700-bed tertiary medical center and the largest hospital in South Korea. The number of ED visits per year is over 100,000, and approximately 10 % of cancer patients in Korea receive their care there. Hospital beds for cancer patients are almost always full. The ratio of solid-tumor patients to hematologic-tumor patients treated at Asan is over 2 to 1. The most commonly treated malignancy is gastric carcinoma. Stem cell transplantation is also provided at Asan.

Asan's Cancer ED is located on a different floor from the primary ED. The Cancer ED consists of 30 beds and serves approximately 30 patients per day. Care is provided to patients on stretchers in an open-ward format. Private rooms are provided for patients who require isolation for airborne infections in the ED intensive care unit, known as the acute care unit. Length of stay in both EDs is limited to 72 h. Cancer patients who are being managed by the Asan Medical Center Oncology/Hematology departments are triaged to the Cancer ED from the main triage intake area. If the Cancer ED is full, the patients are treated in the main ED. Patients who are not currently being treated at Asan for their oncology problems are not admitted to the Cancer ED; they are cared for in the main ED. Patients who are critically ill, presenting for shock

or requiring cardiopulmonary resuscitation or immediate airway placement, are managed in the main ED.

The unit is staffed with an emergency physician assisted by alternating emergency medicine and internal medicine residents. The residents spend a 2-month rotation working in the Cancer ED. The unit is also staffed with two nurse practitioners and four registered nurses during the day and one nurse practitioner and four registered nurses in the evening. Nighttime staffing consists of four registered nurses. The nurses staffing the Cancer ED unit are dedicated to the Cancer ED and do not staff the main ED at other times. Oncology and hematology staff members round on their patients in the ED daily and assist in the decision making and management of these patients as needed. Upon a patient's arrival to the Cancer ED, oncology fellows are notified immediately via a text message through their cellular phones and evaluate the patients once the initial workup and treatments have been completed by the emergency physicians. Simple procedures such as thoracentesis and paracentesis are performed by physicians and midlevel providers. More complicated procedures are usually performed by interventional radiologists. Cellular phones, rather than pagers, are used to communicate between physicians free of charge inside the hospital facility; this is called a "Free Zone" and is sponsored by one of the communication companies in Korea.

The Cancer ED is divided into four zones and a fast track. Patients who present with unstable vital signs or other acute symptoms that are deemed "high risk" are assigned to the fast track and receive close monitoring and expedited evaluation and treatment.

In the first year, 5502 patients were treated in the Cancer ED. The length of stay was approximately 34 h. By opening the Cancer ED, Asan Medical Center reduced its admission rate of oncology patients from 85 to 42 %.

The predominant services provided in the Cancer ED are administration of antibiotics (28.9 %) and pain control (22.9 %) with opioids. Drainage procedures, including percutaneous drainage of effusions, stent insertion for obstructed bowel, drainage of biliary or urinary tract obstructions, repositioning of previously existing catheters, and other procedures, constitute 17.5 % of services provided. Supportive care with nutrition, parenteral hydration (10.7 %), colony-stimulating factor administration for neutropenia (8.3 %), whole-brain radiation or gamma-knife radiosurgery, and palliative radiation for metastatic bone pain or spinal cord compression (6.4 %) were also common treatments. Anticoagulation for newly diagnosed venous thromboembolism and vascular interventions, including occasional placement of inferior vena cava filters or superior vena cava stents, are important treatments done in the Cancer ED. Patients who present with pulmonary emboli begin anticoagulation therapy in the Cancer ED. The most commonly used drugs are dalteparin and rivaroxaban, and the therapeutic decision is made by the oncologists involved in the patients' care. Additionally, 7.8 % of patients received transfusion of blood products.

The hospital does not have specialists in palliative or supportive care and hospice care is not provided in the Asan hospital. When physicians decide that hospice care would be the best choice for the patient, "hospice coordinators" are notified to explain hospice and arrange care at a hospice center near the patients' home.

The Clatterbridge Cancer Centre and Merseyside and Cheshire Cancer Network

The Clatterbridge Cancer Centre (CCC) and Merseyside and Cheshire Cancer Network (MCCN) in England are parts of the British National Health Service. Their dilemma was how to provide emergency care to oncology patients in a system in which much cancer treatment is provided in outpatient environments that are divergent in location and do not have closely associated EDs. This had resulted in oncology patients with acute care needs being seen in EDs that were not closely affiliated with the oncology practices. Common problems were patients being treated by physicians who did not have adequate knowledge about their needs and a lack of communication back to the oncologist regarding the resultant ED visit or hospitalization. The 2008 National Confidential Enquiry into Patient Outcomes and Death highlighted an urgent need to improve the quality, safety, and efficiency of care for cancer patients following emergency presentation to acute general hospitals. In response to this dilemma, CCC and MCCN set up an Acute Oncology Service (AOS) in 2010. This network-wide service was commissioned and implemented on the basis of recommendations from the National Chemotherapy Advisory Group [7].

Through a continuous program of raising awareness regarding both the role of the AOS and the necessity of early patient referral to acute oncology teams, the acute oncology teams have been able to establish an AOS across all acute trusts in their cancer network. The network-wide AOS has improved communication across clinical teams, enabled rapid review of patients by oncology staff, reduced hospital stays, increased understanding of oncologic emergencies and their treatment, and enhanced pathways for rapid diagnosis and appropriate referrals for patients presenting with malignancy of undefined origin (MUO) or cancer of unknown primary (CUP). These achievements have been made by developing a network protocol book for managing common oncologic emergencies, such as febrile neutropenia and malignant spinal cord compression; by introducing local pathways for managing MUO and CUP; and by collaborating with palliative care teams.

MCCN provides cancer services for a population of 2.3 million people in North West England and the Isle of Man and incorporates seven acute hospital trusts. (National Health Service trusts are essentially public sector corporations serving a geographical area or specialized function.) CCC provides tertiary inpatient chemotherapy, radiotherapy, and day-case chemotherapy services and is a stand-alone trust with no acute on-site services. In this trust, over 70 % of systemic cancer treatments are delivered in local hospitals, which are supported by nine satellite chemotherapy clinics and one satellite radiotherapy unit. Chemotherapy services are nurse led, and consultant oncologists may not be on site. Owing to the geography of the region covered by the CCC, cancer patients who require acute medical care present to local hospitals. Before the establishment of an AOS, these patients did not routinely receive specialist oncology review, although 24-h telephone advice was made available by CCC for patients and healthcare professionals alike.

The aim of the AOS is to improve the quality of care for cancer patients following emergency presentation to acute general hospitals because of cancer or treatment-related complications. Reports indicating the need for improved care of cancer patients presenting acutely to hospital show that these patients account for 5 % of all acute hospital admissions, costing the National Health Service approximately £1 billion per year. There is a national increase in the use of systemic cancer treatments and a rapid expansion in the availability of novel agents (including oral drugs). In addition, more treatments are being delivered locally rather than in tertiary cancer centers. These changes all contribute to the increase in patients presenting to local hospitals and being managed by non-cancer specialists [7].

The team model consists of two or three consultant oncologists (one being the lead acute oncology [AO] consultant for the trust), at least one full-time cancer nurse specialist, and secretarial support. The team provides a 5-day service, including one consultant providing 4 h of direct clinical care per day (Monday to Friday) and cancer nurse specialist support for 5 full days. The patients remain under the care of the admitting consultant within the local trust, with the AO providing an advisory service. Each AOS oncologist also provides one or more site-specialized services at the trust where they provide AO support. The annual work plan for each AO team is supported by a local steering committee that includes the lead AO consultant, the local lead cancer clinician, an oncology nurse, a hematology consultant, an emergency medicine consultant, an acute medicine consultant, a palliative care consultant, a rehabilitation lead for malignant spinal cord compression, and a radiologist.

The AOS developed protocols for the management of oncology emergencies presenting to the ED and acute medical units. Individual AO teams provide regular training for the ED and acute medical unit healthcare professionals. In addition, they train physicians who participate in acute "on-take" and liaise closely with the patient's primary oncologist.

Since 2010, the MCCN AOS has seen over 10,000 patients, providing high-quality specialist care and leading to a reduced length of hospital stay of over 3 days. Patients are admitted mostly through the ED, with some also being admitted to the acute medical unit following assessment by their general practitioner either at home or in the practitioner's office. Following presentation to the ED, patients, in line with government targets, have to be seen within 4 h, after which they are either discharged home or (more likely) admitted. The AO team is alerted to all oncology patients and will either see the patient in the ED or more usually on the ward. Of oncology patients presenting for emergency admission, an average of 19 % have newly diagnosed cancer, the most common being lung, gastrointestinal, and MUO/CUP cancers. Thirty-three percent have complications of cancer treatment, the most common being neutropenic sepsis and treatment-induced diarrhea, and 48 % are complications of cancer itself, such as malignant spinal cord compression, superior vena cava obstruction, or disease progression. Most patients are discharged home from the hospital, but on average 10–12 % of patients die during their hospital stay. Of these, over half are patients who are admitted with complications of the cancer itself and are near the end of life. Patients presenting with complications of treatment usually have the shortest hospital stay (approximately 6 days), and lowest risk of inpatient death (6.5 %), whereas patients presenting with complications pertaining to end of life, including those presenting with a new cancer in the advanced stage, have the longest average hospital stay of 10–15 days. Such patients are identified early, and the AO teams work closely with palliative care medicine, discharge planning teams, and local hospice to facilitate symptom control and discharge to the patient's preferred place of care for the terminal phase of their cancer.

The response from patients and their caregivers to this new model has been overwhelmingly positive. Oncology patients can feel vulnerable when being admitted to a non-cancer hospital and worry that the healthcare professionals they see will not understand about their cancer or its treatment. They found that being seen daily by a specialist oncology nurse or doctor, who will advise on the best management and who will also liaise with the patient's primary, tumor specific, oncologist ensuring, for example, that appointments for clinics or cancer treatments are rescheduled or appropriate changes to chemotherapy dosing and scheduling are made if indicated, gives enormous psychological support and feelings of safety to the patient and their caregivers.

The CCC-MCCN AO model provides high-quality specialist care to acutely unwell cancer patients and is a service that has been achieved by positive engagement with each

host trust. AO is now part of the National Peer Review Programme, and any British hospital with an accident and emergency department should have an AOS in situ [8].

The Ohio State University Comprehensive Cancer Center: Arthur G. James Cancer Hospital and Richard J. Solove Research Institute

Several institutions have approached MD Anderson seeking expertise for the design of new emergency services for cancer patients. The Ohio State University Wexner Medical Center is currently in the process of developing a specialized ED to care for its cancer patients, with plans to open in April 2015. The ED currently cares for all cancer patients that arrive seeking emergency care: approximately 70,000 patients per year. They currently evaluate approximately 30 oncology and hematology patients per day. All patients who have active cancer and a potential cancer-related problem will be triaged to the ED at The James, which is integrated within the main ED.

One of the challenges has been to develop triage criteria to perform this function effectively and to maintain equity among all patient types. The plan is to dedicate an area with 15 treatment spaces within the ED that would be allocated to the care of cancer patients. Ten of the rooms are private, four have private bathrooms, and two have negative airflow. The other five spaces are treatment bays with lounge chairs for infusions. On days with a larger number of oncology and hematology patient visits than the 15-bed space can accommodate, additional patients will be evaluated in the main ED. Similarly, when there are fewer James ED patients, non-cancer patients will be evaluated as needed in the James ED. This will ensure equal access to emergency care for all patients, regardless of disease state.

Nurse practitioners who have cross-trained in the ED and the cancer center will staff the cancer ED, along with emergency medicine faculty members who have expressed an interest in cancer care and have a strong background or additional training in internal medicine. During high-volume periods of the day, a dedicated team will care for these patients. During off hours, other faculty members and residents will cross-cover the James ED treatment spaces. The ED group also anticipates that at least two emergency physicians who have completed a palliative care fellowship will lend specialized expertise to the operations of the James ED.

One area already addressed is the difficult issue of the patient with neutropenic fever, a patient type that is often difficult, but critical, to recognize. Many of these patients may appear well and traditionally have had to wait with other patients for further evaluation, even though a prolonged time to antibiotics can result in deterioration and development of sepsis. To improve the management of these patients, The James has added the criterion that any patient with a fever who has received chemotherapy or radiation in the prior 2 weeks will be evaluated under the ED Sepsis Alert process. This process brings together a multidisciplinary team to expedite initiation of IV antibiotics and diagnostic workup for this high-risk population of patients.

Other clinical scenarios The James anticipates is the use of the chair unit to address the time-consuming infusion of electrolytes and blood products. They are developing an expedited admission pathway for patients who have been identified by their oncologist or hematologist as in need of admission. Additionally, a new inpatient service that will handle care for patients without a definite cancer diagnosis but identified as being at high risk for malignancy (i.e., new, large lung mass) has been created to facilitate the care of patients with a presumed diagnosis of cancer who may be attracted to the cancer ED. Patients who are not already receiving their cancer care at The James will be able to be seen in the James ED to facilitate transition of their care to the cancer center.

Considerations for the Cancer ED

Increasing specialization has resulted in a fragmentation of medical care and cancer care is no exception. Many oncology patients are treated by several physicians who are all specialists in cancer therapy. One patient may have one or more surgeons, a medical oncologist, a radiation therapist, a palliative care physician, and other specialists, such as cardiologists, and pulmonologists involved in their care. Patients are often confused as to which doctor is "in charge" and whom to ask which question. The role of the emergency physician in a comprehensive cancer center has some similarities to that of a primary care physician. The ED physician often explains the roles of the different providers and facilitates communication between the various specialties involved in the patients' care. Another important role is that of a safety net, by providing care to the patients when they cannot wait for an office visit or when the office visit results in the discovery of a problem that is beyond the scope of the oncologist or specialist. In these roles the emergency department supports both oncologists and patients. Physicians specializing in oncologic emergencies use unique skills and knowledge of potentially dangerous complications of different treatment modalities and the best supportive therapies as well as understanding of the disease process of multiple different malignancies and their associated emergencies. Also valuable are expertise in pain management, procedures commonly needed in cancer patients, and skillful management of palliative and end-of-life care.

This skill set, which currently, can only be obtained through experience, helps doctors who specialize in the acute care of cancer patients make decisions regarding the aggressive or supportive nature of the care provided in the cancer ED.

Several themes are prevalent in the acute care of cancer patients. One of the concerns expressed by physicians seeking to provide acute care to oncology patients is access to the complete medical record and the expertise of the oncologist. The ED physicians must have a significant understanding of the treatment paths and modalities of the patients they are seeing. In order to make appropriate decisions, communication must be available with the oncologist and other supportive services. With more knowledge and experience, the emergency physician can be more effective in support of the patients and the oncologists and be more confident in their independent decision making. A method of documentation and a process of communication that make the primary oncologist aware of all visits to the ED are optimal. At MD Anderson, an online medical record documents the visit and outcome, and is accompanied by an e-mail notifying the oncologist of the emergency visit, closing the communication loop. Sloan Kettering has gone one step further by posting the ED tracking board throughout the institution. The CCC-MCCN network uses an acute oncologist to liaise with the primary oncologist. These institutions have developed treatment algorithms that further guide and support the care of cancer patients in the ED. Examples of these algorithms are treatment of chemotherapy-induced nausea and vomiting, malignant spinal cord compression, and neutropenic fever. The ED can play an important role in developing and supporting these algorithms.

Another common concern is that caring for this group of patients is very labor intensive. These patients are often very ill; many of them are not independently ambulatory. Most of the patients are on multiple medications and have numerous comorbidities and several complaints. Due to the complexity of their illness, their stay in the ED is longer than that of other populations. Many of the patients require electrolytes or blood replacement as an incidental finding or the reason for the visit. These processes add to the time in the ED and the nursing workload. The ubiquitous admission rate of over 50 % and the high mortality rate of patients admitted through the ED are further testimony to the high acuity level of the patients.

An ED that treats only cancer patients does not have to devise a triage method to identify the cancer patients from the non-cancer patients, and recognition of neutropenic fever, sepsis, and infection with underlying immunocompromised is routine. Other problems, such as managing intractable pain and mixing and adjusting large doses of opiates, are a frequent occurrence. However, these are issues that EDs—who want to support a large cancer population but cannot be dedicated solely to that population—contend with. A frequent issue more unique to a cancer ED is the arrival of patients with a recent diagnosis of suspected or confirmed malignancy. One of the challenges of working in a cancer ED is handling a group of patients with varying degrees of illness, varying knowledge about their condition, and different stages of diagnosis who have recently received difficult news and are emotionally charged. At MD Anderson, several methods are used to defuse the situation and get patients the help they need as best as possible. Patients with a recent diagnosis who do not need admission for a medical emergency are given the name of a self-referral line and contact information for a patient advocate whose job is to aid new patients who have come to the emergency center seeking help. The advocate assists the patients with referral to the appropriate cancer specialist and will provide guidance on funding sources if necessary. MD Anderson also has a "suspicion of cancer" clinic that evaluates new patients and expedites their referral to the appropriate oncology specialist by establishing the diagnosis and/or initiating staging tests. This clinic works closely with the emergency center and is notified via an e-mail that includes doctors, schedulers, and financial specialists while the patient is in the emergency center. In all of the functioning cancer EDs interviewed, avoiding having the cancer ED serve as the intake portal for the cancer institute has been a common theme. Another frequent challenge is patients with late-stage cancer with no prior relationship to the parent institution. Many of these patients have received treatment at other centers and when told that no further treatment options exist, go to the cancer ED hoping for a salvation therapy. These patients are often too sick to be discharged, and without the evaluation of an oncologist in the emergency center will ultimately be admitted to the hospital for an expert opinion and transition to supportive care or hospice. A consulting service that is available to see such patients in the ED would make this process more satisfactory.

Therapeutic procedures frequently utilized in cancer patients necessitate the development of certain services. Oncology patients have a frequent need for invasive procedures such as thoracentesis, paracentesis, stenting, and percutaneous drainage. Some of these procedures can be done by emergency department physicians, but they are time-consuming and difficult to perform in a busy ED. MD Anderson has developed a team of mid-level providers that provide paracentesis, thoracentesis, lumbar puncture, and central-line insertion and port removal throughout the institution during extended hours. At Asan, one of the most common procedures is placement of biliary drains, and the center has developed a pathway for expedited treatment of these patients in partnership with their interventional radiology service.

Another common diagnosis is the incidental finding of pulmonary embolus on CT scans. Many of these patients are handled in the emergency center at Memorial Sloan Kettering, MD Anderson, and Asan Medical Center. These patients are routinely treated as outpatients at all three institutions. At Memorial Sloan Kettering, these patients are seen on a fast track and treated with oral Factor Xa inhibitors if possible. At MD Anderson, low-molecular-weight heparin is the default treatment, and at Asan, a combination of drugs is used depending upon individual physician preference. Both Memorial Sloan Kettering and MD Anderson have anticoagulation clinics for the follow-up of these patients, and pathways have been devised for determining insurance coverage, follow-up visits, and education of the family and patient.

The optimal medical management of many cancer-related emergencies is an excellent area for further research. Many practice patterns are based on expert opinion or prior experience rather than clinical trials. Formal training for treatment of oncologic emergencies is not available and currently must be learned through work experience. Examples of frequently treated problems that could be better supported by research are treatment of hyponatremia and hypercalcemia of malignancy, rescue treatment of chemotherapy- or radiation-induced nausea and vomiting, chemotherapy- or radiation-induced diarrhea and mucositis, chemotherapy-induced peripheral neuropathic pain, pain related to colony-stimulating growth factors, dosage of steroids and radiation in malignant spinal cord compression, and acute management of narcotic-induced constipation. Other important areas include treatment of therapy-associated skin rashes and management of medical problems with unique complications, such as venous thromboembolism and acute coronary syndrome in thrombocytopenic patients and anticoagulation of patients who have metastatic disease to the brain.

In summary, the care model used for patients with oncologic emergencies must be tailored to the local medical and oncology environment; therefore, it naturally follows that different medical systems have developed different processes to care for these patients. A constant among the models discussed here is the underlying goal of care being provided to these patients by clinicians who are knowledgeable about their needs and have integrated communication with the primary oncologists. Acute care of the oncology patient is gaining recognition as an important area that could be improved upon with increased training, research, and emphasis on integration into the oncology system.

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Quality Measures for Oncologic Emergency Medicine

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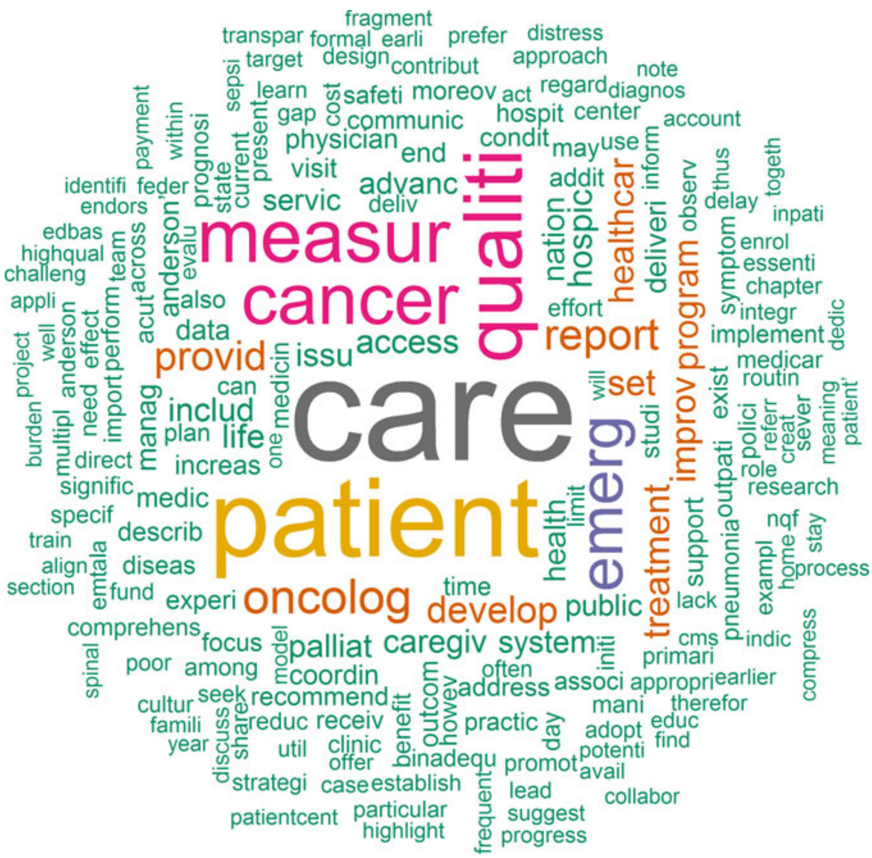

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Introduction/Background

Quality issues in the oncologic emergency care setting are well known. Common emergency department (ED) concerns include overcrowding, long wait times (perceived and actual), boarding, ambulance diversions, inadequate access to specialists, and patient handoffs. Additionally, some issues (e.g., patients with multiple visits near the end of life and those diagnosed in that ED with late-stage cancer) are well recognized in the ED but are not directly related to care delivered in the ED. Instead, they are reflective of broader cancer quality issues, such as inadequate access to and utilization of cancer prevention and diagnostic services, insufficient care coordination, fragmented healthcare delivery, poor symptom management, and underutilized hospice and palliative care services.

To address these and other healthcare quality issues, experts have developed quality measures assessing the underlying structures and processes, as well as outcomes, of care. These quality measures are used by state and federal agencies for purposes of accountability and public reporting. Increasingly, they are being used by payers for value-based payment programs. Despite the face validity and inherent appeal of public reporting and transparency of healthcare quality, there is minimal evidence linking public reporting of healthcare quality measures with meaningful improvements in the safety, appropriateness, effectiveness, and overall quality of US healthcare delivery [1, 2]. In view of these observations, it is important to consider the health policy and practice patterns that have contributed to these issues, as well as a path forward.

This chapter examines the history, current state, and desired future state of health policy for quality in oncologic emergency care. It describes observed quality issues, including upstream drivers, and highlights the important role of quality measures in addressing these issues. Additionally, it outlines recommendations for measuring quality in oncologic emergency care and proposes healthcare policy changes and quality measures that could help effect these changes. Finally, it highlights activities at The University of Texas MD Anderson Cancer Center (MD Anderson) to improve the quality of oncologic emergency care.

History and Current State of Health Policy for Quality in Oncologic Emergency Care

Much of the formal health policy that has shaped oncologic emergency care is not specific to cancer. Instead, it focuses on providers' duty to treat patients in an emergency as well as patient access to emergency medical care. This section describes two key drivers of current health policy for emergency medicine—the no-duty-to-treat principle and the Emergency Medical Treatment and Active Labor Act (EMTALA). The sections that follow explore known issues in oncologic emergency care, factors that have contributed to the current state, and historical efforts to measure the quality of US emergency care.

The No-Duty-to-Treat Principle and the Emergency Medical Treatment and Active Labor Act (EMTALA)

The no-duty-to-treat principle, which affords physicians significant autonomy in determining which patients they will serve, has been the controlling law in the USA for over a century [3]. Several state court cases have supported this principle and have generally held that duty-to-treat begins when the patient-provider relationship is established, regardless of whether the relationship is expressly agreed [4–9]. While the no-duty-to-treat principle remains the controlling law, federal and state entities have established safeguards—through statutes, regulations, and court cases—to prevent discrimination and to ensure access to emergency care [3, 10–17].

Enacted through the Consolidated Omnibus Budget Reconciliation Act of 1986 [18], EMTALA is the most influential US law affecting emergency care. The law obligates EDs to provide care to all people with an emergency medical condition, even those who are not established patients [3]. Specifically, EDs must screen, stabilize, and, where necessary, accept transfer patients, regardless of their insurance status or ability to pay. Moreover, it gives EDs the right to transfer unstable patients based on medical necessity, if the potential medical benefit outweighs the risks (e.g., transferring the patient to a facility for emergency care that is unavailable at the current facility). As an "antidumping" law, it prohibits hospitals from refusing to treat uninsured or underinsured patients, from transferring unstable patients (except where deemed medically necessary, as described above), and from refusing to accept transfer patients that require specialized emergency care that is unavailable elsewhere. EMTALA applies to all EDs at hospitals that care for Medicare beneficiaries, and EMTALA violations can lead to suspension from the Medicare program.

Over time, EMTALA's provisions have been clarified through various statutes, regulations, and court cases [3, 19–25], including the Patient Protection and Affordable Care Act of 2010 (ACA) [26, 27]. Nonetheless, many EMTALA provisions, as clarified, remain controversial. For example, EMTALA is intended to ensure equitable access to and provision of emergency care, but not to regulate the quality of care. Thus, misdiagnosis and medical negligence remain the

purview of state medical malpractice law and do not constitute EMTALA violations as long as the emergency care was delivered in good faith. Additionally, EMTALA's stabilization obligations have been held as absolute, even when care is futile due to an underlying condition or when it conflicts with a physician's moral and ethical judgment and professional standards of care. Other revisions have focused on the physical locations that fall within the jurisdiction of EMTALA, such that EMTALA applies to emergency medical conditions presenting in urgent care and outpatient care facilities (*under certain conditions*) and to hospital parking lots, driveways, and sidewalks. Importantly, outpatients with scheduled nonemergency procedures are excluded, and hospitals' stabilization duties and transfer rights and duties under EMTALA are terminated once the patient is admitted as an inpatient [3, 20, 28–30].

In summary, the no-duty-to-treat principle and EMTALA—as written and subsequently clarified—create a strong policy framework to ensure patient access to emergency medical care in the USA. EMTALA has effectively transformed EDs into a safety net for those who lack access to or cannot afford primary care. A predictable, albeit unintended, consequence is that the US emergency care system is overloaded and inadequately funded to comply with this federal mandate [31]. This compromises the quality and accessibility of emergency care for all patients, including those with a cancer diagnosis. Recognized quality issues for oncologic emergency care are described in the next section of this chapter.

Known Quality Issues

As noted previously, ED cancer patients experience many of the same issues that non-cancer patients experience, while other issues are specific to oncology patients. Moreover, some issues manifest in ED care but are more directly associated with quality issues in the primary care setting or derive from inadequate access to care. Six issues that affect cancer patients in the emergency setting are described below: (1) late-stage cancers presenting to the ED, (2) overutilization of ED services, (3) overcrowding, boarding, and diversion, (4) high costs at the end of life, (5) patient dissatisfaction with emergency care, and (6) caregiver burden. Specific issues for dedicated oncology EDs are also discussed in this section.

Late-Stage Cancers Presenting to the ED

In a well-coordinated healthcare system where patients receive routine primary care and guideline-based cancer screenings, cancer diagnoses should be made in the primary care setting. However, many undiagnosed cancers present to the ED each year [32–35], with approximately 204,000 cancers diagnosed in US EDs in 2006 [36]. This is problematic for a number of reasons. First, these patients often have nonspecific symptoms (e.g., nausea and vomiting, fatigue, and bleeding) that may be attributed to a number of different conditions. Moreover, ED physicians do not have established relationships with these patients and may lack a comprehensive medical background for them. Therefore, cancer may be misdiagnosed and treatment further delayed until the patient seeks follow-up care in the outpatient setting. Second, when patients are diagnosed in the ED, the cancers tend to be of later stage and, therefore, of poorer prognosis. Worsened outcomes, including higher perioperative mortality, lower overall survival, higher readmissions, and longer length of stay, have been observed by Mitchell et al. [33], Hargarten et al. [34], and Amri et al. [35]. Third, ED-based cancer diagnoses suggest disparities in healthcare. For example, a Michigan study of ED-based lung and colorectal cancer diagnoses demonstrated that cancer diagnoses in the ED were disproportionate among older people, African Americans, dual-eligible patients (patients eligible for Medicare and Medicaid benefits), and patients with three or more comorbidities. Of note, these patients had significantly more inpatient, outpatient, and primary care encounters in the months preceding their diagnosis than their counterparts diagnosed in a nonemergency setting [32]. This suggests that the quality, rather than the quantity, of the healthcare services received by some of these patients was insufficient to detect their cancer earlier. These findings highlight gaps in the nation's population health strategies and indicate opportunities for improved patient education, better screening adherence, earlier detection, and improved care coordination—particularly for more vulnerable populations.

Overutilization of ED Services

Cancer patients present to the ED with acute conditions, including sepsis, spinal cord compression, deep vein thrombosis, and respiratory and gastrointestinal obstruction. This is an appropriate use of emergency resources, as ED physicians are trained to diagnose and treat acute illness and injury and to stabilize patients for further treatment. However, in a 2002–2003 prospective observational study from Argentina, Diaz-Couselo et al. demonstrated that only 26 % of oncology patients seeking emergency care represented true oncologic emergencies [37]. Additionally, Wallace et al. determined that 52 % of ED presentations in their study were avoidable [38]. Together, these findings suggest significant overutilization of emergency services, where cancer patients seek care in the ED for symptoms associated with progression of disease and treatment side effects that could be effectively managed in the outpatient setting. Cancer patients seeking emergency care often have several interrelated symptoms, including pain, fatigue, dyspnea, nausea, dehydration, depression, and cognitive impairment. Chronic pain, in particular, is a frequent complaint among cancer patients visiting the ED. Evaluating and managing these symptoms

independently is insufficient. With inadequate attention to and coordination of symptom management, cancer patients make frequent visits to the ED, especially near the end of life [39]. Several observational studies have examined the utilization of ED services among cancer patients at the end of life. The findings of these studies vary, with 27–37 % of the studied cohorts having an ED visit in the last 14 days of life and 7–19 % of the studied cohorts having multiple ED visits in the last 30 days of life [40]. Similarly, in a 2010 study of hospice enrollees, Carlson et al. found that patients that disenrolled from hospice were significantly more likely to have an ED visit compared to their continuously enrolled counterparts (33.9 % vs. 3.1 %) [41].

Frequent ED visits have been identified as an indicator of poor quality of care [42]. Aprile et al. concluded that over 50 % of unplanned visits at an acute oncology clinic were repeat presentations [43]. In some cases, repeat ED visits indicate healthcare access issues, with cancer patients receiving care in the emergency setting that could be delivered in a less costly outpatient setting. In other cases, repeat ED visits indicate that patients—in particular, patients with complex comorbidities, impaired performance status, or poor prognosis—are receiving overly aggressive treatment (e.g., chemotherapy), where the treatment toxicities outweigh the potential clinical benefits. Repeat ED visits may also indicate delayed access to hospice and palliative care services or that caregivers are not adequately prepared to manage and cope with the patient's burden of disease at home. Furthermore, repeat ED visits may indicate that patients are receiving inadequate discharge instructions or follow-up care coordination or that the patients' symptoms were inadequately managed during the initial ED visit. These trends highlight the need for more selective use of aggressive treatment, improved symptom management, and earlier introduction of advance care planning. Likewise, greater access to palliative and hospice care, same-day/next-day physician appointments, and 24/7 access to providers may reduce ED utilization by cancer patients, particularly at the end of life. These care delivery approaches are discussed later in this chapter.

Overcrowding, Boarding, and Ambulance Diversion

The demand for emergency services routinely exceeds ED capacity, with most EDs (especially in large urban areas) reporting problems with overcrowding. ED crowding has worsened over time, due to coalescing system-level issues, including ED closures, inadequate or delayed access to primary and specialty care, and higher rates of uninsurance and underinsurance [44]. ED crowding is worsened by ED "boarding," where admitted patients remain in the ED for hours—*even days*—until a hospital bed becomes available. ED boarding has become routine for most EDs and is the product of high inpatient census rates and inefficient admission processes [31]. ED overcrowding and extended ED boarding have been associated with treatment delays, increased risk for medical errors, patients leaving the ED without being seen, compromised quality of care and patient experience with care, and poorer outcomes, including longer lengths of stay and higher inpatient mortality rates [45–48].

Unmanaged ED crowding and prolonged ED boarding contribute to ambulance diversion. Once a practice reserved for catastrophic events, diversion has become increasingly common, particularly in urban areas. Diversion can place patients with acute conditions at significant risk by delaying treatment or by redirecting patients to EDs that lack the resources and expertise to optimally care for their severity of illness [31]. Furthermore, extended diversion time has been associated with adverse patient outcomes, particularly for patients with life-threatening conditions [49–52]. Together, ED overcrowding, extended boarding, and ambulance diversion contribute to a stressful work environment for ED providers and increase patients' risk for adverse events and poorer outcomes. Accordingly, experts have advocated for stronger standards to reduce these practices [31]. While these findings and recommendations are generalized to emergency care and are not specific to oncologic emergency care, they nonetheless have important implications for cancer patients seeking ED care.

High Costs at The End of Life

In 2010, an estimated $38 billion was spent on end-of-life care for cancer patients in the USA. By 2020, those costs are projected to increase to between $49 billion and $74 billion, representing up to 36 % of total spending for cancer care in the USA [53]. This high level of spending at the end of life has been attributed to fragmented healthcare delivery, frequent transitions between care settings, inadequate care coordination, lack of access or delayed access to palliative and hospice care, and overutilization of aggressive treatment for patients with advanced disease. Additionally, under the current fee-for-service environment, providers are paid based on the quantity, rather than the quality, of services delivered. This creates financial incentives for providers to deliver low-value, high-cost, and high-intensity services, even at the end of life. For example, Vera-Llonch et al. estimated total healthcare spending at nearly $126,000 and $129,000 for patients receiving chemotherapy for metastatic lung cancer and metastatic breast cancer, respectively [54, 55]. Additionally, in a study of patients with stage IV breast, colon, lung, and prostate cancers, Hu et al. determined that one-third of patients received a high-cost advanced imaging study (computerized topography or CT, magnetic resonance imaging or MRI, positron emission tomography or PET, and nuclear medicine or NM) in the last month of life, with the

top 10 % receiving three of these imaging studies in the last month of life [56]. Moreover, research from the Dartmouth Atlas Project suggests that Medicare beneficiaries with terminal cancer receive overly aggressive treatment at the end of life, with 29 % dying in an acute care setting [57]. Aggressive treatment at the end of life is not associated with better survival, quality of life, or access to care, but it contributes to unsustainable national healthcare spending on end-of-life care. Since Americans have ranked treatment costs and financial burden to family members as their biggest concerns when faced with a life-limiting illness [58, 59], healthcare costs exacerbate emotional distress among patients with a poor prognosis.

Significant variation in end-of-life costs has been observed between geographic areas and between hospitals, and a seminal study by the Dartmouth Atlas Project identified the availability of healthcare resources, rather than patient acuity or patient preference, as the most significant contributing factor [60]. Moreover, in 2013, a committee convened by the Institute of Medicine (IOM) found that variation in acute care and post-acute care contributed to 89 % of variation in total Medicare spending [61]. This has important implications for the overutilization of services at the end of life (including ED visits) and suggests that better care coordination may reduce spending for these patients.

Patient Dissatisfaction with Emergency Care

Overcrowding, poor patient handoffs, and extended wait times—perceived and actual—in the ED compromise patient experience and contribute to patients leaving the ED without being seen [39, 62–64]. Historically, patient experience with ED care has not been systematically measured in the USA. However, a number of studies in the USA and abroad have attempted to identify factors that influence patient satisfaction (and dissatisfaction) with emergency care. The findings are mixed [65–67]. Provider communication, courtesy, empathy, and competence, together with patient perception regarding wait time, have been associated with overall satisfaction [67–69]. Because ED physicians often lack an established relationship with patients and because they balance multiple patients of varying acuity, they face significant challenges to timely and accurate communication [70]. Therefore, patient satisfaction may be improved by expanding ED provider access to patient records across care delivery systems and by training ED providers to initiate more frequent and targeted communication, particularly regarding wait times.

Some studies have shown higher satisfaction among ED patients of higher acuity (and vice versa) [71–73]. Additionally, lower-acuity patients have expressed greater dissatisfaction with wait times and costs of care than their higher-acuity counterparts [72]. This difference may be attributed to two factors. First, urgent or emergent ED patients likely will be triaged more quickly than their nonurgent counterparts. Second, the fact that lower-acuity patients could be seen more quickly—and at a lower cost—in an outpatient setting may contribute to their dissatisfaction. Redirecting lower-acuity patients from the ED to more appropriate outpatient settings may help address this issue.

In 2012, the Centers for Medicare & Medicaid Services (CMS) contracted with the RAND Corporation to develop and validate a Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey for emergency care—the Emergency Department Patient Experience of Care (EDPEC) Survey. Three preliminary survey instruments were developed, based on patient disposition (i.e., discharge to the community vs. hospital admission). These instruments include four composites that measure patient experience with timeliness of care, communication regarding medications, physician and nurse communication, and discharge communication. Of note, preliminary testing identified poorer experience with provider attentiveness and communication among patients discharged to the community when compared to their counterparts that were admitted to an inpatient setting [74]. Clearly, further testing is needed to understand these differences in patient experience. Following further validation and adoption by CMS, these surveys likely will yield important findings regarding patient experience with ED care.

Caregiver Burden

Family caregivers experience significant financial, social, physical, and psychological distress while caring for relatives with debilitating and chronic conditions, such as cancer. As cancer care continues to shift to the outpatient setting, caregivers face increasing pressure to help their loved one navigate a complex and fragmented care delivery system and to manage much of their loved one's burden of treatment and disease at home while receiving limited training and support [75]. In a 2011 survey conducted by AARP, Inc. and the United Hospital Fund, 46 % of caregivers of patients with multiple chronic conditions reported performing medical care (e.g., medication management and operating specialized medical equipment) for their loved one. Additionally, 53 % of caregivers reported serving as care coordinators [76]. To prepare family members to meet the demands of their caregiver role, the IOM recommended that healthcare agencies, including the Department of Health and Human Services (HHS), fund demonstration projects to train caregivers of cancer patients for their demanding role [75].

Several studies have described morbidity in caregivers of cancer patients [77–79]. For example, Braun et al. reported significant symptoms of depression in nearly 39 % of caregivers of patients with advanced cancer [80]. Moreover,

Grunfeld et al. observed that caregivers of patients with advanced breast cancer experienced anxiety and depression that were equal to or greater than the patient's anxiety and depression [81]. Place of death was also shown to affect caregiver well-being. Wright et al. associated ICU death and inpatient death with increased caregiver risk for post-traumatic stress disorder and prolonged grief disorder, respectively, when compared with death at home [82]. Researchers have also described lifestyle interference among caregivers of cancer patients. Wadhwa et al. determined that 25 % of caregivers experienced a change in work status while caring for someone with advanced cancer [83]. Furthermore, Mazanec et al. estimated a 23 % loss of work productivity among caregivers [84]. This is problematic, since increased lifestyle interference due to caregiver duties increases caregiver emotional distress [85]. High stress among caregivers can interfere with their ability to provide logistical and emotional support to the cancer patient [86]. Caregiver emotional distress can also negatively affect the patient's well-being. Through two longitudinal studies of partners of breast cancer patients, Segrin et al. observed increased fatigue, symptom distress, anxiety, and depression among patients as emotional distress among caregivers increased [87, 88]. Therefore, it is essential for providers to assess patient and caregiver emotional well-being, burden, unmet needs, and social support through routine monitoring and to provide targeted psychosocial support for patients and their caregivers throughout the continuum of care. Additionally, it is imperative for professional and patient advocacy organizations to develop educational materials and support programs to help caregivers manage their distress.

Specific Issues for Dedicated Oncologic EDs

Dedicated oncologic EDs face additional pressures to coordinate care. For example, some patients with a cancer diagnosis seek entry to a free-standing cancer center [89] or another National Cancer Institute-designated comprehensive cancer center [90] through a dedicated ED at that center, if one exists. Thus, for some cancer patients, the ED serves as an interface or gateway into specialized oncology care systems. However, entry into a dedicated oncology ED is no guarantee of access to oncology care. Additionally, EDs at other hospitals may seek to transfer an uninsured or underinsured cancer patient to a specialized cancer center through its dedicated ED on the basis of an oncologic emergency that the transferring center is unable to manage. While the receiving ED has the duty to screen and stabilize the patient in the ED, there is no duty to admit the patient, once stabilized, for further treatment of the patient's health issue or underlying cancer. Thus, cancer patients may be bounced between multiple care settings, placing them at greater risk for receiving unsafe and poorly coordinated care.

Upstream Drivers

In the preceding section of this chapter, we discussed six quality issues affecting oncologic emergency care. We also described specific issues for dedicated oncologic EDs. Often, these issues arise when cancer patients seek ED care, but they are more directly associated with care delivery issues in the primary care setting or with inadequate access to care. Six upstream drivers that compromise ED-based oncology care are described below: (1) poor care coordination, (2) underutilized advance care planning, (3) inadequate access to palliative care, (4) delayed hospice referral and the hospice reimbursement model, (5) limited availability of immediate and after-hours outpatient care, and (6) unrealistic patient/caregiver expectations regarding prognosis and treatment.

Poor Care Coordination

Fragmented healthcare delivery and poor care coordination are well documented for the elderly, for the uninsured and underinsured, and for patients with chronic and life-threatening conditions. Because cancer patients frequently move between care settings—including oncology care, primary care, community and specialty hospitals, EDs, hospice, and long-term care—their treatment is often fragmented. Yet, strong care coordination is imperative for superior management of a complex disease, such as cancer, where care is typically delivered by multiple providers and, increasingly, on an outpatient basis. Outpatient intravenous chemotherapy and radiation therapy are delivered to an estimated 1.1 million Americans each year [91]. Moreover, increasing numbers of complex procedures, such as bone marrow transplant, stem cell transplant, and mastectomy without immediate reconstruction, are performed in the outpatient setting. Shifting these services to outpatient settings has many benefits for patients, reduces healthcare costs, and eases the demand for inpatient resources. However, it places patients at increased risk for unmanaged pain, infection, febrile neutropenia, anemia, dehydration, nausea and vomiting, gastrointestinal distress, and dyspnea that lead patients to seek care in the ED. Thus, ED visits and, in particular, repeat ED visits indicate that patient needs are unmet elsewhere, such as in the outpatient setting, or that caregivers are unprepared to care for their loved one's disease at home. This is principally true at the end of life, where cancer patients with poorly managed symptoms or with symptom distress associated with progression of disease frequently present at the ED.

Inadequate care coordination by the primary oncology team places ED care teams in the challenging and unlikely role of oncology care coordinator. However, as previously noted, ED physicians are trained to manage acute injury and illness and to stabilize patients for further treatment. Moreover, many ED physicians are uncomfortable with

addressing end-of-life issues in cancer patients [64]. Therefore, inadequate coordination in other care settings places added pressure on overextended ED physicians to ensure that they direct patients to appropriate follow-up care (including hospice or palliative care) and to connect with patients' primary care physicians and oncology providers.

Underutilized Advance Care Planning

Advance care planning allows patients to consider their end-of-life preferences, to communicate those preferences to their family members, caregivers, and healthcare providers, and to document their preferences regarding life-sustaining procedures in a legally binding advance directive. Ideally, advance care planning begins during treatment planning and is revisited periodically throughout treatment and if the patient's prognosis worsens. For cancer patients, it should include ongoing communication between patients, caregivers, and providers across care delivery settings in order to tailor treatment choices (including decisions regarding the intensity of care at the end of life) to align with patient goals and preferences. The National Comprehensive Cancer Network (NCCN) recommends initiating advance care planning for patients with a life expectancy of 1 year or less [92]. For patients with advanced disease, advance care planning is critical to delivering patient-centered care and is essential to align treatment plans with patient values and preferences for quality of life, treatment intensity, and life-prolonging treatment. Early findings indicate that advance care planning has several benefits: reduced aggressive treatment and increased hospice referral at the end of life [93], better alignment between patient preferences and care at the end of life [94], and improved satisfaction and reduced stress and anxiety for patients and their families [95].

Despite the potential benefits of advance care planning, end-of-life care discussions are often delayed until death is imminent [96] and all curative treatment options are exhausted [97]. Furthermore, researchers have observed large proportions of cancer patients presenting to the ED without an advance directive [98, 99]. Even when patients have an advance directive, its usefulness in the emergency care setting is limited if the ED care team is unaware of its existence or lacks access to it. With the sudden onset of an acute, life-threatening illness or critical decline of health status, the absence of, or delayed access to, a patient's advance directive may prevent the ED team from honoring patient wishes regarding life-prolonging treatment since these patients frequently are unable to communicate their wishes to their ED care team.

Of note, efforts to improve advancing care planning have focused on executing advance directives for patients with poor prognosis. Completion of advance directives is an integral component of advance care planning. However, advance care planning is much broader and includes thoughtful consideration of patient preferences regarding life-sustaining procedures and place of death as well as treatment intensity and quality of life at the end of life. Thus, future efforts should focus on implementing coordinated, systematic, and patient-centered approaches to initiate advance care planning much earlier in the trajectory of disease, especially for patients with later-stage diagnoses.

Inadequate Access to Palliative Care

Palliative care can ease the burden of cancer throughout the continuum of care by addressing the physical and psychosocial effects of the disease and its treatment. Researchers propose that early palliative care initiation improves symptom management and quality of life [100, 101] while reducing healthcare spending and utilization of acute care and emergency services [102–104]. It has also been associated with improved survival in some patients [105], whereas poor health-related quality of life has been associated with poorer survival [106–109]. Moreover, early palliative care referral has been associated with more realistic expectations regarding cancer prognosis [110]. Despite recent growth in palliative care programs across the USA [111, 112], most palliative care programs are inpatient-based, and outpatient palliative care clinics are offered more frequently in National Cancer Institute-designated cancer centers [111, 112]. Therefore, palliative care services are not readily accessible for many cancer patients. Additionally, palliative care referrals may be delayed due to perceptions among oncologists that palliative care and curative treatment must follow sequential, rather than concurrent, pathways [113]. Consequently, palliative care needs often are unmet in the healthcare system and in the ED, and patients with distress associated with advanced disease or high symptom burden frequently seek care in the ED, particularly at the end of life.

To reduce barriers to timely palliative care, experts have recommended integrating palliative care with ED services [114–116]. However, the benefits of ED-based palliative care are as yet unproven, and researchers have identified several barriers to integrating palliative care practice in the ED; these include inadequate palliative care training, an ED culture that favors aggressive treatment, and provider fear of being sued [117, 118]. This highlights opportunities for health services research to investigate formally the barriers to ED-based palliative care and to test strategies to address those barriers. Four research priorities were defined in 2009 by a joint workgroup of the Agency for Healthcare Research and Quality (AHRQ) and the American College of Emergency Physicians (ACEP):

1. Which patients are in greatest need of palliative care services in the ED?
2. What is the optimal role of emergency clinicians in caring for patients along a chronic trajectory of illness?

3. How does the integration and initiation of palliative care training and services in the ED setting affect healthcare utilization?
4. What are the educational priorities for emergency clinical providers in the domain of palliative care? [119]

Focused research in these areas will reveal potential clinical and economic benefits of ED-based palliative care and can help expedite the development of validated models for integrating palliative care with ED services. Moreover, continued experimentation with, and early adoption of, best practices and guidelines for ED-based palliative care, such as those made available through the *Improving Palliative Care in Emergency Medicine* (IPAL-EM) initiative, will provide important insights into the benefits of and roadblocks to delivering ED-based palliative care [120].

Delayed Hospice Referral and the Hospice Reimbursement Model

Hospice programs can deliver excellent end-of-life care for cancer patients with a life expectancy of 6 months or less. Ideally, these programs offer team-based comprehensive and interdisciplinary palliative care in the patient's home, thereby maximizing patient comfort and quality of life at the end of life. Electing hospice care requires patients to forgo curative treatment and is an appropriate choice for patients with poor prognosis or when the risks or complications of treatment outweigh the potential benefits. Hospice referrals have increased significantly since the Medicare hospice benefit was created by the Tax Equity and Fiscal Responsibility Act of 1982 [121], with 1.27 million Medicare beneficiaries receiving hospice services in 2012. From 2000 to 2012, hospice enrollment among Medicare decedents more than doubled (from 22.9 % in 2000 to 46.7 % in 2012). The timing of hospice referral, although delayed, has also improved. Average length of hospice stay for Medicare decedents was 88 days in 2012 vs. 54 days in 2000. Median length of hospice stay remained relatively stable, however (18 days in 2012 vs. 17 days in 2000). This indicates longer hospice stays for patients with the longest hospice stays, along with opportunities to extend hospice stays for all enrolled beneficiaries—principally for cancer patients. Moreover, it indicates that many patients are enrolling in hospice too late to benefit fully from the team-based comprehensive and interdisciplinary palliative care that hospice programs offer. In 2012, cancer patients continued to lag behind non-cancer patients, with average length of hospice stay at 51 days for cancer patients vs. 139 days and 112 days for patients with neurological conditions and chronic obstructive pulmonary disease, respectively. Likewise, the share of hospice decedents with cancer declined from 52 to 32 % between 2000 and 2012 [122]. These findings highlight opportunities to introduce hospice referral earlier for patients with a terminal cancer diagnosis.

Several barriers have been identified to earlier hospice referral. These include patient and family difficulty accepting a terminal cancer prognosis, provider discomfort with introducing end-of-life discussions, and financial incentives to keep patients in the acute care system [122]. Desired intensity of care also represents a significant barrier to earlier hospice enrollment due to the eligibility criteria and benefit design. In the USA, hospice care delivery is largely defined by the Medicare Hospice Benefit. To qualify for the Medicare Hospice Benefit, patients must have a life expectancy of 6 months or less (as certified by two physicians) and must agree to forgo curative treatment. Once patients are enrolled, Medicare pays hospice providers a per diem rate per enrollee—$156/day base payment rate for routine home care and $694/day base payment rate for general inpatient care in 2014—regardless of the intensity of care required by the patient [122]. Hospice providers then assume financial responsibility for all care related to the patient's terminal illness. Patients with advanced cancer often benefit from palliative radiation and chemotherapy, opioids, and parenteral nutrition. These treatment costs may be substantial [123] and may greatly exceed the Medicare Hospice Benefit. Accordingly, hospice providers may be discouraged from enrolling high-cost cancer patients [124]. Many hospice providers have implemented restrictive enrollment policies aimed at reducing these costs. A 2008–2009 survey of US hospice providers found that 55 % of respondents restricted total parenteral nutrition, while 61 and 30 % of respondents restricted chemotherapy and palliative radiation, respectively [124]. These restrictions present many patients and caregivers with the dilemma of electing hospice care or comfort care at the end of life [123].

The ACA mandated a 3-year pilot of concurrent hospice and traditional care to determine its effect on the quality and costs of care [125]. As of 2014, this demonstration project has not been funded. However, Aetna conducted a similar pilot—extending hospice eligibility to patients with a life expectancy of 12 months or less—and observed increased hospice enrollment, lower utilization of acute care services, and a 22 % reduction in costs [126]. Additional demonstration projects should be conducted to help public and private payers design benefits that promote better quality of life, appropriately timed hospice enrollment, and, where appropriate, integrated hospice and acute care delivery.

Limited Availability of Immediate and After-Hours Outpatient Care

Experts suggest that many ED visits are for non-emergent complaints that could be effectively and affordably managed in the outpatient setting. For example, Hansagi et al. observed that two-thirds of ED patients in their study were primary care cases, but the patients could not get in to see their physician or were referred to the ED for care [71]. Similarly, Mayer et al. conducted an observational study of ED visits in North

Carolina and found that 44.9 % of ED visits occurred during normal clinic hours. Less than one-fifth of those patients were admitted to the hospital [127]. These findings suggest opportunities to manage these patients by providing more immediate access to outpatient oncology care, such as through same-day/next-day appointments or 24/7 provider access.

The effectiveness of these practices is being tested through oncology-specific patient-centered medical homes (PCMH). The PCMH is a primary care delivery model designed to provide comprehensive, well-coordinated, patient-centered care (including preventive, chronic, and acute care) by promoting access to care and a systems-based approach to safety and quality [128]. When applied to oncology, this model is proposed to support integrated primary and oncology care in the community setting. Consultants in Medical Oncology and Hematology (CMOH) is the first oncology practice designated as a level III PCMH by the National Committee for Quality Assurance (NCQA). CMOH began reengineering its processes in 2004 to improve patient engagement and symptom management. CMOH experienced a 68 % decrease in ED referrals by 2010, due to the following interventions: expanded patient access to clinical staff, standardized patient assessments, patient empowerment, and utilization of advanced health information technology (health IT or HIT), including an oncology-specific electronic health record (EHR) and a telephone triage system [129, 130]. A broader pilot—Community Oncology Medical HOME (COME HOME)—is now underway with funding from the CMS Innovation Center [131]. COME HOME is piloting similar approaches, such as 24/7 provider access and a telephone triage system, to deliver more coordinated cancer care. The findings of the COME HOME pilot, together with CMOH's experience, should be studied to determine the generalizability of these approaches to cancer care in the community and at academic medical centers.

Unrealistic Patient/Caregiver Expectations Regarding Prognosis and Treatment

Patient preference regarding treatment intensity is influenced by health literacy, provider mistrust, family dynamics, religious beliefs, and other cultural and religious factors [132, 133]. For cancer patients to make treatment decisions that are consistent with their preferences and values, they must have an accurate understanding of their treatment options and prognosis. Moreover, this is essential to reduce unnecessary and futile care, since patients who understand their prognosis prefer symptom-directed care [94], whereas patients that overestimate their prognosis are more likely to receive aggressive treatment of questionable benefit [134]. A number of studies have confirmed that patients with advanced disease frequently overestimate their prognosis or misunderstand the intent of their cancer treatment [101, 135–138]. For example, Temel et al. published a study of newly diagnosed patients with metastatic lung cancer in 2011, noting that 32 % of respondents considered their cancer curable and that 69 % of respondents believed they were receiving curative, rather than palliative, treatment [110]. Likewise, Weeks et al. reported that 69 and 81 % of patients with metastatic lung and colorectal cancer, respectively, did not understand that they were receiving palliative chemotherapy [139].

Patient and caregiver misunderstandings about prognosis or treatment intent reflect communication challenges between patients, their caregivers, and providers. In some cases, patients receive accurate prognostic information, but do not understand or do not accept their prognosis. In other cases, physicians may be reluctant to provide this information, will do so only when asked by the patient, or will provide inflated survival estimates to their patients [136, 138–140]. Mack and Smith attributed provider communication issues to discomfort with these discussions and concerns regarding patient depression, reduced hope, cultural appropriateness, and uncertainty in estimating prognosis [141]. In 2013, the IOM recommended five strategies for improving patient-centered communication and shared decision-making for cancer patients:

1. Making more comprehensive and understandable information available to patients and their families.
2. Developing decision aids to facilitate patient-centered communication and shared decision-making.
3. Prioritizing clinician training in communication.
4. Preparing cancer care plans.
5. Using new models of payment to incentivize patient-centered communication and shared decision-making [75].

Implementing these approaches will assist providers in communicating prognosis and treatment intent and would contribute to more realistic assessments among patients and their caregivers. Most importantly, physicians should seek to understand their patients' preferences for prognostic information and adapt their communication styles accordingly.

Role of Quality Measures

Healthcare quality measures provide objective and subjective assessments of the consequences of healthcare, transforming medical practical into a quantitative discipline. Experts have developed quality measures to evaluate multiple components of care, including the underlying structures and processes of care as well as the outcomes of care and, to a limited degree, the costs of care. Moreover, there is continued interest in measuring patient experience with care and, increasingly, caregiver burden and experience with care. Some measures are developed for a specific health condition (e.g., breast cancer) or care delivery setting (e.g., ED). Other measures are crosscutting, applying to a variety of health conditions or care delivery settings.

In this section, we describe the history of quality measurement in emergency medicine, provide examples of existing ED quality measures that are relevant to cancer care, and discuss the limitations of these measures.

History of Quality Measurement in Emergency Medicine

National quality measurement for emergency medicine began in the early 2000s as part of CMS' Reporting Hospital Quality Data for Annual Payment Update (RHQDAPU) program. The RHQDAPU program was a voluntary CMS quality reporting program that became the Inpatient Quality Reporting (IQR) program in 2010. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) introduced financial incentives for hospitals to report data on ten quality measures for pneumonia, acute myocardial infarction (AMI), and congestive heart failure via the RHQDAPU program [142, 143]. These measures were developed through the Hospital Quality Alliance, a public/private partnership whose members included CMS, the Joint Commission, the American Hospital Association, and healthcare consumer groups [144]. In 2004, these data were published as the first national comparative dataset for ED quality. The financial incentives created under the MMA were later strengthened by the Deficit Reduction Act of 2005 (DRA) [145] and expanded to include measures for hospital-based outpatient care under the Tax Relief and Health Care Act of 2006 [146].

Subsequent public and private sector efforts have also focused on enhancing ED quality measurement. For example, in 2006, the American Medical Association's Physician Consortium for Performance Improvement (AMA-PCPI), ACEP, and NCQA jointly developed physician-level ED measures for pneumonia, chest pain, and syncope [147, 148]. Additional independent measure development projects were undertaken by hospitals, by CMS, and by professional organizations, such as ACEP. These efforts focused on specific aspects of care (e.g., timeliness of care and ED communication). Attention was also directed toward disease-specific measures of morbidity, mortality, and resource use [148–151]. Likewise, two Performance Measures and Benchmarking Summits were convened in 2006 and 2010, and participants proposed a wide range of metrics: operational metrics (e.g., ED census), timestamp and interval metrics (e.g., ED length of stay), proportional metrics (e.g., left without being seen), and utilization metrics (e.g., specialty consultations) [152, 153]. More recently, Stone-Griffith et al. developed the ED Dashboard and Reporting Application to support data-driven ED performance improvement projects by routinely measuring ED throughput [154].

In parallel, the National Quality Forum (NQF) launched a two-phase project endorsing a national measure set for ED care. The NQF is a nonprofit organization that uses a consensus development process to endorse healthcare quality measures for use in federal public reporting programs. Between 2007 and 2009, the NQF endorsed 22 measures for ED care, including nine measures that were given time-limited endorsement (temporary endorsement, pending completion of measure testing and validation) [149, 155]. These measures are included in Table 1. Some of these measures were adopted for CMS public reporting programs, including the IQR program, Meaningful Use (MU) Stage 2 EHR Incentive Program, Outpatient Quality Reporting (OQR) program, and Physician Quality Reporting System (PQRS) program. Over time, many of these measures have been retired from these federal reporting programs or are no longer endorsed by the NQF [156]. As of January 2015, there are 24 ED quality measures endorsed by the NQF, including 11 ED quality measures used in CMS reporting programs (Table 1). ED measures relevant to cancer care and the limitations of those measures are summarized in the following section and in Table 2.

Limitations of Existing Quality Measures for Emergency Departments

Despite the ED measure development efforts to date, existing measures have substantial limitations. For example, ED measures have been incorporated in federal public reporting programs, including the IQR, MU, OQR, and PQRS programs. However, there is no nationally mandated public reporting program specific to emergency care. Hence, patients lack a clear, dependable resource for information on ED provider performance. Additionally, the ED measures currently collected and publicly reported by CMS are largely provider-oriented, reflect fragmented care delivery, and lack a clear method to address upstream care delivery challenges that often present in the ED. Due to these factors, current reporting efforts offer limited potential to improve substantially the quality of ED care for cancer patients. Five limitations of ED quality measurement in the USA are briefly discussed below: (1) gaps in existing ED measures, (2) fragmented measure development, (3) difficulty defining an episode of oncologic emergency care, (4) measurement without a clear mechanism for improving ED care, and (5) challenges in obtaining ED quality data.

Gaps in Existing ED Measures

A robust ED measure set for cancer patients should assess multiple dimensions of oncologic emergency care, such as access to care, care coordination, advance care planning, patient and family engagement, and evaluation and management of acute and chronic conditions and psychosocial needs. Routine measurement of the outcomes and costs of care as well as appropriate resource utilization is also essential. Yet, no existing measure set or quality reporting program adequately measures these aspects of oncologic emergency care. As noted above, 24 ED quality measures are

endorsed by the NQF as of January 2015. Thirteen of these measures are relevant to cancer care, including one cancer-specific measure. An additional ED measure has been developed specifically for cancer care, but it has not been endorsed by the NQF. Current ED measurement gaps relevant to cancer care span all measure categories (i.e., outcomes, structure, process, cost-of-care, efficiency, and patients' perception-of-care) and include cancer-specific ED measures. These measurement gaps, together with recommendations to address these gaps, are summarized in Table 2.

Fragmented Measure Development

Historically, ED measure development efforts in the USA were academic-led and focused on specific patient populations or clinical conditions. These initiatives were conducted independently of payers and state and federal agencies, leading to a "patchwork of measures" for ED care [148]. These independent measure development efforts have contributed to the fragmented ED quality measurement observed today, which undermines efforts to deliver high-quality, patient-centered care. With the exception of AMI ED measures (e.g., NQF measure #0286—*Aspirin at Arrival*), which have been adopted in several public reporting and reimbursement programs, the existing measures have not been widely adopted by providers or payers [148]. Thus, most ED care is not routinely measured, and existing quality measures provide an incomplete view of the nation's ED system. A well-coordinated approach to developing ED quality of care measures for oncology is discussed later in this chapter.

Difficulty Defining an Episode of Oncologic Emergency Care

Defining an episode of emergency care is challenging for most conditions, since the expected prognosis, treatment time, and time to recovery can vary greatly by condition and across patients. Moreover, patients can receive care for their acute health event from multiple providers and across multiple care settings, all of which contribute to the patient's final health outcome [31]. For cancer patients, defining standardized episodes of emergency care is problematic for two reasons. First, cancer patients move frequently—and often unpredictably—between care settings throughout the continuum of care. Therefore, cancer patients may present to the ED before diagnosis (for late-stage cancers presenting to the ED), at any point during treatment, and at the end of life. Second, the sequelae of cancer and its treatment vary greatly across patients. Therefore, cancer patients can present to the ED with symptoms of varying severity, ranging from moderate dehydration to life-threatening sepsis, making it difficult to standardize oncologic emergency treatment pathways across patients. Because episodes of oncologic emergency care can vary so greatly across patients, it is difficult to develop quality measures and appropriate benchmarks for care. Focused health service research is needed to develop episodes of oncologic emergency care with well-defined endpoints to support the development of relevant quality measures for this setting.

Measurement Without a Clear Mechanism for Improving Care

Quality measures designed for performance improvement and accountability should align with evidence-based guidelines, be actionable by clinicians, and have a clearly defined relationship with patient outcomes. Moreover, measures should be reported publicly to inform healthcare consumers and to drive improvements in care. Public reporting of ED performance data has been proposed as a critical lever for improving the nation's emergency care system [31]. Experience with publicly reported ED measures has produced mixed results, however. Some public reporting initiatives (e.g., AMI performance measures) have led to significant improvements in care, while others (e.g., pneumonia performance measures) have yielded disappointing results or—even worse—poorer quality of care. In those cases, the measures were misaligned with the existing guidelines, were based on weak evidence, or included arbitrary time points [148]. These factors limit the utility of existing quality measures to support meaningful improvements in care.

Faulty or unclear provider attribution can also impede efforts to address quality of care issues. For example, NQF measure #0211—*Proportion with more than one emergency department visit in the last days of life*—is designed for reporting by hospitals and acute care facilities. However, as previously described, end-of-life ED visits can be associated with poor care coordination or inadequate symptom management in other settings. Therefore, ED reporting of this important end-of-life measure will fail to uncover—and ultimately improve—quality of care issues in upstream care settings and may lead to erroneous conclusions regarding the quality of care in some EDs. Furthermore, because cancer patients move between a variety of care settings, multiple providers and care settings share responsibility for their outcomes of care. Ideally, existing quality measurement programs could be leveraged to measure the quality of care across providers and care settings. However, the current programs are too narrowly focused to support a broad, system-level approach to measuring the quality of emergency care. Currently, federal quality reporting programs are organized around CMS' payment programs (e.g., the PQRS program applies to physician payments under the Medicare Physician Fee Schedule.). Measures in these programs often leverage administrative claims data, which differ between physician and hospital payment programs. Thus, ED quality measures adopted for the PQRS program (e.g., NQF measure #0092—*Emergency Medicine: Aspirin at Arrival for Acute Myocardial Infarction (AMI)*) are not easily applied to hospital-level reporting, which limits their ability to improve

Table 1 NQF-endorsed measures for emergency care: past and present

NQF ID	Measure title (1)	Measure description (1)	Reporting level	Measure owner (1, 2)	Measure target (type) (1)	Year endorsed	Current status	CMS program (3)	Relevant to cancer care? (4)
0025	Management plan for people with asthma	Percentage of patients for whom there is documentation that a written asthma management plan was provided either to the patient or the patient's caregiver OR, at a minimum, specific written instructions on under what conditions the patient's doctor should be contacted or the patient should go to the emergency department	Clinician	IPRO	Asthma (process)	2009	Endorsement removed (*Oct 2012*)		No
0090	Emergency Medicine: 12-Lead Electrocardiogram (ECG) Performed for Non-Traumatic Chest Pain	Type of score: proportion percentage of patients aged 40 years and older with an emergency department discharge diagnosis of non-traumatic chest pain who had an ECG performed	Clinician	AMA-PCPI	Cardiovascular (process)	2007	Endorsed	PQRS	No
0092	Emergency Medicine: Aspirin at Arrival for Acute Myocardial Infarction (AMI)	Type of score: proportion percentage of patients, regardless of age, with an emergency department discharge diagnosis of AMI who had documentation of receiving aspirin within 24 h before emergency department arrival or during emergency department stay	Clinician	AMA-PCPI	Cardiovascular (process)	2007	Endorsed	PQRS	No
0093	Emergency Medicine: 12-Lead Electrocardiogram (ECG) Performed for Syncope	Type of score: proportion percentage of patients aged 60 years and older with an emergency department discharge diagnosis of syncope who had an ECG performed	Clinician	AMA-PCPI	Cardiovascular (process)	2007 (6)	Endorsement removed (*Feb 2014*)	PQRS	No
0094	Assessment of Oxygen Saturation for Community-Acquired Bacterial Pneumonia	Percentage of patients aged 18 years and older with the diagnosis of community-acquired bacterial pneumonia with oxygen saturation assessed	Clinician	AMA-PCPI	Pneumonia (process)	2007 (6)	Endorsement removed (*Dec 2011*)		No
0095	Assessment Mental Status for Community-Acquired Bacterial Pneumonia	Percentage of patients aged 18 years and older with the diagnosis of community-acquired bacterial pneumonia with mental status assessed	Clinician	AMA-PCPI	Pneumonia (process)	2007 (6)	Endorsement removed (*Dec 2011*)		No
0148	Blood cultures performed in the emergency department prior to initial antibiotic received in hospital	Percentage of pneumonia patients 18 years of age and older who have had blood cultures performed in the emergency department prior to initial antibiotic received in hospital	Facility	CMS	Pneumonia (process)	2007	Endorsement removed (*Oct 2012*)	IQR; VBP	No
0151	Initial antibiotic received within 6 h of hospital arrival	Percentage of pneumonia patients 18 years of age and older who receive their first dose of antibiotics within 6 h after arrival at the hospital	Facility	CMS	Pneumonia (process)	2009	Endorsement removed (*Oct 2012*)		No

0211	Proportion with more than one emergency department visit in the last days of life	Percentage of patients who died from cancer with more than one emergency department visit in the last days of life	Population; health plan; integrated delivery system; facility; group; clinician	ASCO	Cancer-specific (process)	2009	Endorsed		Yes
0286	Aspirin at Arrival	Percentage of emergency department acute myocardial infarction (AMI) patients or chest pain patients (with probable cardiac chest pain) without aspirin contraindications who received aspirin within 24 h before ED arrival or prior to transfer	Population; facility	CMS	Cardiovascular (process)	2007 (5)	Endorsed	OQR	No
0287	Median Time to Fibrinolysis	Median time from emergency department arrival to administration of fibrinolytic therapy in ED patients with ST-segment elevation or left bundle branch block (LBBB) on the electrocardiogram (ECG) performed closest to ED arrival and prior to transfer	Population; facility	CMS	Cardiovascular (process)	2007 (5)	Endorsement removed (*Jan 2012*)	OQR	No
0288	Fibrinolytic Therapy Received Within 30 Min of ED Arrival	Emergency department acute myocardial infarction (AMI) patients receiving fibrinolytic therapy during the ED stay and having a time from ED arrival to fibrinolysis of 30 min or less	Population; facility	CMS	Cardiovascular (process)	2007 (5)	Endorsed	OQR	No
0289	Median Time to ECG	Median time from emergency department arrival to ECG (performed in the ED prior to transfer) for acute myocardial infarction (AMI) or chest pain patients (with probable cardiac chest pain)	Population; facility	CMS	Cardiovascular (process)	2007 (5)	Endorsed	OQR	No
0290	Median Time to Transfer to Another Facility for Acute Coronary Intervention	Median time from emergency department arrival to time of transfer to another facility for acute coronary intervention	Population; facility	CMS	Cardiovascular (process)	2007 (5)	Endorsed	OQR	No
0291	Emergency Transfer Communication Measure	Percentage of patients transferred to another healthcare facility whose medical record documentation indicated that required information was communicated to the receiving facility prior to departure (Subsection 1) or within 60 min of transfer (Subsection 2–7)	Facility	UMRHRC	Care coordination (process)	2007 (5)	Endorsed		Yes
0292	Vital Signs	Percentage of patients transferred to another healthcare facility whose medical record documentation indicated that the entire vital signs record was communicated to the receiving facility within 60 min of departure	Facility	UMRHRC	Care coordination (process)	2007 (5)	Endorsed		Yes

(continued)

Table 1 (continued)

NQF ID	Measure title (1)	Measure description (1)	Reporting level	Measure owner (1, 2)	Measure target (type) (1)	Year endorsed	Current status	CMS program (3)	Relevant to cancer care? (4)
0293	Medication Information	Percentage of patients transferred to another healthcare facility whose medical record documentation indicated that medication information was communicated to the receiving facility within 60 min of departure	Facility	UMRHRC	Care coordination (process)	2007 (5)	Endorsed		Yes
0294	Patient Information	Percentage of patients transferred to another healthcare facility whose medical record documentation indicated that patient information was communicated to the receiving facility within 60 min of departure	Facility	UMRHRC	Care coordination (process)	2007 (5)	Endorsed		Yes
0295	Physician Information	Percentage of patients transferred to another healthcare facility whose medical record documentation indicated that physician information was communicated to the receiving facility within 60 min of departure	Facility	UMRHRC	Care coordination (process)	2007 (5)	Endorsed		Yes
0296	Nursing Information	Percentage of patients transferred to another healthcare facility whose medical record documentation indicated that nursing information was communicated to the receiving facility within 60 min of departure	Facility	UMRHRC	Care coordination (process)	2007 (5)	Endorsed		Yes
0297	Procedures and Tests	Percentage of patients transferred to another healthcare facility whose medical record documentation indicated that procedure and test information was communicated to the receiving facility within 60 min of departure	Facility	UMRHRC	Care coordination (process)	2007 (5)	Endorsed		Yes
0489	The Ability for Providers with HIT to Receive Laboratory Data Electronically Directly into their Qualified/Certified EHR System as Discrete Searchable Data Elements	Documents the extent to which a provider uses certified/qualified electronic health record (EHR) system that incorporates an electronic data interchange with one or more laboratories allowing for direct electronic transmission of laboratory data into the EHR as discrete searchable data elements	Facility	CMS	Care coordination (structure)	2008 (6)	Endorsement removed (*Apr 2014*)	OQR	Yes
0491	Tracking of Clinical Results Between Visits	Documentation of the extent to which a provider uses a certified/qualified electronic health record (EHR) system to track pending laboratory tests, diagnostic studies (including common preventive screenings) or patient referrals. The Electronic Health Record includes provider reminders when clinical results are not received within a predefined timeframe	Facility	CMS	Care coordination (structure)	2008 (6)	Endorsement removed (*Apr 2014*)		Yes

0495	Median Time from ED Arrival to ED Departure for Admitted ED Patients	Median time from emergency department arrival to time of departure from the emergency department for patients admitted to the facility from the emergency department	Facility	CMS	Care coordination (outcome)	2008 (5, 6)	Endorsed	IQR; MU	Yes
0496	Median Time from ED Arrival to ED Departure for Discharged ED Patients	Median time from emergency department arrival to time of departure from the emergency department for patients discharged from the emergency department	Facility	CMS	Care coordination (outcome)	2008 (5, 6)	Endorsed	MU; OQR	Yes
0497	Admit Decision Time to ED Departure Time for Admitted Patients	Median time from admit decision time to time of departure from the emergency department for emergency department patients admitted to inpatient status	Health Plan; facility; group; clinician	CMS	Care coordination (process)	2008 (5, 6)	Endorsed	IQR; MU	Yes
0498	Door to Diagnostic Evaluation by a Qualified Medical Personnel	Time of first contact in the ED to the time when the patient sees qualified medical personnel for patient evaluation and management	Facility; clinician	LSU	Care coordination (outcome)	2008 (5, 6)	Endorsement removed (*May 2012*)	OQR	Yes
0499	Left Without Being Seen	Percent of patients leaving without being seen by a qualified medical personnel	Facility; clinician	LSU	Care coordination (outcome)	2008 (5)	Endorsement removed (*May 2012*)	OQR	Yes
0500	Severe Sepsis and Septic Shock: Management Bundle	This measure will focus on patients aged 18 years and older who present with symptoms of severe sepsis or septic shock. These patients will be eligible for the 3 h (severe sepsis) and/or 6 h (septic shock) early management bundle	Integrated delivery system; facility	HFH	Disparities (outcome)	2008 (5, 6)	Endorsed		No
0501	Confirmation of Endotracheal Tube Placement	Any time an endotracheal tube is placed into a patients airway in the emergency department (ED) or a patient arrives to the ED with an endotracheal tube already in place (via EMS or hospital transfer) there should be appropriate confirmation of ETT placement and documentation of its performance in the medical record	Population; integrated delivery system; facility; group; clinician	CCF	Pulmonary (process)	2008 (5, 6)	Endorsement removed (*June 2012*)		No
0502	Pregnancy test for female abdominal pain patients	Percentage of female patients aged 14 to 50 who present to the emergency department (ED) with a chief complaint of abdominal pain for whom a pregnancy test ordered	Facility; group; clinician	ACEP	Perinatal (process)	2008 (5, 6)	Endorsement removed (*May 2012*)		No
0503	Anticoagulation for acute pulmonary embolus patients	Number of acute embolus patients who have orders for anticoagulation (heparin or low-molecular weight heparin) for pulmonary embolus while in the ED	Facility; group; clinician	ACEP	Cardiovascular (process)	2008 (5, 6)	Endorsement removed (*Jan 2013*)	PQRS	No
0504	Pediatric weight documented in kilograms	Percentage of emergency department visits by patients < 18 years of age with a current weight documented in kilograms in the ED electronic health record; measure to be reported each month	Facility	AAP	Safety (process)	2008 (5, 6)	Endorsement removed (*Jan 2013*)		No

(continued)

Table 1 (continued)

NQF ID	Measure title (1)	Measure description (1)	Reporting level	Measure owner (1, 2)	Measure target (type) (1)	Year endorsed	Current status	CMS program (3)	Relevant to cancer care? (4)
0549	Pharmacotherapy Management of COPD Exacerbation (PCE)	This measure assesses the percentage of COPD exacerbations for members 40 years of age and older who had an acute inpatient discharge or ED encounter on or between January 1–November 30 of the measurement year and who were dispensed appropriate medications	Population; health plan; integrated delivery system; facility; group; clinician	NCQA	COPD (process)	2009	Endorsement removed (*Jul 2012*)		No
0604	Adult(s) with diabetes mellitus that had a serum creatinine in last 12 reported months	This measure identifies adults with diabetes mellitus that had a serum creatinine test in last 12 reported months	Population; health plan; integrated delivery system; facility; group; clinician	Optum	Endocrine (process)	2009	Endorsement removed (*Dec 2013*)		No
0605	Patient(s) with hypertension that had a serum creatinine in last 12 reported months	This measure identifies patients with hypertension (HTN) that had a serum creatinine in last 12 reported months	Population; health plan; integrated delivery system; facility; group; clinician	Optum	Cardiovascular (process)	2009	Endorsement removed (*Dec 2013*)		No
0644	Patients with a transient ischemic event ED visit that had a follow up office visit	Patient(s) with a recent emergency department encounter for a transient cerebral ischemic event that had any physician visit within 14 days of the acute event	Population; health plan; integrated delivery system; facility; group; clinician	Optum	Stroke (process)	2010	Endorsement removed (*Mar 2013*)		No
0649	Transition Record with Specified Elements Received by Discharged Patients (Emergency Department Discharges to Ambulatory Care [Home/Self Care] or Home Health Care)	Percentage of patients, regardless of age, discharged from an emergency department (ED) to ambulatory care or home health care, or their caregiver(s), who received a transition record at the time of ED discharge including, at a minimum, all of the specified elements	Integrated delivery system; facility	AMA-PCPI	Care coordination (process)	2010	Endorsed		Yes
0652	Rh immunoglobulin (Rhogam) for Rh negative pregnant women at risk of fetal blood exposure	Percent of Rh negative pregnant women at risk of fetal blood exposure who receive Rhogam [at] the ED	Group; clinician	ACEP	Perinatal (process)	2011	Endorsement removed (*Jul 2014*)	PQRS	No
0660	Troponin Results for Emergency Department acute myocardial infarction (AMI) patients or chest pain patients (with Probable Cardiac Chest Pain) Received within 60 min of arrival	Emergency department acute myocardial infarction (AMI) patients or chest pain patients (with probable cardiac chest pain) with an order for troponin during the stay and having a time from ED arrival to completion of troponin results within 60 min of arrival	Facility	CMS	Cardiovascular (process)	2011	Endorsement removed (*Nov 2012*)		No
0661	Head CT or MRI Scan Results for Acute Ischemic Stroke or Hemorrhagic Stroke Patients who Received Head CT or MRI Scan Interpretation Within 45 min of ED Arrival	Emergency department acute ischemic stroke or hemorrhagic stroke patients who arrive at the ED within 2 h of the onset of symptoms who have a head CT or MRI scan performed during the stay and having a time from ED arrival to interpretation of the head CT or MRI scan within 45 min of arrival	Population; facility	CMS	Stroke (process)	2011	Endorsed	OQR	No

0662	Median Time to Pain Management for Long Bone Fracture	Median time from emergency department arrival to time of initial oral or parenteral pain medication administration for emergency department patients with a principal diagnosis of long bone fracture (LBF)	Facility	CMS	Musculoskeletal (process)	2011	Endorsed	OQR	No
0664	Patient(s) with an emergency medicine visit for syncope that had an ECG	This measure identifies patients with an emergency medicine visit for syncope that had an ECG done as part of their evaluation	Population; health plan; integrated delivery system; facility; group; clinician	Optum	Cardiovascular (process)	2011	Endorsement removed (*Dec 2013*)		No
0665	Patient(s) with an emergency medicine visit for non-traumatic chest pain that had an ECG	This measure identifies patients with an emergency medicine visit for non-traumatic chest pain that had an ECG done as part of their evaluation	Population; health plan; integrated delivery system; facility; group; clinician	Optum	Cardiovascular (process)	2011	Endorsement removed (*Dec 2013*)		No
0666	Ultrasound guidance for Internal Jugular central venous catheter placement	Percent of adult patients aged 18 years and older with an internal jugular central venous catheter placed in the emergency department (ED) under ultrasound guidance	Group; clinician	ACEP	Pulmonary (process)	2011	Endorsed		No
0667	Inappropriate Pulmonary CT Imaging for Patients at Low Risk for Pulmonary Embolism	Percent of patients undergoing CT pulmonary angiogram for the evaluation of possible PE who are at low-risk for PE consistent with guidelines (1, 2) prior to CT imaging	Facility; group; clinician	ACEP	Pulmonary (efficiency)	2011	Endorsed		No
1381	Asthma Emergency Department Visits	Percentage of patients with asthma who have greater than or equal to one visit to the emergency department for asthma during the measurement period	Population; health plan	ALMA	Asthma (outcome)	2011	Endorsement removed (*Feb 2014*)		No
1824	L1A: Screening for preferred spoken language for health care	This measure is used to assess the percent of patient visits and admissions where preferred spoken language for health care is screened and recorded	Facility; group; clinician	GWU	Disparities (process)	2012	Endorsed		Yes

Source: This table is based on the authors' analysis of ED quality measures that are endorsed as of January 2015 or were previously endorsed by the NQF, including measures used in CMS reporting programs. [156]

Note:

1. The measure titles, descriptions, and owners in this table are based on the information listed on the NQF website as of January 2015 [156]. These fields may differ from the measure titles, descriptions, and owners when the measures were initially endorsed by the NQF

2. Measure owners are listed below: AAP - American Academy of Pediatrics (www.aap.org/); ACEP - American College of Emergency Physicians (www.acep.org/); ALMA - Alabama Medicaid Agency (www.medicaid.alabama.gov/); AMA-PCPI - American Medical Association - Physician Consortium for Performance Improvement (www.ama-assn.org/ama/home.page); ASCO - American Society of Clinical Oncology (www.asco.org); CCF - Cleveland Clinic Foundation (http://my.clevelandclinic.org); CMS - Centers for Medicare & Medicaid Services (www.cms.gov/); GWU - Department of Health Policy, The George Washington University (http://publichealth.gwu.edu/departments/health-policy); HFH - Henry Ford Hospital (www.henryford.com/homepage_hfh.cfm?id=37471); IPRO (http://ipro.org/); LSU - Louisiana State University (www.lsuhospitals.org); NCQA - National Committee for Quality Assurance (www.ncqa.org); Optum (https://www.optum.com/); UMRHRC - University of Minnesota Rural Health Research Center (http://rhrc.umn.edu/)

3. CMS public reporting programs are listed below: IQR - Inpatient Quality Reporting (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/HospitalRHQDAPU.html); MU - Meaningful Use Stage 2 EHR Incentive Program (www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/Stage_2.html); OQR - Outpatient Quality Reporting (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/HospitalOutpatientQualityReportingProgram.html); PQRS - Physician Quality Reporting System (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/PQRS/index.html)

4. Relevance to cancer care is based on the authors' analysis of the measure specifications. Some measures (e.g., NQF #0090-Emergency Medicine: 12-Lead Electrocardiogram (ECG) Performed for Non-Traumatic Chest Pain) may apply to cancer patients with other comorbidities as well as health status changes. However, the measures are not directly relevant to cancer care

5. ED measures endorsed by the NQF between 2007 and 2009 based on the NQF report: National Voluntary Consensus Standards for Emergency Care: A Consensus Report. [149]

6. Measure was given time-limited endorsement. Time-limited endorsement is granted to measures that meet NQF evaluation criteria, but have not been adequately field-tested. Measure developers are given up to 2 years to demonstrate the reliability, validity, and feasibility of the measure based on testing at multiple provider sites [155]

Table 2 Existing ED measures relevant to cancer care, current gaps, and measure development priorities

Cancer-specific ED measures
Description: Measure aspects of emergency care that are unique to cancer patients. Include measures of the processes, outcomes, structure, efficiency, and costs of care as well as patients' perception-of-care
Rationale: Cancer patients visit the ED throughout the continuum of care and often present with complex, interrelated symptom burden. Most ED measures focus on cardiovascular disease and are not relevant to oncologic emergency care. In addition, many cancer patients experience unique quality of care issues (e.g., late-stage cancers presenting to the ED) that reflect quality issues in other care settings. The existing measures are not sensitive to these issues. Widespread adoption of cancer-specific ED measures will help stimulate improvements in emergency oncologic care
Current measures: Two cancer-specific ED measures have been developed, and one measure is NQF-endorsed. They assess overutilization of ED services, due to poor symptom management, aggressive treatment, poor care coordination, or inadequate access to care
Examples:
– NQF measure #0211—Proportion with more than one emergency department visit in the last days of life
– Potentially Avoidable Admissions and Emergency Department Visits Among Patients Receiving Outpatient Chemotherapy, not endorsed by the NQF as of January 2015
Health services research priorities: *Listed below by measure type*
Measure development priorities: *Listed below by measure type*
ED outcome measures
Description: Measure the outcomes of emergency care, including the sustainability of health post-ED discharge, timeliness of ED care, and treatment complications during and after ED discharge
Rationale: Cancer patients frequently visit the ED for symptom management (e.g., management of acute pain and fatigue) due to cancer treatment or cancer progression. In addition, ED care delays are associated with ED overcrowding and boarding and, ultimately, poorer outcomes and compromised quality of life. Failure to measure the timeliness of care—in particular, timely symptom improvement—represents a failure to measure the most important outcomes for these patients
Current measures: There are only two NQF-endorsed ED outcome measures. These are "time to" ED measures, which evaluate ED throughput and the timeliness of care
Examples:
– NQF measure #0495—Median Time from ED Arrival to ED Departure for Admitted ED Patients
– NQF measure #0497—Admit Decision Time to ED Departure Time for Admitted Patients
Health services research priorities:
– Develop protocols to adopt validated patient-reported outcome surveys as a standard of care for EDs to collect data on symptom burden and quality of life in the ED and post-ED discharge. Focus on minimizing patient burden and leveraging telehealth and other emerging technologies, where possible
– Study clinical and patient characteristics that are associated with repeat ED visits and health decline post-ED discharge in the cancer population
Measure development priorities:
– "Time to" patient-reported symptom improvement in the ED, stratified by chief complaint
– "Time to" cancer diagnosis, for patients presenting to the ED with an undiagnosed cancer
– Sustainability of patient-reported symptom improvement post-ED discharge, stratified by chief complaint
– Repeat ED visits within 2, 7, and 14 days of ED discharge, stratified by chief complaint
– ED length of stay for cancer patients, stratified by: (1) patients admitted to an inpatient unit, (2) patients transferred to another facility, and (3) patients discharged home
ED process measures
Description: Assess compliance with established standards of ED care that have been linked to improved patient outcomes, reductions in unnecessary care, and more equitable care. Include a wide array of measures, such as adherence to: guideline-based diagnostic testing and treatment; protocols around patient intake, discharge, and care coordination; and policies to ensure equitable care for vulnerable patient populations
Rationale: Routine measurement of adherence to guideline-based care can highlight practice variations across providers that ultimately contribute to poorer outcomes or higher costs of care for some patients. In particular, measuring care coordination by ED providers is important to ensure that patients are guided to appropriate follow-up care and to prevent repeat ED visits and inpatient admissions
Current measures: There are twenty NQF-endorsed ED process measures. Eleven of these measures are disease-specific, including one cancer-specific ED measure; the remaining measures focus on care coordination across all conditions. Only one ED process measure evaluates care coordination for patients discharged to outpatient care
Examples:
– NQF measure #0092—Emergency Medicine: Aspirin at Arrival for Acute Myocardial Infarction (AMI)
– NQF measure #0291—Emergency Transfer Communication Measure
Health services research priorities:
– Develop algorithms to identify patients at potential risk of presenting to the ED with an undiagnosed cancer
– Test methods to promote care coordination between outpatient oncology and ED providers

(continued)

Table 2 (continued)

– Model episodes of oncologic emergency care, with well-defined endpoints and treatment pathways
– Develop algorithms to identify patients at risk for disparities in care that present to the ED
Measure development priorities:
– Screening and diagnosis for high-frequency complications that present to the ED (e.g., pain, fatigue, dyspnea, nausea, dehydration, depression, and cognitive impairment)
– Patients discharged with a referral to an appropriate outpatient oncology provider
– Advance care planning discussions for patients with advanced cancer
– Cancers diagnosed in the ED, stratified by: (1) cancer type and (2) stage of disease
ED cost-of-care measures
Description: Calculate direct and indirect costs for a specific medical condition, episode of care, or healthcare service. Demonstrate variations in costs across medical conditions, care delivery settings, and between providers
Rationale: Cost-of-care measures can increase transparency around cost inefficiencies (perceived and actual) as well as higher costs associated with adverse events, delayed diagnosis and treatment, and individual patient factors, such as comorbid conditions [170]. Furthermore, these measures can provide important insights into cost variation between providers and care delivery settings, among patients with similar diagnoses, and across the continuum of cancer care
Current measures: There are no NQF-endorsed ED cost-of-care measures
Examples: None
Health services research priorities:
– Model episodes of oncologic emergency care, with well-defined endpoints and treatment pathways
Measure development priorities:
– Costs of care per ED visit, stratified by chief complaint
– Cost of diagnosing asymptomatic or quasi-symptomatic cancers in the ED
– Costs of managing patient comorbidities in the ED
– Costs of care by adverse event
– Costs of ED care in the last 7, 14, and 30 days of life
ED efficiency measures
Description: Examine the relationship between inputs and outputs in emergency care; they compare resource use (and associated costs) with the level of health outcome achieved
Rationale: Significant resources are expended in managing the complex—and often interrelated—symptoms, comorbidities, and psychosocial needs of patients presenting to the ED, particularly cancer patients
Current measures: There is one NQF-endorsed ED efficiency measure that evaluates the overuse of advanced imaging; it is not applicable to cancer
Examples:
– NQF measure #0667—Inappropriate Pulmonary CT Imaging for Patients at Low Risk for Pulmonary Embolism
Health services research priorities:
– Understand the overuse, underuse, and misuse of ED resources in cancer patients; this is largely unstudied beyond the frequency of ED visits. Develop guidelines for appropriate ED resource utilization for cancer patients
– Evaluate the relationship between ED resource utilization and outcomes for cancer patients
– Study the relationship between resource utilization (in the ED and in the outpatient setting) and repeat ED visits for cancer patients. Develop protocols to reduce repeat ED visits for cancer patients, particularly at the end of life
Measure development priorities:
– Efficient utilization of advanced imaging studies for cancer patients
ED patients' perception-of-care measures
Description: Evaluate patients' satisfaction with the healthcare received
Rationale: While restoration of health is a priority among cancer patients, equally important is patient (and caregiver) experience with care throughout the cancer care continuum. This is particularly true for patients with advanced cancer whose treatment may be noncurative
Current measures: One ED patients' perception-of-care survey has been developed, but further validation is required
Examples:
– Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey
– Emergency Department Patient Experience of Care (EDPEC) Survey, not endorsed by the NQF as of January 2015
Health services research priorities:
– Strategies to address the psychosocial needs of cancer patients with advanced disease and their caregivers
– Potential modifications to the EDPEC survey to make it applicable to oncologic emergency care
Measure development and research priorities:
– Modified EDPEC survey (or new patient experience with ED care survey), applicable to oncologic emergency medicine
– Survey of caregiver experience with emergency care and overall caregiver burden

Source: This table is based on the authors' analysis of existing ED measures relevant to cancer care [156], current gaps, and measure development priorities as of January 2015

quality across the entire emergency care system. In some cases this has led to duplicative measures for different programs (e.g., NQF measure #0286—*Aspirin at Arrival*, which is essentially the same as NQF measure 0092 but has been adopted for the OQR program). While these examples are specific to AMI, they nonetheless have important implications for oncologic emergency care.

Challenges in Obtaining ED Quality of Care Data

Much has been published in recent years regarding the limitations of existing data sources to support robust, actionable quality measurement. Historically, quality measurement relied upon administrative claims data, which are relatively easy to access but are not designed for quality reporting. Accordingly, the accuracy, relevance, and completeness of these data are questionable. At best, they offer an incomplete view of healthcare quality, particularly for cancer patients. Federal agencies and EHR vendors have promoted EHRs as a viable alternative to address these data issues. However, EHRs were designed to support healthcare operations, rather than quality measurement, and early assessments of EHR-based quality reporting have produced disappointing results [157–159]. Hence, manual chart review and data entry remain a primary method of collecting data—or supplementing electronic data—for purposes of quality measurement. Manual chart review is resource-intensive and is rarely performed on a real-time basis. Therefore, reliance on manual chart review limits access to the data that are critical for timely, actionable, and meaningful ED quality measurement. Moreover, because ED physicians often lack an established and ongoing relationship with their patients, they often lack access to data on the outcomes of ED patients immediately post-discharge as well as longitudinal data to support robust quality measurement for these patients. Potential strategies to address these issues are described later in this chapter.

Desired State of National Quality Measurement for Oncologic Emergency Care

In reviewing the history and current state of national quality measurement for emergency medicine, several important themes emerge:

1. There is widespread acknowledgement of the essential role that EDs serve in the nation's public health system.
2. Quality issues in emergency medicine are well documented, and healthcare experts have developed practical recommendations to address many of these issues.
3. Some quality issues observed in the ED are unrelated to the quality of emergency care and, instead, reflect broader social issues (e.g., inadequate access to healthcare) or quality of care issues in other healthcare settings.
4. Public and private organizations have recognized that quality measurement is integral to ED quality improvement, and early successes in cardiovascular emergency medicine have demonstrated how ED-based national quality measurement can be leveraged to improve patient outcomes.
5. HIT advancements, together with increased adoption of EHRs, offer the potential to give ED providers greater access to the data needed to care for their patients and to evaluate their quality of care on a more real-time basis.

While not specific to oncologic emergency care, these accomplishments represent a solid platform on which to develop national reporting for oncologic emergency care. In general, public reporting for cancer care has experienced minimal progress in more than a decade and has lagged behind public reporting for other conditions, such as diabetes and cardiovascular disease. These findings apply to public reporting for oncologic emergency care as well. Five factors that contribute to this inertia were described earlier in this chapter: (1) gaps in existing ED measures, (2) fragmented measure development, (3) difficulty defining the episode of oncologic emergency care, (4) measurement without a clear mechanism for improving ED care, and (5) challenges in obtaining ED quality data. Many of these factors stem from substantial shortcomings in funding, oversight, and coordination of measure development and public reporting for cancer care.

In this section, we outline a vision for measuring quality in oncologic emergency care, through the implementation of the IOM's recommendation to create a comprehensive national quality reporting program for cancer care. This includes a well-coordinated approach to developing cancer-specific ED quality of care measures. We also propose healthcare policy changes that will promote better alignment between public reporting and reimbursement for oncologic emergency care and that will promote shared accountability across providers. Additionally, we describe how the IOM's recommendation to implement a learning healthcare system for cancer could address many of the challenges in obtaining ED quality of care data. Finally, we share initiatives at MD Anderson to measure and improve the quality of oncologic emergency care delivered in its ED.

Vision for National Quality Measurement in Oncologic Emergency Care

Since 1999, the IOM has promoted national quality measurement as an essential lever to improve the quality of US cancer care delivery. In 2013, the IOM released *Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis*, which outlined six components of a high-quality cancer care delivery system: (1) engaged patients, (2) an adequately staffed, trained, and coordinated workforce,

(3) evidence-based cancer care, (4) a learning healthcare information technology system, (5) translation of evidence into clinical practice, quality measurement, and performance improvement, and (6) accessible, affordable cancer care [75]. The report identified the nation's inability to systematically measure and improve cancer care delivery as a primary contributor to existing gaps in cancer quality and offered the following recommendation:

Recommendation 8: Quality Measurement

Goal: Develop a national quality reporting program for cancer care as part of a learning healthcare system.

To accomplish this, the Department of Health and Human Services should work with professional societies to:

- Create and implement a formal long-term strategy for publicly reporting quality measures for cancer care that leverages existing efforts.
- Prioritize, fund, and direct the development of meaningful quality measures for cancer care with a focus on outcome measures and with performance targets for use in publicly reporting the performance of institutions, practices, and individual clinicians.
- Implement a coordinated, transparent reporting infrastructure that meets the needs of all stakeholders, including patients, and is integrated into a learning healthcare system [75].

Implementation of this national quality reporting program for cancer care would enhance quality measurement across multiple care delivery settings, including the ED. It would support purposeful, well-coordinated, and patient-centered quality measurement in the ED, with an emphasis on care coordination and shared accountability across providers and care delivery settings. Through public reporting, it would encourage evidence-based care delivery and patient engagement, while discouraging unnecessary—*and potentially harmful*—care. By increasing transparency around the outcomes, processes, and costs of cancer care, the national reporting program envisioned in the report could expedite progress toward a high-quality cancer care delivery system, of which the ED is an essential component. Adequate funding, formal leadership, strong collaboration, and HIT enhancements, together with a well-developed framework and a unified strategy, are essential to its successful implementation, as discussed below.

Health Policy for Measuring Quality in Oncologic Emergency Care

As described earlier in this chapter, EMTALA and the no-duty-to-treat principle form the health policy base for emergency care in the USA. While EMTALA ensures patient access to emergency medical care, it does not regulate the quality of that care. More recently, the MMA, DRA, and Tax Relief and Health Care Act of 2006 introduced and incentivized national quality reporting for emergency care. The quality reporting stimulated by this legislation did little to promote high-quality oncologic emergency care, because it focused largely on other conditions, such as cardiovascular disease.

To advance quality in the nation's oncologic emergency care, national quality reporting for cancer care is essential, as recommended by the IOM. The frequency, complexity, and costs of oncologic emergency care, particularly at the end of life, necessitate a well-coordinated and unified approach to address current measurement gaps in oncologic emergency care. Thus, we offer the following policy recommendations in support of this effort:

- *Leadership and Collaboration*: *Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis* identified HHS as the appropriate organizer of this work. Through collaboration with patient advocacy organizations, professional societies, payers, and other stakeholders, HHS could ignite national development of quality measures for oncologic emergency care. Designating CMS and the NQF as key partners in this effort could accelerate progress in developing validated cancer-specific ED quality of care measures.
- *Formal Long-Term Strategy*: Create and enforce a formal long-term strategy (with shorter-term milestones) and a well-defined framework for the development and public reporting of measures for oncologic emergency care (as part of a broader strategy and framework for cancer). This long-term strategy would address the needs of all cancer patients, with a particular focus on cancer patients seeking emergency care at the end of life. Moreover, it would promote shared accountability by providers, by moving away from quality measurement focused on specific Medicare payment programs.
- *Research*: Fund health services research and clinical trials to expand the scientific evidence for oncologic emergency care, including:
  - Effective care coordination between outpatient oncology and ED providers.
  - Outpatient care delivery models that reduce unnecessary ED utilization among cancer patients.
  - Approaches to mitigate the overutilization of ED services by cancer patients, particularly at the end of life.
  - Episodes of oncologic emergency care, with well-defined endpoints and treatment pathways.
  - Strategies to address the psychosocial needs of cancer patients with advanced disease and their caregivers.
  - Drivers of late-stage cancers presenting to the ED.
  - Care delivery models that integrate palliative care with ED services.
- *Measure Development*: Fund the development of a robust set of meaningful measures for oncologic emergency care (including performance targets) for use in public

reporting. Measure development should focus on the outcomes of care as well as access to care, care coordination, advance care planning, patient and family engagement, and evaluation and management of acute and chronic conditions and psychosocial needs. High-priority measurement gaps are described in Table 2 of this chapter. Prioritization of measure development should align with the formal long-term strategy guiding this effort and target likely healthcare disparities. Moreover, measure development should have a well-defined cost-benefit relationship and should foster shared accountability across providers and including patients. Where appropriate, the developed measures should address multiple care delivery settings. Measures available from existing data sources should receive higher priority. However, lack of data should not constitute a barrier to measure development. A formal tool should be developed to assist the collaborative in prioritizing measure development [160].

- *Transparent Reporting Infrastructure*: As recommended by the IOM, implement a reporting infrastructure (including IT infrastructure and reporting methodologies) that promotes transparency of the outcomes that are most meaningful to patients and their caregivers and that meets the information needs of all stakeholders (patients and their caregivers, providers, payers, and state and federal agencies). Public reporting should be understandable by patients and their caregivers to support healthcare decision-making.

Expedited adoption of health policy in support of these priorities would do much to address the existing measurement gaps for oncologic emergency care. With multi-stakeholder collaboration among organizations that share a vested interest in oncologic emergency medicine as well as proper funding and authority, robust national quality measurement for oncologic emergency care could become a reality within a few years.

HIT Support through the Learning Healthcare System for Cancer

Providers face significant obstacles in obtaining timely, actionable, and comprehensive data to support the robust quality measurement described herein. Additionally, because ED providers lack an established and ongoing relationship with their patients, they often do not have access to post-discharge and longitudinal outcomes data to support meaningful quality measurement. To advance meaningful quality measurement and public reporting, *Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis* advocated the creation of a learning healthcare system for cancer [75]. A learning healthcare system streamlines provider data collection and reporting and enables real-time data analysis for performance improvement, quality measurement, and clinical decision support. The cancer-specific learning healthcare system described by the IOM would support more rapid innovation in cancer care delivery by addressing critical data gaps in two ways: (1) by capturing provider-driven clinical data, patient-reported outcomes, and patient and caregiver experience with care in a structured format and (2) by integrating structured, unstructured, and semi-structured data. National endorsement of this recommendation would address many of the data gaps described in this report and would enable development and reporting of quality measures for oncologic emergency care. To be successful, federal incentives to promote HIT adoption (e.g., Meaningful Use) should incorporate the principles of a learning healthcare system for cancer [161]. Likewise, public and private payers should reward providers for participating in a learning healthcare system for cancer. Aligning provider incentives with adoption of a learning healthcare system for cancer would enhance the current IT infrastructure and promote widespread access to the information needed to catalyze national public reporting for oncologic emergency care.

Role of Targeted Quality Measures in Driving Practice Change

As noted earlier in this chapter, quality measures provide a standardized, objective means of evaluating healthcare quality and hold an important role in the US healthcare delivery system, including emergency care. State and federal agencies utilize quality measures to promote provider accountability and to inform the public. Increasingly, payers are using quality measures in value-based payment programs to align reimbursement with quality of care. Because cancer patients experience unique quality of care issues and because most disease-specific ED measures focus on cardiovascular disease, the existing ED quality of care measures offer minimal opportunity to improve the quality of oncologic emergency care. Despite these limitations, *appropriately selected* quality measures have the potential to inform consumer decision-making and care planning, accelerate improvements in care, and highlight variation between providers and over time within a given practice setting [75]. Additionally, routine quality measurement and reporting enables payers and providers to test whether new care delivery and payment models have a positive effect on the accessibility, quality, and affordability of healthcare.

Public reporting of well-designed quality measures for oncologic emergency care represents a powerful policy lever to encourage more appropriate ED resource utilization, better care coordination, shared accountability, and, ultimately, superior outcomes and patient (and caregiver) experience with care. Lamb et al. observed that the act of measuring performance at the provider level can ignite an interest in self-improvement or a spirit of competition among providers,

leading to improvements in care [162]. Pay-for-performance programs are another promising policy lever, which could lead to improvements in the quality of oncologic emergency care. The effectiveness of pay-for-performance has been the subject of much debate, given current measurement gaps across multiple conditions and in various aspects of care. However, designing a pay-for-performance program around targeted quality measures for oncologic emergency care (such as those listed as measure development priorities in Table 2) could stimulate significant and lasting improvements in care.

Case Study: MD Anderson Experience

Background

Founded in 1941 and located in Houston, Texas, MD Anderson is one of the world's most respected centers devoted exclusively to cancer patient care, research, education, and prevention. The institution is one of the nation's original three comprehensive cancer centers designated by the National Cancer Act of 1971 and is one of 41 National Cancer Institute-designated comprehensive cancer centers as of January 2015 [90]. MD Anderson's mission is to eliminate cancer in Texas, the nation, and the world through outstanding programs that integrate patient care, research, and prevention and through education for undergraduate and graduate students, trainees, professionals, employees, and the public. Underlying MD Anderson's mission is a strong focus on delivering high-quality cancer care.

Between 1944 and 2014, nearly 1,000,000 patients turned to MD Anderson for cancer care in the form of targeted therapies, surgery, chemotherapy, radiation and proton therapy, immunotherapy, or combinations of these and other treatments. Additionally, more than 24,000 patients annually visit MD Anderson's 43-bed Emergency Center for acute oncologic emergencies associated with disease progression, treatment-related side effects, and comorbidities. Moreover, many individuals with confirmed or suspected cancer seek entry into MD Anderson through its dedicated ED. Thus, MD Anderson's ED represents an important safety net for patients in two ways: (1) by coordinating care across a number of disciplines for established patients with cancer-related emergencies and (2) by helping prospective patients navigate the oncology care system and directing them to appropriate follow-up care. MD Anderson's ED is strategically aligned within the institution to create, implement, monitor, and evaluate quality improvement efforts as part of the continuum of cancer care. This essential role highlights the importance of well-coordinated, high-quality care in MD Anderson's ED. In this section, we describe three structural elements that promote high-quality care in MD Anderson's ED: (1) culture of safety and quality, (2) availability of comprehensive services, and (3) oncologic emergency protocols.

Culture of Safety and Quality

Experiences from other industries, such as aviation and nuclear power, suggest that culture has an enormous impact on safety. Likewise, a strong safety culture has been proposed as a critical lever to reduce harm in the healthcare setting. Nevertheless, hospitalized patients continue to experience adverse events, with recent estimates suggesting that between 210,000 and 400,000 patients die from harm each year [163]. This suggests the need for a renewed focus on hospital safety culture to protect patients, their families, and healthcare staff.

The culture of safety and quality within MD Anderson's ED starts with a highly efficient team-based framework, with clearly defined and well-aligned expectations, open communication, shared accountability, and transparency. The ED's Quality Officer leads quality initiatives within the department and is a member of MD Anderson's Division of Internal Medicine Quality Council. Together, the ED and the Quality Council monitor patient care in the ED to ensure alignment with the IOM's six aims for quality care [164]. ED staff members meet monthly to review safety events and near misses reported via MD Anderson's event reporting system and to consider relevant peer-review cases. The team uses this information to identify opportunities for system-based improvement, in collaboration with staff from MD Anderson's Office of Performance and other internal stakeholders. ED faculty monitor progress on quality improvement initiatives through data collection and routine quality measurement. A dashboard is available for physicians to monitor their progress on high-priority metrics, including patient satisfaction with physician care, length of ED stay, patients returning within 48 h of ED discharge, and other productivity metrics.

Provider education is a cornerstone of the culture of safety and quality within MD Anderson's ED. ED leaders leverage internally developed educational materials to increase transparency around medical errors. For example, MD Anderson has developed a video series that highlights system-level issues that could lead to a medical error. The "stories" are based on near misses and promote interventions to improve patient safety [165]. ED staff routinely review and discuss these videos to direct attention to situations that could lead to patient harm. Additionally, ED physicians receive intensive training via MD Anderson's Faculty Leadership Academy and Clinical Safety and Effectiveness (CS&E) course. The CS&E course is an 8-day course, modeled after a program developed by Dr. Brent James at Intermountain Health Care in Utah [166]. It is designed to embed validated quality improvement techniques within frontline care delivery teams

and emphasizes routine quality measurement. During the course, ED providers are able to put these skills into practice by completing a quality improvement project in the ED. Continuing education in patient safety and cultural competency training also support the ED's culture of safety and quality.

Comprehensive Services Available

To ensure timely and effective care for patients with acute oncologic emergencies, MD Anderson's ED offers a comprehensive array of services. Patients have access to standard emergency services, including diagnostic imaging, internal medicine consults, and chaplaincy. Specialty consults are readily available, including neurosurgery, interventional radiology, and palliative care. Clinical pharmacists are also on staff to help prevent adverse drugs events. This comprehensive and multidisciplinary approach enables MD Anderson's ED to address acute oncologic emergencies for established patients in an effective and efficient manner. Furthermore, it allows many ED patients to be discharged to home, avoiding unnecessary hospitalizations.

Five percent of patients visiting MD Anderson's ED are not established patients. In some cases, these patients do not present with a true oncologic emergency but are attempting to gain access to MD Anderson. Patients suspected of having cancer—based on clinical or radiographic findings—receive a full evaluation, and a patient advocate orients them to MD Anderson. Stable patients are referred to MD Anderson's Suspicion of Cancer Clinic and are typically seen within three business days. Thus, as noted previously, MD Anderson's ED serves as a gateway into MD Anderson's care delivery system for prospective patients. More importantly, it functions as a safety net by directing patients with a confirmed or suspected cancer diagnosis to appropriate follow-up care.

Oncologic Emergency Protocols

Because of the large number of patients that visit MD Anderson's ED each year, its providers are uniquely positioned to observe quality and patient safety issues for patients with acute oncologic emergencies. Thus, MD Anderson's ED has initiated numerous quality improvement initiatives, with some having a short duration and others requiring years to develop and implement. Some quality improvement initiatives have focused on operational efficiency, including reducing ED length of stay through a physician-nurse triage team and reducing boarding by creating an observation unit in the ED. Other initiatives have targeted end-of-life care and pain management. This experience has enabled MD Anderson's ED to develop, validate, and implement evidence-based approaches to improve the outcomes of patients that visit MD Anderson's ED. Three examples are described below: (1) pneumonia pathway, (2) early goal-directed therapy for patients with sepsis, and (3) spinal cord compression management.

Pneumonia Pathway

Pneumonia is a common complication of cancer treatment. In 2005, a multidisciplinary team with representation from the ED, infection control, pulmonary medicine, respiratory therapy, nursing, and pharmacy was formed to evaluate the process of care for cancer patients presenting to the ED with pneumonia. The team conducted a four-phase quality study that included a baseline practice evaluation, an extensive literature review, and an analysis of the pathogens responsible for community-acquired pneumonia. They concluded that MD Anderson patients experienced healthcare-associated pneumonia more frequently than community-acquired pneumonia and developed an institutional pneumonia algorithm and order set to establish best practices for evaluation and management of pneumonia in cancer patients. An intensive hospital-wide educational program was launched, which led to significant utilization of the institutional pneumonia order set and reduced variation in care. Because treatment of cancer patients with pneumonia falls outside established guidelines for treating community-acquired pneumonia, adherence to the internally developed pneumonia pathway is essential [167]. MD Anderson continues to monitor adherence to the pneumonia pathway to optimize outcomes in patients with healthcare-associated pneumonia.

Early Goal-Directed Therapy for Patients with Sepsis

The development of sepsis in cancer patients can be life-threatening. However, recognizing sepsis in cancer patients can be challenging, due to altered inflammatory responses. Early goal-directed therapy (EGDT) has been recommended as an effective means of managing severe sepsis and septic shock in cancer patients, through aggressive surveillance and management of hemodynamics. Therefore, in 2010, MD Anderson's ED implemented a noninvasive sepsis EGDT protocol to assess its impact on patient outcomes. A multidisciplinary team of ED physicians, nurses, respiratory therapists, and pharmacists designed an algorithm focused on early identification at triage, timely clinical management, and rapid antibiotic administration and hemodynamic management. A sepsis documentation tool was created to support timely documentation of vital signs as well as communication with the treating physician. Hanzelka et al. associated adoption of MD Anderson's sepsis order set and algorithm with a significant improvement in interim outcomes, such as mean arterial pressure and urine output, and a decreased 28-day in-hospital mortality rate [168]. Through provider education and routine quality measurement, MD Anderson's ED encourages compliance with the noninvasive sepsis EGDT protocol. Implementation of this protocol improves the timeliness and efficacy of care for patients

with severe sepsis or septic shock and, most importantly, saves patient lives.

Spinal Cord Compression Management

Spinal cord compression in cancer patients can greatly diminish quality of life, leading to severe pain, paralysis, and sensory loss [169]. To ensure timely diagnosis and treatment of spinal cord compression, MD Anderson's ED began development of a spinal cord compression management protocol in 2012. A multidisciplinary team, with ED physicians and representation from neuro-oncology, neuroradiology, radiation therapy, and neurosurgery, evaluated best practices of care for patients presenting with back pain, metastatic spine disease, and suspicion of spinal cord compression. A comprehensive algorithm and order set were developed and adopted by MD Anderson [169], as described in more detail in Chapter 13 of this book. Adoption of this protocol as a best practice has led to an increase in palliative care consults for patients with spinal cord compression associated with metastatic disease. Moreover, it has allowed MD Anderson's emergency care team to quickly recognize and treat spinal cord compression, leading to improved symptom control and function preservation.

Conclusion

In this chapter, we examined the history, current state, and desired future state of health policy for quality in oncologic emergency care. We discussed five quality issues that cancer patients experience when seeking care in the ED, together with upstream drivers. We also described specific issues for dedicated oncology EDs. We highlighted the essential role of quality measures in addressing these quality of care issues, along with five limitations of the existing quality measures that apply to emergency care. We also shared the quality measures for emergency care that are currently endorsed by the NQF and used in CMS quality reporting programs. We outlined recommendations for national quality measurement for oncologic emergency care, through the implementation of the IOM's recommendation to create national quality reporting for cancer care, as part of a learning healthcare system. We proposed health policy changes—in the form of leadership and collaboration, formal long-term strategy, research, measure development, and transparent reporting infrastructure—to accelerate progress toward national quality measurement for oncologic emergency care. We emphasized the importance of adequate funding, formal leadership, strong collaboration, and HIT enhancements to make this reporting a reality. We also explained how a learning healthcare system for cancer and targeted quality measures can catalyze change and advance progress toward the national reporting program described herein. Finally, we shared MD Anderson's efforts to promote high-quality care within its Emergency Center through a culture of safety and quality, by offering comprehensive services to its patients, and through implementation of oncologic emergency protocols.

The recommendations outlined in this chapter are ambitious, but are necessary to accelerate the development of targeted quality measures for oncologic emergency medicine. To be successful, measure developers and other stakeholders must abandon the historical practice of siloed development of highly specific measures that apply to a small proportion of the population or to a single care delivery setting. With adequate funding, unified leadership, and multi-stakeholder commitment, national quality reporting for oncologic emergency medicine could become a reality within a few years, leading to more patient-centered and higher-quality cancer care in the ED.

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Ethics of Emergency Department Cancer Care

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Introduction

Bioethical issues often arise when treating emergency department (ED) and prehospital care patients. Actual or anticipated bioethical dilemmas commonly occur among patients with hematological and oncologic diseases, and these dilemmas may require slightly different approaches than in other ED patients due to people's attitudes toward and the nature of the disease processes. Bioethical dilemmas raised by emergency hematological-oncologic patients fall into four categories (Table 1): decision-making, treatment demands and refusals, system problems, and notifications.

Bioethics can be a nebulous concept, so the first order of business will be to lay the groundwork by describing bioethics and discussing how it fits into our societal and professional value systems. Then, I will briefly review basic ethical (foundational) theories and the methods used to think through ethical dilemmas, followed by a discussion of the mid-level ethical principles with which clinicians may be more familiar. While they may appear superficial or oversimplified, these mid-level principles provide an easy way to think about the issues posed in bioethical dilemmas and policy development. Therefore, when treating emergency patients with hematological and oncologic illnesses, we use them to convey common moral themes, such as decision-making, demands for and refusals of treatment, and system constraints. Finally, I will move into the area of virtues to discuss notifications to patients and survivors.

Table 1 Categories of bioethical issues encountered when working with patients with hematological-oncologic diseases and their families

Decision-making (*autonomy*)
1. Dying. Surrogates and advance directives (PHAD, also)
2. Decision-making capacity
Treatment demands/refusals (Beneficence; Nonmaleficence)
1. Demands to "do everything"
2. Palliative care decisions (demand to do "nothing"—care only)
3. Refusal of analgesia
4. Refusal of possibly beneficial treatment (including decisions based on religious beliefs)
System dilemmas (*distributive justice, confidentiality*)
1. System problems (inability to pay, intentional/unintentional release of patient information, undocumented alien, "wrong" insurance or medical system/group)
2. Collegial problems (refusal to see patient, abandonment, etc.)
3. Research protocols
Notification (*honesty with sensitivity*)
1. Notifying patient/family of diagnosis
2. Died. Notifying survivors

How Bioethics Fits into Our Societal and Professional Value Systems

Bioethics, or clinical ethics, describes how we apply professional and societal values in an organized way to find reasoned and defensible solutions for moral dilemmas. Moral dilemmas are those situations in which an individual must make a decision between conflicting or competing values. The resolutions to such dilemmas, however, do not always hinge on determining right versus wrong or good versus evil. Rather, moral dilemmas more often deal with "gray areas," where the situations or resolutions initially seem to be equivalent, i.e., situations with seemingly equal merit or apparently equal injury. In these more ambiguous situations, we use ethical values to help determine a morally acceptable course of action.

In a pluralistic society, we derive these values from a variety of sources, including the general cultural, philosophical, and religious moral traditions, the social norms embodied in law, and our professional oaths and ethical codes. Each of these sources claims moral superiority. The goal of bioethics is to help us understand, interpret, and weigh these competing moral values [1].

Values in Emergency Medicine

Values describe the standards that individuals, institutions, professions, and societies use to judge human behavior. We learn values, usually at an early age, through indoctrination into the birth culture, from observing behavior and through secular (including professional) and religious education. They are moral rules derived from ethical principles that promote those things we think of as good and minimize or avoid those things we think of as bad. Societal institutions incorporate and promulgate values, often attempting to retain old values even in a changing society.

In pluralistic societies, clinicians must be sensitive to alternative beliefs and traditions, since they treat people with multiple and differing value systems. Not only religious but also family, cultural, and other values contribute to patients' decisions about their medical care; without asking the patient, there is no way to know what decision they will make [2].

Although many people cannot answer the question "What are your values?", physicians can get concrete expressions of patients' uncoerced values by asking what they see as their goal of medical therapy and why they want specific interventions. In patients who are too young or who are deemed incompetent to express their values, physicians may need either to make general assumptions about what a normal person would want done or to rely on surrogate decision-makers [2].

Institutions, including healthcare facilities and professional organizations, have their own value systems. Healthcare facilities often have specific value-related missions. Religiously oriented or affiliated institutions may be the most obvious of these, but charitable, for-profit, and academic institutions also have specific role-related values. Professional organizations' values often appear in their ethical codes [3].

Clinicians also have their own ethical values, based on religious, philosophical, or professional convictions. While conscience clauses permit clinicians to "opt out" when they feel that they have a moral conflict with professionally, institutionally, or legally required actions, they are generally required to provide timely and adequate medical care for the patient—which may be particularly difficult to achieve in emergency medicine [3].

Virtues in Emergency Medicine

Virtues describe admirable personal behavior that Aristotle and other philosophers claim is derived from natural internal tendencies [4]. The virtuous person concept can be summed up with the ancient saying: "In a place where there are no men, strive to be a man" [5]. Virtuous behavior stems from a sense of duty and the perception that it is the right thing to do, rather than from a desire to garner personal benefits. These ideal, morally praiseworthy character traits (e.g., showing kindness) are evident across many situations throughout the person's lifetime. Virtues that may be inherent in emergency medicine clinicians include courage, safety, impartiality, personal integrity, trustworthiness, and fidelity [1].

Courage allows one to fulfill an obligation despite reasonable personal risk. The courageous clinician also advocates for patients against incompetent practitioners and those who attempt to deny them care, autonomy, or confidentiality. *Safety* balances unreasoned courage. *Impartiality* prompts the emergency physician to provide unbiased, unprejudiced, and equitable treatment to all patients, without regard to their race, creeds, customs, habits, or lifestyle preferences. *Personal integrity* incorporates *trustworthiness*, which prompts clinicians to protect their sick and, often, vulnerable emergency patients' interests by exercising ethical principles. *Truth telling* (fidelity, honesty) prompts clinicians to provide patients with the known facts, but tempered with humility and sensitivity.

Bioethics, Religion, and Law

Religion. Organized religions have long been recognized as the guardians of a society's values. Religious values have therefore been an important component of ethical deliberations in medicine, as elsewhere in society. Modern secular bioethics incorporates many religion-originated decision-making methods, arguments, and ideals [6]. Although various religions may appear to be dissimilar, most have as a basic tenet (no matter how it is stated) the Golden Rule: "Do unto others as you would have them do unto you." Religious values are important from two perspectives: the patient's in the exercise of autonomy and the practitioner's in placing limitations on what he or she can morally do. Given the overwhelming importance of patient autonomy in modern Western bioethics and law, however, a practitioner's religious convictions can only guide his or her actions. If their values differ, clinicians must follow the patient's wishes, as long as they are legal and practicable, and they do not violate medicine's basic ethical precepts.

Law. Laws are rules of conduct established by legislatures, administrative agencies, courts, or other governing bodies. They often vary from locale to locale and are enforceable only in the jurisdiction where they prevail. Law and bioethics both provide rules of conduct to follow based on societal values. But, while good ethics often makes good law, good law does not necessarily make good ethics [6].

So, how does bioethics differ from law? The law, unlike bioethics, is relatively rigid and, particularly in the case of scientific and medical issues, can lag years or even decades behind modern developments. Societal values are incorporated both within the law and within ethical principles and decisions. By contrast, ethics is more inclusive within a culture, incorporating the broad values and beliefs of correct conduct. The primary differences between law and bioethics are shown in Table 2 [3].

Emergency physicians often look to the law for answers to thorny dilemmas. Yet, except for the rare cases of

Table 2 Relationship between the law and bioethics

Bioethics	Function	Law
✓	Case based (casuistic)	✓
✓	Has existed since ancient times	✓
✓	Mutates over time	✓
✓	Strives for internal consistency	✓
✓	Incorporates societal values	✓
✓	Healthcare policy source	✓
–	Some unchangeable directives	✓
–	Formal process rules	✓
–	Adversarial	✓
✓	Relies heavily on individual values	✓
✓	Interpretable by medical personnel	–
✓	Ability to respond relatively rapidly to changing environment	–

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Table 3 Comparing ethics codes of EM organizations

	AAEM/AMA	SAEM	AOA/AOCEP	ACEP
Protect patient confidentiality	×	–	×	×
Professional excellence through CME	×	×	×	×
Be a good citizen	×	×	–	–
Change laws to be in patients' best interests	×	–	×	×
Obtain consultation when necessary	×	–	×	–
Choose whom to serve except in emergencies	×	–	×	–
Avoid discriminatory practices	×	×	×	×
Promote highest quality of healthcare	×	×	–	×
Protect patient welfare	×	×	–	×
Honesty	×	×	–	×
Respect the law	×	–	×	×
Respect patient autonomy	×	–	×	×
Report clinical research honestly	×	×	×	–
Prevent patient exploitation	–	×	–	×
Encourage public health thru education	×	×	–	–
Protect patient dignity	×	×	–	–
Full disclosure to patients	×	–	×	×
Expose incompetent/dishonest physician	×	–	–	×
Patient free choice of physician	×	–	×	–
Do not abandon patients	×	–	×	–
Perform duties objectively/accurately	×	–	–	–
Promote harmony with other health professionals	×	–	–	×
Assure death with dignity	×	–	–	–
Transplant/donation conduct	×	–	–	–
No participation in torture/inhumane practices	×	–	–	–

The following is a comparison of five ethical codes used by emergency medicine professional organizations: the American Medical Association (AMA) used by the American Academy of Emergency Medicine, the Society for Academic Emergency Medicine (SAEM), the American Osteopathic Association (AOA) used by the American Osteopathic College of Emergency Physicians, and the American College of Emergency Physicians (ACEP)

"black-letter law" wherein very specific actions are mandated, clinicians can best resolve these issues by turning to bioethical reasoning, using bioethics consultations, or applying previously developed institutional bioethics policies.

Modern bioethics developed because the law often has remained silent or inconsistent on matters vital to the biomedical community. The rapid increase in biotechnology, the failure of both the legal system and legislatures to deal with new and pressing issues, and the increasing liability crisis drove the medical community to seek answers to the difficult questions that practitioners have to work through on a daily basis [3].

Oaths/Codes

Medical ethics, or bioethics, differs from ethics in other fields just as medicine differs from other professions. This is because physicians treat ill people who are dependent on them and vulnerable to exploitation. For this reason, physicians have used ethical codes since ancient times to guide their behavior. Modern physicians who deliver critical hematologic and oncologic emergency medical services still rely on this guidance to help resolve dilemmas.

Many healthcare professional organizations, including most involved with emergency care, have developed their own values statements, which they often incorporate into their ethical codes. These codes (and the associated oaths) promote moral standards that their members presumably agree with and are expected to follow. The interpretation of those principles often evolves, albeit sometimes slowly, as the larger society changes. For example, although the American Medical Association's Code of Ethics was first published in 1847, it was not until 2001 that it stated that the physician's primary responsibility should be to their patient. While existing medical professional codes differ markedly (Table 3), all try to provide a "bottom line"—that is, a minimally acceptable course of action [2].

Some professional oaths and codes conflate bioethics and professional etiquette. However, these two areas differ markedly: professional etiquette deals with standards governing

the relationships and interactions between practitioners, while bioethics is concerned with basic moral values and patient-centered issues [7]. Specifically, bioethics deals with relationships between providers and their patients, providers and society, and society and patients.

Review of Basic Ethical (Foundational) Theories

Foundational ethical theories embody grand philosophical ideas that attempt to coherently and systematically answer two fundamental questions: What ought I do? How ought I live? Philosophers continue to elaborate or reconstruct fundamental ethical theories based on ancient ethical systems. Many were developed in India and China or within the Jewish, Christian, Islamic, and Buddhist religions. Clinicians generally have difficulty directly applying these theories to individual situations. Rather, they rely on "casuistry," a case-based application of bioethical values (described later in this chapter).

There are two main "foundational" theories of ethics: utilitarianism and deontology.

Utilitarianism, sometimes called consequentialism or teleology, is one of the more functional and commonly used ethical theories. Based on writings by John Stuart Mill and Jeremy Bentham, it focuses on getting good or valued results rather than using the right means to achieve those results. This theory promotes achieving outcomes that benefit the majority in the most impartial way possible. In its simplest form, this theory proposes achieving the greatest good (or the greatest sum of pleasure or the least amount of pain) for the greatest number of people. It is often advocated as the basis for broad social policies. Health planners often employ concepts of utility to develop more equitable health delivery systems. Such systems attempt to encourage and maximize the use of treatment that results in the most beneficial outcome for the least resource expenditure. Nevertheless, trying to define what is "good" or who comprises the affected community exposes the major problems with this theory [8].

Utilitarian principles apply to ED triage systems that regulate the resources given to each patient to maximize overall benefit. However, physicians should not use the utility concept as an excuse to deny an individual patient needed and available resources merely to add to society's greater good. In doing this, the physician would be abandoning the traditional healer's role and violating the bioethical principle of beneficence.

Deontology (*rule-based ethics*) is based on moral absolutes—something is either right or wrong. Adherents hold that certain unbreakable moral rules govern the most important aspects of our lives, even if following the rule leads to results that may not be "good." One example of a list of "unbreakable" rules is the Ten Commandments. The philosopher Immanuel Kant is often identified with this theory.

However, major problems can arise in applying rule-based ethics. The first is that moral rules may vary depending on one's culture or subculture. This can lead to great divisiveness over the interpretation of what might seem, at first glance, to be an obvious and straightforward rule. For example, does the common stricture "Do not kill" prohibit passive euthanasia (allowing death without intervening) or physician-assisted suicide (providing a patient with a lethal medication prescription)? The rigidity inherent in rule-based ethics causes difficulties when confronted with real-life situations. For some individuals, however, such a system provides necessary guidelines on how to conduct oneself in life.

Other commonly cited ethical theories include:

Natural Law. This system, often attributed to Aristotle, suggests that man should live life according to his inherent human nature, in contrast to man-made or judicial law. Natural law is often associated with particular religious beliefs, especially Catholicism. The claim that the medical profession has an inherent morality mirrors natural law.

Virtue Theory. This theory asks what a "good person" would do in specific real-life situations. It stems from the writings of Aristotle, Plato, and Thomas Aquinas in which they discuss such timeless and cross-cultural character traits as courage, temperance, wisdom, justice, faith, and charity. The Society for Academic Emergency Medicine adopted a virtue-based Code of Conduct.

Mid-level Ethical Principles

"Mid-level principles" that guide clinical practice and bioethical thought are derived from ethical theories, but are more specific and less abstract. Instead, these ethical principles are "action-guides," basically role-specific duties that physicians owe to patients, consisting of various "moral rules" that comprise a society's values [9].

By melding medicine's goals with societal morality, law, religious values, and societal expectations for the profession, Beauchamp and Childress popularized the most commonly cited mid-level principles: autonomy, beneficence, nonmaleficence, and distributive justice. These four principles provide a handy medical ethics template and a practical, although often difficult to apply, checklist to use when considering the moral implications of specific cases [8, 9].

A question that naturally arises is whether ethical principles are universal. For individual clinicians, the bioethical principles they follow, and the values that stem from them, do not change because of geography. Clinicians practicing or

teaching within cultures other than their own have a responsibility to continue applying their core ethical principles while being sensitive to the local population's values [10].

I will discuss autonomy in more depth (below), since it directly affects many decisions and ethical dilemmas that emergency clinicians face when caring for patients with hematological-oncologic problems. These include whether a patient has the capacity to make his or her own decisions, who can act as surrogate decision-makers, and what is the role of advance directives. The other principles—and virtues—will be discussed in relationship to specific ethical dilemmas, such as demanding and refusing treatment, constraints imposed by healthcare systems, and patient/survivor notifications.

Decision-Making Capacity

Autonomy means, as Justice Cardozo said, "Every human being of adult years and sound mind has a right to determine what shall be done with his own body" [11]. Physician adoption of patient autonomy has been a major change from the millennia-old tradition of medical paternalism (or parentalism), that is, doing what the physician thinks is good for the patient regardless of what the patient desires. Grounded in the moral principle of respect for persons, autonomy recognizes the right of adults with decision-making capacity to accept or reject recommended healthcare interventions, even to the extent of refusing potentially lifesaving care. Physicians have a concomitant duty to respect their choices. Over the past several decades, autonomy has become the predominant value in US medicine and society, although paternalism is still the prevailing attitude in most of the world.

One important, and often misunderstood, aspect of autonomy is that individuals who retain decision-making capacity can voluntarily and verbally assign decision-making authority to other people (e.g., family) for a specific decision or time period, such as when they are in the emergency department. Since patients may exercise their autonomy only if they have decision-making capacity, emergency clinicians must be able to determine this at the bedside so that if necessary, surrogate decision-makers may become involved.

While autonomy has become ingrained in US medical professionals, clinicians need to be sensitive to *communitarianism*, which is a counterbalance to autonomy. Communitarianism considers the larger picture of the patient's life, including his or her family and community, when puzzling through a bioethics case or developing public policy. This principle generally holds that the community's welfare outweighs an individual's rights or good and thus requires that deliberations involve communal (e.g., family, elders) discussions [8]. Many cultures rely on communitarian deliberations when making medical choices and use this pattern for public policy decisions. When making bedside ethical decisions, physicians should determine, whenever possible, not only their patient's individual values but also whether the patient subscribes to an individualistic or communitarian ethic [6].

Evaluating Decision-Making Capacity

Many ethical dilemmas in emergency medical care revolve around ascertaining a patient's decision-making capacity. In clinical settings, the question of decisional capacity is most often linked with consent to (or, more often, refusal of) a medical procedure.

Capacity refers to a patient's decision-making ability that, in the ED, emergency physicians determine at the bedside rather than by the courts, a psychiatrist or a lawyer. ("Competence" is a legal term and can only be determined by the court.) Decisional capacity is always related to the type of decision involved, although it is unclear whether it should be based on the potential seriousness or irreversibility of the outcome of a patient's decision (e.g., refusing lifesaving intubation) or on the complexity of the information needed to make the decision (e.g., whether to enter an experimental cancer treatment protocol). In current practice, most clinicians and ethicists use the seriousness or irreversibility of the outcome as the key to determining decisional capacity.

To have adequate decision-making capacity in any circumstance, an individual must understand (a) the options, (b) the consequences of acting on the various options, and (c) the personal costs and benefits of these consequences related to a relatively stable framework of personal values and priorities (Table 4) [12]. Assessing this last criterion can be especially difficult when clinicians have poor verbal skills in the patient's language. An easier, albeit incomplete, method of assessing this criterion is to ask the patient "why" a particular decision was made. This often provides an approximation of the last (and most important) criterion for assessing decisional capacity.

Table 4 Components of decision-making capacity

1.	Knowledge of the options
2.	Awareness of consequences of each option
3.	Appreciation of personal costs and benefits of options in relation to relatively stable values and preferences

From Buchanan AE. The question of competence. In Iserson KV, Sanders AB, Mathieu DR (eds). *Ethics in Emergency Medicine*, 2 ed., Tucson, AZ: Galen Press, Ltd,. 1995, pp 51–56. © 1995 by Galen Press, Ltd., Tucson, AZ. Used with permission

Disagreement with the physician's recommendation is not in itself grounds for determining that the patient is incapable of making his own decisions. In fact, even refusal of lifesaving medical care may not prove that the person is incapable of making valid decisions if he or she makes it on the basis of firmly held religious beliefs, as when a Jehovah's Witness patient refuses a blood transfusion.

Patient Consent

If a patient has decision-making capacity, a clinician who respects a patient's autonomy must get the patient's consent for any intervention. The consent need not be associated with a formal document, although an appropriate level of explanation is always required.

There are three general types of consent: presumed, implied, and informed. Presumed consent, sometimes called emergency consent, covers the necessary lifesaving procedures that reasonable people would usually wish to have performed on them. *Presumed* consent conjoins a patient's "best interest" with physician beneficence. Stopping hemorrhage and securing an airway in an unconscious, unknown patient are common examples of procedures performed under this type of consent. *Implied* consent occurs when a patient with decision-making capacity simply cooperates with a procedure, such as holding out their arm to give blood or to allow placement of an intravenous line. Indeed, this is the most common type of consent in medical practice [13].

Informed consent occurs when a patient who retains decision-making capacity is given all the pertinent facts regarding a particular procedure's risks and benefits, understands them, and voluntarily agrees to undergo the procedure. The requirement for informed consent varies in practice and law from area to area and even among practitioners and institutions in the same area. If a patient lacks decision-making capacity, get a surrogate decision-maker involved.

Advance Directives and Surrogate Decision-Makers

Advance directives loosely include durable powers of attorney for healthcare, living wills, prehospital advance directives [14], and similar documents initiated or approved by physicians, such as prehospital DNAR, inpatient DNAR forms, and Physician Orders for Life-Sustaining Treatment (POLST). They do not, however, include nonstandard and indecipherable directives [15]. The standard and generally recognized documents often express the patient's autonomous wishes about the treatment he or she will receive. However, they only go into effect if the patient lacks decision-making capacity. Otherwise, ask the patient what he or she wants done.

When patients do not have the capacity to make medical decisions for themselves, someone must make the decision for them. Four major classes of decision-makers have been proposed, and actually used, in these situations: family, bioethics committees, physicians, and courts.

Traditionally, and usually in practice, the family, especially the spouse, makes medical decisions when a patient does not have decision-making capacity. A typical prioritization list of those empowered to act as surrogate decision-makers is often stipulated in state statutes, similar to Arizona's landmark law (Table 5) or in a hospital's policy. When no surrogates exist, all potential surrogates refuse to act in that capacity, or an irresolvable conflict exists between surrogates at the same level (such as siblings), the court will intervene.

Table 5 Statutory surrogate decision-maker list: an example

Arizona Revised Statute: Living Wills and Health Care Directives Act, Title 36, Chap 32. 1992. Revised 2005
1. The patient's *spouse*, unless the patient and spouse are legally separated
2. An *adult child* of the patient. If the patient has more than one adult child, the healthcare provider shall seek the consent of a majority of the adult children who are reasonably available for consultation
3. A *parent* of the patient
4. If the patient is unmarried, the patient's *domestic partner* if no other person has assumed any financial responsibility for the patient
5. A *brother or sister* of the patient
6. A *close friend* of the patient. For the purposes of this paragraph, "close friend" means an adult who has exhibited special care and concern for the patient, who is familiar with the patient's healthcare views and desires and who is willing and able to become involved in the patient's healthcare and to act in the patient's best interest
7. If the healthcare provider cannot locate any of the people listed [above], the patient's *attending physician* may make healthcare treatment decisions for the patient after the physician consults with and obtains the recommendations of an *institutional ethics committee*. If this is not possible, the physician may make these decisions after consulting with a second physician who concurs with the physician's decision. For the purposes of this subsection, "institutional ethics committee" means a standing committee of a licensed healthcare institution appointed or elected to render advice concerning ethical issues involving medical treatment

Surrogates make decisions in one of two ways. The first is *substituted judgment*, which is used when the surrogate is not certain what the patient would want done in a particular situation. The second is absent advance directives or other explicit direction, which attempts to determine and act in accordance with the patient's values based on the patient's prior statements and behavior. This is the most worrisome type of surrogate decision-making, because it is based on the most ambiguous grounds. The second way is used when the patient has never had adequate decision-making capacity, and the surrogate must simply act in the patient's best interest. Unless there is already a court-appointed guardian, these cases often end up being resolved in a courtroom.

Children pose a special situation. Individuals less than the age of majority (and unemancipated) are usually deemed incapable of making medical decisions for themselves, although clinicians normally explain the situation to the child and ask for his or her assent. In most cases, the same rules for decision-making capacity that apply to adults also apply to children. The more serious the consequences, the more important it is that the child understands the options and consequences and can articulate the values involved in making their decision. Especially in cases involving religiously or culturally based refusal of potentially lifesaving treatment or when the parents disagree, the court or child protective services may intervene on the child's behalf.

Methods of Applying Bioethics Principals

To apply bioethical principles to a clinical situation, one first must recognize that a bioethical dilemma exists, which is not always an easy task. Once identified, addressing the problem brings its own challenges. Clinicians adhere not only to basic bioethical principles but also, at least tacitly, to a number of professional, religious, and social organizations' ethical oaths, codes, and statements. This complexity can produce a confusing array of potentially conflicting bioethical imperatives.

When dealing with bioethics cases, clinicians need to use ethical reasoning, which includes the application of foundational theories, mid-level principles, and case-based reasoning. This helps us systematically identify elements within moral problems that we otherwise might overlook.

Casuistry, or case-based ethics, attempts to define problems and correct courses of action based on the intricacies of a particular case. It puts an emphasis on what Aristotle called *phronesis*, or "practical wisdom," and is the basis for the emergency rapid decision-making model, described below. To use this method, examine each case for its similarities and differences with select previous cases paradigms, for which you have determined a suitable course of action. Where the present case is similar enough to the paradigm, use the same course of action. When significant differences exist, clinicians must apply the broader mid-level principles derived from rulebased, utilitarian, and other ethical systems, usually giving the most weight to patients' autonomy and values.

In practice it can be difficult to identify and extract the most appropriate and useful principles to apply to a particular case. Some principles may appear too vague, or perhaps several conflicting principles appear to apply to a given case. The key is to prepare for bioethical problems as one would for critical medical events, by reading about, reflecting on, and discussing how to approach these issues. This leads not only to increased personal preparation but also to more general policies that provide guidance for dealing with difficult bioethical issues [2].

Prioritizing Conflicting Principles: The Bioethical Dilemma

Applying bioethical principles can be confusing. When two or more seemingly equivalent principles or values appear to compel the clinician to act in different ways, a bioethical dilemma exists. This situation is often described as being "damned if you do and damned if you don't," where any potential action appears, on first reflection, to be an option between two seemingly equivalent "goods" or "evils." In bioethics, although there may be disagreements regarding the optimal course of action using a specific set of values, there is often general agreement as to what constitutes ethically wrong actions. While we theoretically have a duty to uphold each bioethical principle, none routinely "trumps" another.

Working through bioethical dilemmas generally requires a case-based approach. The key is to use paradigm and analogy (the first step in the rapid decision-making model, described below). Thus, when faced with a troubling case, first identify relevant mid-level principles and alternative courses of action. Then, compare it to similar but much clearer paradigms, that is, cases having resolutions with which virtually any "reasonable person" will agree. Identifying such cases may be difficult; it takes experience and a significant knowledge base. Using bioethics committees and bioethical or legal case databases may help.

Application to Emergency Medicine: The Rapid Decision-Making Model [16, 17]

When faced with bioethical dilemmas, emergency clinicians often must make ethical decisions with little time for reflection or consultation. Ethical problems, like clinical prob-

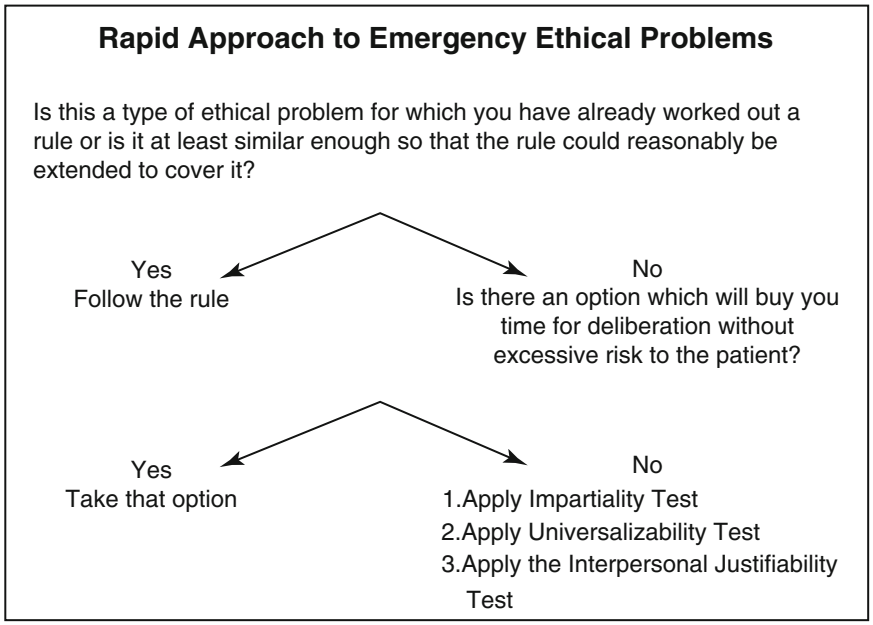

Fig. 1 Rapid decision-making model. From Iserson KV. An approach to ethical problems in emergency medicine. In: Iserson KV, Sanders AB, Mathieu D (eds.). *Ethics in Emergency Medicine, 2nd ed.*, Figure 2, pg 45. © 1995 by Galen Press, Ltd. All rights reserved. Used with permission of Galen Press, Ltd., Tucson, AZ

lems, require action for resolution. For that reason, a rapid decision-making model was developed, based on accepted bioethical theories and techniques (Fig. 1). It provides guidance for emergency medicine practitioners who are under severe time pressures and wish to make ethically appropriate decisions [16, 17].

When using this approach, the clinician must first ask: "Is this an instance of a type of ethical problem for which I have already worked out a rule?" Or, at least, is it similar enough to such cases that the rule could be reasonably extended to cover it? In other words, if there had been time in the past to think coolly about the issues, read about them, discuss them with colleagues, and develop some rough guidelines, could they be used in this case? Just as with the indications for any clinical emergency procedure, emergency physicians should be prepared with a course of action for at least the most common ethical dilemmas likely to occur in the ED. If the case in question does fit under one of those guidelines arrived at through critical reflection, and there is not time to further analyze the situation, then the most reasonable step would be to follow that rule—if it is still appropriate. In ethics, this step follows from casuistry or case-based reasoning.

If the case does not fit under any previously generated ethical rule, the practitioner should consider if there is an option that will buy time for deliberation. If there is such an option, and it does not involve unacceptable patient risks, then it would be the reasonable course to take. Using a delaying tactic may afford time to consult with other professionals, the bioethics committee, and the family.

If there is no acceptable delaying tactic, the clinician should weigh what she considers the best option using a set of three tests, drawn from three different philosophical theories, to help make a decision:

Impartiality Test. "Would you be willing to have this action performed if you were in the other person's (the patient's) place?" A version of the Golden Rule, it helps correct one obvious source of moral error—partiality or self-interested bias.

Universalizability Test. "Would you be comfortable if all clinicians with your background and in the same circumstances act as you are proposing to do?" This generalizes the action and asks whether developing a universal rule for the contemplated behavior is reasonable—an application of Kant's categorical imperative. This helps eliminate not only bias and partiality but also short-sightedness.

Interpersonal Justifiability Test. "Can you give reasons that you would be willing to state publicly? Will peers, superiors, or the public be satisfied with the answers?" This uses a theory of consensus values as a final screen.

When ethical situations arise in cases for which no time exists for further deliberation, it is probably best to go ahead and act on the previously determined ethical rule or take the course of action for which the clinician was able to answer all three tests in the affirmative with some degree of confidence. Once the crisis has subsided, clinicians can hone their ethical decision-making abilities by reviewing the decision with colleagues and bioethicists.

Bioethics Committees and Consultants

Another resource for complicated ethical dilemmas is to use your institution's bioethics committee. Most US hospitals now have multidisciplinary committees or bioethics consultants to help resolve bioethical dilemmas. Bioethics committees and consultants have four roles: (a) education, (b) policy development (proactive ethics), (c) retrospective case review, and (d) concurrent case review (ongoing clinical cases in which they often mediate between dissenting parties) [18]. Some experienced committees and consultants also perform "stat" consultations that can assist in emergency department cases.

Other Principles and Virtues

Other mid-level bioethics principles and virtues often guide clinician behavior. They also may conflict with the principle of autonomy or with each other, posing a bioethical dilemma. In their practice, emergency clinicians commonly use the principles of beneficence and nonmaleficence, as well as the virtue of truth telling. When developing policy, they often use the principle of distributive justice. Therefore, it is instructive to examine how these principles relate to specific clinical scenarios with ED patients, including those with hematological or oncologic illnesses.

Beneficence is the principle of doing good or producing benefits. This principle is one of the medical profession's universal tenets. Society's view of physicians as altruistic reflects the profession's long history of beneficence. In addition, all medical students are taught the basic tenet of nonmaleficence: *primum non nocere* (first, do no harm). This stems from recognizing that physicians can harm, as well as help, their patients.

Clinicians use the principle of distributive justice to develop policies, including triage protocols, affecting patient groups and healthcare systems. Truth telling is the virtue that guides clinicians in what and how they communicate with patients and families, rather than the decisions they must make.

Beneficence

Clinicians enter the healthcare field to help others—to be beneficent or to do good. While ED interventions for hematology-oncology patients will not provide a long-term solution, they often relieve symptoms or provide time to begin more definitive treatments. However, when opportunities to clearly benefit a patient present themselves, clinicians feel intense anguish when a patient or surrogate decision-maker refuses the interventions. This sets up a struggle between patient autonomy and physician beneficence. Probably the most common ethical dilemma in modern US medical practice, it exemplifies physician paternalism, that is, the desire to do what he or she thinks is best for the patient no matter what the patient (or surrogate decision-maker) wants.

Yet, when made by patients with decision-making capacity, clinicians should respect these refusals. That does not mean that the clinician should not clearly explain the options, potential outcomes, and costs involved. If the patient holds firm to the decision, the clinician must follow the patient's wishes, even if they conflict with his or her own values. This is the most difficult part of adhering to patient autonomy.

The only exceptions to this are when a surrogate makes a decision that the clinician believes is contrary to the patient's expressed wishes or is masking (possibly illegal) ulterior motives, or when a child is involved. In any of these situations, obtain legal assistance immediately. In the case of a child, including religion-based refusals of treatment, most courts will order clinicians to institute therapy if any reasonable chance of benefit exists.

Beneficence: Withholding and Withdrawing Treatment

As noted above, resuscitating patients who present to the ED with unknown illnesses and injuries is both ethically appropriate and virtuous behavior. A common fear, and unfortunate misunderstanding, is that once treatment is initiated, it cannot be withdrawn. Actually, there is a much higher ethical and legal bar to withholding treatment in uncertain cases than there is to withdrawing treatment once complete information is known [19].

Withholding treatment. Not infrequently, a patient is brought into the ED in extremis, unable to interact with clinicians, and without any history or direction about care. For example, the patient may be in cardiorespiratory failure or the patient may have metastatic cancer and now be suffering from hypercalcemia, a frequent terminal event. While some have advocated that allowing the patient with hypercalcemia to have a "good death" may be humane and medically appropriate [20], emergency physicians do not have this option. Without knowing the patient, the disease prognosis, or any prior wishes, they are obligated to intervene to preserve life. This obligation is based on the principles of beneficence and nonmaleficence, which are societal values placed on emergency physicians. Our society sees the entire emergency medical care system as being the caregivers of last resort. Arbitrary decisions to do less than everything reasonable to preserve a life signal a lapse in this entrusted function. Unknown and unknowing patients deserve the presumption of life.

Withdrawing treatment. Contrary to popular myth, if the emergency physician (or inpatient physician) later learns that, given the patient's condition or wishes, lifesaving interventions such as ventilation and vasopressors are not appropriate, it is both ethical and legal to withdraw them. This follows the dicta to use only beneficial interventions and to preserve a patient's autonomous wishes. Morally, withdrawing treatment is identical to initially withholding it. That is, withdrawing an IV drip or stopping a ventilator is equivalent to withholding the next drop of medication or the next ventilation. The problems that generally arise with withdrawal under these circumstances are emotional, not ethical [19].

Even though treatment has been withdrawn, clinicians must continue to provide analgesia and any other appropriate care. Healthcare professionals never cease providing care.

Beneficence vs. Patient Autonomy: Refusing Lifesaving Treatment

The following common case demonstrates the ethical dilemma produced by the tension between the physician's motivation of beneficence and the patient's (or surrogate's) desire to determine which treatments to authorize based on his or her values. In the case, the decision is religiously based.

An exsanguinating adult leukemic patient, awake and still with medical decision-making capacity, arrived in the ED and explicitly stated that, owing to long-standing religious beliefs, she wanted no blood or blood products. The physician, with a professional duty and moral commitment to preserve life, did not personally agree with the patient's decision. Yet, society (through the benchmark of court decisions) has repeatedly sided with the patient's right to refuse such treatment.

In this case, the patient's autonomy and right to practice her religion are recognized as the overriding values. The case becomes somewhat less clear when the patient lacks decision-making capacity, is a minor, or appears to be under external pressures (such as from relatives) to make what is a life-threatening decision. In my experience, however, when clinicians truthfully tell patients that they will die quickly without the transfusion, most consent. Some clinicians, steeped in the idea of patient autonomy, forget that informed consent includes informing the patient of all the relevant benefits and risks—including death.

Beneficence vs. Patient Autonomy: Refusing Analgesia

Physicians are expected to follow the medical maxim "cure sometimes, relieve often, comfort always" [21]. In some cases, patients or their surrogates may refuse analgesics to relieve acute pain. This may be due to misguided concepts of drug abuse and addiction or to a fear that taking analgesics will hasten death. Rarely, refusal may stem from religious or cultural values.

The final decision may come down to a balance between autonomy and beneficence. While there may be unique instances when analgesics should be withheld, at least in the short term (e.g., so that the patient can be awake when relatives arrive), beneficence generally outweighs any countervailing argument and the patient should receive analgesia.

Nonmaleficence

The principle of nonmaleficence includes not doing intentional harm to patients, preventing harm, and removing harmful conditions. Nonmaleficence is the profession's protective shield for patients. The following two situations demonstrate how this may not only conflict with other principles, such as autonomy, but also how it forms the basis for the rules regarding clinical research.

Nonmaleficence: Demands to "Do Everything"

No one gets every possible medical intervention. Yet, ED clinicians commonly hear surrogates demand that they "do everything," even for terminally ill hematology-oncology patients for whom further intervention will not change the disease course and may prolong an unpleasant dying process. This request, often coming from distraught and guilt-stricken relatives, poses difficult ethical dilemmas for clinicians. While patient autonomy plays a key role in any decision, surrogates may be unaware that clinicians' interventions must not harm the patient without providing them with a countervailing benefit (nonmaleficence).

The "do everything" request usually presents as one of three scenarios: where a patient knowingly requests intervention, where a patient asked for intervention via an advance directive, or where surrogates ask for the intervention.

The first situation occurs when a patient with decisional capacity who is informed of the options selects a probably non-beneficial and definitely painful course of therapy. In the ED, that may mean intubating and ventilating a terminal cancer patient in severe pain. These decisions fall under the question of patient autonomy, and even if the physician thinks she would not make the same decision herself, she should help the patient implement this choice.

The second scenario occurs when a patient has left instructions via an advance directive to "do everything." This directive carries much less weight than the patient's actual informed decision, described above, because the exact situation with

which the medical team is presented could not have been anticipated. Nevertheless, clinicians should make all reasonable efforts to comply with the patient's wishes.

The third situation occurs when families of a terminally ill patient demand non-beneficial care for their relative. Emergency physicians are usually reluctant to provide this, since it only prolongs the predictable dying process. On the other hand, to be beneficent, clinicians frequently admit end-stage cancer patients if they come for pain relief that cannot be provided at home, to temporarily relieve a family of the stress of caring for the patient (respite care), as an interlude to get a patient into a hospice or nursing facility, or who are in the terminal stage of the disease presaging death. However, interventions which simply prolong dying usually violate the ethical principle of nonmaleficence.

Legally, the representative for a patient lacking decisional capacity can make any informed decision that the patient could make about healthcare. After explaining the options and that the interventions will not be beneficial, physicians should abide by these surrogates' requests, even if they seem unreasonable. Note, however, that a physician is never required to offer any treatment through a surrogate that they would not offer directly to a patient, such as cardiopulmonary resuscitation in an imminently dying metastatic cancer patient. This is a struggle between autonomy and nonmaleficence, and the medical team's responsibility is to follow the legal surrogate's instructions to the extent that they would follow a patient's instructions. The assumption is that in most cases, the patient believed that this individual would best represent his or her wishes. When clinicians question whether the agent is acting in the patient's best interest, they can ask a court intervene.

Nonmaleficence and Autonomy: Research Protocols

The horrors inflicted under the guise of scientific research during World War II led to the Nuremburg Code and subsequently the Helsinki Declaration, enumerating basic ethical principles for research studies [22]. With a basis in autonomy, the respect for persons as individuals, these research principles arose from the desire to no longer harm research subjects, as had been done both during WWII and subsequently in the civilian sector.

Research is vital to medicine. In the past, most medical care, including that in emergency medicine, has relied on experience that was unsupported by investigation, so-called nonvalidated practice. Recently, however, clinicians have begun to use evidence-based medicine, which requires research. Over the past three decades, research done within emergency medicine and that done elsewhere but applied to emergency medical practice has improved the elegance of patient encounters, significantly benefiting ED patients. In hematology-oncology, research has driven diagnostic and treatment breakthroughs, and emergency physicians can often assist in these projects.

Yet some aspects of clinical research and research oversight fall short of meeting the ethical standards of safety and patient benefit. Overall, emergency medicine research has been and continues to be a moral endeavor. Even more important than the institutional safeguards, such as the institutional review boards (IRBs), is the individual researcher's moral compass, which must serve to protect the subject-patients of clinical research. Perhaps the greatest moral lapse has been the lack of attention to key populations, such as women and children, within emergency medicine research, with the result that patients most needing acute intervention are the ones who suffer [23].

Funding availability, both from private industry and from government agencies, still drives research agendas. This raises questions about clinical researchers' fiduciary responsibility to their subject-patients.

Finally, the moral responsibility to ensure that any research protocol and its execution are ethical extends to the journals in which the research is published [24]. While emergency medicine has an excellent record of ethical research, a large percentage of human research studies published in the major EM journals fail to mention either IRB review or informed consent [23, 25].

System Constraints: Distributive Justice and Confidentiality

Distributive or comparative justice suggests that comparable individuals and groups should share similarly in the society's benefits and burdens. In contrast to the judicial system's retributive and compensatory justice, this basic bioethical principle does not apply to individual practitioners for ad hoc use in limiting healthcare resources for individual patients [26]. Rather, it is meant to be used at the policy-making level to allocate limited healthcare resources.

For example, triage decisions conform to this principle when they are applied uniformly and impartially to all patients [27]. Other typical issues in emergency medicine for which distributive justice plays a part in designing policies and protocols include admission prioritization; how to work with patients who cannot pay for treatment; patients who have the "wrong" insurance, or belong to the "wrong" medical system or group for the particular hospital or clinic; intentional or unintentional release of patient information; and how to work with patients who are undocumented aliens.

Other principles have also had long-standing importance to medical practice, one of the most important being confidentiality, that is, the nondisclosure of patient information.

Based on a respect for persons (as is autonomy), patient confidentiality has been a cornerstone principle of the medical profession since antiquity. The *Hippocratic Oath*, for example, states, "Whatever, in the course of my practice, I may see or hear (even when not invited), whatever I may happen to obtain knowledge of, if it be not proper to repeat it, I will keep sacred and secret within my own breast." Confidentiality presumes that, unless they first obtain the patient's permission, physicians will not reveal to any other person or institution what patients tell them during the medical encounter. Various US federal and state laws have both emphasized (e.g., HIPAA) and carved out exceptions (mandatory reporting) to this stricture. With the advent of minimally secure electronic medical records, the ability to maintain patient confidentiality has become even more difficult.

Note that privacy, often confused with but related to confidentiality, is a patient's right to sufficient physical and auditory isolation such that he or she cannot be seen or heard by others during interactions with medical personnel.

Truth Telling

Truth telling remains a somewhat controversial virtue within the medical community. While many champion absolute honesty to the patient, honesty must be tempered with sensitivity and compassion; it should not equate to brutality. In recent years, poor role models, a lack of training in interpersonal interactions, and bad experiences may have diminished the perception of truth telling as a physician virtue. There are multiple tales of the champions of absolute fidelity who, nevertheless, were appalled by their own physician's lack of sensitivity when relating unfavorable medical news to them [28].

The degree to which physicians fail to disclose the truth varies with the circumstances. When failure to disclose the truth will do physical harm to the patient, such as in the infamous Tuskegee experiments on patients known to have syphilis, it is not only immoral but also probably illegal to withhold the information. Likewise, if failure to disclose information is strictly for the physician's benefit, such as telling a patient who calls in the middle of the night to "take two aspirins and call in the morning," although there is a strong suspicion of serious disease, there are serious ethical and legal deficits in the clinician's behavior. The issues become somewhat murkier when truth telling involves a third party, such as a sex partner who the patient has exposed to an infectious disease [29].

The following cases demonstrate two scenarios involving this principle that commonly occurs with ED hematology-oncology patients. The first deals with relating a probable diagnosis to a woman in a strong communitarian culture. The second deals with death notification, emphasizing the need for strong communication skills and sensitivity.

Truth Telling (Fidelity) and Communitarianism: Diagnosis Notification

A 54-year-old Hispanic woman came to the ED with her family because of a persistent cough and poor health for at least several weeks. Before the patient could be examined or any tests could be done, the patient's husband intercepted the emergency physician and told him that if the patient had a lifethreatening disease, she was not to be told because "she didn't want to know." The adult children agreed. The evaluation showed that the woman had a hard new breast lump, honeycomb lesions, and multiple pulmonary nodules consistent with cancer. The physician had a policy to tell the truth to all his patients but believed that the family might be accurate in their assessment.

Many patients come from cultures that embrace communitarianism, rather than autonomy. Communitarianism stresses the interactions between group members, which may be just the family, but may also include elders, religious figures, or the entire tribe, group, or community. In this case, the family implied that the patient was part of such a culture.

Doing good in these cases often means respecting the patient's personal or cultural desire not to be explicitly informed about a serious disease. This is the norm for many Asians (particularly Japanese), Hispanics, and Native Americans. The enormity of this information (and slight possibility of error in this case), coupled with the minimal physician-patient relationship established in the ED, might also suggest that, at least at this stage, stating the presumed "diagnosis" could be avoided.

The question for the physician is, how much does the patient want to know? The best way to find out is to ask her both what she wants to know and, if she does not want to know anything, with whom does she want the physician to speak. If she wants the information, the physician is obligated to gently tell her what he knows about her illness, including the next steps in the diagnostic process. If she designates someone else to receive this information, this fully complies with the patient autonomy principle and should be followed.

Truth Telling (Fidelity): Survivor Notification

Nowhere in emergency medicine is truth telling with sensitivity more important than when the clinician must deliver the news of a death, which is often an emotional blow, precipitating life crises, and forever altering the survivors' world. Emergency physicians must repeatedly do death notification as part of their daily work.

Excellent communication skills represent the basis for correctly delivering tragic news to survivors. Directness,

truth, consistency, and clarity are the key factors in delivering information about a sudden, unexpected death—and complying with the virtue of fidelity. Perceptive survivors can easily tell which notifiers care and which are only "going through the motions" [30, 31].

Poor clinician-patient communication disappoints both the patients and clinicians. Often, this failure is due to clinicians:

- Using highly technical language.
- Not showing appropriate concern for problems voiced by patients.
- Not pausing sufficiently to listen.
- Not verifying that the listener has gotten the information presented.
- A generally impersonal approach to the interaction, including their manner of speech [32].

Delivering the news about sudden unexpected death provokes strong emotions in both the notifier and survivors. Communication is improved if the notifier acknowledges those emotions, being prepared to vocalize and demonstrate their sadness and to recognize and acknowledge it in the survivors. Using the voice to communicate does not always mean talking. In some instances, para-verbal behavior is what is called for. These sounds, such as mmmmm, ahhhh, or mhmmm, are often sufficient to show that a person is listening and understands, particularly if they are accompanied by appropriate nonverbal cues, such as nodding the head.

It often takes imagination to put oneself in the position of a grieving survivor, especially when wide cultural or age differences exist. Even if you cannot learn to empathize with survivors, you can learn to behave appropriately, speak correctly, and assist them in their time of grief. Imagination, studying people, advance planning, or taking the lead from experienced mentors is the only way to successfully perform this necessary, but tragic task [30, 31].

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Patient Navigation

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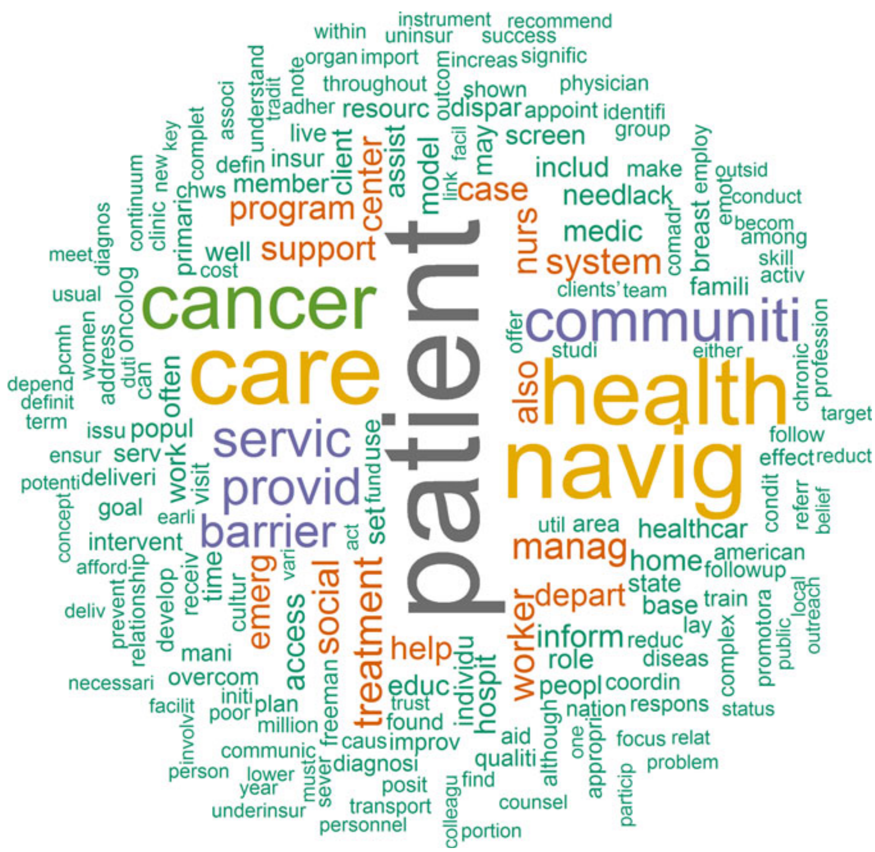

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Introduction

How Patient Navigation Is Defined

The term *patient navigation* was created by Dr. Harold P. Freeman, who partnered with the American Cancer Society (ACS) to create the first patient navigation program in Harlem, New York [1]. Patient navigation refers to the assistance offered to patients living with cancer in navigating through the complex health-care system to overcome barriers in accessing quality care and timely diagnosis and treatment. Navigation programs most often focus on helping patients with positive screening tests complete the diagnostic workup expeditiously [2, 3]. Navigation has also targeted patients undergoing initial cancer treatment [4] and in palliative care [5]. Navigation encompasses several potential forms of instrumental (defined as the provision of tangible aid and services that directly assist a person in need) [6] and emotional support for individuals with cancer. Navigators assess patients' needs and, in collaboration with the patient, develop a plan to overcome barriers to high quality care [7].

Instrumental navigation services help patients access the cancer care system and overcome barriers to care. Navigators provide assistance with insurance, finances, transportation, language barriers, communication with the doctor, securing childcare, obtaining relevant information, and coordination of cancer care [2, 7]. Because cancer is usually an emotionally charged and life-changing experience, navigators also may offer emotional support to patients and families by responding to emotional distress, expressing empathy, listening supportively, and providing comfort. Several definitions of patient navigation have been published [2, 8–10]. Although variations do exist, patient navigation generally is described as a barrier-focused intervention that has the following common characteristics:

- Patient navigation is provided to individual patients for a defined episode of cancer-related care (e.g., evaluating an abnormal screening test). Navigation in cancer-related care is not episodic (per clinic basis) but encompasses the phases of cancer treatment. The navigation skill sets employed may vary depending upon whether a patient is in the early or advanced stage of disease, palliative care, clinical trial, etc.
- Although tracking patients over time is emphasized, patient navigation has a definite endpoint when the services provided are complete (e.g., the patient achieves diagnostic resolution after a screening abnormality).
- In low-income women with breast and other gynecological-related cancers, patient navigation has improved adherence to their radiation and chemotherapy regimens [11].
- Patient navigation targets a defined set of health services that are required to complete an episode of cancer-related care.
- Patient navigation services focus on the identification of individual patient-level barriers, as well as systemic barriers, to accessing cancer care.
- Patient navigation aims to reduce delays in accessing the continuum of cancer care services, with an emphasis on timeliness of diagnosis and treatment, reduction in the number of patients lost to follow-up, and increasing the quality of the clinical encounter.

Background

Former president of the American Cancer Society (ACS), Harold Freeman, has been extensively credited as the founder of patient navigation programs that were specifically designed to explore cancer care barriers among poor Americans [12]. The ACS-funded Breast Health Patient Navigation Program used patient navigators to provide support to women that sought diagnosis and treatment of breast cancer [13]. Dr. Freeman developed the patient navigator program at the Harlem Hospital Center in 1990 in response to the complex barriers that marginalized Americans faced while trying to access cancer care services. Those complex barriers to health care included (1) extensive financial constraints resulting in the lack of health insurance and inexpensive cancer care services, Medicaid or Medicare exclusion, and lack of employment-related health insurance; (2) operational barriers including shortages in transportation services, geographic restrictions between patient and health-care facilities, lack of patient reminders, and confusing cancer-related health information; and (3) sociocultural barriers including a lack of social support and poor health literacy [14]. Parker and colleagues [15] found that these marginalized patients were at an increased risk of receiving ineffective care throughout the cancer continuum: screening, prompt follow-up of suspicious results, adequate treatment, and survivorship observation.

Dr. Freeman's patient navigation program was instrumental in expanding screening and education services in the Harlem community by having specific community members offer services to women that had a suspicious result [14]. More than 40 % of patients diagnosed with breast cancer between 1995 and 2000 were diagnosed early in the course of the disease as compared to less than 10 % between 1964 and 1986 at the same facility; there was also an increase in 5-year survival rates to around 70 % during that same time period [12].

The work of Dr. Freeman and the success of the patient navigation program have more recently encouraged governmental support. In 2001, community-based programs such as patient navigation programs were recommended to obtain funding to provide cancer education, screening, treatment, and other support services [14]. The Patient Navigation Outreach and Chronic Disease Prevention Act of 2005

approved $25 million in funding for more than 5 years from programs that successfully used patient navigation to improve health outcomes [13]. In the same year, the National Cancer Institute's Center to Reduce Cancer Health Disparities supported the Patient Navigation Research Program (PRNP) to examine the effectiveness of community-based patient navigation programs [14]. Wells and colleagues [14] also noted that in 2006, there were six sites supported by the Center for Medicare Services to reduce access barriers to screening, diagnosis, and cancer treatment in minority Medicare beneficiaries.

Key Personnel

The complexity of cancer care requires patients to navigate the cancer center system for treatment as well as the community system for health, community, and social resources between treatment appointments. Hospital-/cancer center-based navigation enables patients to effectively navigate the hospital system, while community-based navigation enables patients to effectively engage and navigate community-based services and support systems that can facilitate the cancer center/hospital system interactions and potentially improve the cancer treatment experience.

There is no accepted definition of patient navigation, nor is there an assumption of who would be most competent to provide patient navigation activities [13]. In a study conducted by Wells and coauthors [14], the results from their literature review identified four areas in which patient navigators frequently intercede: (1) providing social support, (2) addressing patient barriers to cancer care, (3) providing health education about cancer across the cancer continuum from prevention to treatment, and (4) overcoming health system barriers. In a nutshell, these same duties have been categorized by Jean-Pierre et al. [16] into two types of interventions: instrumental and relationship. Instrumental interventions are organizational or operational, such as transportation services and cancer information, but relationship interventions are personal ones that build and strengthen the connection between the patient and provider [16].

After reviewing published literature [14–21], the patient navigator also has several alternate titles, but the role and responsibilities are yet the same. Originally, the patient navigator was a hands-on patient representative that concentrated on addressing the specific needs of patients by recognizing and eliminating barriers to timely receipt of care [26]. Dohan and Schrag [25] noted that the role of a patient navigator needs more refining accompanied by specialized training. Defined roles and standardized training should allow the representative that best serves the patients to fulfill the patient navigator role. Currently, patient navigators have many titles, including *nurses*, *community health workers*, *case managers*, *social workers*, *community health aides*, *lay health workers*, *comadres*, and *promotoras*. These services are often provided by a lay patient navigator, but there are many programs that utilized navigators with undergraduate degrees, graduate degrees, nurse navigators, social workers, health educators, clinicians, research assistants, as well as cancer survivors [14]. The following sections will highlight four types of individuals who provide patient navigation services.

Nurse Navigator

The term nurse navigator was introduced to the oncology health-care setting in recent years but seems to continue to fall under the broad heading of patient navigation [28]. In 2011, the National Comprehensive Cancer Network [29] stated that the patient navigator is most often a nurse and used the term patient navigator interchangeably with case manager. Nurse navigation is defined as patient navigation services implemented by a bachelor's prepared RN, often with oncology experience, who offers cancer education, supportive care, and appropriate referrals after diagnosis and throughout treatment for breast cancer [21]. These trained professionals assist patients with scheduling doctor's appointments as well as making knowledgeable decisions regarding treatment. Nurse navigation also consists of providing tips on coping with patients' prognoses, making sure that patients stay on track with their treatment plans, handling insurance issues, and offering emotional support [29, 30].

Seek and Hogle [29] noted that due to the complex responsibilities of a patient navigator, a nurse practitioner or advanced oncology nurse would be best suited for the role [30]. A nurse navigator is able to provide services at the initial diagnosis and can enhance cancer care throughout the cancer care continuum, whether it ends in survivorship or end-of-life care [31]. However, their focus is on treatment delivery issues within the hospital/cancer center system. Oncology nurses are an essential component to the education of not only patients but family members of patients, as well as the community [32]. They can translate complicated information into lay terminology for cancer patients, family members, and care givers [33]. One of the most essential responsibilities of an oncology nurse is to explain cancer-related information that is given to the patient by other health-care providers and to help them in comprehending any treatment plans [31]. Oncology nurses provide information needed to understand treatment side effects, nutrition, coping strategies, and other behaviors that improve care [34]. They can show patients how to effectively navigate the cancer medical system until that patient has the ability to navigate alone [20]. Oncology nurse navigators are also active members of the health-care team who can provide input

on treatment schedules, education provided to the patient and family, and any other valuable information to support the patient [32]. They can also initiate difficult discussions between either the patient and family members or physicians and help them make difficult choices that affect their individual cancer care [20].

Case Managers

Case managers are health-care professionals who help provide a variety of services that assist individuals and families cope with complex physical or mental health medical conditions. The purpose of the case manager is to increase effectiveness, enhance treatment adherence, offer patients with needs services with the health-care facility and community, and guarantee patient-centered care [35]. To do so, the case manager job description is centered on working closely with clients and their families to identify their needs, goals, and the necessary resources to meet those goals. Instead of managing the clients, case managers help clients manage their own difficult situations. Case managers are vital members of the health-care professional team. When a client reaches the optimal quality of life, all additional support systems benefit, including the client, their family, and their health-care providers. Since case managers can be found in both medical and social service work environments, duties can vary depending on employment. The duties of a case manager are as follows [36]:

- Reach out to clients assigned by his or her supervisor to assess their most urgent needs, appraise the situation, and listen to the clients' concerns.
- Develop a detailed plan of action to meet these needs, set goals, and find necessary resources to meet the goals.
- Offer counseling for patients in either individual or group settings.
- Consult with other external agencies to provide support services and resources.
- Keep comprehensive records of clients' progress throughout the process, including every call, referral, and home visit.
- Maintain confidentiality, respect privacy, and preserve the clients' routine and independence as much as possible.
- Stay in touch with clients to ensure the services were beneficial and that their needs are still met after pointing clients in the right direction for services.

Medical case managers usually work in various health-care facilities, such as hospitals, nursing homes, clinics, and rehabilitation centers. Social service case managers are employed mostly by public and nonprofit organizations, including schools, housing commissions, and homeless shelters. Typically, case managers specialize in a particular area, such as physical health, mental health, aging, disability, child welfare, addiction, or occupational services. Hesselgrave [37] noted that case managers bear a responsibility for coordinating oncology services, in addition to counseling services, home health services, physical therapy, and more.

Most case managers are professionals who have a background in either social work or nursing. Successful case managers must possess strong communication skills and problem management strategies. He or she must also be organized, detail oriented, and knowledgeable. Usually, they obtain a bachelor's or master's degree, while some states also require licensing since the managers play such a prominent role in patient care. Case managers hold positions where they are strong advocates to ensure clients' unique needs are met.

Social Workers

Although patient navigation is thought to be a very recent idea, it borrows many concepts from social work [13]. A health-care social worker takes on a variety of tasks depending on the environment in which they choose to work. They work with people who have chronic and acute health-care needs such as HIV, diabetes, heart conditions, and trauma [21, 26, 38]. They work in clinics, hospitals, nursing homes, assisted living, mental health, and other health-care settings as well. In the hospital, they help clients plan their discharge home. They coordinate services such as home health care, medical equipment rentals, transportation to follow up doctor visits, and other related activities. They will help clients get admitted to inpatient and outpatient services, find funding sources, fill out paperwork, and find support resources for families. They assist with educational classes on things such as childcare, Alzheimer's management, living with cancer, and HIV. They are concerned with all components of health and mental health care. They also participate in and advise on health-care policy, services, and legislative issues [39]. Although many social workers primarily work in an office setting, they also spend a great deal of time outside of their office setting to visit and check on the status and health of their client.

Social workers have been known to serve the most economically disadvantaged populations [39]. Those disadvantaged populations include those that are unaware of available services; discouraged from taking advantage of services due to lack of trust, difficult programming, or poor access to available services; refuse to participate in available programs; or withdrawn from available services [40]. With a dedication to assist vulnerable populations, social workers have become a very cost-effective resource [24]. They have been utilized as patient navigators because of the ability to help cancer patients get services and coordinate the health-care team of

cancer patients [31]. The Affordable Care Act indicates the duties of a patient navigator include increasing public awareness about health insurance, cultural and linguistically sensitive health-care information, assist in health-care selection, and offer recommendations to appropriate services that handles grievances, complaints, or other questions [23]. Darnell [23] maintains that social workers are well suited to do the previously mentioned duties effectively.

Community Health Aides, Lay Health Workers, Comadres, and Promotoras

In contrast to social workers and hospital-based navigators, community health aides, lay health workers, comadres, and promotoras spend the majority of their time in the field working directly with their patients/clients and little time in the office setting. Since they usually live in the community, and often neighborhoods they serve, they and their patients/clients daily lives overlap professionally as well as socially. This facilitates the development of richer interpersonal trust relationships and understanding of community-based barriers and perceptions that may exist with navigators living outside of the community or neighborhood.

Community health workers (CHWs) have been described as serving in areas of community outreach and follow-up by helping patients to access health-related services. In contrast to social workers and other personnel listed, CHWs are lay people who commonly live (rather than work) in the community and have received training through formal (state certification) or informal (local organization/position specific) training. They also have provided informal counseling, social support, health education, screening, detection, and basic emergency care [41, 42].

By identifying and addressing barriers to adherence to cancer screening or treatment recommendations and working with patients to negotiate tailored plans of care, CHWs have improved care access and cancer screening behaviors, as well as reduced health-care costs in minority communities, including Black and Hispanic communities [43–45]. Community health workers (CHWs) can be broadly defined as community members who serve as connectors between health-care consumers and providers to promote health among groups that have traditionally lacked adequate access to care [46]. CHWs are referred to by more than 40 different terms. These names include "lay health advisors," "paraprofessionals," "health aides," "comadres," "promotoras," "patient navigators," and "natural helpers." Community health workers play influential roles in the health-care delivery system even though they are not often considered to be formal members of a medical team. They often help link people to the necessary health-care information and services that they may be lacking at the time. Community health workers work in all geographic settings, including rural, urban, and metropolitan areas; border regions (colonias, i.e., comadres and promotoras); and the Native American nations. Community health workers that are hired by health-care agencies often have a disease- or population-based skill set such as providing education or enhancing the nutrition of those who may be living with the various forms of cancer, heart disease, or diabetes. Teaching home-based chronic disease self-management skills is also an important component of their skill set. Community health workers may [47]:

- Staff tables at community events.
- Provide health screenings, referrals, and information.
- Help people complete applications to access health benefits.
- Visit homes to check on individuals with specific health conditions.
- Drive clients to medical appointments.
- Deliver health education presentations to schoolchildren and their parents and teachers.

Although their roles vary depending on locale and cultural setting, they are most often found working in low-resource communities where people may have limited resources, lack access to quality health care, lack the means to pay for health care, speak English fluently, or have cultural beliefs, values, and behaviors different from those of the dominant Western health-care system [18, 22, 39, 48]. In these communities, community health workers play an integral role in bridging the chasm between the community and the health-care system. The role and responsibilities of a community health worker may consist of the following [2, 42, 47–51]:

- Helping individuals, families, groups, and communities develop their capacity and access to resources, including health insurance, food, housing, quality care, and health information.
  - Facilitating communication and client empowerment in interactions with health-care/social service systems.
  - Helping health-care and social service systems become culturally relevant and responsive to their service population.
  - Helping people understand their health condition(s) and develop strategies to improve their health and well-being.
  - Helping to build understanding and social capital to support healthier behaviors and lifestyle choices.
  - Delivering health information using culturally appropriate terms and concepts.
  - Linking people to health-care/social service resources.
  - Providing informal counseling, support, and follow-up.
  - Advocating for local health needs.

- Providing health services, such as monitoring blood pressure and providing first aid.
- Making home visits to chronically ill patients, pregnant women and nursing mothers, individuals at high risk of health problems, and the elderly.
- Translating and interpreting for clients and health-care/social service providers.

The success of CHWs' efforts has caused many government agencies, nonprofit organizations, faith-based groups, and health-care providers to create paid positions for community health workers to help reduce, and in some cases eliminate, the persistent disparities in health care and health outcomes in underprivileged communities [47]. Something very unique about CHWs is that they oftentimes reside in the community that they regularly serve.

Patient Navigation Intervention Sites

Patient navigation has quickly grown into a nationally recognized model for the delivery of health-care services [2]. As the patient navigation model is becoming more and more utilized within the health-care delivery system, it is important to note that patient navigators are not just found within the hospital system. In order to improve health outcomes for cancer patients that often have to overcome daunting barriers, patient navigation is now being utilized outside the hospital in facilities such as community cancer centers. There has also been a push for primary care providers to employ the patient-centered medical home model to aid in the reduction of cancer care disparities. Dr. Freeman understood that there needed to be a more innovative way to attack cancer, one that eliminated economic and cultural barriers to health care, early screening, and treatment and that needed to be implemented in the communities around America [2]. The implementation of patient-centered medical homes, as well as the overall evolution of the patient navigation model has helped to breathe new life into this fight against cancer and cancer care disparities.

Patient-Centered Medical Home

The patient-centered medical home (PCMH) model of care was given considerable backing because of how the Patient Protection and Affordable Care Act of 2010 promoted the expansion of innovative styles of primary care and coordination of care services [51]. Henderson and colleagues [51] noted that the purpose of the PCMH is to offer patients a facility where they are seen by the same members of a health-care team, including a care coordinator, who is usually a nurse [51]. Patient-centered care is thought to be a very important component in reducing racial, ethnic, and socioeconomic disparities in health outcomes and access to care [52]. The PCMH has become a widely accepted approach to primary care delivery in the United States, with no signs of deviating from this approach [53]. The PCMH has focused on providing coordinated care, which has been shown to improve health outcomes, enhance patient satisfaction, and minimizing costs [52]. This health-care model is built of general principles that balance one another and feed into an inclusive idea of primary care delivery including (1) having a personal physician, (2) comprehensive orientation, (3) physician-led medical practice, (4) coordinated care, (5) focus on quality and patient safety, and (6) improved access [53]. Patient navigators are influential in this coordination of care that makes the PCMH model of care so popular. The oncology patient-centered medical home (OPCMH) model has stemmed from PCHM. Studies have shown that OPCMH model reduces cancer-related hospital admissions, as well as the number of hospital admission days for chemotherapy patients [54].

Community Cancer Centers

Based on the notion that community members trained to be patient navigators can be valuable in eliminating diagnosis and treatment barriers of cancer, community patient navigation programs denote the prevention component of the Freeman model in encouraging the community to get screened, potentially reducing disparities in cancer care [55]. With the anticipation of patient-centered care from not only cancer patients but also from accrediting bodies, community cancer centers have considerable demands to implement patient navigation programs [56]. The Avon Foundation Community Education and Outreach Initiative (CEOI) addresses barriers to cancer care through the use of community-based patient navigation. Patient navigation programs within community cancer centers use both untrained and trained volunteers to (1) inform the community about routine breast care, breast cancer, and screening options; (2) coordinate breast health events such as seminars, lunch and learns, and community health fairs; (3) lectures on breast health and breast cancer in the workplace, places of worship, and town hall settings; (4) extend reminders to encourage the community to make and attend all mammogram appointments; and (5) offer educational support through educational outreach activities [55]. The CEOI is a single documented case of where a community patient navigation model was utilized within a community cancer center, but more centers are adopting this trend of incorporating patient navigation to address cancer care barriers of its community members.

Patient Navigation in the Emergency Department

Patient navigation programs give assistance and direction to persons with the objective of enhancing access to cancer care while eliminating the barriers to timely, quality of care [12]. Barriers such as low socioeconomic standing and cultural and religious beliefs often are the foundation for disparities in ethnic groups, but poverty is the most significant cause of disparities in Americans [57]. Along with the previously mentioned barriers, insurance status has also proven to be a significant barrier to adequate cancer care. Although cancer is often associated with patients of advanced age, Calhoun and associates [26] noted that compared to Whites, racial and ethnic minorities receive poorer health care even with comparable insurance status, age, income, and disease severity. Adding to the issue of lower-quality cancer care, there are difficulties in obtaining timely cancer care that include medical distrust, poor health literacy, lack of cultural and language concordance, and misunderstanding about cancer [58]. For patients that live in rural areas, barriers to access of health care and transportation to health-care facilities has been shown to inhibit prompt cancer treatment [57].

Patient navigation is a model of care that has been proposed to alleviate the effects of health disparities [26], but significance of this concept does not end there. Patient navigation has developed into a model that has grown from addressing the needs of marginalized populations to navigating every cancer patient throughout the cancer continuum [35].

Barriers surrounding lack of insurance have been shown to have a negative impact on cancer-related health outcomes. One major resource for medical care for the under- or uninsured is the emergency department. Emergency department use has increased to almost 25 %, to around 110 million visits between 1992 and 2002 [61], According to the 2003 National Hospital Ambulatory Medical Care Survey, there were about 114 million emergency department visits that year, with less than 20 % considered actual emergencies [60]. Although health-care costs in the United States are more than in other nations across the globe, 13 million Americans are underinsured with 46 million Americans uninsured [61].

Long recognized as a safety net provider, the emergency department is one usual source of care for those who are affected by barriers to continuity relationships with physicians [62]. Community health centers (CHC) also provide health care, but CHCs only provide a portion of care needed for people without usual access to care [61]. CHCs also come with their own set of barriers, because patients often have to pay a portion of the costs for any services that are needed during the appointment [63]. Although emergency departments are guaranteed medical care for many patients, there are far less acute settings that can provide much of medical care that is needed [64].

Patient navigation has traditionally addressed barriers to access of care to underserved and underinsured populations and that utility has now been seen in action in the emergency department. A study conducted by Enard and Ganelin [27] found that patient navigation decreased the chances of return emergency department visits among those that use the emergency department for usual care. This study also found that there was a considerable decrease in those that did make return visits to the emergency department for usual care over a 12-month time span [27]. A 2010 study by Roby and associates [65] found that over a 19-month time frame, patients were less likely to make multiple emergency department visits if they had previously received case management through medical homes. In a study that utilized rigorous clinical case management for frequent emergency department users in urban areas, the researchers found considerable reductions to acute hospital services, including psychosocial issues [66].

Patient navigation has the potential to remedy another issue that emergency departments are presented with and that is the issue of overcrowding. Emergency department use that leads to overcrowding has the misconception of being attributed solely to those patients that are either underinsured, uninsured, or lack a primary care physician. The barrier that is often overlooked in the scenario is the possibility of a poor patient provider interaction. Patient provider relationship factors such as mistrust and poor communication styles have been associated with poor patient satisfaction, lack of preventive care services, lack of referral options, and poor patient follow-up on treatment [67]. Successful communication is a crucial component in cancer care and allows patients to make informed treatment decisions and also adherence to treatment options [68]. Weber and associates [59] found that the misconception that patients who utilize the emergency department either do not have a primary care physician or health insurance coverage can contribute to the assessment that emergency department overcrowding is only the result of misuse by a small marginalized segment of the US population. Policy makers and health-care officials should understand that not all issues of overcrowding or improper use of emergency departments are due to poor patient provider relationships but can be attributed to other systemic barriers that contribute to health disparities among vulnerable populations in the United States.

Summary

Patient navigation has been shown to be an intervention whose sole purpose is to reduce barriers to cancer care throughout the entire cancer care continuum. The success of this approach has led to its implementation in the management of non-oncologic chronic disease management. This

intervention has been met with governmental support to ensure that the goals and aims of the patient navigation model are achieved. The evolution of patient navigation has not caused the model to deviate from Dr. Freeman's initial goals for the first patient navigation program, but it has grown to include many different key players in the health-care system. Not only has patient navigation evolved to include other key health-care personnel, but it has also expanded outside the traditional health-care system to better serve the marginalized underserved population Dr. Freeman set out to help in 1990. This chapter has shown how patient navigation is a model of care that not only ensures timely care for cancer patients, but its principles are now being used in the emergency department to help eliminate disparities in primary care of those who are marginalized, underinsured, or uninsured. The patient navigation model is proving to be an intervention that has shaped how patients, whether they have cancer or not, navigate through the health-care system and receive optimal care.

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The Interface of Emergency Department, Oncology, and Palliative Social Work: Psychosocial Interventions in Oncologic Emergencies

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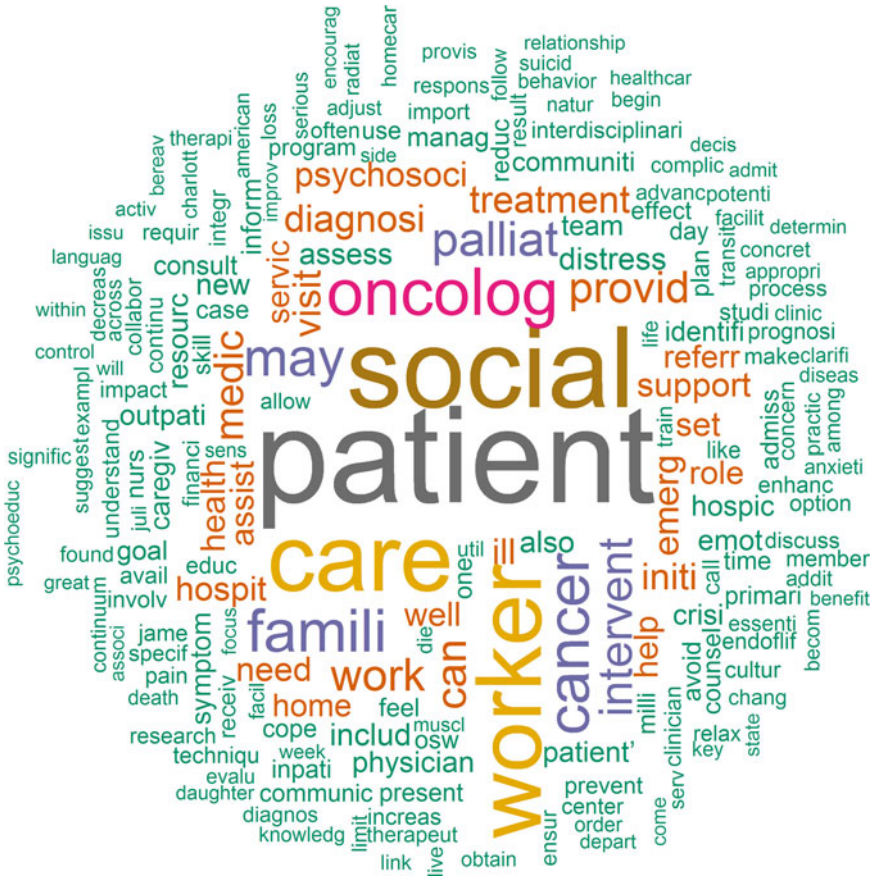

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Introduction

Cancer patients may require emergency department (ED) care as a result of symptoms or complications of the disease itself, from the side effects of cancer treatment, including chemotherapy or radiation therapy, or from intercurrent injury or illness unrelated to cancer. Sepsis, pain, neutropenia, fever, deep vein thrombosis, nausea/vomiting, and failure to thrive are common symptoms that prompt oncologic emergency care [1–3]. Despite the overall decrease in cancer death rates, ED visits for cancer-related emergencies are on the rise [4]. The impact of a new cancer diagnosis, worsening prognosis, or transition to end-of-life care exacts physical, emotional, financial, and psychosocial distress on patients and families. Medical social workers are key interdisciplinary team members within the inpatient, outpatient, and home care settings who intervene along the continuum of illness. They are specifically trained to assess the patient's adjustment to illness and treatment, as well as any social and financial concerns that may impact medical decision-making. Social workers also provide therapeutic interventions to enhance patient coping, reduce caregiver distress, and ensure continuity of care across settings [5].

When patients with oncologic emergencies and their families present to the ED, social workers may be called upon to intervene with issues involving the entire spectrum of cancer, from a new diagnosis to end-of-life care. In both inpatient and outpatient settings, oncology social workers are trained to provide a variety of interventions to assist patients and families coping with cancer, including assessment of psychosocial needs, adjustment to illness and side effects of treatment, and linkage to community resources. Palliative social workers may also intervene to assist oncology patients in crisis where primary attention may be placed on pain and symptom management, decision-making, advance care planning, or education and counseling regarding end-of-life care. This chapter examines social work's involvement with oncology patients in the ED, as well as the oncology social work role in the outpatient setting, and suggests potential partnerships and collaboration among ED, oncology, and palliative social work.

The Role of the ED Social Worker

The role of the ED social worker varies greatly, given the diversity of the patient population and the emergent nature of many social work referrals in this setting. ED social workers are frequently consulted for patients who present with psychiatric symptoms, sexual assault, and abuse/neglect [6]. Due to the time-intensive nature of these referrals, it may be difficult for the ED social worker to consult on less urgent referrals, including patients who, after a diagnostic evaluation, confront a newly diagnosed cancer. Despite these constraints, ED social workers may be the first psychosocial clinicians to see patients with life-limiting illnesses who present with distressing symptoms or who may be actively dying [7].

ED social workers strive to maintain a careful balance by blending their responsibility to provide concrete services such as community resource referrals, medical equipment setup, and placement in short-term or long-term care facilities, with therapeutic interventions, including crisis intervention. ED social workers also conduct psychosocial assessments and provide bereavement counseling when deaths occur in the ED [8]. While no one doubts the importance of ED social work, there is very little research examining the types or effectiveness of interventions provided by ED social workers [9].

Crisis Intervention

For ED social workers, priority referrals that require immediate intervention include domestic violence and sexual assault and elder or child abuse and neglect. In addition to providing support and crisis intervention, these referrals may also require consultation with law enforcement or state agencies as well as hospital security, locating and supporting family members or friends, and maintaining constant communication with the ED physician and nurse. Given the sensitive and complicated nature of this work, the ED social worker may spend a great deal of time on such consultations. Crisis intervention skills utilized with victims of sexual assault and domestic violence include re-establishing coping skills, problem solving to identify next steps, assessment for suicidality, provision of emotional support, and the resolution of concrete needs such as safety, housing, and financial support.

For patients who present with symptoms of depression, anxiety, suicidal ideation, or alcohol and drug abuse, but do not require inpatient admission, the ED social worker typically completes an assessment and provides brief counseling as well as linkage to community resources to ensure follow-up support. ED social workers with strong backgrounds in mental health may identify appropriate referrals to psychiatry or outpatient mental health agencies and provide brief interventions and education to interdisciplinary team members on strategies to help patients in this setting.

Complex Case Management

When a patient's ability to care for himself or herself is diminished but admission is not required, the ED social worker may be responsible for obtaining support through home-based health services. They also assist with applying for financial assistance to facilitate admission to a skilled nursing facility, as well as coordinating a plan for family and friends to support

caregiving at home. For patients who need additional services, preventing a "social admission" by facilitating a safe discharge from the ED is important. Effective discharge planning reduces unnecessary hospital admissions and coordinates the outpatient services a patient needs to allow them to safely remain in their home environment. The expertise and range of skills implicit in crisis intervention, mental health assessment, and complex case management are essential to the care of oncology patients and their families who present to the ED for help.

ED Social Work Role with Oncology Patients

When oncology patients present to the ED with complications from their disease or treatment, the ED social worker may be asked to see patients with concomitant symptoms of depression, anxiety, or suicidal ideation, while also evaluating caregivers who may be exhausted from providing care. Newly diagnosed cancer patients, as well as cancer patients who come to the ED in lieu of a visit with their primary physician or oncologist, may be referred to the ED social worker for assistance with medical follow-up, evaluation, and treatment, as well as provision of concrete services such as home health care or medical equipment.

When oncology patients present to the ED at the end of life, the ED social worker provides emotional support to the patient and family, communicates with the hospital chaplain as requested by the family, and helps identify a private space for family members to gather and grieve. While there is no published research delineating the role of ED social work with oncology patients, many of the skills outlined above are integral to assisting oncology patients and their families.

Psychosocial Issues for Cancer Patients in the ED

Diagnosis of Cancer in the ED

A new diagnosis of cancer may elicit strong emotions and can induce a great deal of stress for patients and families. It may cause the patient to experience feelings of loneliness, abandonment, and loss of control over their situation [10]. The ED social worker may be called upon to provide emotional support while identifying and clarifying, in consultation with the emergency physician, any real or perceived fears surrounding a new diagnosis, prognosis, or treatment. Providing patients and families with the necessary time to integrate a new diagnosis is essential to allowing them to consider decisions about appropriate treatment and continuing medical care [10]. For patients who decline further evaluation and treatment, it is essential that the patient understand the potential consequences of avoiding further care. An ED social work assessment of concerns and fears following a new diagnosis of cancer may provide the patient with an alternative plan of care aside from hospitalization, such as follow-up with an oncologist to review and integrate medical options. Below is a case study of a newly diagnosed cancer patient in the ED that demonstrates the ED social worker's role with patients/families and the interdisciplinary team.

Case Study with Emergency Department Social Worker

The ED social worker receives a call from an emergency physician to see a 63 year-old Latina woman, who, with her three adult children, is anxiously awaiting the results of a CT scan of her pelvis and abdomen. Prior to this ED visit, her medical history includes diabetes and asthma. She presents with rectal bleeding, severe abdominal pain, and dizziness. The emergency physician informs the ED social worker that the patient has a new diagnosis of metastatic anal cancer and that he would like the social worker to assist as he provides this information to the patient and her family. The patient has no primary care physician and must be admitted to the hospital for further evaluation and consideration of treatment options.

The ED social worker had spoken with the patient earlier in the day while the patient was waiting. The patient confided, "I bleed every time I'm on the toilet, for the last few months." When the social worker inquires if she had told anyone, the patient states that she did not want to tell her family because she was scared. As the social worker begins to explore the patient's fears about telling family, the patient begins crying and pulls out rosary beads from her pocket. The patient explains that her youngest daughter is getting married in a few months and that the focus should be on the young, not the old. She goes on to say she has led a full and happy life and that it is up to God to decide her fate.

With the patient's permission, the ED social worker contacts the Catholic chaplain on call for the ED, to be present at the family meeting. The ED social worker secures a private space for the patient and family to meet so that they can process this new diagnosis in a quiet setting. As the emergency physician explains the results of the tests done in the ED and describes the patient's diagnosis, prognosis, and treatment options, the patient and her children begin to cry. While the social worker and the chaplain comfort the patient/family, the emergency physician sits quietly, in order to allow them time to process this information.

After a few minutes, the emergency physician confirms with the patient that she has heard the words and

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is beginning to integrate the significance of her medical condition and the treatment options. Following this discussion, the ED social worker acknowledges the unique emotional responses of the patient and family and describes the oncology and/or palliative services that can be provided concurrently with the chemotherapy or radiation that the patient may receive while in the hospital. The emergency physician concurs with the ED social worker, describing how the patient may benefit from specialized symptom management and the provision of psychosocial and spiritual services for both the patient and family. The patient is admitted to the hospital late that evening and is seen by oncology and palliative consultants the next day. The ED social worker ensures a seamless transition by communicating with the inpatient unit social worker.

Communication in the ED

Due to the often chaotic and busy environment, ED clinicians are often unable to spend significant periods of time with patients/families. As most patients arrive to the ED in crisis and distress, it may be difficult for them to comprehend a complete picture of their medical problem and proposed treatment. The medical jargon and complex terms used by health-care professionals may represent a foreign language to patients/families, regardless of their educational level. ED social workers can assess the patient's/family's health literacy and understanding of medical information and then work with the physician to clarify that the patient understands the care they are receiving. The essential role that social workers play as part of the healthcare system is evidenced by their frequent initiation, implementation, and support of end-of-life discussions with patients, families, and other caregivers [11]. Furthermore, social workers advocate on behalf of patients to physicians and nurses, increasing awareness of psychosocial issues along the continuum of illness and the benefits of early referrals to palliative care or hospice.

In addition to normalizing the challenge of integrating information when in crisis, the care taken to help patients and families to anticipate the next steps in resolving their medical crisis models a relationship that highlights both the emotional and informational needs of patients and families. Despite the often limited time that is spent with a patient, all clinicians who care for seriously ill patients contribute to the meaning making and processing of coping with illness. While ED interactions may be brief, they can forever impact patients and families.

ED as Primary Health-Care Site

Patients who typically use the ED as their primary healthcare site are more likely to learn of their cancer diagnosis in the ED. The fragmentary nature of emergency care may limit the possibility of establishing continuity of care and a predictable relationship with a provider after diagnosis [12]. Among patients who use the ED for primary health care, one small study suggested that limited access to office-based practitioners in their community, lengthy wait times, and rapidly progressing illness were the proximal causes of seeking ED rather than office-based care [13].

For those who are without insurance, social work involvement can be pivotal to helping patients organize their medical care and access available financial assistance, without which, treatment for their disease can be delayed and suboptimal. In working with patients/families to identify alternative care plans, as well as available community resources to assist with integrating a new diagnosis, the ED social worker serves as the link between the community, primary care, and hospital settings.

Language/Cultural Barriers

In one Michigan study, those diagnosed with cancer in the ED were found to come from lower socioeconomic backgrounds, were older, and more often disabled [12]. A large number of these patients were found to be dually eligible for Medicaid and Medicare up to 12 months prior to diagnosis compared to those diagnosed with cancer in other settings. Racial differences were also found in this study, with African Americans being significantly more likely to receive a cancer diagnosis in the ED [12].

A small study of Spanish-speaking patients in New York City found that they were frustrated both due to their inability to comprehend their prognosis, as well as difficulty in accurately expressing to clinicians their feelings surrounding cancer diagnosis and prognosis [13]. Advocating for the use of an interpreter for patients/families whose first language is not English can enhance understanding of medical information and minimize the emotional distress and confusion that emanates from such misunderstandings. An ED social worker's assessment of specific cultural concerns related to hospitalization, caregiving, and in some cases, receipt of medical treatment, allows the ED team to practice more culturally sensitive care.

A key tenet of social work practice is cultural competence or the ability to work in the context of cultural differences. Health disparities in ED pain management have been demonstrated, with one study showing that Hispanics were twice as likely not to receive pain medication for bone fractures as compared to non-Hispanic whites [14]. ED social workers can take the lead role in educating their interdisciplinary team members about these and other disparities as well as specific cultural concerns and traditions that may impact medical decision-making.

Caregiver Distress

Whether driven by distressing symptoms that are unmanageable at home, exhaustion from the intensity and/or longevity of caring for a cancer patient, or feeling overwhelmed by the responsibilities of caregiving, caregiver distress may be the root cause of an ED visit. ED social workers who screen for caregiver distress can work to determine additional sources of support in the caregiver's life and ensure a link to these services. A case example of an oncology social work intervention for a distressed caregiver is provided at the end of the chapter.

The Role of the Outpatient Oncology Social Worker

In addition to the acute medical needs that prompt ED visits and invite the interventions of ED social workers, oncology social workers serve to address the unique psychosocial stressors that accompany a cancer diagnosis. These may include adjustment to a new cancer diagnosis, alterations in role and identity, changes in caregiver needs and family roles, impact on work and finances, and goals of care planning. For cancer patients, these transitions can be markers of ambiguous loss, or the unclear, indeterminate losses that are less acknowledged than death, but can greatly impact coping, sense of control, and psychosocial functioning in both the patient and family [15, 16]. These losses can also trigger feelings of anticipatory bereavement, in which patients and families begin the process of mourning, coping with loss, and psychosocial reorganization in preparation for death. This process can trigger mixed emotions such as helplessness, denial, confusion, and guilt but, if managed effectively, may provide patients and their families with improved communication and meaningful interactions at the end of life [17].

Prior to a cancer diagnosis, patients may not have had needs that would necessitate an interaction with a social worker. The oncology social worker may be their first introduction to such services. Once this connection is made, the oncology social worker can link patients and their families to concrete resources in the community, as well as provide therapeutic interventions to address psychosocial needs. The oncology social worker becomes the conduit of communication, linking the work done in the ED with the work of the outpatient oncology team; thus avoiding a "new beginning" for patients and families and supporting continuity of care in the process. It is the author's experience that oncology and ED social workers typically collaborate and communicate to ensure smooth transitions for patients in need between specialties and across outpatient and inpatient settings.

Social workers are the primary psychosocial professionals available to patients receiving medical treatment [18, 19]. While medical social workers have become more broadly available in healthcare settings, oncology social workers have evolved as a subspecialty within the field [20]. The psychosocial needs of patients with cancer have become increasingly complex as treatment has shifted to the outpatient setting. The broader range of treatment options available to patients has complicated decision-making and increased both patients' and families' care management responsibilities [21, 22].

Traditional social work interventions in outpatient oncology settings include biopsychosocial assessments, psychoeducation, counseling, linking patients to community resources, and coordinating the provision of concrete services including home care, hospice, durable medical equipment, and transportation. Social workers are highly skilled practitioners who are trained to provide screening, assessment, and therapeutic interventions across the cancer continuum including primary prevention, diagnosis, treatment, survivorship, palliative care, end of life, and bereavement [20]. Oncology social workers are knowledgeable about cancer and its treatments as well as psychosocial aspects of illness, cultural and spiritual influences, pain and symptom management, finances, community resources, and research in the field of psychooncology [20, 21].

Clinical Interventions

Oncology social workers spend considerable time with patients and/or family members discussing their adjustment to a cancer diagnosis. Individual counseling can help the patient determine specific concerns and set priorities [21]. The focus of clinical work in health care is on enhancement of coping rather than psychopathology [23, 24]. The goals of clinical interventions are to reduce anxiety and assist in clarifying misconceptions and correct misinformation, as well as decrease feelings of isolation [20, 25]. Researchers have shown that psychological interventions can improve the emotional and physical health outcomes in patients with cancer [25, 26].

Cognitive Behavioral Interventions

Cognitive behavioral therapy (CBT) combines cognitive psychotherapy with behavioral interventions. It seeks to reduce emotional distress by identifying, challenging, and eliminating irrational beliefs and encouraging patients to change their maladaptive preconceptions and behaviors [27]. These techniques may include hypnosis, guided imagery, progressive muscle relaxation, and biofeedback, which are utilized during individual or group sessions [21, 25]. Social workers frequently obtain specialized training for this type of work [21]. Used either alone or in conjunction with medication, behavioral methods are effective for treating side

effects associated with cancer. These include anticipatory nausea and vomiting associated with treatment, heightened anxiety, and pain [28, 29].

Relaxation Techniques

Relaxation techniques guide patients to achieve control over their muscles and thoughts, in order to reduce emotional distress [27]. Progressive muscle relaxation involves systematic tensing and relaxing of various body parts. The practitioner describes comfortable sensations in muscle groups usually progressing from head down to feet or from feet up to head. Patients are encouraged to practice these techniques at home to enhance competence and achieve mastery [27]. Visualization of restful scenes associated with pleasurable thoughts is another technique used to promote a sense of relaxation and calmness, allowing patients to feel more in control of their feelings. Social workers practicing these techniques should obtain specific training in these areas [21]. The growing use of complementary therapies (such as, meditation, relaxation, hypnosis, and visualization) has resulted in their increasing availability in hospitals and oncology centers [30, 31].

Supportive Counseling

Counseling helps patients and their families manage the multiple problems associated with chronic illness [21]. Individual supportive counseling can decrease the distress and disruption experienced with a cancer diagnosis. While there is no clear definition for supportive psychotherapy, this approach is generally considered an intervention that can be used intermittently or continuously. This patient-centered flexible approach assists patients in dealing with distressing emotions by reinforcing strengths [27, 32]. Supportive counseling emphasizes the importance of compassion, empathy, and support in working with patients [25]. An important goal of counseling in oncology social work is to help the patient and/or family maintain or redefine hope [21], moving beyond equating hope with cure to broader meanings, values, and intentions that are beyond the limits of an illness.

Crisis Intervention

A significant crisis can be triggered with the initial cancer diagnosis, throughout the course of treatment, when the disease recurs, and at the termination of curative therapy. Therefore, oncology social workers may use crisis intervention techniques on a recurring basis throughout the illness trajectory. Oncology social workers help the patient and family explore and clarify feelings, understand how to manage these feelings, and teach new ways of coping [29].

Psychoeducation

Providing education to cancer patients serves to reduce the sense of helplessness that results from uncertainty and lack of knowledge. Psychoeducation can provide patients with a sense of mastery over their illness. It can involve disease-specific information and may also include information about coping, side effects, and wellness [25]. The goal of this intervention is to enhance coping skills and empower patients to become active participants in their care [25]. The information provided should be tailored to meet the patient's expectations, preferences, diagnosis, treatment, and prognosis. Information can also be related to maintenance of maximal health, coping, and financial/legal concerns.

A patient's educational needs change over time, such as during and after treatment [33]. A patient's primary language and reading comprehension level are also important factors for social workers to consider when adapting psychoeducational materials to cancer patients and their families. Oncology social workers often provide patients with brochures, booklets, and materials from well-known sources, such as the Leukemia and Lymphoma Society, CancerCare, and the American Cancer Society, or refer patients to resource libraries and/or trusted websites. An understanding of patient health literacy is essential to effectively using these resources. Table 1 lists national resources that provide support, information, and/or financial assistance to those with cancer and their families.

Table 1 Resources for general cancer support

Resource	Website/phone
AMC Cancer Information and Counseling Line	800-525-3777
American Cancer Society	cancer.org 800-227-2345
cancer.net	cancer.net 888-651-3038
CanCare	CanCare.org 888-461-0028
CancerCare	cancercare.org 800-813-HOPE
Cancer Hope Network	CancerHopeNetwork.org 800-552-4366
Cancer Financial Assistance Coalition	cancerFAC.org
Cancer Support Community/ Gilda's Club	CancerSupportCommunity.org 202-659-9709
Fertile Hope	FertileHope.org 866-965-7205
Imerman Angels	Imermanangels.org 877-274-5529
Kids Konnected	Kidskonnected.org 800-899-2866
Livestrong	Livestrong.org 866-673-7205
Mautner Project of Whitman Walker, National Lesbian Health Organization	whitman-walker.org/ mautnerproject 202.797.3570
National Cancer Institute	Cancer.gov 800-4CANCER
National Comprehensive Cancer Network	nccn.org 215-690-0300
RA Bloch Cancer Foundation	BlochCancer.org 800-433-0464

[a]This listing represents national organizations providing information to cancer patients. There are many more excellent disease-specific organizations and local organizations

Table 2 Description of psychosocial interventions that may be used with oncology patients in the ED

Intervention	Description	Outcome
Cognitive behavioral therapy	Assists patients in identifying and changing maladaptive thinking and behaviors, in order to reduce negative emotions and facilitate psychological wellness	Reduces anxiety, increases problem-solving skills, increases understanding of maladaptive cognitions, and enhances coping
Relaxation techniques	Encompasses a variety of techniques to calm thoughts and muscles, in order to allow patients to feel more in control and at ease	Reduces anxiety, increases sense of control, enhances coping
Supportive counseling	Focuses on helping patients to cope with distressing emotions, reinforces pre-existing strengths, and promotes adaptive adjustment to illness	Enhances coping by establishing a therapeutic alliance, reduces anxiety
Crisis intervention	Time limited, used intermittently; focuses on symptom reduction; expression of feelings are encouraged and tangible support is provided	Reduces psychosocial symptoms, mobilizes social supports, increases sense of self-competency
Psychoeducation	Utilizes educational resources and provides information to reduce feelings of helplessness while increasing the patient's knowledge and sense of control	Prevents ED admissions (i.e., may increase compliance to medical recommendations), fosters improved decision-making, reduces anxiety, increases sense of control

Cancer patients may benefit from numerous intervention techniques and programs. Psychiatric interventions play a significant role in the comprehensive care of cancer patients. The list provided in Table 2 is not an exhaustive list of interventions but rather a compilation of interventions that are utilized by oncology social workers in practice, which may also be applicable to oncology patients in the ED.

Case Example Oncology Social Worker Interventions to Prevent an ED Visit

"Charlotte" was a 57 year-old African American female with metastatic triple-negative breast cancer. Charlotte was well known to her outpatient oncology social worker (OSW), who had been working with her since she was initially diagnosed with cancer a year before. The OSW assisted with referral to a home hospice program which had an inpatient unit affiliated with the cancer center. Several days later, the OSW received a call from her adult daughter, "Julie." She was upset because the hospice nurse told her that Charlotte was entering the dying stage and they were unwilling to transfer her to the inpatient unit. Julie had a four year-old daughter at home and had been explicit at enrollment that she did not want her mother to die at home. She was very frustrated that the hospice staff was not helping her to facilitate an inpatient admission as they believed her symptoms could be managed at home. Julie stated that she was going to call an ambulance to bring Charlotte to a hospital, if the hospice agency did not transfer her mother immediately. In order to avoid the crisis of an ED visit and added distress for Charlotte and her daughter, the OSW intervened and advocated for an immediate inpatient admission since Julie was going to call 911/ambulance if the agency did not act right away. The OSW also spoke to Julie and educated her about alternative options (other hospice programs with inpatient facilities), in order to avoid her calling 911/ambulance to have her mother brought to an ED. Within an hour Charlotte was brought to the inpatient hospice unit. This case example demonstrates one way that continuity of relationship with an outpatient OSW, even in the setting of a hospice admission, assisted in preventing an ED visit/hospital admission and optimized the care of a dying patient, containing further risk of complicated bereavement for Julie and her four year-old child.

The Role of the Palliative Social Worker

Palliative social work developed as palliative care teams sought to increase patient and family-centered care for seriously ill patients and because of the need for the unique assessment and interventional skills provided by social workers. Building on the fields of hospice, oncology, critical care, and other established areas of practice [34], early leaders in palliative social work helped identify specific competencies in palliative care, targeted psychosocial interventions, and areas of research [35]. Social workers are core interdisciplinary clinicians on palliative care teams whose multifaceted role includes education and counseling on one's adjustment to illness, with special attention to the multidimensional aspects of pain and other symptoms, including the impact of life-limiting illness on the patient's mood, goals, and relationships [36]. Palliative social workers also help facilitate patient/family decision-making regarding goals of care and advance care planning and provide therapeutic interventions to help reduce anxiety and distress in patients and families.

Palliative Social Work Initiative in the ED

As increasing numbers of ED's strive to integrate palliative care into their clinical setting with the goal of improving care for seriously ill patients and encouraging earlier palliative care consults and hospice referrals [37], there are opportunities for palliative social workers to provide consultation to patients, families, and clinicians in the ED. One study of ED utilization found that visits for palliative care, dehydration, and an altered level of consciousness were higher during the final two-week period of life than during the last 6 months preceding death [38]. Palliative social workers may be called upon to consult in the ED to help patients and families integrate the meaning of the medical crises while attending to issues such as advance care planning, goals of care discussions, and facilitating transitions in care.

The palliative social worker can obtain medical information, specify functional limitations in the patient, and complete symptom assessments [39], as well as discover the patient's narrative of the event that led them to the ED. The ability to ascertain unmet palliative care needs and communicate the benefits of a palliative consult or a hospice referral to the emergency physician encourages their initiation from the ED [40]. The palliative social worker can be expected to communicate with the palliative care team regarding symptom management needs for seriously ill patients in the ED.

Visibility of the palliative care team is important in the eyes of emergency clinicians. The palliative social worker may become the "face" of palliative care by regularly consulting in the ED, through collaboration with the ED social worker to assist seriously ill patients, or by providing education on palliative care principles to ED clinicians. Whether helping to increase collaboration between emergency medicine and palliative care, identifying patients who are appropriate for palliative care consults and hospice referrals, or providing specific psychosocial interventions to patients in the ED [40], palliative social work can play a key role in assisting oncology patients and families.

Goals of Care Conversations in the ED at End of Life

The ED is often where changes in the patient's illness trajectory are recognized, and new plans of care are established; thus identifying end-of-life patients who may be appropriate for a transition in care is appropriate in this setting. For oncology patients who present to the ED and are actively dying, or for those whose prognosis is poor, facilitating goals of care discussions can help clarify options for ongoing disease-modifying therapies. Within these discussions, it is important to understand the patient's or surrogate's wishes related to initiating, continuing, or foregoing potentially life-prolonging treatment (e.g., endotracheal intubation). With the assistance of the emergency physician, the palliative social worker can help guide goals of care conversation to enhance patient and family's understanding of diagnosis, prognosis, and treatment options at the end of life, including palliative care and hospice.

The nature of an oncology patient's emergency may also invite a conversation about advance directives or MOLST/POLST to include decisions about resuscitation, treatment preferences, and goals of care [40]. Palliative social workers have the clinical skills and knowledge to work with the physician to obtain, interpret, and assist in completing these advance care-planning documents. ED social workers are also knowledgeable about advance care-planning documents as well as pertinent state laws that may pertain to this process.

Social Work Initiatives to Prevent ED Visits

As a result of the recent changes in the health-care system, it is highly likely that hospitals will embark on initiatives to decrease the number of ED visits [41]. Based on the acuity of cancer patients, initiatives will likely involve social workers who are most often responsible for making and following up on home care and hospice referrals. An initiative to assist in the prevention of ED visits requires screening, anticipatory guidance, and knowledge of resources. For example, caregivers experiencing distress and exhaustion might be connected to community resources that provide respite care. Below is a case example highlighting one such instance.

Case Study of OSW Connecting an Oncology Patient's Caregiver to Community Resources

James is a 63 year-old, African American male with pancreatic cancer living in Tennessee. James' sister, Millie, his only caretaker, lives in New York City. When Millie found out about his diagnosis, she moved him to New York City, as he had no family in Tennessee. James sleeps on Millie's living room sofa and she assists him by coming to his medical appointments, chemotherapy appointments, making sure he eats properly, etc. Millie met with the oncology social worker (OSW) to discuss her feelings of being overwhelmed by the level of care that he required and she indicated that she felt she needed help. The OSW offered to make a home care referral and Millie agreed. After several weeks of home care, Millie reported that she was still feeling stressed and overwhelmed, and she requested that James be admitted to a nursing home. James has Medicaid,

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prompting the OSW to suggest that Millie try a day program at a nursing home close to where she lived. Millie agreed to the referral and James began attending the day program four days per week. The day program provided James with meals, activities, and transportation to and from Millie's apartment, all covered by his insurance. Millie was relieved by the referral, since the facility was one that she liked and was in her neighborhood. Millie had originally asked the oncologist for James to be admitted to the hospital in order to have him transferred to a skilled nursing facility. However, once the OSW suggested the day program, Millie no longer felt the need for James to stay full time at the nursing home. In this case, the OSW's involvement, recommendation, and referral to a community resource resulted in the avoidance of an ED admission.

Radiation Oncology ED Initiative: Preventing Admissions

At an urban academic medical center in New York City, the radiation oncology interdisciplinary team has undertaken an initiative focused on head and neck cancer patients (D. Belloise, personal communication, 2014 May 1). The team has partnered with a large home care company to make referrals for weekend nurse visits for wound care and hydration, as needed. Because patients come to the medical center for treatment 5 days per week, this initiative would allow for monitoring by a nurse for 6–7 days per week. This pilot program will follow ED visits among patients receiving daily radiation for head and neck cancer over time to determine if the weekend home care initiative reduces ED visits/hospital admissions. The oncology social workers are involved in this initiative because of their role in arranging home care referrals and interventions to prevent the emotional distress created by emergent hospital visits.

Psychiatry

One initiative to avoid ED visits and an additional crisis for patients and families is through partnering or making psychiatry services readily available. The accessibility to a psychiatrist can be helpful in avoiding ED visits for suicide assessment(s). In outpatient cancer centers, if a psychiatrist is not available and a social worker determines that a patient is at risk, the patient would likely be sent to the ED for further assessment. This is not a beneficial allocation of ED resources as it is a potentially avoidable visit that can be upsetting for the patient. If a psychiatrist is on staff at the outpatient cancer center, or psychiatric services are readily available in the community, then ED visits to assess for suicidality may be avoidable.

Health Home Initiative

As more cancer patients are living longer with the disease, cancer is increasingly viewed as a chronic illness [42]. Due to the ongoing evolution of the American healthcare system and changes in reimbursement for services, hospitals will no longer be reimbursed at the same rates for readmissions and ED visits [41]. Therefore, many hospitals are making efforts to lower and contain costs through initiatives that have the potential to decrease readmissions and ED visits. The "Independence at Home" (IAH) initiative for Medicare beneficiaries who have been hospitalized and received rehabilitative services in the past 12 months targets those with two or more chronic conditions. This health home initiative offers home-based primary care services aimed at reducing repetitive ED visits and hospitalizations. Under a collaborative care model of multidisciplinary team members, one IAH initiative utilizes nurses and social workers to do the majority of home visits with the support of physicians [43]. Health homes are one example of a program in which social workers can play a pivotal role to reduce ED visits and readmissions for oncology patients.

Suggestions for Future Research

More research is needed to understand the optimal role of ED social work in caring for oncology patients, as well as to identify therapeutic interventions and their effectiveness with patients/families in enhancing their ED experience. There is also a need to identify collaborations and initiatives between ED, oncology, and palliative social work that have the potential to strengthen the psychosocial care of the patient, avoid duplication of services, and possibly prevent unnecessary ED visits and hospitalizations.

Conclusion

Clinical social workers are trained to conduct a comprehensive biopsychosocial-spiritual assessment of patients and their families, to better inform goals of care, enhance communication, and ensure smooth transitions in care [5, 44]. In working with cancer patients who present to the ED in crisis, the ED social worker can identify psychosocial, financial, and cultural concerns that may impact future medical care. ED, oncology, and palliative social workers are in key posi-

tions to help identify and test new initiatives aimed at strengthening services for oncology patients throughout the continuum of their illness. Collaboration among these social workers allows for earlier outreach to oncology patients with unmet psychosocial and concrete needs and supports continuity of care across settings. Attention to the psychosocial needs of oncology patients and their families can help patients, caregivers, and medical providers optimize the delivery and efficacy of healthcare services while managing the emotional and social aspects of illness [33]. Bridging biomedical and psychological well-being aids in the promotion of better health.

The current healthcare climate focuses on market-driven, cost-containment strategies for the provision of medical care. As such, social workers serve an essential function in the cost-efficient delivery of health care. Social workers are well positioned to contribute to the psychosocial care of oncology patients in the ED and can identify and coordinate alternative plans of care that may reduce the number of unnecessary ED visits.

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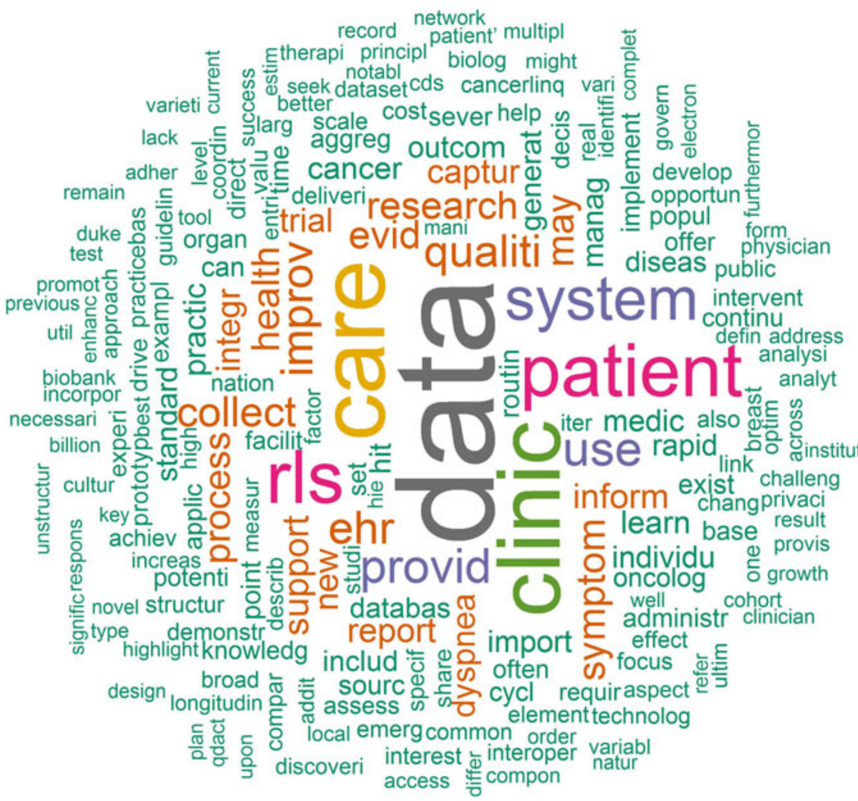
Rapid Learning Systems

Krish Patel and Amy P. Abernethy



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Health-care systems and their providers and patients face notable challenges in the form of questions about the viability, value, and quality of health-care delivery. Rapid knowledge growth and rising costs further complicate these challenges. Notable variation in quality of care has been demonstrated through large variations in implementation of evidence, health-care spending, and aggregate health outcomes [1–3]. Further, biological discovery sciences are often disconnected from the realities of health care and generalized patient populations, thereby slowing time to relevant clinical investigation. In oncology and emergency medicine, evidence to identify best practices and inform care delivery with respect to therapies and novel health technologies is often not available, equivocal, or of low quality [4]. Improving the quality of care delivering and personalization of care requires rethinking how data is collected, aggregated, and applied to individual patients. This is the conceptual underpinning of rapid learning systems (RLS), also referred to as learning health systems (LHS).

RLS seek to collect data from routine clinical practice, research databases, administrative datasets, and patient-facing data collection interfaces and integrate these data into a continuously growing ecosystem of information to support individualized patient care, health-care optimization, and clinical discovery. RLS "learn" by recursively collecting specific, discrete data elements from routine clinical care and linked databanks, uniformly organizing these data, generating new evidence or new hypotheses for testing, supporting retrospective and prospective analyses, and promoting implementation of new evidence into subsequent clinical practice (Fig. 1) [5]. This "learning" process perpetuates a continued emphasis on novel evidence generation, promotion of comparative effectiveness research, better implementation of existing evidence, and iterative delivery of value-driven care. Furthermore, by incorporating practice-based clinical data, RLS offer the opportunity to better inform clinical evidence on populations that are often underrepresented in large clinical trials. Such populations might include elderly patients, patients with high degrees of comorbid illnesses, or patients with rare medical conditions.

A major foundation of RLS is the use of health information technology (HIT). HIT is necessary to facilitate the

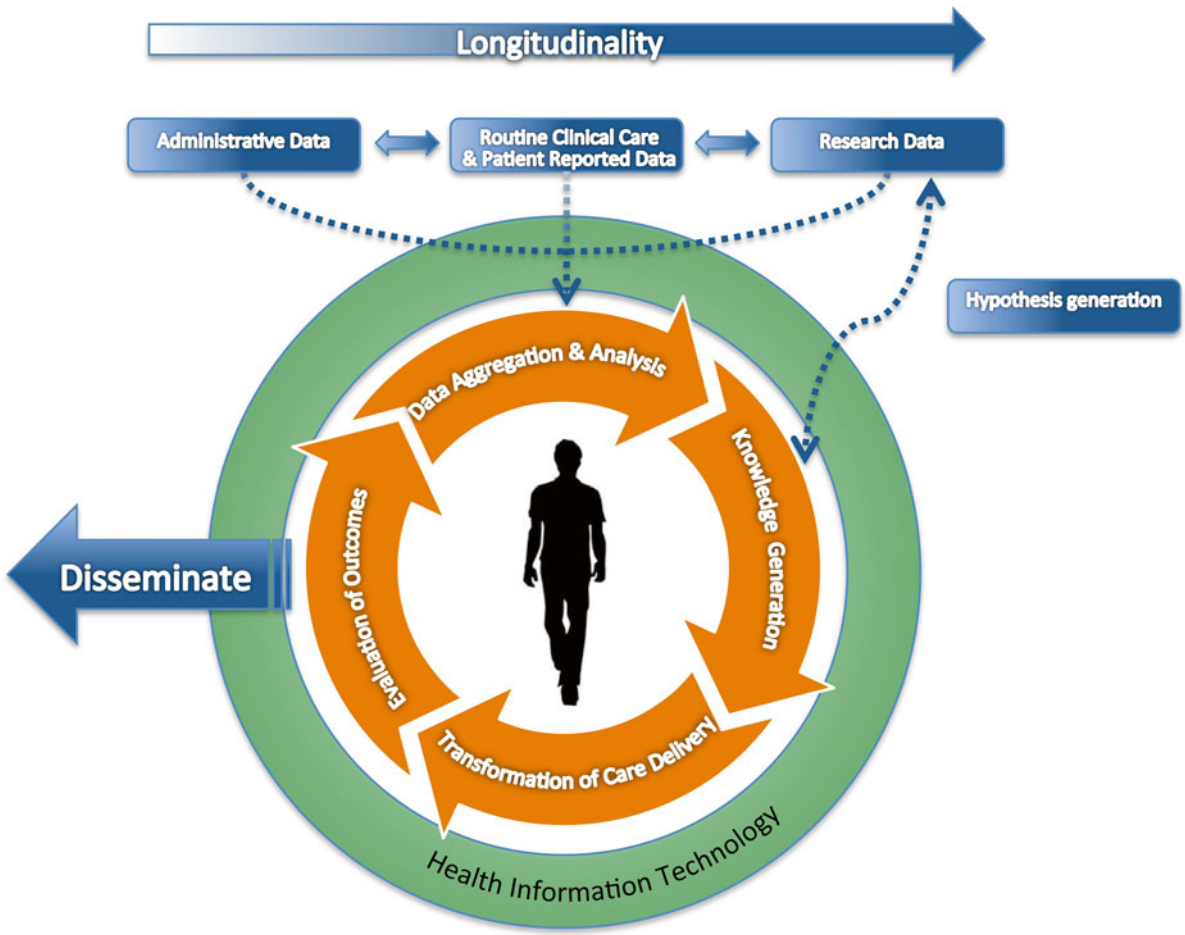

Fig. 1 Rapid learning systems continuously aggregate data from routine clinical care, patient-reported data, and linked administrative and research databases. These data are recursively analyzed to generate new knowledge and evidence. This knowledge and evidence then informs care transformation

large-scale data collection required for RLS, as well as the distribution of data to be used for multiple purposes. In a RLS, the same data point may be used for clinical care, assessment of health-care quality, comparative effectiveness research, and biological discovery sciences, at the same time or at different points in time. The HIT environment facilitates data integration and multiple analytic frameworks, which enhances the value of the data collected and stored. HIT broadly encompasses any electronic interface that can be used to capture clinically relevant data and may include a diversity of systems ranging from electronic health records (EHRs), pharmacy and physician order entry systems, administrative billing systems, and scheduling systems, to research data and disease registries. Perhaps the most familiar of these elements to clinicians are EHRs. The broad adoption of EHRs catalyzes RLS [5, 6]. EHRs are designed to capture, store, and display clinically important data in a manner conducive to clinical workflow. They can also be used as electronic tools that help provide care through electronic prescribing and physician order entry. As such, they are centrally poised to operate in both the data-gathering elements of RLS as well as implementation of evidence and process improvement.

Similarly, paramount to RLS are quality sources of data. EHRs allow for the capture of practice-based clinical data. EHR data can be augmented with data from clinical trials, laboratory research, biomarker repositories, and tissue banks, thereby facilitating rapid translation of medical research into clinical practice and vice versa [5, 6]. Large-scale linkage between datasets optimizes understanding, such as better information on patterns of care and changes in disease outcomes garnered by combining administrative data with cancer registries (e.g., United States Medicare data linked to the Surveillance Epidemiology and End Results (SEER) national cancer registry to generate SEER-Medicare). Further, incorporation of patient-reported data such as symptoms and quality of life information into RLS datasets provides care providers real-time feedback on a patient's experience of clinical care and ensures that data about the individual patient experience are embedded in the aggregating registries underpinning the RLS.

The process of iterative data collection, aggregation into linked datasets, analysis, and applications of new knowledge learned from analyses in RLS is based upon Plan-Do-Study-Act cycles used in various industries to achieve continuous quality improvement. The coupling of this process with advanced HIT systems and linked clinical, research, and administrate databases forms the foundation of RLS. Several terms used throughout this chapter to describe aspects of RLS are listed in Table 1.

Technologic Components of RLS

The core of RLS is the clinical data generated through routine care processes. To date, data from routine clinical care have been largely underused in driving care improvement or growing the evidence basis that informs care delivery [6]. There are likely several reasons for this including the variable quality of the data collected at the point-of-care delivery, barriers to aggregation, storage and exchange of such data, and a lack of quality analytic systems necessary to meaningfully utilize such data. The rapid growth and increasing availability of HIT systems offer the potential to circumvent some of the challenges involving inadequate collection, organization, and storage of routine clinical care data. The similarly rapid growth of informatics science and technology offers the opportunity to optimize and harness collected data to drive new discoveries and improve care delivery. As such, HIT and clinical informatics represent important pillars upon which RLS are based. Here we will describe several aspects of RLS that highlight the principles of HIT and clinical informatics.

Table 1 Terminology used to describe aspects of rapid learning systems

Term	Definition
Rapid learning system (RLS)	A system that aggregates data from routine clinical care with research, administrative, and other databases and uses iterative cycles of data collection, data aggregation, data analysis, new knowledge generation, and application of new knowledge for the purpose of continuously improving clinical care
Health information technology (HIT)	The application of information processing involving both computer hardware and software that deals with the storage, retrieval, sharing, and use of health-care information, data, and knowledge for communication and decision-making
Electronic health record (EHR)	A longitudinal electronic record of patient health information generated by one or more encounters in any care delivery setting
Clinical decision support (CDS)	A process for enhancing health-related decisions and actions with pertinent, organized clinical knowledge and patient information to improve health and health-care delivery
Health information exchange (HIE)	The access and securing sharing of a patient's vital medical information electronically between all patient providers and health-care settings

Electronic Health Records

EHRs are among the most recognizable elements of HIT. EHRs are systems designed to capture, store, and display clinically important data for use during patient care episodes. They often include patient demographics, progress notes, problem lists, medications, vital signs, past medical history, immunization records, laboratory data, and radiology reports [7]. EHRs often also interface with, or contain systems for, administrative and financial tasks such as scheduling and billing. Increasingly, EHRs also incorporate systems for direct care provision such as medication management and electronic prescribing, physician order entry for laboratory, radiology, and ancillary care services and clinical decision support systems [8]. With a broad array of functions, EHRs are a powerful tool for both capturing the data from clinical practice that drive RLS and implementing RLS discoveries to then reshape patient, provider, and health systems behaviors.

Data Capture, Organization, and Processing

As a tool for data entry, storage, and display during clinical care of individual patients, many EHRs are optimized primarily for clinical workflows. However, the design of EHRs suitable for RLS should extend beyond the simple capture and display of data. For practice-based clinical data to be successfully aggregated for use in population health studies, data collected for a potential variable of interest would ideally be structured data, which refers to data that is highly organized and can be seamlessly entered from an EHR into a database capable of being queried. Examples of clinical data in an EHR that might easily be structured are listed in Table 2. Data structure can be accomplished at the point of data entry (point of care) in EHRs by requiring standardized entry. This standardization ultimately ensures interoperability of captured data between connected databases and distinct EHRs. Without structured data, significant post entry data processing may be required to use such data in analytic systems and avoid loss of valuable data [9].

Not all pertinent data from an EHR can be structured at the point of entry. Some data may be recognized as important to RLS much after data entry. Some data may require narrative reporting that cannot be routinely structured. Examples of EHR data that might be considered unstructured are also listed in Table 2. The use of such unstructured data in RLS requires processing to impart structure and afford interoperability [10, 11]. Analytic systems for natural language processing can be used to impart structure to unstructured data. This approach has been less successful in cancer than in other settings such as diabetes. In response, large-scale technology-enabled abstraction is quickly becoming the standard approach to generate structured data from unstructured cancer information. Data processing approaches often seek to harmonize data according to standardized clinical language vocabularies (a.k.a. common ontologies) so that the processed data can then be used for multiple purposes in the RLS [12]. Limitations to use of unstructured data include potential data loss, delay in data capture, requirement of processing systems, and lack of a consensus standard clinical language vocabulary.

Clinical Decision Support

In addition to the data capture and organization features of EHRs, the integration of clinical decision support (CDS) systems is a key element of EHRs that support RLS. CDS is an EHR system feature that alerts, reminds, or directs providers to a manner consistent with some pre-stated standard such as according to a clinical practice guideline [13]. CDS can range from simple messaging reliant upon one or two data elements (e.g., date-driven influenza vaccination reminders) to more complex systems that integrate multiple clinical variables from disparate data sources in order to provide advice for decisions such as appropriate antibiotic ordering, adherence to optimal best practices for chronic disease management, and improved awareness of medication interactions and dosing. The use of such systems has demonstrated improvement in provider adherence to clinical guidelines and evidence-based medicine and improvements in patient safety outcomes [14–18]. CDS may also help providers avoid cognitive biases that lead to errors [19]. In RLS, CDS equipped EHRs serve to improve adherence to existing evidence and best practices while also providing an opportunity to rapidly and broadly incorporate new evidence and guidelines into clinical practice [20].

EHRs alone are not sufficient to drive RLS. They do, however, offer the opportunity to connect real-time practice-based data from millions of patients for the purpose of discovery and evidence generation on a scale not otherwise achievable. At their best, EHRs simultaneously offer clini-

Table 2 Examples of structured versus unstructured clinical data

Structured data	Unstructured data
Gender	Radiology reports
Date of birth	Pathology reports
Vital signs	Narrative histories
Numerical laboratory values	Narrative exams
ICD 9 codes	Narrative assessments

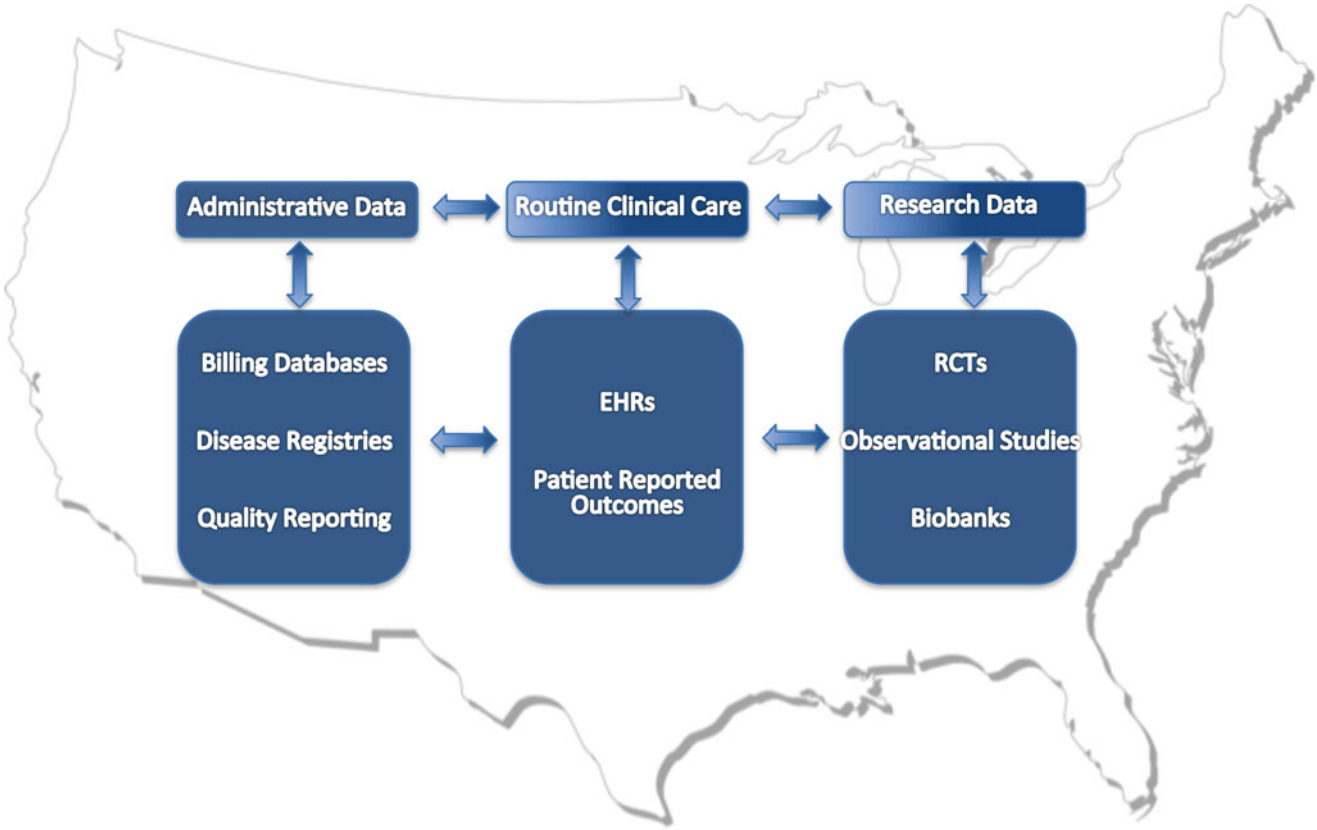

Fig. 2 Health information exchange is a crucial aspect of rapid learning systems. To achieve the goals of improving individual patient care and supporting health system-level research requires real-time, multidirectional integration of data from varied sources. Such information exchange occurs on a national level across public and private domains

cians optimized clinical workflows, provide the capability to capture and categorize important clinical data elements for real-time analytics, and provide decision support to promote integration of clinical evidence and guidelines.

Shared Access to Databases

EHRs and practice-based clinical data are a centerpiece for RLS. In a RLS, linking EHRs across provider networks permits individual patient data to be integrated and accessible nationally. Additionally, integration of pooled EHR data with existing clinical research databases, biobanks, disease registries, and epidemiologic databases facilitates novel evidence generation and application of existing clinical evidence. The integration of such data using patient-level identifiers is broadly termed *health information exchange* (HIE, Fig. 2).[1] To achieve the point-of-care accessibility envisioned in RLS, such coordinated databases require notable HIT planning and infrastructure. Linkage of coordinated databases should be rapid, ideally in real time and multidirectional. This can be accomplished by pooling individual patient data into central repository-type databases (e.g., a data warehouse) or by creating distributed data networks that house data on local systems and distribute data of interest when queried by other networked systems [21]. Interoperability of data is required to achieve this, and again systems for structuring and standardizing data are necessary to allow databases across private, public, and academic sectors to communicate meaningfully with one another. Furthermore, such systems must be scalable to sustain the growing expanse of data to be collected and linked in such systems.

Sources of Data for RLS

RLS endeavor to harness potential learning from combining practice-based clinical data with that of varied datasets that have traditionally existed in isolation from one another. The sources, quality, and interoperability of these data are key factors in building RLS. Here we will describe several important data sources anticipated to be included in next generation RLS.

[1]Conceptually, HIE implies the facilitation of movement of patient-level information to support patient care and learning. Practically, the term HIE is commonly used to imply public or private organizations coordinated to support information movement within a region or among certain institutions.

Clinical Trials

Practice-based data from EHRs are a key feature of RLS that are intended to augment, not replace, the valuable data gathered from prospective clinical trials. Prospective randomized clinical trials often provide high-quality data that may broadly facilitate changes in practice patterns and improve health outcomes. Many trials, however, may underrepresent specific populations of interest or lack optimal comparator arms [22–24]. In a RLS, patient-level data collected from existing and future clinical trials can be integrated with practice-based data and other data sources to help address knowledge gaps not directly addressed in clinical trials [24]. This can be accomplished upfront, at the time of data collection for the clinical trial, and through the creation of publicly accessible linked clinical research databases for existing datasets.

Traditionally, clinical data collected for use in clinical trials is captured and stored in systems separate from the clinical interfaces (i.e., EHRs) used in direct patient care. One approach to improve efficiency of clinical trials and direct integration into RLS would be to repurpose clinical data collected by EHRs during routine care so that it is used for clinical research purposes in addition to documenting routine care. There is significant data redundancy that exists in collecting data for actual care provision and data collection that occurs strictly for clinical trial purposes. Using EHRs to obtain some data elements required for clinical trials may reduce redundancy of collection and facilitate standardization of data to achieve the interoperability required to integrate different data sources in RLS. Several models that integrate EHR data into clinical trial workflows serve as an example [25]. In order for this vision to be achieved, it is critical that there is continued improvement in data collection and processes that enhance the quality of routinely collected clinical data so that it meets a research standard.

Promoting public reporting and sharing of de-identified patient-level data obtained from clinical trials is an additional method to better integrate these data sources for RLS. Many clinical trials rely on external funding for completion. The National Institutes of Health (NIH) directly funded $3.1 billion for clinical trials in 2013 alone [26]. Industry funding of clinical trials was estimated to exceed that figure in 2013 at an estimated $8–9 billion. Requiring that publicly funded and industry-funded clinical trials seeking FDA approval for devices or pharmaceuticals submit collected datasets from ongoing and concluding trials into publicly accessible databases would facilitate rapid incorporation of vast quantities of clinical trial data to RLS. To date, one of the most remarkable clinical trial data sharing activities has been spearheaded by the pharmaceutical industry; companies are donating de-identified data from comparator arms in phase III cancer clinical trial datasets plus the study protocols to a common repository for aggregate analyses (www.projectdatasphere.org). Availability of the entire collected datasets for integration and analysis with other data sources may facilitate the novel evidence generation sought by RLS [27].

Biobanks

The completion and publication of full sequence data from the Human Genome Project in 2003 enabled an unprecedented research focus on the interplay of genomics, therapeutics, and patient environmental factors in human diseases. This increasing research focus and continued improvements in molecular biology and bioinformatics technologies have resulted in an increased interest in molecular and genomic analysis of biological specimens (blood, tissue, DNA) to support and drive new knowledge. Analyses of these biologic samples may help reveal important disease biomarkers and genomic signatures that translate into improved clinical diagnostics and therapeutics. But, despite the emergence of new technologies to drive biomarker and "omic" research, direct translations of this research into clinical applications remain slow [28].

Population-based national biobanks have been proposed to support these translational research efforts [29]. A biobank is a repository of a large number of donated biological specimens from a general population of individuals who might or might not have a certain disease. It is estimated that as of 2012, over 400 biobanks containing millions of biological specimens exist in the USA [30]. Creating open-access biobanks and linking them with individual EHRs in a RLS connects biological data with patient's medical histories, lifestyle information, and clinical outcome data. This longitudinal clinical annotation of biospecimens, a.k.a. "clinical phenotyping," may facilitate the identification of biologic markers that correlate with disease diagnosis, disease prognosis, or response to specific therapies. Ultimately, such correlations could be used to drive development of new therapies or highlight areas of new hypothesis testing. Furthermore, linking biospecimen data to practice-based clinical data could be used to enhance comparative effectiveness research, providing an additional data to help identify best practice for an individual patient [6].

Patient-Reported Outcomes

A fundamental goal of RLS is to continually drive improvement of care for individual patients. The integration of patient-reported outcomes (PROs) with population-level data in RLS is an important mechanism to help achieve individually targeted care [31]. PROs include measures of physical symptoms (e.g., nausea, pain, diarrhea), psychosocial

experiences (e.g., anxiety, fear, worry), functionality (e.g., tolerance of exertion, ability to perform ADLs), quality of life (QOL), and overall satisfaction of care. They may include any end point or data reported directly by patients or their documented surrogate. Often they are captured in diaries, event logs, symptom reports, or formal assessment instruments [32]. The rapid growth of consumer technology, including use of tablet computers, smartphones, and other Internet-enabled devices, offers multiple avenues by which patients can report their experiences. Further, the concept of PROs has recently been expanded to the concept of "patient-generated data" (PGD), to acknowledge other patient-enabled (but not necessarily reported) data sources such as biometric sensors (e.g., accelerometers, bioimpedance), home laboratory testing (e.g., glucometers), and other data sources that patients oversee themselves.

As new knowledge, therapies, and technologies penetrate into the clinic, understanding their impact on a patient's experience of care and life outside of clinical care settings is a vitally important aspect of comparative effectiveness research (CER). Traditionally, clinical research has focused on assessing the effect of an intervention on fixed outcomes such as clinical event rates or survival. These outcomes may not accurately reflect the patient's experience of care, an important factor to clinicians and patients when considering a specific intervention. In practice, symptom management remains a critical focus of oncology care and toxicity monitoring, and the evidence base for many aspects of symptom data collection and management remains poor [33, 34]. By enabling patients to submit their own standardized reports of their symptoms and integrating these data with EHRs, longitudinal assessment of symptoms, alleviating and aggregating factors, and potential approaches to management are possible. In RLS, integration of EHRs with research databases and evidence-based guidelines can then permit clinical decision support systems to prompt clinicians to address these symptoms in an evidence-based fashion ultimately leading to improvements in quality of care [35].

Integrating PROs and PGD with practice-based clinical data, clinical research databases, and biobank data in RLS offers an unprecedented opportunity to personalize medical care and enhance CER.

Administrative Data

Understanding disease incidence, patterns of care, utilization of clinical resources, and patient outcomes related to such factors are an important focus of RLS. Existing administrative databases such as SEER and the Medicare Master Beneficiary Summary File are examples of administrative datasets that can facilitate RLS. SEER, a population-based cancer registry, includes 13 US states and ~25 % of the US population to track cancer incidence and mortality statistics over time. The Medicare Master Beneficiary Summary File contains demographic, mortality, and cost and resource utilization information. Linkage of such datasets to one another and to other datasets offers the potential to identify disparities in care outcomes, resource utilization, and patterns of care before and after cancer diagnosis. Linking these data to EHRs and clinical research databases may help clinicians better understand the relative value of the care they provide and identify areas for quality improvement.

Process of RLS

Application of Iterative Plan-Do-Study-Act Cycles

A core principle of a RLS is the iterative cycle of data collection, aggregation, analysis, generation of new knowledge and evidence, and the application of these new insights to drive clinical improvements (Fig. 1) [5, 36, 37]. This approach employs the basic tenets of Plan-Do-Study-Act (PDSA) cycles (a.k.a. Deming cycles) frequently utilized in various industries to support continuous quality improvement. The "Plan" portion of the cycle involves defining the outcome of interest to be improved in a given process; structuring the observation, intervention, or process change to be enacted in the study; and planning data collection. The "Do" steps carry out the planned action and implement the data collection plan. Analysis of the data and the formulation of conclusions from the data collection are made in the "Study" step. Finally, in the "Act" portion of the cycle, the new knowledge generated in the "Study" step is used to design and implement changes in the process being studied. The cycle is repeated to validate the process change and continues to generate new knowledge and further process improvements (Fig. 3). The principles of PDSA cycles permit the use of smaller scale, iterative testing of process changes. The advantage of such an approach is more rapid assessment of the process change and a flexibility to adapt the change to feedback directly from the system. This helps ensure that process changes introduced into a system are a good fit for the system they are implemented in and for the outcome improvements desired [38].

Applying the concept of PDSA cycles clinically, the use of such cycles in RLS can be implemented in a variety of manners to facilitate continuous clinical quality improvement. These iterative cycles may facilitate the study of conclusions from RCTs in real-world clinical populations to help validate the generalizability of such RCT data. Alternatively, in RLS, these cycles might be employed in populations underrepresented in traditional clinical research to generate new knowledge and hypotheses about these

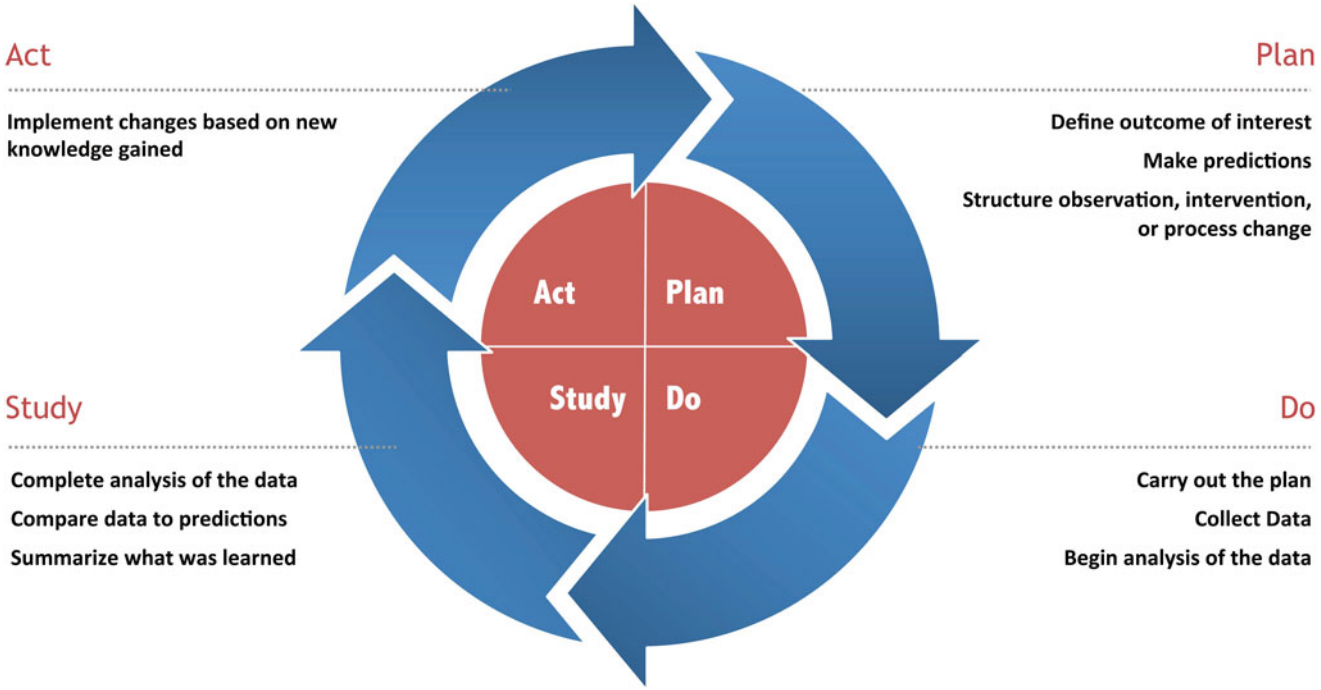

Fig. 3 PDSA cycle. Iterative cycles of Plan, Do, Study, and Act are employed to achieve continuous quality and process improvement and drive new knowledge generation

patients. The cycle might be used to improve the fidelity of evidence-based practice by introducing, testing, and validating stepwise care process changes that integrate important research evidence into the point of care.

Using PDSA concepts to successfully improve health outcomes has been previously demonstrated in the literature [39–41]. Marrying the quality improvement principles of iterative PDSA cycles with the integration of broad datasets and a coordinated HIT infrastructure forms the core platform of RLS.

Coordination and Optimization of Care Processes

RLS seek to simultaneously improve individual patient outcomes, high-value and cost-conscious care, and research and discovery. Focusing on the value and efficiency part of this equation, fragmentation of the current health-care system contributes significantly to medical waste and excess health spending. In 2009, an estimated $765 billion was spent on wasteful care. Of this sum, approximately $210 billion was spent on unnecessary care. Such care includes overuse beyond the evidence base and unnecessary use of higher cost care without expectation of increased benefit compared to use of lower cost care. An additional $130 billion of the total was estimated to have been spent on inefficiently delivered care. This included care resulting in preventable medical errors and redundant care due to care fragmentation. Finally, an additional $55 billion was estimated to be waste on account of missed opportunities for preventive care [19]. RLS has the potential to reduce such wasted health-care spending by improving upon coordination of care processes and aligning care provision with current evidence.

Patients, including those in oncology, often have multiple medical providers in varied practices [42]. They may include primary and specialty physicians, pharmacists, nurses, and technicians [19, 43]. Further fragmentation may occur between inpatient, outpatient, and emergency care settings. Information about the care provided by each of these providers is often not available to all practitioners at the point of care [44]. As a result, duplicate care leading to excess spending or inadequate care due to missing information may result [19, 44]. The use of a single EHR or distinct EHRs that are interoperable across the boundaries of multiple health-care settings in real time improves the availability of pertinent clinical information at the point of care for a given provider [45, 46]. This is termed health information exchange (HIE). The use of EHRs that integrate across inpatient, outpatient, and emergency care settings in a health system to improve HIE has been shown to result in improvement of health outcomes, decreased laboratory and imaging utilization, and cost savings [47–50]. Furthermore, in systems with effective HIE, creation of individualized, multidisciplinary, coordinated care plans may provide further cost savings and help providers direct patients to most appropriate care settings

[51]. By leveraging interoperable EHRs supporting quality HIE, RLS offer an important opportunity to improve coordination of care processes and support high-value care.

Time constraints and lack of knowledge are among the most commonly identified barriers to provider adherence to evidence-based medicine and clinical guidelines [52–56]. A limited understanding of the cost of care is often cited as a barrier to the practice of high-value care [19, 57]. In RLS, interoperability of research and administrative data with EHRs would permit review of care efficacy, experience, cost, and value by providers and patients at the point-of-care provision. Integration of these data into decision support systems may further enhance effective application of these data [58, 59]. By improving the knowledge deficit concerning clinical evidence and cost factors at the point of care through interoperable databases and HIT, RLS offer the opportunity to align individual patient care with current evidence and clinical guidelines, provide valuable feedback to practicing physicians on cost-conscious care, and provide a platform for improved comparative effectiveness research efforts.

Culture of Learning

Thus far, we have described several integral components of RLS: HIT, data sources, and the process of rapid learning. A culture of learning is as paramount to RLS as these previously described components. Organizational factors have an important impact on patient outcomes and care quality. For example, a study on organizations with high-quality clinical measures (including mortality) about acute myocardial infarction demonstrated that high performance correlated with organizations demonstrating shared values and culture, good communication and care coordination, and experience with problem solving and learning [60]. Another study demonstrated that staff and hospital leadership engagement influenced the success of a program aimed at reducing nosocomial infections [61]. A shared focus on continuous learning is accordingly a critical component of a RLS.

In a RLS, new knowledge is generated through the use of practice-based data combined with data from research, administrative, and other databases. Thus, in practice environments, a culture that is accepting of processes that facilitate rapid learning during routine care provision is vital. Use of HIT to improve data capture and coordination of care processes should be engineered and implemented to maximize ease of work and support efficient clinical workflows. Providers and patients should embrace the use of RLS tools such as EHRs and clinical decision support systems to improve safety, care efficiency, and ultimately patient outcomes. Simply put, an organization that supports continuous learning should be one that "make[s] the right thing easy to do" [62]. Leadership organization is an important aspect of this. Leaders from the top of an organization to the leaders in subunits of the organization should have a shared support for the culture of continuous learning. This culture of learning drives the iterative learning cycle at the heart of RLS.

Applications of RLS

We have described in detail the concepts, components, and culture of learning that encompass RLS. The applications of RLS are broad and scalable. RLS can be implemented on an institutional scale to address local clinical interests or on a broader national scale to address aspects of health care that pose national interest. Here we describe several applications of RLS for oncology patients, including systems exploring symptom management of a population on a local level and a prototype system designed at improving quality of breast cancer care on a national level.

RLS for Dyspnea Management

Dyspnea is a major cause of morbidity in patients with chronic diseases. In the US, chronic obstructive pulmonary disease or asthma affects up to 24 million adults [63]. Dyspnea has a reported prevalence of 56–90 % depending on the stage of their disease [64, 65]. Dyspnea is also among the most common symptoms reported by oncology patients and among the most common reasons for oncology patients to seek emergency medical care [66]. The American Thoracic Society defines dyspnea as "a subjective experience of breathing discomfort" derived from physiological, psychological, social, and environmental factors. The subjective nature of dyspnea highlights the importance of patient reporting as a critical aspect of dyspnea assessment. Assessments of dyspnea by providers in practice are often described narratively to capture the patient experience and severity. Furthermore, patients may report symptoms of dyspnea to a number of different types of providers (primary care physicians, emergency physicians, oncologists, mental health providers, chaplains, etc.), and the data capture of this experience may exist in isolated records not readily integrated for these providers. Given the multifaceted nature of dyspnea (deriving from physiologic, psychological, social, and environmental factors), management of dyspnea is often challenging. A biopsychosocial approach to the management of dyspnea is needed to provide optimal care. In 2012, a group at Duke University proposed their RLS model to better inform care of patients with dyspnea by using standardized assessment tools for dyspnea evaluation, longitudinal collection of patient-reported data, and incorporated evidence from existing dyspnea clinical trials.

In 2006, the Duke Cancer Care Research Program and the Duke Cancer Institute began a longitudinal collection of PROs as part of several clinical research studies. The program

expanded into the medical oncology clinics and became a part of routine clinical care. Patients presenting for clinic visits with their medical oncologists used tablet computers to complete a validated 80-item (86 items for women) review of symptoms while in the waiting room prior to their scheduled appointments [35]. The data collected were uploaded into a centralized secure location, and a summary of the symptom reports was provided to clinicians. The reports highlighted symptoms concerning to the patient and as well as the magnitude and direction of symptoms since last assessment. Values for the same symptom at the prior three visits were also included on the report. These patient-reported data could be thus then be used by providers to find areas for symptom improvement and assess longitudinal responses to symptom-directed therapies.

These data were used to study disease-specific symptom burden, with a focus on dyspnea. The clinical and research team combined efforts and opened a series of clinical trials evaluating new interventions for patients with refractory dyspnea. Patients whose dyspnea scores were over 6 out of 10 on a 0–10 scale (i.e., severe) were potentially eligible for studies of new treatments; based upon their scores, they were automatically triaged to be visited by the research team to determine whether their eligible for the trial and interested in participation. In this way, case finding for potentially eligible patients was build directly into the PRO system, the dyspnea clinical trials were efficiently conducted, and each new intervention was evaluated quickly. New interventions with sufficient evidence were suggested to physicians caring for dyspneic patients. Quality measures aligned with routine dyspnea assessment and treatment were developed in order to reinforce implementation of evolving best evidence [37].

In 2008, members of the same research group at Duke formed a partnership with four North Carolina community palliative care organizations to collect point-of-care data on patient distress and issues needing attention by palliative care providers. Dyspnea was again a key issue. A web-based instrument called Quality Data Collection Tool (QDACT) was developed, mimicking the clinic-based system previously used to capture point-of-care patient-reported symptoms and outcomes, including dyspnea [37]. The tool is accessible to patients and providers across several domains (home, hospital, long-term care centers, outpatient clinics). QDACT also records pharmacologic and non-pharmacologic interventions used for dyspnea management. QDACT is used to monitor the quality of dyspnea care provided in the outpatient palliative care setting, through wide-scale implementation of the quality measures developed by the Duke team using the clinic-based system. QDACT will ultimately provide providers with rapid individualized feedback on how their practice in dyspnea management conforms to evidence-based standards and potential new interventions to consider. Hence, QDACT represents the statewide dissemination of the clinic-based PRO RLS initially developed for the cancer clinic.

Standardizing the process of data capture across different care domains, collecting the data longitudinally, and incorporating existing evidence into routing clinical practice form a robust platform for rapid learning in dyspnea management. As data is iteratively collected in this process, data about response to dyspnea interventions from the individual patient and from the system at large may be then used to build decision support pathways that support personalized care provision.

RLS for Gastrointestinal Symptoms

Gastrointestinal (GI) symptoms are common for patients with a variety of chronic medical diseases and particularly in patients with oncologic diseases. Symptoms may be caused by oncologic treatment or by the underlying disease itself. GI symptoms range from nausea and/or vomiting, to diarrhea, constipation, anorexia, dysphagia, and pain. Symptoms may be present in as many of 70–80 % of patients receiving cancer chemotherapy [67]. Such symptoms are associated with a significant compromise in quality of life, may interfere with adherence to treatment schedules, and result in frequent emergency medical care encounters [31, 68]. The varied types of GI symptoms, the varied causes of these symptoms, and the subjective reporting of symptoms make them challenging to manage. Furthermore, while professional society guidelines, such as those from the National Comprehensive Cancer Network (NCCN), exist for more common symptoms such as nausea or vomiting, they are lacking for other types of GI symptoms. Recognizing the subjective nature of GI symptoms, the variation of underlying causes, and the relative lack of robust evidence to guide GI symptom management in a broad group of oncology patients, in 2010 the Duke University group published their experience with a prototype RLS, focusing on management of GI symptoms for medical oncology patients [31].

Using tablet computers to record patient-reported symptoms outlined in the prior example of dyspnea management, data was collected on various types of GI symptoms experienced by patients with breast, lung, and GI cancers. Each distinct disease cohort had varying prevalence and severity of common GI symptoms such as nausea, vomiting, diarrhea, constipation, and anorexia. Each patient's most severe problems were identified and highlighted by the reporting system for provider review. The incidence of nausea was highest in breast cancer patients compared to lung and GI cohorts (17 % vs. 4 % vs. 14 %). Moderate to severe diarrhea was more prominent in

patients with GI cancers compared to breast and lung cohorts (31 % vs. 22 % vs. 11 %). Moderate to severe anorexia was notable in all three cohorts (36 % vs. 30 % vs. 28 % in GI, lung, and breast, respectively). The study demonstrated that through the use of electronically reported patient outcomes, the varying incidence of GI symptoms could be established for various cancer cohorts, and the system ultimately could be used by providers to anticipate the occurrence of symptoms in a given disease cohort, and the system could be used to monitor patient experiences in response to clinical interventions [69]. A standardized system for data capture collected longitudinal data from routine clinical care for analysis to inform subsequent areas for improving patient care; this model demonstrates several of the key aspects of RLS.

CancerLinQ

In 2012, the American Society for Clinical Oncology (ASCO) recognized the potential of RLS for improving oncology care and undertook an initiative to develop a proof of principle HIT prototype called CancerLinQ [70].[2] Using the foundational principles of RLS, the prototype system was engineered to capture and aggregate routine clinical data from a variety of existing EHR formats, to provide real-time, guideline-based, clinical decision support system in a novel EHR, to measure clinical performance on a subset of quality improvement measures, and to explore and generate hypotheses from clinical data using analytic software.

To create the CancerLinQ prototype, individual patient data from 170,000 previously treated breast cancer patients from 19 different oncology practices were collected and structured for use in the prototype system. The process successfully captured billing, pharmacy, and administrative datasets into the prototype system without regard to the source EHR format. This demonstrated the ability to allow any practice to participate in a fully scaled version of CancerLinQ. Using an open-source resource (OpenMRS), an EHR (with built-in breast cancer-specific clinical decision support modules) was created to interface with the collected data. The CDS modules included embedded primary reference materials so that the provider could review reference materials during CDS prompts. CDS modules were entered into the system individually so that updates to the material or data on which each module was based could be incorporated into the system without having to reprogram the entire CDS decision tree. The prototype system was able to provide decision support whenever breast cancer case data was entered for a specific patient. For example, the system could make recommendations such as avoiding sentinel lymph node biopsy in women with larger (T3 or T4) breast cancer tumors when a patient's tumor size was reported. In addition, ten breast cancer quality improvement measures from ASCO's Quality Oncology Practice Initiative (QOPI) were programmed into the CancerLinQ prototype. This allowed the measurement of provider compliance with the quality measures in the prototype's patient population. Finally, the system was integrated with a data analytic module (from Galileo Analytics) to permit visual exploration, mapping, and analysis of patient data variables in the system to support hypothesis generation. The prototype system was demonstrated in November of 2012 at the ASCO Quality Care Symposium [70].

The CancerLinQ prototype RLS was created in approximately 8 months. The CancerLinQ prototype successfully demonstrates the ability to collect and aggregate routine clinical, billing, and administrative data from a variety of practice settings, integrate accepted clinical guidelines and evidence into a clinical decision support-driven EHR, provide real-time performance feedback to providers, and offer a platform for hypothesis generation from analysis of data collected during routine care. Based on the success of the prototype, ASCO is currently pursuing the development of a production version of CancerLinQ, the first elements of which are expected to be complete in 2015.

RLS in Emergency Medicine

The previously described applications demonstrate two examples of using RLS to improve the management and palliation of symptoms experienced by patients with chronic diseases and one example of using RLS to enhance the quality of care and support new evidence generation in a large cohort of breast cancer patients. While the applications are specific, the principles of RLS employed in each example are shared. Similar to our examples, RLS may be applied in emergency medical care to improve management of symptoms commonly presenting in the emergency department or to generate new evidence to inform the management of specific disease processes encountered in the emergency department (ED). One such application could be in the management of pain and analgesia. Longitudinal collection of standardized pain assessments for individual patients and collection of data about pharmacologic interventions may provide a platform on which to better assess efficacy of analgesia management. The continuous, real-time aggregation and analyses of such data may be informative to improving individual patient management as well as providing important insights about analgesia in specific populations of patients such as those with cancer.

[2]This example was generated from published information and/or publically presented information about CancerLinQ.

Barriers to Implementing Rapid Learning Systems

Data Sharing and Privacy

The core of RLS is the capture of patient-level data from routine care processes and their subsequent linkage with other HIT systems. A notable challenge to implementing and maintaining such an interconnected system is ensuring patient privacy, data security, and compliance with Health Insurance Portability and Accountability Act (HIPAA) rules. Patients are increasingly cared for in a variety of settings and institutions, and portability of health information across these varied settings is necessary for the high-quality patient data needed to drive RLS. Many existing HIT systems such as EHRs offer built-in ability to de-identify or conceal certain elements of patient health information on the local system level. Such privacy safeguards, however, may unintentionally conceal the sharing of vital clinical information with interlinked components of RLS [71]. Furthermore, to effectively and accurately link a patient's data from one HIT system to another, some minimum amount of individually identifiable health information may be necessary [72, 73]. Large-scale health delivery systems such as Kaiser Permanente, Geisinger Health System, and the Veterans Health Administration have successfully achieved large-scale data sharing and may offer valuable insights into questions of balancing privacy with data fluidity [19]. The creation of regional health information organizations (RHIOs) to aggregate data from community stakeholders in a regionally focused manner may help improve the capture and sharing of valuable data in RLS [73]. RHIOs could be achieved through creation of central repository-type databases or the use of distributed data networks where data is held on local HIT systems until requested [21]. Privacy policies could then be handled on a regional basis by RHIOs or remain locally governed in the case of distributed data networks. Patient confidentiality and privacy are as important in RLS as in existing models of care delivery; however, to accomplish the real-time interconnectivity envisioned in RLS, new policies and methods for regulating issues of privacy will be needed.

Data Quality

Data sources form the engine of RLS and, accordingly, the quality of data in RLS is an important consideration. While the use of advanced HIT, such as an EHR with natural language processing systems or wide-scale abstraction of unstructured data, may help improve data capture, completeness and accuracy of the data recorded remain at least partly dependent upon completeness and accuracy at the point of provider entry [74]. We have discussed that data standardization is important to promote the interoperability of data between different HIT systems in RLS. Standardization is also an important aspect of promoting quality data capture. Defining the data to be captured and providing standards on how it should be collected and reported are important considerations in capturing high-quality data from routine clinical care. For example, CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone) chemotherapy is a standard regimen for patients with non-Hodgkin's lymphoma, but there may be tremendous variability in its administration (dosages, interval, concurrent supportive care medicines). Even in the context of implementing evidence-based care directly from clinical trial protocols, actual adherence to trial protocols exists and can lead to variable data quality [75]. For RLS to achieve quality data capture, it is important to specifically define and capture variables that most accurately and specifically describe the actual care provisioned. These standards must then be applied equally across the spectrum of clinical, research, and non-clinical data sources that drive RLS.

Data Governance

Questions about data sharing, privacy, quality, and standardization highlight the challenge of data governance. Data governance refers to the stewardship of data quality, access, storage, management, and security [71]. In other words, who defines data standards for a RLS? Who monitors data quality and enact process improvements when data quality is poor? Who is responsible for maintaining data security? Optimal governance is partly dependent on the scope and scale of a RLS. It also requires consideration of balanced participation of stakeholders to avoid conflicts of interest. Data governance may include cooperation between patients, providers, and researchers in a local RLS. Alternatively, it may be achieved through a partnership of public interests, private companies, and professional clinical societies, in the case of larger RLS such CancerLinQ [20]. Finally, given the national health interests, it may be necessary to establish a national health data stewardship entity (NHDSE) to broadly support governance. Whether such a national entity should be a wholly public service or a collaboration of public and private entities is currently debated [76]. Defining policies and methods for data governance in a RLS are of fundamental importance to support data quality and patient privacy and remain a significant challenge to address.

Summary

There are increasing questions about the cost, quality, and value of care provided to patients in the current US health-care system. The rapid growth of new knowledge and development of new medical therapies and technologies has added to the complexity of health-care delivery. The ultimate applicability and benefits of new discoveries to specific individual patients are often unclear to providers. Accordingly, there are notable variations in care patterns and quality of care nationally. Rapid learning systems have the potential to inform medical care delivery at the point of care and improve health outcomes and quality. RLS seek to aggregate data from routine patient care, clinical and biomedical research, administrative data, and patient-reported outcomes to form rich integrated data sources for application in real-time care. Using advanced HIT such as EHRs with clinical decision support and iterative cycles of data collection, aggregation, and analysis, RLS leverages these rich, integrated data sources to better inform care delivery at the point of care as well as generate new evidence and hypotheses for testing.

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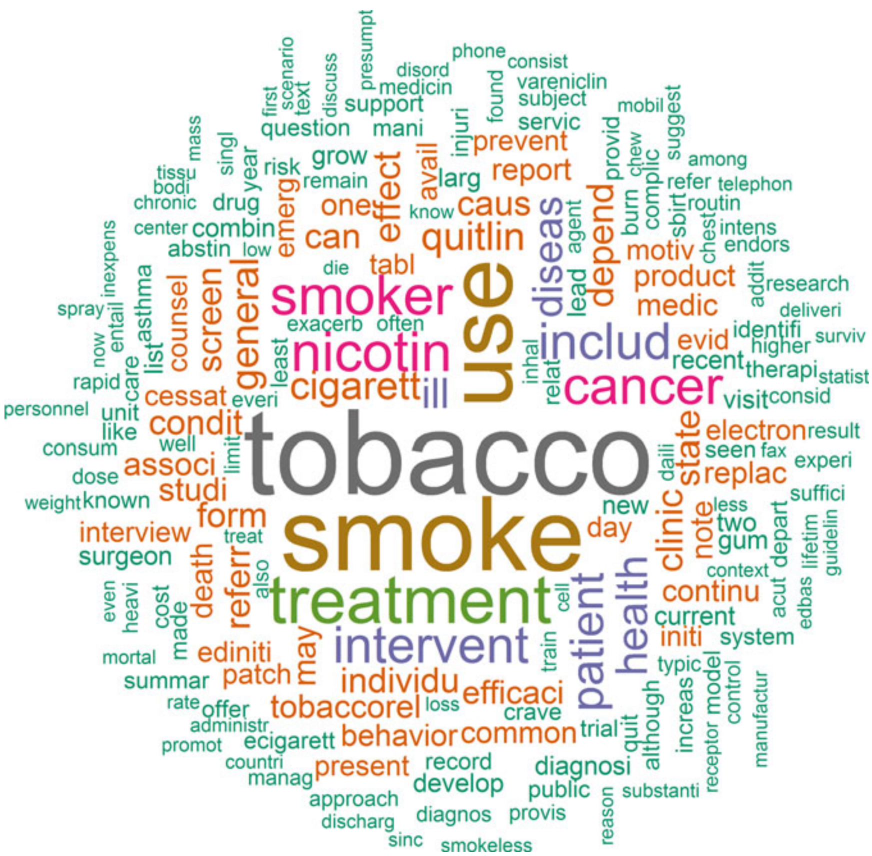
Part II

Prevention

Tobacco-Related Illnesses and Management

Steven L. Bernstein



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Background

Fifty years after Surgeon General Luther Terry's landmark report on smoking and lung cancer, tobacco use remains the leading cause of death in the United States and the leading cause of preventable death [1]. Worldwide, tobacco use is a growing cause of morbidity and mortality. In many developing countries, it is overtaking infectious diseases as a leading public health hazard. Although great progress has been made in curbing this man-made epidemic, the human and economic costs associated with smoking remain enormous.

In the United States, each year about 437,000 Americans die from smoking [1]. An additional 41,000 die from exposure to secondhand smoke, largely as a result of living with a smoker. The conditions associated with death from secondhand smoke exposure include lung cancer and coronary artery disease, residential fires, and prenatal and perinatal conditions such as sudden infant death syndrome [1]. Smoking is a causative agent in dozens of diseases, enumerated in Surgeon General's reports dating back to 1964 and summarized in the most recent 2014 report [1]. These diseases are listed in Table 1. Of note, even half a century after publication of the first major Surgeon General's report on smoking, epidemiologic research continues to reveal new associations between smoking and certain cancers, such as renal cell carcinoma, pancreatic cancer, and acute myeloid leukemia.

The terms "smoking" and "tobacco use" are often used interchangeably. They are not. "Smoking" refers to the consumption of burned tobacco, in the United States, that is largely in the form of cigarettes. Other forms of burned tobacco include cigars, cigarillos, and hookah. In developing countries, bidi and kretek are also popular forms of consuming burned tobacco.

Smokeless tobacco may be consumed as well, in the form of snus (moist pouched tobacco placed between the lip and gum), chewing tobacco, dip, and snuff (dried, insufflated tobacco). Newer products include nicotine-containing water.

Electronic cigarettes, which consist of a heating element that vaporizes a nicotine-containing solution, which is then inhaled, constitute a new and rapidly growing product. E-cigarettes, as they are known, come in a variety of delivery devices. Most solutions contain nicotine; some do not. There is no uniformity in the design or manufacture of these products,

Table 1 Relative risks for adult mortality from smoking-related diseases, adults 35 years of age and older, based on Cancer Prevention Study II, United States

	Males		Females	
Disease category (ICD-10 codes)	Current smoker	Former smoker	Current smoker	Former smoker
Malignant neoplasms				
Lip, oral cavity, pharynx (C00–C14)	10.89	3.40	5.08	2.29
Esophagus (C15)	6.76	4.46	7.75	2.79
Stomach (C16)	1.96	1.47	1.36	1.32
Pancreas (C25)	2.31	1.15	2.25	1.55
Larynx (C32)	14.60	6.34	13.02	5.16
Trachea, lung, bronchus (C33–C34)	23.26	8.70	12.69	4.53
Cervix uteri (C53)	n/a	n/a	1.59	1.14
Kidney and renal pelvis (C64–C65)	2.72	1.73	1.29	1.05
Urinary bladder (C67)	3.27	2.09	2.22	1.89
Acute myeloid leukemia (C92.0)	1.86	1.33	1.13	1.38
Cardiovascular diseases				
Coronary heart disease (I20–I25) persons 35–64 years of age	2.80	1.64	3.08	1.32
Persons ≥65 years of age	1.51	1.21	1.60	1.20
Other heart disease (I00–I09, I26–I28, I29–I51)	1.78	1.22	1.49	1.14
Cerebrovascular disease (I60–I69)	3.27	1.04	4.00	1.30
Persons 35–64 years of age				
Persons ≥65 years of age	1.63	1.04	1.49	1.03
Atherosclerosis (I70)	2.44	1.33	1.83	1.00
Aortic aneurysm (I71)	6.21	3.07	7.07	2.07
Other arterial disease (I72–I78)	2.07	1.01	2.17	1.12
Respiratory diseases				
Influenza, pneumonia (J10–J11, J12–J18)	1.75	1.36	2.17	1.10
Bronchitis, emphysema (J40–J42, J43)	17.10	15.64	12.04	11.77
Chronic airways obstruction (J44)	10.58	6.80	13.08	6.78

From the 2014 Surgeon General's report
ICD international classification of diseases

which have recently come under the regulatory purview of the Food and Drug Administration's (FDA's) Center for Tobacco Products. The potential for e-cigarettes to cause illness, including cancer, cardiovascular disease, and addiction, is not well understood. They are currently the subjects of intense study, as well as substantial marketing efforts by the traditional tobacco companies, many of which have acquired e-cigarette manufacturers. Because of the paucity of data surrounding their health effects, they will not be discussed at length.

Diagnosis of Tobacco Use

Tobacco-related illness is common in the ED. A complete listing would include diseases directly caused by smoking, such as chronic obstructive pulmonary disease (COPD), and conditions like asthma whose acuity or treatment is complicated by co-occurring tobacco use. Table 1 summarizes the list of tobacco-caused illnesses. An early paper found that about 5 % of all ED visits, 7 % of all admissions, and 10 % of ED charges are attributable to smoking [2].

Emergency physicians and nurses screen for smoking irregularly. Tobacco use is more likely to be solicited for patients with conditions that are clearly tobacco related, less so for others.

There are various ways to screen for tobacco use. In research contexts, a two-question screener is often used. The screener is used by two large annual surveys, managed by the Centers for Disease Control and Prevention: the Behavioral Risk Factor Surveillance System (BRFSS) and the National Health Interview Survey (NHIS).

The two questions are:

1. Have you smoked at least 100 cigarettes in your entire life?
   ☐ No
   ☐ Yes
   ☐ Don't Know/Not Sure
   ☐ Refused
2. Do you now smoke cigarettes every day, some days, or not at all?
   ☐ Every day
   ☐ Some days
   ☐ Not at all
   ☐ Don't know/Not sure
   ☐ Refused

Individuals who endorse having smoked at least 100 cigarettes in a lifetime and are every- or some-day smokers are considered to be current smokers. Individuals who endorse at least 100 cigarettes in a lifetime but do not currently smoke are considered to be former smokers. Those smoking less than 100 cigarettes in a lifetime are considered never-smokers.

Of note, these questions do not capture the use of other forms of burned tobacco: cigars, cigarillos, and hookah or unburned forms, such as smokeless tobacco, chew, and snus. Electronic cigarettes (e-cigarettes) and related products, known collectively as electronic nicotine delivery systems (ENDS), constitute a new and growing means of nicotine administration. The oncogenic and pathogenic potential of ENDS is only starting to be studied, although the market share of these products is growing rapidly.

However, in the context of routine clinical care, it is probably sufficient to ask the patient if he or she currently smokes. In our experience, smokers tend to be forthcoming in disclosing their tobacco use. In the current era of data capture via electronic medical records (EMRs), there is typically a defined field in the social history (or elsewhere) to record smoking status. In that case, the provider's choices may be constrained by the responses offered in the "smoking box" of the EMR.

Diagnosis of Tobacco-Related Illness

The list of conditions in Table 1 is extensive but does not cover all clinical scenarios in which EM practitioners might discuss smoking with patients. For example, wound healing is often compromised in smokers, with higher risks of poor cosmesis and infection [3]. Injury comprises about 22 % of all ED visits [4], so smokers with injuries are common. Tobacco abstinence should be advised for all smokers with lacerations, fractures, abscesses, and other skin, soft tissue, and musculoskeletal injuries. Discharge summaries generated by electronic medical records should mention tobacco avoidance for patients with traumatic injury.

Illnesses Associated with Tobacco Use

The number of diseases associated with tobacco use is profound, and Surgeon General's reports since 1964 continue to identify new conditions associated with smoking. The list of tobacco-related illnesses, along with their associated relative risks for mortality, is summarized in Table 1.

Note that many of these conditions are commonly seen in the ED. These are largely the cardiovascular diseases, such as chest pain, acute coronary syndromes including myocardial infarction and unstable angina pectoris, and respiratory disease including pneumonia, influenza, exacerbations of chronic bronchitis and emphysema, and asthma. Patients with cancer are, of course, seen in the ED. They generally present with a complication of treatment or the cancer itself.

Cancer is occasionally, albeit rarely, diagnosed de novo in the ED. It is important to note that these diagnoses are presumptive, because no tissue diagnosis has yet been made.

Some possible scenarios in which cancer may be presumptively diagnosed include:

- A heavy smoker who presents with a cough, dyspnea, or weight loss and has a new pulmonary mass seen on chest x-ray.
- A heavy smoker who presents with marked weight loss, progressive difficulty swallowing, and a mediastinal mass contiguous with the esophagus seen on chest x-ray or CT scan.
- A woman who presents with vaginal bleeding and has an irregular appearance to the uterine cervix.
- A previously healthy person who presents with fever and generalized bleeding and is found to be thrombocytopenic with many blast cells in the peripheral blood smear.

For ED patients with a known diagnosis of cancer who continue to smoke, clinicians (and patients) may question the value of treating tobacco dependence. While interventions should be individualized and patient centered, there is considerable evidence to support tobacco cessation attempts in those with a cancer diagnosis. Continued smoking reduces the efficacy of all forms of cancer treatment, including surgery, radiotherapy, and chemotherapy. As is true for other tobacco-related diseases, cancer patients who continue to smoke experience an increase in treatment-related complications, including postoperative complications [5] and treatment-related adverse effects [6]. After successful cancer treatment, continued smoking increases the risk of cancer recurrence as well as the incidence of developing a second primary cancer. For all patients, continued smoking decreases disease-specific survival and overall survival [7].

Of note, tobacco use also is relevant in the ED management of conditions not formally associated with smoking. For example, acute exacerbations of asthma are commonly treated in the ED [8]. Although asthma is not caused by smoking, tobacco use is common in ED asthmatics. It increases the frequency and severity of attacks and prolongs the duration of the exacerbation.

Emergency Department Treatment of Tobacco Dependence

Because of tobacco's great burden of illness and death, its disproportionate use by individuals of low socioeconomic status (SES), and the heavy use of EDs by low SES individuals, the ED has been regarded as an opportune venue in which to initiate treatment for smoking. Interestingly, tobacco treatment is not part of the training curriculum for emergency medicine residents. Much of the research in this area has entailed understanding provider facilitators and barriers to ED-initiated interventions for smoking.

The general approach to ED-initiated intervention for smoking is adapted from the model known as Screening, Brief Intervention, and Referral to Treatment (SBIRT) [9]. SBIRT entails using one or two questions to identify an individual with a risky health behavior, offering an abbreviated form of motivational interview [10] to promote behavioral change and then referring to an appropriate source of aftercare. Initially developed to identify and intervene with persons with alcohol use disorders, SBIRT has been endorsed by the Substance Abuse and Mental Health Services Administration and other professional bodies for use in the ED [11]. ED-based studies with more intensive interventions have generally offered a combination of SBIRT (tailored for smokers) and motivational interviewing.

There are numerous evidence-based treatments for tobacco dependence. These may be divided into two broad categories: medication and counseling. Each is effective; used in combination, they provide even greater efficacy.

There are seven FDA-approved medications: nicotine patch, gum, lozenge, nasal spray, inhaler, varenicline, and bupropion. Counseling strategies with proven efficacy include one-on-one in-person sessions, group counseling, and telephone quitlines. The evidence base supporting these treatments is reviewed extensively in the 2008 Public Health Service guideline on tobacco dependence treatment and in the 2014 Surgeon General's report on smoking.

Of note, quitlines are widely available in all 50 states. They can be accessed by a single phone number: 1-800-QUIT NOW. Services vary somewhat from state to state, but as a rule include counseling by a trained provider, provision of written materials, starter doses of nicotine replacement, Web-based services, and, increasingly, smartphone-based texting services. Quitlines are open 7 days a week, and languages other than English are available. Referrals can be made by providers or smokers. There is no cost to individuals or health systems, and insurance is not needed. Additional information is available at www.naquitline.org, the home page of the North American Quitline Consortium.

Most smoking cessation counseling uses principles of motivational interviewing or cognitive behavioral therapy. Of note, neither hypnosis nor acupuncture have demonstrated efficacy.

These treatments are summarized in Table 2.

The pharmacotherapy of nicotine dependence treatment is relatively straightforward. Smokers who consume five or more cigarettes daily are good candidates for treatment. Medication is typically begun with a single agent, usually the nicotine patch or gum. A single cigarette contains 1–3 mg of nicotine, which can be used to guide dosing. In general, nicotine should be replaced milligram for milligram. A 21-mg

Table 2 Tobacco dependence treatment medications

Products OTC	Dosage	Duration	Precautions	Adverse effects	Patient education
Nicotine patch 21 mg 14 mg 7 mg	One patch per day >10 cpd: 21 mg 4 weeks, 14 mg 2 weeks ≤10 cpd: 14 mg 4 weeks, 7 mg 2 weeks	8–12 weeks	Do not use if Pt has severe eczema or psoriasis Caution within 2 weeks of MI	Local skin reaction Insomnia	Apply each day to clean, dry, hairless skin Focal rash is common: Rotate site daily. Available without prescription
Nicotine gum 2 mg 4 mg	First cigarette ≤ 30 min after waking, 4 mg First cigarette > 30 min after waking, 2 mg One piece every 1–2 h	12 weeks	Caution with dentures Do not eat or drink 15 min before or during use. Limit 24 in 24 h	Mouth soreness Stomachache Hiccups	*Do not chew like ordinary gum* Alternate chewing and parking between cheek and gum (chew until mouth tingles, then park for 1 min, and continue for 30 min) Nicotine absorbed across buccal mucosa Avoid food and acidic drinks before and during use. Available without prescription
Nicotine lozenge 2 mg 4 mg	First cigarette ≤ 30 min after waking, 4 mg First cigarette > 30 min after waking, 2 mg 1 every 1–2 h	12 weeks	Do not eat or drink 15 min before use One lozenge at a time Limit to 20 in 24 h	Heartburn Local irritation of mouth and throat Coughing Hiccups	*Do not bite, chew, or swallow* Dissolve in mouth slowly Each lozenge takes 20–30 min to dissolve Avoid food and acidic drinks before and during use. Available without prescription
Nicotine inhaler Nicotrol Inhaler®	6–16 cartridges/day Each cartridge = 2 cigs Use 1 cartridge q 1–2 h	6 months; taper	Reactive airway disease	Mouth and throat irritation Cough	Patient is not to puff like a cigarette. Gentle puffing recommended Absorption via the buccal mucosa Avoid food and acidic drinks before and during use
Nicotine nasal spray Nicotrol NS®	1–2 sprays each nostril/h 8–40 doses/day	3–6 months; taper	Not for patients with asthma	Nasal irritation Sneezing Cough Teary eyes	Instruct patient to tilt head back and spray Tolerance to local adverse effects develops first week after use
Bupropion SR150 Zyban® or Wellbutrin®	Start 1–2 weeks before quit date Days 1–3, 150 mg each morning Days 4–end, 150 mg BID	2–6 months	Contraindications: Seizure disorder Current use of MAO inhibitor Eating disorder Alcohol dependence Head trauma	Insomnia Dry mouth Anxiety	Take second pill early evening to reduce insomnia Never double dose
Varenicline Chantix®	Start 1 week before quit date 0.5 mg/d for 3 days then 0.5 mg BID for the next 4 days After the first 7 days, 1 mg/BID	3–6 months	Persons with kidney problems require dose adjustment Serious psychiatric illness	Nausea Insomnia Abnormal dreams	Take after eating and with water (full glass) Never double dose. Take missed dose as soon as remembered. If close to the next dose, wait and take at regular dose time Nausea is usually transient. If nausea persists, dose reduction is recommended

patch, applied daily, would be a typical treatment for someone who smokes ten or more cigarettes daily. Higher dosing or additional forms of nicotine replacement therapy (NRT) may be added if the patient experiences cravings. Recent studies suggest combination therapy, using both a long-acting and a short-acting agent (e.g., patch and gum or nasal spray or inhaler), may be more effective than monotherapy. The reason is that transdermal nicotine generally does not replace enough nicotine to prevent cravings and other symptoms of withdrawal. NRT products that cross the blood–brain barrier quickly and easily can offer rapid relief for smokers with cravings.

Bupropion is a drug whose mechanism of action is incompletely understood. It was initially approved for treatment of mood disorders, but also shows efficacy in smoking cessation. Varenicline is an interesting drug that blocks nicotinic receptors in the brain that mediate reward and craving. It is an agonist–antagonist. Varenicline prevents nicotine from binding to receptors, but stimulates the release of a small amount of dopamine, generally sufficient to prevent symptoms of withdrawal. These drugs are beyond the scope of practitioners of emergency care and are not indicated for initiation in the ED.

The clinical trials of ED-initiated tobacco dependence treatment are summarized in Tables 3 and 4 [12–20]. These trials have all been conducted since the 2000s. They were largely single-institution studies with modest sample sizes and limited methodological rigor, including poorly specified inclusion criteria, inadequate attention to fidelity of the intervention, and limited use of biochemical confirmation of cessation. Only two followed subjects up to 1 year after enrollment.

Most studies did not show an effect of the intervention. One recent study [16] found that a multicomponent intervention was able to produce a statistically significant higher rate of tobacco abstinence in subjects at the primary endpoint, 3 months, compared to controls. At 1 year, the effect attenuated but nearly reached statistical significance. The intervention consisted of provision of 6 weeks of nicotine patches and gum, initiation of the patch in the ED, a brief motivational interview (10–15 min) by a trained interventionist, a referral faxed to the state smokers' quitline, a phone call 2–3 days after enrollment, and a smoking cessation brochure. This study was the first to demonstrate the efficacy of ED-initiated tobacco dependence treatment. Although efficacious, the intervention has limited generalizability because of the use of nonclinical personnel to perform the motivational interview and the provision of a substantial supply of nicotine replacement medication. Future work for ED-based tobacco treatment should focus on effective interventions that are scalable. The use of mobile health technologies to "push" behavioral change messages to smokers, such as short-message-service (SMS) texting, is one possibility [21].

Table 5 reviews the components of an effective ED-initiated tobacco intervention. The individual components are all supported by evidence from high-grade clinical trials in various settings, with at least one high-quality ED trial to support their use.

Cost

Tobacco dependence treatment is among the most inexpensive, most cost-effective interventions in clinical medicine [23]. Integrating tobacco dependence screening, treatment, and referral into ED clinical workflows can be quite inexpensive. Several models of practice are available. The cheapest is to allow providers—physicians, nurses, and midlevel practitioners—to perform the screening as part of routine clinical care. Brochures advertising the state tobacco quitline, generally available from health departments in bulk from little to no cost, can be distributed to smokers. Advice to quit, a referral to the quitline, or perhaps a visit to a locally available smoking cessation clinic can be templated and added to discharge summaries. Directed referrals to quitlines via fax can be made by clinical or clerical personnel. Some electronic medical records are integrating quitline referrals into their order sets for tobacco dependence [24].

A more intensive, and expensive, model of care entails placing lay educators, or health promotion advocates, in EDs to screen patients for tobacco use and other risky health behaviors [25]. These models are effective in identifying and referring patients, but their impact on long-term abstinence rates is unclear.

Conclusion

Tobacco use is widely prevalent in emergency department patients, and tobacco-related illness is a common reason for presentation. Recent evidence suggests that an approach that combines nicotine replacement therapy, behavioral counseling, and referral to a telephone quitline may result in sustained tobacco abstinence. As a result of the accumulating evidence regarding the efficacy of ED-initiated tobacco control, both the US Public Health Service clinical practice guideline [26] and a report by the Institute of Medicine [27] recommend EDs as effective loci for tobacco screening and treatment. Tobacco use carries a sufficient burden of illness and death to warrant routine screening and intervention in ED patients.

Table 3 Characteristics of studies included in a meta-analysis of emergency department-initiated tobacco control. Adapted from Rabe et al. [19]

Year of publication, authors, country	Number of participants randomized, intervention, control group, target group	Setting, size of yearly patient load	Smoking definition	Treatment in the intervention group	Treatment in the control group	Definition of tobacco abstinence
2000, Antonacci and Eyck, USA	42, 21, 21, adults	Military ED, 30,000	Answer "yes" to the question "Do you smoke?"	Referral to a formal smoking cessation program	Brief counseling	Answer "no" to the question "Do you smoke?"
2000, Richman et al., USA	152, 78, 74, adults	Suburban ED, 47,000	Answer "yes" to the question "Do you smoke cigarettes now?"	Referral to a smoking cessation program	Two-page "Stop Smoking" pamphlet from the AHA	Answer "no" to the question "Do you smoke cigarettes now?"
				+ Counseling		
				+ AHA pamphlet and information packet		
2007, Horn et al., USA	75, 41, 34, adolescents	Suburban ED, 40,000	Smoking on 1 or more days in the past 30 days	≤30 min MI on site	Brief advice (<2 min)	7-day tobacco abstinence
				+ Workbook with audio	+ QL referral	
				+ Personal postcard + Maximum three booster phone calls	+ Follow-up phone call at study end	
2007, Schiebel and Ebbert, USA	40, 20, 20, adults	Urban ED, 70,000	Current daily cigarette smoking for at least 1 year	Proactive telephone counseling (≤45 min)	Self-help manual	7-day tobacco point prevalence abstinence
				+ Maximum four booster phone calls		
2008, Bock et al., USA	543, 271, 272, adults with acute chest pain	Urban ED (24-h observation unit), >100,000	Current, regular smokers (>5 cigarettes/day for the past 3 months)	≤30 min MI on site	One-page referral sheet to local smoking cessation resources	7-day tobacco point prevalence abstinence
				+ Maximum two booster phone calls		
2008, Boudreaux et al., USA	90, (36; 37)[a], 17, adults	Urban ED, 47,000	At least one cigarette per day	Group 1. ≤30 min MI on site	Self-help brochures (from the AHA and the hospital's tobacco dependence clinic)	7-day tobacco abstinence
				+ Self-help brochures		
				+ Maximum three booster phone calls		
				Group 2. Same treatment but all MI sessions by phone after discharge[a]		
2009, Neuner et al., Germany	1044, 515, 529, adults	Urban ED, 40,000	Minimum of one cigarette smoked per day during the last 7 days	≤30 (–45) min MI on site	Counseling at study end	7-day tobacco abstinence
				+ Maximum four booster phone calls		
2011, Bernstein et al., USA	338 adults, 168, 170	Urban ED, 90,000	100 cigarettes in a lifetime + current or everyday smoker	6-week patch, passive quitline referral, MI, booster phone	Brochure	7-day tobacco point prevalence abstinence + carbon monoxide confirmation or cotinine
2014, Bernstein et al., USA	778 adults, 390, 388	Urban ED, 90,000	100 cigarettes in a lifetime + current or everyday smoker	6-week patch + gum begun in ED, active quitline referral, MI, booster phone call, brochure	Brochure	7-day tobacco point prevalence abstinence + carbon monoxide confirmation

Efficacy of emergency department-initiated tobacco control—systematic review and meta-analysis of randomized controlled trials. Adapted from Rabe et al. [19]
MI motivational interviewing, *QL* quitline, *AHA* American Heart Association
[a]This study randomized two intervention groups and one control group

Table 4 Number and proportion of abstinent smokers at follow-up, results of individual studies

			Number and proportion of abstinent smokers at follow-up			
Year of publication, authors	Type of group	No. of randomized participants	1 month	3 months	6 months	12 months
2000, Antonacci and Eyck	Intervention	21			0 (0 %)	
	Control	21			1 (4.8 %)	
2000, Richman et al.	Intervention	78		5 (6.8 %)		
	Control	74		6 (7.7 %)		
2007, Horn et al.	Intervention	41	2 (4.9 %)	1 (2.4 %)	1 (2.4 %)	
	Control	34	NEV	NEV	1 (2.9 %)	
2007, Schiebel and Ebbert	Intervention	20		2 (10.0 %)	4 (20.0 %)	
	Control	20		1 (5.0 %)	0 (0 %)	
2008, Bock et al.	Intervention	271	44 (16.2 %)	39 (14.4 %)	30 (11.1 %)	
	Control	272	27 (9.9 %)	29 (10.7 %)	29 (10.7 %)	
2008, Boudreaux et al.	Intervention	73		8 (11.0 %)		
	Control	17		1 (5.9 %)		
2009, Neuner et al.	Intervention	515	33 (6.4 %)	45 (8.7 %)	61 (11.8 %)	73 (14.2 %)
	Control	529	26 (4.9 %)	41 (7.8 %)	55 (10.4 %)	60 (11.3 %)
2011, Bernstein et al.	Intervention	170		25 (14.7 %)		
	Control	168		22 (13.2 %)		
2014, Bernstein et al.*	Intervention	390		47 (12.2 %)*		62 (16.3 %)
	Control	388		19 (4.9 %)		45 (11.7 %)

*$P = 0.0003$

Table 5 Components of an effective ED-initiated intervention for tobacco dependence

Component	Comments
Counseling	Brief counseling intervention employing principles of motivational interviewing; cognitive behavioral treatment may be efficacious
Medication	Provision of at least 4 weeks of nicotine replacement therapy. Combining short- and long-acting forms, e.g., patch and gum, likely to be more efficacious than monotherapy
Post-discharge treatment: quitline, texting	Aftercare should extend at least 30 days beyond visit. Active referral to state smokers' quitline, via fax or electronic health record, may achieve that. Newer interventions such as the use of cell phone texting warrant further study
Interventionist	Ideally, a nonclinical individual, such as a health promotion advocate or health educator. Can be delivered by physicians, midlevel providers, and nurses, but constraints of time and clinical burden are substantial

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Ionizing Radiation

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Introduction

CT Is a Transformative Tool in Medicine

Computed tomography (CT) has numerous benefits that impact emergency care including but not limited to decreasing the negative appendectomy [2–6] and exploratory laparotomy rates, decreasing the need for hospitalization [7], allowing for safe discharge after exclusion of coronary disease [8], increasing provider [9] and patient [10, 11] confidence in diagnoses, and possibly even increasing mortality [12] and life expectancy [13]. Indeed, CT is fast, easy to obtain, relatively inexpensive, widely available, and highly sensitive and results in relatively low radiation exposure for the benefits obtained. The benefits of a CT with appropriate indication far outweigh the risks.

The Explosion in CT Utilization

In light of this, it is perhaps not surprising that the use of CT skyrocketed during the last two decades, with a growth rate of 14 % per year for about a 12-year period [14]. In 1981, 3 million CT exams were performed, increasing to over 67 million exams by 2006 (Fig. 1) [1]. One in ten Americans undergo a CT scan every year, and many undergo more than one [15].

Increasing awareness about cumulative radiation in addition to other policies and guidelines may have contributed to a plateauing of CT imaging rates observed in the years 2008–2010 onward. [16, 17] Though this trend is true for overall CT rates, utilization in the ED has continued to increase [18]. It is estimated that one in seven ED patients undergoes CT and that 25 % of CTs in the USA are performed in the ED [7]. In one study, 70 % of the nearly one million non-elderly adults underwent at least one imaging study that included ionizing radiation resulting in mean effective doses that nearly doubled the cumulative radiation expected from natural sources alone [19]. Similar patterns of CT use have been observed in pediatric populations as well, though more so in non-pediatric EDs [20, 21].

CT's Contribution to Cumulative Radiation

Because of the much higher exposures that are imparted by CT when compared to radiographs, discussion of this modality drives the discussion about concerns over cumulative radiation exposure as well as costs [22]. Though by volume, radiographs comprise the majority of imaging studies, these account for a relatively small amount of cumulative radiation exposure on a population basis [23]. Interventional diagnostic studies and therapeutic procedures, such as thallium scans and radiotherapy, can impart much higher doses of radiation than CT but are not as commonly performed as CT. In 2006, CT comprised about 17 % of imaging procedures but was the source for over half the medical radiation dose in the USA (Fig. 2) [1]. The delayed nature of the carcinogenic effects of radiation exposure makes overutilization an insidious problem that fails to signal the usual alarms among patients or providers. Of concern, cumulative radiation from diagnostic imaging is projected to account for up to 5 % of future cancers in the USA [15, 24, 25].

Reasons for Increased CT Utilization

Many reasons for the observed increases have been proposed, including but not limited to an aging population, the wide availability of CT, the replacement of older (X-rays) with newer technology (CT), its speed and ease to obtain, concerns about malpractice and other factors, and the reasons that are surely multifactorial [18]. With hospital crowding, time pressures, the need to make decisions based on limited information, and a mandate to never miss life-threatening disease, the ED is fraught with the potential for error. This generally leads to a bias toward testing, including advanced imaging. It is important to appreciate that the increases in CT imaging in the ED have occurred in the context of a significant shift in the USA in the setting in which acute care is provided. The ED now accounts for nearly a third of the 354 million annual acute care visits in the USA, practically all acute care provided after hours and on weekends, more acute care for the uninsured than in all other settings combined, and nearly 50 % of hospital admissions in the USA [26, 27]. To some degree, this shift in location of care explains some of the increases in volume of imaging performed in this setting, though early studies demonstrated that increases in CT utilization outpaced increases in ED visits [28]. Studies demonstrate that increased CT utilization far exceeds the amounts expected by replacement of technology [29] and that changes in tort law have had mixed findings as relates to CT utilization [30, 31].

Patterns of Repeat/Multiple CT Imaging in the ED

Though head and abdominopelvic CTs are the most commonly performed studies in the ED, it is known that certain indications for CT (kidney stones, suspected pulmonary embolus) predominate among patients who are repeatedly or multiply imaged [25, 32, 33]. It has been observed that significant proportions of CTs performed are unnecessary and/or could be replaced with other imaging modalities that do not impart radiation [34][ref]. Studies identifying patients

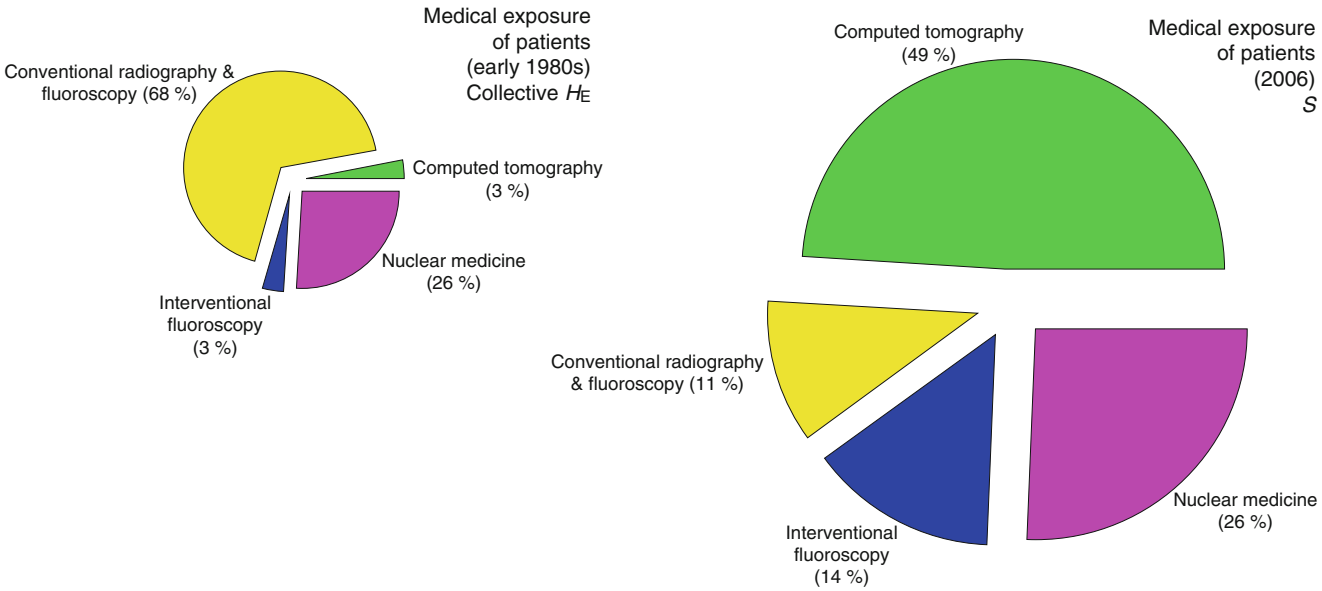

Fig. 1 Growth of CT from 1980 to 2006 as a contributor to cumulative radiation exposure (reprinted with permission of the National Council on Radiation Protection and Measurements, http://NCRPpublications.org)

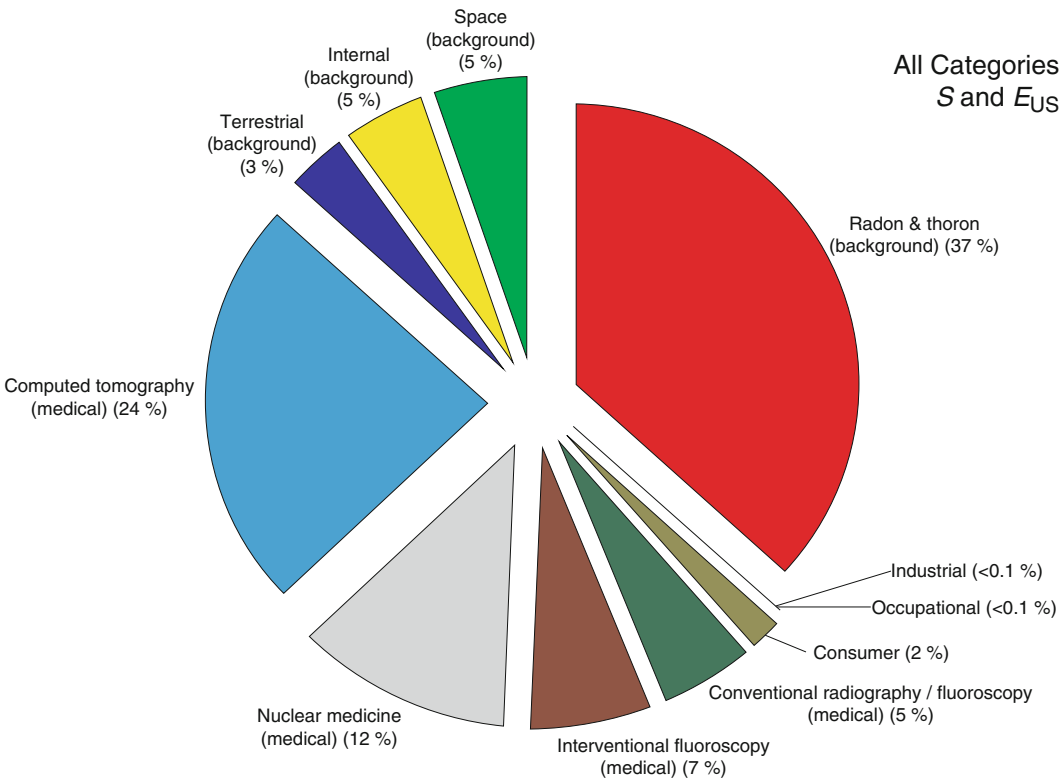

Fig. 2 CT accounts for over half of the cumulative radiation exposure from medical imaging (reprinted with permission of the National Council on Radiation Protection and Measurements, http://NCRPpublications.org)

Organ	Effects	Thresholds (Sv)	
		Single absorption (Sv)	Prolonged absorption (Sv-year)
testis	permanent infertility	3.5 - 6.0	2
ovary	permanent infertility	2.5 - 6.0	> 0.2
lens	cataract	5.0	> 0.15
bone marrow	Blood forming deficiency	0.5	> 0.4

Fig. 3 Examples of deterministic effects of ionizing radiation (reprinted from ICRP, 1991. 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Ann. ICRP 21(1–3), with permission of ICRP)

who are heavily imaged at a given point in time find that these patients tend to have multiple imaging generally and patients heavily imaged in the ED are also highly imaged in settings outside the ED [32, 33, 35].

Radiation and Its Effects

Radiation is the passage of an electromagnetic wave through space. At one end of the electromagnetic spectrum, lower-frequency and lower-energy waves, including radio waves, microwaves, infrared, visible and ultraviolet light, as well as ultrasound, comprise *non-ionizing radiation*. At the other end of the spectrum, the higher-energy, higher-frequency waves, including X-rays and gamma rays, are said to be *ionizing radiation*. X-rays are produced when electrons are emitted from electron clouds as a result of electron excitation. Gamma rays are emitted from unstable nuclei as part of radioactive decay. Radiation is considered ionizing if it is of high enough energy to remove electrons from an atom. This is the basis for ionizing radiation causing cellular injury at the atomic and molecular level.

A displaced electron can cause direct injury if it hits and damages a strand of DNA or can indirectly damage DNA if the electron reacts with water, causing a hydroxyl radical that then interacts with DNA. When just a single strand of DNA is damaged, the cell is usually able to repair this, but when both strands are damaged, an abnormal reconnection of strands can occur, which is believed to account for the negative effects of radiation in humans. This may include a rejoining of strands incorrectly, leading to cell death or rejoining as a symmetrical translocation. This can result in oncogene expression during division and subsequent development of a malignancy or abnormal division in the gonads potentially leading to hereditary disorders [36].

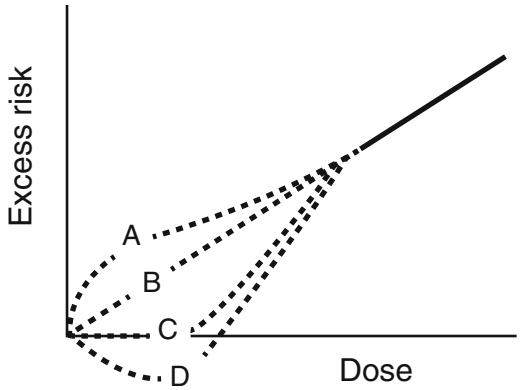

Fig. 4 Possible dose response curves for cancer induction at low doses. *A*: supralinear, *B*: LNT (linear non-threshold), *C*: threshold, *D*: hermetic. Summing up the epidemiological data and biological findings, we are still unsure about the shape of the dose response curve in the low dose range. While several dose response curves are possible as illustrated in the figure, the LNT model is usually adopted as a best estimate for low dose risk (reprinted with permission from Anzai K, Ban N, Ozawa T, Tokonami S. Fukushima Daiichi Nuclear Power Plant accident: facts, environmental contamination, possible biological effects, and countermeasures. J Clin Biochem Nutr. 2012 Jan; 50(1): 2–8)

Deterministic vs. Stochastic Effects of Ionizing Radiation

At high doses, high-energy radiation causes direct cellular injury resulting in what are called *deterministic effects*. These effects are dose related, occurring at threshold levels of radiation to cause sufficient cellular death within a tissue that then results in functional impairment of that organ or tissue (Fig. 3). Deterministic effects are discrete and specific and occur within specific time frames following exposure. These effects are typically due to single large overdoses of radiation. Some examples include:

- Skin erythema, necrosis, and sloughing
- Cataract formation

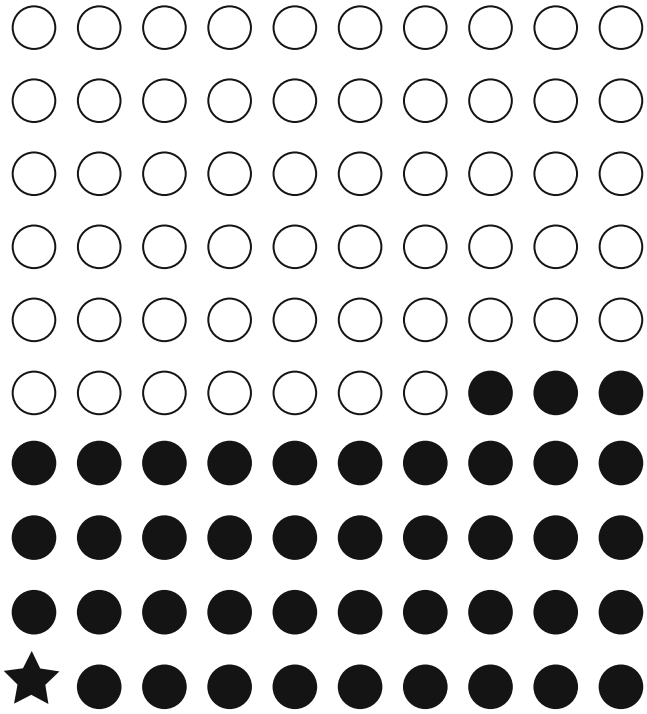

Fig. 5 In a lifetime, approximately 42 (*solid circles*) of 100 people will be diagnosed with cancer from causes unrelated to radiation. The calculation in this report suggest approximately one cancer (*star*) in 100 people could result from a single exposure 100 mSv of low-LET radiation (reprinted with permission from BEIR VII Phase 2, 2006 by the National Academy of Sciences, Courtesy of the National Academies Press, Washington, D.C.)

- Sterility
- Radiation illness (nausea, vomiting, diarrhea related to injury of the GI tract, bone marrow, and CNS)
- IUGR, teratogenesis, and fetal death

By comparison, so-called *stochastic effects* of radiation are due to DNA mutations whose effects become apparent after cell division. By definition, these are random and are not guaranteed to occur and develop in an unclear time frame. Stochastic effect occurrence is thought to follow a linear, no-threshold (LNT) exposure where cumulative low doses result in increasing risk, not requiring some threshold level in order to lead to these effects.

The Link Between Low-Dose Ionizing Radiation and Cancer

Without the benefit of direct observation to quantify amounts, considerable debate has existed about the nature of radiation exposure and the relationship to cancer. Questions about the relationship between radiation and cancer causation include whether cancer due to radiation results only from discrete exposures to some threshold amount or whether risk of cancer due to low levels of radiation increases in a linear (or other) fashion. Studies exploring this relationship have been largely based on data from observed vs. expected solid and liquid cancer rates among people who were in the blast zones of Hiroshima and Nagasaki approximately 2000–3000 yards from ground zero that included radiation in the 5–100 mSv range. Among 93,000 survivors followed over 55 years, 31,650 received a dose of 5–100 mSv. 44 % of leukemia and 8 % of solid tumor cases were attributable to radiation [37, 38]. Studies among survivors of the Chernobyl nuclear accident have also established the role of radiation as a precursor to malignancy. Other studies report increased all-cause mortality (primarily due to dose-related increases of cancer mortality) of nuclear workers related to cumulative low-dose exposure [39] and both projected cancers [40] and effects on cognition among infants exposed to low-dose radiation [41, 42]. In 2005, the US National Research Council's Seventh Biologic Effects of Ionizing Radiation Conference (BEIR VII) adopted the most widely used risk model for the effects of low levels of ionizing radiation [43]. The BEIR VII model, accepted by the International Commission or Radiological Protection and the UN Scientific committee on the Effects of Atomic Radiation, holds that the risk of cancer from cumulative low level radiation proceeds in a linear, no-threshold fashion so that low levels of radiation are cumulative and do not require a threshold level to increase the risks of cancer (Fig. 4). Further, this risk model states that a 10 mSv exposure increases the risk of cancer by approximately 1/1000. In the USA, where the lifetime risk of cancer is approximately 42 %, this means very crudely that a cumulative 10 mSv exposure increases this risk to 42.1 %. Approximately half of cancers are fatal, and so by this risk model, a 10 mSv exposures translate to a risk of fatal cancer of approximately 1/2000 (Fig. 5). This model remains highly controversial with major bodies including the French Academy of Sciences, the American Nuclear Society, and the National Academy of Medicine feeling that this model overestimates risk. It is important to appreciate that though this remains controversial, it is nonetheless the most widely accepted risk model. It is important to recognize that this model is unadjusted for gender and age at exposure. The American Association of Physicists in Medicine considers a cumulative dose in excess of 100 mSv to be of concern. The quantity of radiation that is considered to be "low dose" is generally in the range of 5–100 mSv.

Who Is Most at Risk?

It is known that age at exposure and gender are modifiers of risk. Women are scanned more frequently and are more sensitive to the effects of radiation, primarily due to increased radiosensitivity of female gonadal tissues [25]. Children

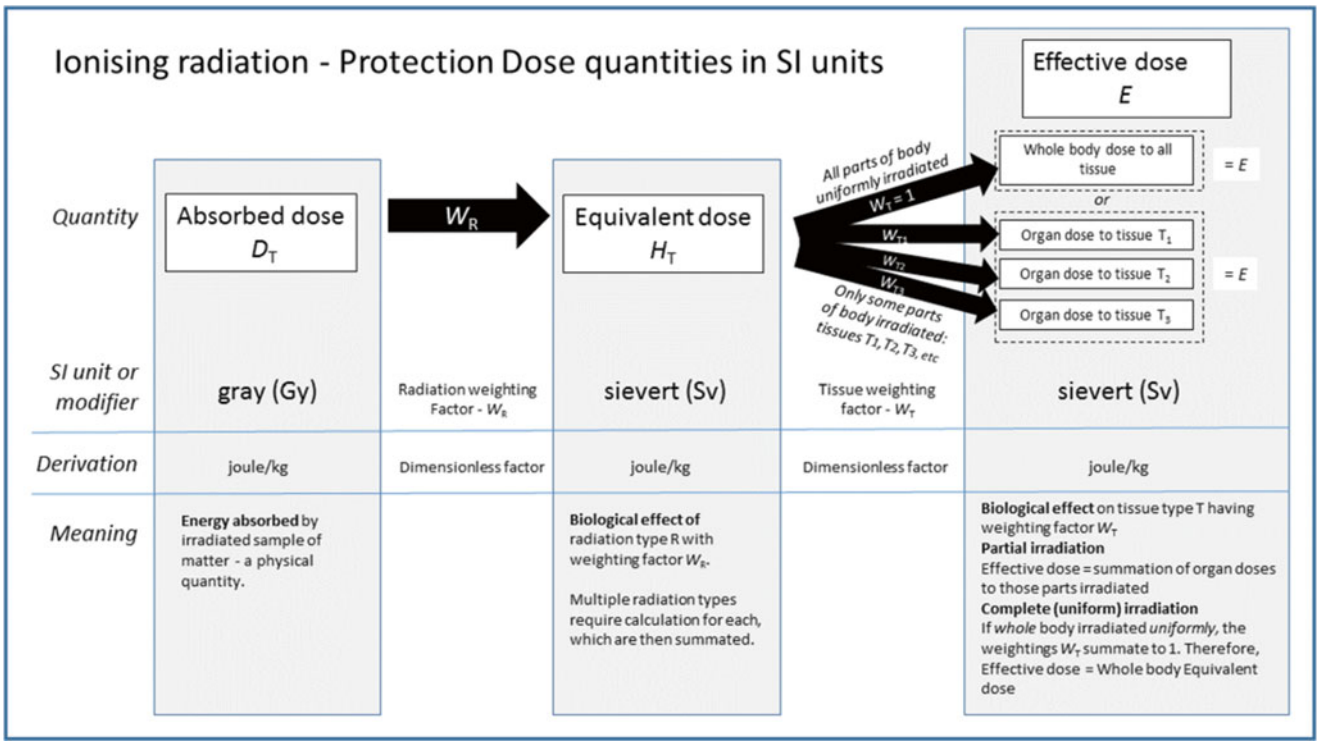

Fig. 6 Units and naming conventions for ionizing radiation (reprinted from https://commons.wikimedia.org/wiki/File:SI_Radiation_dose_units.png with permission. Accessed: 16 Oct 2015)

have both a longer lag time to develop mutations or for mutations to result in malignancies as well as increased radiosensitivity that declines with age [24]. However, recent models suggest that this decrease continues until middle age, but that then cancer risks may then increase in a U-shaped distribution [15]. An additional risk factor is high cumulative radiation exposure due to multiple imaging. Certain conditions are known to be at increased risk for multiple imaging [32, 33, 44–49] including but not limited to inflammatory bowel disease (IBD), kidney stones [20, 50, 51], and shunted hydrocephalus. This leads, in some patients, to very high cumulative doses and increases in lifetime attributable risk (LAR) of cancer. Patients who already have cancer may be at increased risk from developing second malignancies due to radiation. This is documented for radiotherapy, particularly for the lung, esophagus, sarcoma, and breast cancer [52–54]. Cumulative low-dose radiation could represent another potential source of risk.

Measures of Radiation

There are many different units of radiation in use, and these can be difficult to remember for those who do not use them regularly. Measures of radiation relate to different aspects of radiation: exposure, absorption, biological effects, and for comparing effects and values of different exposures.

- *Exposure* to radiation can be measured in Roentgens [R]. Exposure is the strength of a radiation field at some point in the air.
- *Absorption* is entry of radiation into body tissues and is measured in rads where 1 rad = 100 ergs/g or the International System of Units (SI) version and grays (Gy). A gray is defined as the absorption of one joule of energy by one kilogram of matter. One gray = 100 rad. Absorbed dose is therefore expressed as a concentration, not an absolute amount. Absorption depends on the strength of the radiation, the distance from the source and the duration of the exposure.
- The *biological effects* of absorbed radiation are measured in rems or sieverts (Sv), which is the SI unit.
- Important but sometimes confusing concept that is widely used and that can be somewhat controversial is that of *effective dose* (Fig. 6). This relates absorbed dose and biological effects. Effective dose is also used in comparing cancer risks and is not a dose but is rather a concept to reflect the risk of cancer from an exposure reflected over age and gender. It is expressed in millisieverts. Effective dose is determined by taking the sum of organ or tissue

doses, multiplying these by the respective tissue weighting factors, based on an assumed uniform, whole body exposure. Because it is an average, is unadjusted for age and gender, and is mathematically derived using a standard body, it is not a true reflection of risk for an individual (Table 1).

Table 1 Adult effective doses for various diagnostic radiology procedures

Examination	Average effective dose (mSv)	Values reported in literature (mSv)
Skull	0.1	0.03–0.22
Cervical spine	0.2	0.07–0.3
Thoracic spine	1.0	0.6–1.4
Lumbar spine	1.5	0.5–1.8
Posteroanterior and study of chest	0.1	0.08–0.24
Posteroanterior study of chest	0.02	0.007–0.050
Mammography	0.4	0.10–0.60
Abdomen	0.7	0.04–1.1
Pelvis	0.6	0.2–1.2
Hip	0.7	0.18–2.71
Shoulder	0.01	–
Knee	0.005	–
Other extremities	0.001	0.0002–0.1
Dual x-ray absorptiometry (without CT)	0.001	0.001–0.035
Dual x-ray absorptiometry (with CT)	0.04	0.003–0.06
Intravenous urography	3	0.7–3.7
Upper gastrointestinal series	6[a]	1.5–12
Small-bowel series	5	3.0–7.8
Barium enema	8[a]	2.0–18.0
Endoscopic retrograde cholangiopancreatography	4.0	–
Head	2	0.9–4.0
Neck	3	–
Chest	7	4.0–18.0
Chest for pulmonary embolism	15	13–40
Abdomen	8	3.5–25
Pelvis	6	3.3–10
Three-phase liver study	15	–
Spine	6	1.5–10
Coronary angiography	16	5.0–32
Calcium scoring	3	1.0–12
Virtual colonoscopy	10	4.0–13.2

[a]Includes fluoroscopy

(Reprinted from: Mettler FA, Huda W, Yoshizumi TT, Madadevappa M. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology 2008. Vol 248 Issue 1, with permission from Radiological Society of North America)

Dose Estimates

Common units in estimating radiation dose include CT dose index (CTDI) and dose length product (DLP). Most current CT scanners generate these data based on the information provided in determining the protocol used, and these metrics can be reported with interpretations or in other lags. Reporting of CTDI and DLP may soon be required for all scans. CTDI can be thought of as the amount of radiation dose imparted in a single axial CT "slice" through the body with associated scatter and is measured by radiation detectors in a standardized acrylic "phantom" designed to detect doses to specific organs. Different variants of this measure exist but the volume CTDI is most commonly used, measuring the amount of radiation delivered to the scan volume of a standardized phantom. DLP is the slice thickness multiplied by the number of slices acquired or length of the body scanned. When considering doses of radiation provided by a scanner, it should be remembered that these are not direct measurements for the patient on the gantry but rather are estimates based on the protocol used as determined by detection in phantoms. In addition to age and gender, weight or body habitus also impacts absorbed dose.

Efforts to Reduce Radiation and Optimize Imaging

Technological Improvements

At its most basic, CT is an X-ray tube that rotates around a patient. The X-rays passing through the patient are attenuated differently by different body tissues resulting in the detection of a pattern of photons by the detector opposite the tube. As a patient passes through the scanner, it acquires numerous "pictures" in a 360-degree helical fashion that are then mathematically computed and joined to create an image that can be reconstructed in three dimensions. A number of technological improvements can greatly reduce dose per study.

- Standardizing the doses and protocols of CT studies so that for a given patient and a given study, the same dose is delivered. One study of four hospitals in the SF area found that for the same CT study in the same patient, doses varied by up to 13-fold. This sort of variability had significant implications as to projected cancer risk [55] and is unnecessary and wasteful.
- Optimizing aspects of data acquisition (e.g., speed with which the table passes through the scanner, length of body scanned, pitch at which patient passes through the

scanner, minimizing amount of overlapped areas occurring due to the helical nature of the scan) may help reduce exposure.
- New detector technology, increasing detector number, and dual source imaging also offer the potential for lower doses.
- Accepting more noise in images where high resolution is unnecessary, such as for detecting ureteral stones, can decrease the radiation associated with this CT.
- Minimizing multiphase scanning, where patients are scanned, for example, without then again with a contrast agent.
- Modulating tube current, where the amperage from the X-ray tube of a CT scanner is modified as it spins around the patient on the gantry such that a sufficient higher amperage is used in the plane in which the patient is wider and a lower mA setting is less used in the plane in which the patient is thinner.
- Use of shields, such as breast shields, may reduce dose to sensitive tissues. However, these also have limitations and can introduce noise and artifacts.
- Other technical features such as iterative reconstruction can provide high-quality images by eliminating sources of noise, for example, in the reconstruction of the data into images.

Though technological solutions hold promise to minimize the dose per scan, the biggest payoff in terms of radiation and certainly with respect to costs associated with imaging may come at the point of order entry and optimizing ordering to scan those who need it and avoid scanning those who do not. Changing provider behavior is difficult to do, however, as a number of different efforts have demonstrated.

Provider and Patient Awareness

Numerous studies have demonstrated lack of physician awareness of the risks of imaging, disbelief in risks of cancer related to radiation from imaging, and poor performance in estimating risks and equivalent doses of radiation between imaging modalities. This lack of knowledge crosses specialties in some cases even including radiologists [56–61]. While these are mostly older studies that predate the current focus on this area, the few studies specific to EPs confirm these findings [56, 62, 63]. That said, it is not entirely clear what the right knowledge is: does it matter whether EP knows the number of chest X-rays that are equivalent to an abdominal CT or is it more important to know the increase in lifetime attributable risk imparted by an abdominal CT? What is the right knowledge needed for good decision-making? Raising awareness, though helpful, is likely insufficient on its own to make a difference. In one study, training house staff on radiation risks failed to change ordering behavior, though it made them more comfortable with discussion risks with patients [64].

Approaches to raising awareness have included a number of efforts providing information cards for physicians that outline radiation risk for patients, though studies of the effectiveness of these have not been published in the medical literature. One successful program in raising awareness is the Image Gently campaign, started in 2007, and directed at improving the safety and effectiveness of the imaging of children. This includes "raising patient and provider awareness, providing education and advocacy on selection of appropriate imaging studies and minimizing radiation dose to levels as low as reasonably achievable (ALARA) when imaging children" [65]. This successful campaign has subsequently led to the Image Wisely campaign directed at achieving similar goals for adults [66].

The few studies that have looked specifically at ED patient knowledge about radiation and their preferences found that patients generally prefer imaging and definitive diagnoses without concern for radiation or its risks [10, 11]. Studies among pediatric populations found that discussions of radiation risk with parents improved their understanding without causing them to decline necessary imaging studies [67]. In a survey of radiology department chairs at academic medical centers, two-thirds reported having guidelines at their institutions related to informed consent for non-emergent CT studies. And though informed decision-making related to imaging recommended as a best practice [68, 69], only 15 % included discussions about possible radiation risk of CT with their patients [70].

Clinical Decision Support

Appropriateness Criteria

A number of bodies have developed appropriateness criteria for imaging [71, 72], perhaps most notable of these is the American College of Radiology (ACR) Appropriateness Criteria, which consists of consensus-derived rankings of imaging studies and modalities for specific clinical indications for imaging. Particularly when radiologists are not available for consultation, rankings of appropriateness may help guide imaging selection and potentially curb overutilization. Providers board-certified in emergency medicine may find these criteria less useful in selecting appropriate imaging in the ED since this is part of their training and since daily practice and local resource availability inform selection of appropriate imaging modality. In addition, rankings in the ACR's Appropriateness Criteria are not impacted by the amount of radiation a study imparts, which is listed in a separate column called "relative radiation level."

Clinical Decision Rules

Clinical decision rules have been developed in medicine to help guide clinical practice in an evidence-based manner. Though this term is sometimes used casually, scientifically sound clinical decision rules require rigorous derivation and validation methods that are time-consuming and costly and require expertise to ensure their ultimate appropriate use. Clinical decision rules relating to imaging have been developed to help determine whether patients require head CT imaging following minor traumatic brain injury and whether patients suspected for possible pulmonary embolus require chest CT.

Even when a CDR is demonstrated to be effective, valid, and reliable, it is only useful if it is used. A number of studies describe how various imaging decision rules are underutilized [73, 74, 75]. One study estimated that use of a decision rule could prevent up to one-third of pulmonary embolus CTs [34].

Computerized Interventions

A common way to help promote use of CDRs and appropriateness criteria is to embed them in computerized order entry systems. A limited number of studies have explored the effectiveness of computerized decision support in the ED. There have been limited or no studies evaluating use of computerized decision support in providing information on dose associated with commonly ordered CT studies, patients' individual CT study counts, associated cumulative radiation exposure, or lifetime attributable risks of cancer. One study did describe computer-assisted identification of patients who had accumulated certain threshold numbers of lifetime CTs, which then required a peer-to-peer conversation with a radiologist to proceed [76]. Though it has been proposed that patients might carry a card with them that specifies the amount of cumulative radiation they have had, it is unclear what providers should do with this information. One survey of EPs confirmed that though providers were interested in all forms of decision support and information described above, they were inadequately familiar with information on radiation dose to make use of this clinically.

Shared Decision-Making with Patients

Emergency physicians want computerized tools to help guide decision-making and would like information that provides them with ways to discuss risks with their patients [77]. The data suggest that despite being recommended as best practice, discussions with patients regarding risks rarely occur [78]. A main limitation of shared decision-making as relates to CT imaging in the ED is that the decision to image is infrequently preference sensitive or at equipoise with some other diagnostic option. Conveyance of complex information is challenging enough in patients with adequate literacy and numeracy, let alone among those without these skills, which is prevalent in the ED setting.

Quality Metrics and Regulatory Efforts

In addition to physician-initiated efforts to optimize imaging, a number of organizations and regulatory bodies have taken an interest in incentivizing improvements. Preauthorization is one approach taken by payers that has been successful to reduce imaging. However, this is frustrating for physicians who have to seek approval to care for their patients and would be highly impractical for use in the ED. Quality measures related to imaging have been advanced by various bodies, including proposals to report and track patient-specific dose information. Existing or proposed legislation in some states tracking CTDI and DLP. In addition, tracking and documentation of CTDI and DLP in each patient's record are required by the TJC for accreditation effective 7/1/14. Hospitals must compile and analyze data on patient CT radiation doses and compare these with external benchmarks when available.

The Center for Medicare and Medicaid (CMS) adopted six imaging efficiency measures for 2014 that are included as part of the Hospital Outpatient Quality Reporting (OQR) Program reporting requirements. One of these measures, directed at utilization of head CT in the ED for atraumatic headache, is currently under review, having generated a fair amount of debate in the EM community. This measure, OP-14, was controversial because its derivation applied data obtained in a younger population toward an older Medicare population, its exclusion criteria were felt to be insufficient, and it failed to include indications that were indicated in the American College of Emergency Physicians' clinical policies related to atraumatic headache and was felt to be invalid for public reporting.

Summary

It is hard to imagine the practice of emergency medicine without the use of CT imaging. But it may be very important, for the benefit of patients, to imagine practice with more judicious use of this tool, particularly for those at increased risk of cancer. Although the nature of the relationship of low-dose radiation and cancer remains controversial, it is accepted that radiation is a carcinogen and that high cumulative doses increase the risk of cancer. Awareness of the risks of CT imaging in young and female patients, particularly for those at repeat and multiple imaging, is a start toward appropriate use. A number of technological improvements are promising to reduce the dose per study. Decision support tools may be useful in helping risk-stratify patients to help in

decision-making, and more study is needed to evaluate their effectiveness. Quality measures and regulatory statutes related to tracking of cumulative doses may also help drive improvement. Much work remains in order to make clinical use of this information. Finally, providing emergency physicians with options to CT imaging for high-risk patients including alternate imaging modalities is essential to help reduce utilization.

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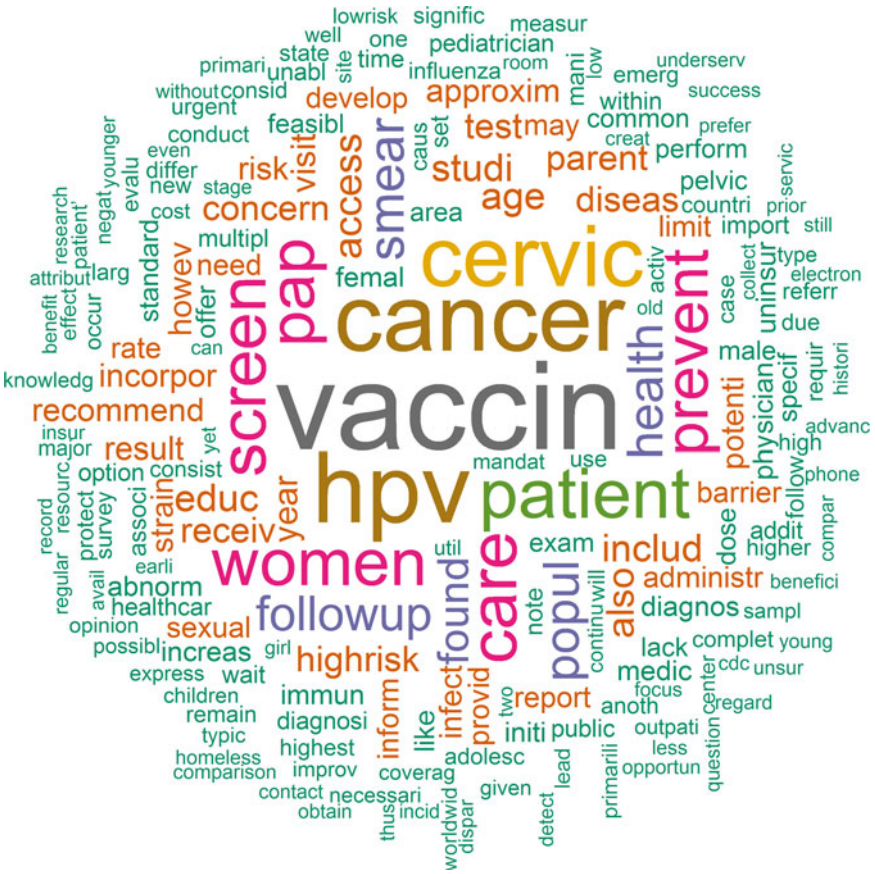
Cervical Cancer Prevention

Larissa May and Chelsea Ware



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Background

Cervical cancer is the third most commonly diagnosed cancer worldwide, only behind breast cancer and colorectal cancer. There are significant disparities in the incidence of cervical cancer between high- and low-resource settings. Cervical cancer is the second most commonly diagnosed cancer (453,300 women in 2008) compared to the ninth most common (76,500 women in 2008) in developing versus developed countries, respectively [1]. These incidence rates have additional ramifications for public health, as developing countries are less likely to have readily available access to preventive care, including cervical cancer screening and the decreased financial capacity to obtain the human papillomavirus (HPV) vaccine, which is a newly available preventive option [2].

In the United States, there are approximately 12,000 new cases and 4000 deaths due to cervical cancer each year. A 2014 report released by the Centers for Disease Control and Prevention (CDC) noted that 93 % of cervical cancer diagnoses could be prevented through screening and HPV vaccination. Eight million (11 %) US women between the ages of 21 and 65 did not receive cervical cancer screening within the last 5 years [2].

Worldwide, there were 529,800 new cases in 2008, with approximately 85 % of these cases occurring in developing countries, primarily Central and South America, sub-Saharan Africa, Southern Asia, and the Caribbean [1, 3]. Nonetheless, the majority of deaths associated with cervical cancer occur in developing countries—approximately 90 % in 2008. The disparities in new cases and deaths are largely attributed to the lack of screening in low-resource areas, specifically the lack of availability of Papanicolaou (Pap) smear [3].

High-Risk Populations

Globally, women in developing countries are at the highest risk to develop cervical cancer. The burden of cervical cancer in these underserved areas has been attributed to limited resources [1, 2, 4]. Poverty, race and ethnicity (primarily African American and Hispanic), and the inability to obtain preventive care are also linked to areas with high rates of cervical cancer diagnosis [4, 5]. A large proportion of women diagnosed with cervical cancer, approximately 80 % in developing countries, present with advanced stages of the disease [6].

In comparison, in the United States, cervical cancer has one of the highest successful treatment rates of all cancer types, approximately a 91 % survival rate, when diagnosed during the early stages of the disease. However, survival rates drop to 17 % if diagnosed during the more advanced stages of the disease [3]. Low-income women are at the highest risk for cervical cancer diagnosis due to their lack of access to preventive care, including Pap smears. Regions of the United States with higher diagnosis rates are also underserved and stricken with poverty, consistent with regions around the world with the higher diagnosis rates [4]. The incidence of cervical cancer in the United States is highest in African American and Hispanic women, which has been attributed to the population's lack of screening, which is likely due to diminished access to health care within these groups [5]. Populations at high risk are also less likely to complete follow-up after an abnormal Pap smear result [7].

In a study of male and female patients visiting an emergency department (ED) in New York City, immigrants received less preventive health care when compared to non-immigrants, even after adjusting for level of income, education, health insurance coverage, language, and length of residence. Limited access to preventive health care leaves these populations at higher risk for illnesses than patients with regular access to health care [8]. In many areas, immigrants are only guaranteed health-care services by emergency medical services; however, some areas offer federally qualified health centers (FQHCs) or public health clinics as alternatives for uninsured or low-income patients. However, there may be limited knowledge of these options. Thus, a large proportion of populations with limited access to care visit the ED for primary care, including their preventive health concerns [8].

Tools for Cervical Cancer Prevention and Detection

Papanicolaou (Pap) Smear

A Pap smear is a laboratory test performed on a sample of cervical cells collected during a pelvic examination and detects abnormal cells associated with cervical cancer [3, 9]. Current recommendations are for women between the ages of 21 and 65 to have a Pap test every 3 years. After the age of 30, it is recommended that women also have an HPV test every 5 years [2]. According to 2010 survey responses, the US Preventive Services Task Force found that 83.0 % of women reported having a Pap smear performed in the previous 3 years. However, only 64.9 % of women with no usual preventive health care and 63.8 % of uninsured women reported having had a Pap test within 3 years [10].

HPV Vaccine

Gardasil, one of the two HPV vaccine options, is a prophylactic, quadrivalent vaccine licensed in 2006 and protects against the four most common HPV strains that cause cervical cancer and genital warts [11]. It is recommended for adolescent girls between the ages of 11 and 12 years old.

For females who do not receive the vaccine at that time, the CDC recommends a "catch-up" vaccination for females between the ages of 13 and 26 years old [12]. The CDC also recommends vaccination of males at the ages of 11–12 years old and up to 21 years of age for prevention of anal cancer and genital warts. Vaccination is also recommended for any male that has had sex with another male or men diagnosed with human immunodeficiency virus (HIV) through the age of 26, only if they had not been vaccinated at a younger age [13]. A second option, Cervarix, protects against two of the most common high-risk types [11].

Several types of HPV strains have been associated with cervical cancer. HPV is the most common sexually transmitted disease (STD), with multiple different strains causing approximately 6.2 million new infections annually [12]. Approximately 15 strains of HPV are linked to cervical cancer, with 70 % of cervical cancer diagnoses caused by two strains, types 16 and 18 [1, 3, 14]. Approximately 90 % of HPV infections, primarily low-risk strains, typically clear without medical intervention within a few years of initial infection [3, 11, 14]. The infections that are unable to be eliminated may lead to the formation of lesions and tumors [11].

The number of adolescent girls who have received the HPV vaccine has increased significantly over the past few years. From 2012 to 2013, HPV vaccine coverage, with one or more doses, increased from 53.8 % to 57.3 % in females. For males, coverage with one or more doses increased from 20.8 % to 34.6 %. Of females who received one or more doses of HPV vaccine in 2013, 70.4 % completed the three-dose series compared to 48.3 % of males [15]. Even after HPV vaccination, patients need to be reminded of the necessity for future cancer screening and continued Pap testing.

Prior research has found that women are interested in education surrounding the risk of HPV and cervical cancer. A study employing focus groups of women found differences between the preferred information of women with different demographic information, including age and ethnicities. For instance, younger women preferred more low-risk HPV strain information, specifically the associated symptoms of an infection, whereas older women preferred more information on risks of the high-risk HPV strains commonly associated with cervical cancer [16]. The study participants also expressed confusion over whether they should be concerned following a positive HPV test result, as well as the differences between low-risk and high-risk HPV strains. They also found that women of all ages were aware of the connection between HPV and cervical cancer but overestimated the possibility of a cervical cancer diagnosis following a positive HPV result. This concern and disconnect of information among adult women could be alleviated or improved if more information is provided in a nontraditional way to patients without regular health-care access [16]. Education could be incorporated into the ED waiting room through the use of public health advocates or through additional discharge education materials and referrals for further follow-up.

HPV Vaccination Barriers

After the HPV vaccine was approved, several states attempted to mandate vaccination for girls between the ages of 11 and 12 with varying success. States with success in mandating HPV vaccination incorporated a parental "opt-out" option, but some parents still questioned whether they should vaccinate their children against HPV. Parental concerns included: the possibility of promoting early sexual activity, the use of unsafe sexual practices, and the unknown long-term effects of the vaccine [12, 17].

The majority of parents have been enthusiastic in regard to vaccinating their daughters against STDs [18]. Olshen et al. found that parents who considered their children at risk for HPV infection were more likely to accept vaccination, while parents who did not consider their children to be at immediate risk were more likely to decline the vaccine. Parents also report concern for vaccine administration at a young age, which could possibly condone premature sexual activity and the possibility for an increase in risky behavior [14, 19].

Public health authorities have expressed concerns surrounding HPV transmission in comparison to other diseases with mandated vaccinations for children. Since HPV is only spread through sexual activity, many parents opposed to vaccination question the immediate risk of spreading the disease in a school environment. Many public health authorities have also noted that mandated vaccination would not create herd immunity within the population but would reduce the number of infections [12]. Herd immunity occurs when majority of a population is vaccinated against a specific contagious disease, which leads to protection for the portion of the population unable to receive the vaccines. This is observed in many diseases with vaccines, including influenza, measles, and mumps [18]. The justification for mandatory HPV vaccination is that women will be protected against the high-risk HPV strains, which would decrease the likelihood of future cervical cancer diagnosis as a result of HPV infection [12].

Another potential barrier to HPV vaccination is its cost, which is $300–$900 for the three-dose regimen charged to the patient [11, 12]. This also concerns physicians and pediatricians because acquiring, stocking, and offering the vaccine are costly, and they are unsure they will receive full reimbursement of the total cost for uninsured patients [12]. This creates yet another barrier for high-risk populations because they are typically uninsured or unable to afford their standard health-care needs, let alone an additional three-dose vaccine regimen.

Physician Attitudes Regarding HPV Vaccination

Pediatricians come in contact with the patients and parents requiring HPV and cervical cancer risk education. In a survey, pediatricians noted strategies that might increase vaccination including: insurance coverage, reasonable cost, and affordability for the uninsured and underinsured [20]. Pediatricians responded they were more likely to recommend the vaccine and educate the parents of a female patient rather than male patients on HPV and the connection to cervical cancer. Many studies have found that parental acceptance of HPV vaccination could increase with pediatrician recommendation [20, 21].

Some pediatricians report reluctance to recommend HPV vaccination to younger patients due to their beliefs that these patients have not yet started sexual activity and thus are low risk for HPV infection. Some also report discomfort discussing sexual topics with young patients and the parents [21]. However, studies have found that approximately 28 % of female adolescents entering the ninth grade have initiated sexual activity [22]. Vaccine administration is recommended prior to an individual's first sexual contact; thus HPV vaccine administration prior to age 14 would provide adequate protection [21]. Having these difficult and potentially uncomfortable conversations may need to occur earlier than previously thought.

Cervical Cancer Prevention and Screening in the ED

Screening

For women lacking regular medical care access, the ED could evaluate the patient's potential need for preventive care screening. These patients could benefit, not only from education on screening and contraceptive use but also having an initial Pap testing and/or HPV vaccine administration with a referral for follow-up visits and vaccinations [23].

Current standard of care pelvic exams in the ED do not include a Pap smear. Many preventive health measures have not been incorporated into ED standard of care for a variety of reasons, including being outside the scope of urgent or emergent care and due to the potential necessity of multiple follow-up visits after receiving results. However, patient expectations of ED care may differ from standard practice. For instance, a prospective, observational study conducted at an urban ED found that 74 % of women believed a Pap test was performed during their pelvic exam. These patients did not receive education from the physician. On the other hand, 56 % of participating women who received Pap test education from the physician still believed they had a Pap smear completed [9]. They also noted that women who correctly answered what a Pap smear tested for were still under the impression that they had a Pap smear during their ED visit [9].

This leads to a false sense of cervical cancer screening compliance among women. Patients unsure of when Pap smears are collected could potentially inform their physicians that they have completed the necessary screening, when in fact, a standard pelvic examination was performed. If providers ask more specific questions about their patient's preventive health screening history, they will have the opportunity to educate the patient on specific areas of concern.

Despite recent advances in the screening and prevention of cervical cancer with the development of the HPV vaccine, there remains a significant gap in knowledge of preventable diseases in high-risk populations that frequent the ED for primary care. Studies have shown gaps in knowledge of what Pap smears test for, primarily in known high-risk populations. The limited knowledge has been associated with women opting out of preventive health screenings, underutilization of the necessary exams, and the misperceptions of their health-care needs [9, 24].

A self-administered survey of female ED patients in a Rhode Island hospital found that those who expressed negative opinions about cancer screening and contraceptive measures were more likely to never have had screening or did not use contraceptives. Pap smears had the highest percentage, 46 %, of negative opinions. Survey respondents with negative opinions described Pap smears as "embarrassing" or "painful" [23]. Interestingly, women expressing negative opinions also viewed the screenings as necessary for preventive health [23].

Up to 25 % of women surveyed in a Canadian ED reported that they were overdue for a Pap smear. These women were offered a Pap smear in the ED; however, all women elected for a referral for outpatient care instead. At follow-up, consisting of phone calls at 1, 2, and 3 months following the initial visit, fewer than half of the respondents had received their outpatient Pap smear [25], suggesting that there may be an important role for incorporating cervical cancer screening in the ED. A separate randomized trial of cervical cancer screening in an urgent care setting found that 22 % of women had an abnormal Pap smear result, with only five returning for follow-up [26], demonstrating patient follow-up as a potentially major barrier to recommending routine cervical cancer screening in the ED, as well as time constraints, lack of personnel with appropriate training, and poor linkages to care outside of the ED. Additional research needs to be conducted to determine the best methods for delivery of cervical cancer screening, as well as improving access to care and follow-up for patients seen in the ED.

Incorporating preventive health screening into an ED visit could be beneficial to high-risk populations. For example, patients receiving a pelvic exam in the ED could be offered additional information concerning HPV, Pap smears, and

cervical cancer, as well as the option to have a Pap smear performed during the physical exam. Multiple studies have determined the feasibility of Pap tests in the ED and urgent care settings, but follow-up is constantly a limitation in ED [7, 27, 28].

Concerns exist the ability of the ED or urgent care to provide proper follow-up to patients with abnormal Pap smear results, especially in regard to high-risk populations, where incorporating cancer screening and education into ED is most beneficial [26]. This population includes women who are homeless, uninsured, and with limited access to a primary care physician.

Women considered high risk for cervical cancer likely utilize the ED because they are unable to see their PCP, are unsure if their PCP can treat their symptoms, or are uninsured, while others may utilize other sites, such as community health centers, FQHCs, homeless shelters, or mobile vans. These sites are typically unable to provide timely follow-up, so patients requiring follow-up after their initial ED visit typically require a referral to another medical facility [7]. A randomized study at an ED with a large population of high-risk patients evaluated the efficacy of high-intensity follow-up after an abnormal Pap smear result, consisting of multiple follow-up phone calls and case management. They found that 65 % of participants went to a follow-up appointment within 6 months [7]. Interventions that could improve or incorporate high-intensity follow-up in EDs with limited resources should be further evaluated.

A study performed at an urban ED found that cervical cancer screening was more effective when completed during the ED pelvic exam instead of referring the patient to screening at a later time. A high prevalence of abnormal cervical sample results was noted in the study's population. Of the abnormal results, it was noted that there was a higher prevalence of dysplasia, in this specific ED population, approximately 8 %, in comparison to the 2 % rate observed in populations with access to and compliance with routine screening and medical care [28]. This same study found a higher rate of follow-up, approximately 70 %, after high-intensity follow-up methods, which included: multiple follow-up phone calls, sending mail, home visits, and contacting the patient's family members [28]. In addition, the quality of the samples was found to be consistent with the hospital's outpatient offices, and physicians reported minimal difficulty during sample collection [26, 28].

Although cervical cancer screening can be improved by incorporating Pap smears into a standard of care pelvic exam, follow-up will continue to be a barrier for the high-risk population, including the homeless. Evaluation of patient follow-up in this population is necessary, because noncompliance with care following abnormal results leads to loss of the benefits the initial screening process provides [7].

HPV Vaccination

No studies to date have been conducted on HPV vaccination in the ED setting. There is, however, a precedent for potentially offering vaccinations in the ED, given the significant waiting that may occur in the ED [28]. A cross-sectional study focused on patient willingness vaccination by a pharmacist in the ED for influenza found that 41 % (62/149) agreed to be vaccinated. Eighty-seven patients declined vaccination, with 38 (44 %) reporting a perceived low risk for infection [29]. Implementation of decision support tools in the electronic health record may assist urgent care and ED settings in increasing vaccination uptake [30]. Another study found that incorporating immunization protocols enhanced vaccination feasibility for pneumococcus and influenza [31]; however, the challenge is that multiple doses of the vaccine are required for HPV. Implementation of the initial dose of HPV vaccination as standard of care in the ED is beneficial to a large portion of urban ED populations. Ensuring each patient who receives the vaccine is given a referral to the appropriate follow-up care will be essential. This could even be incorporated into the patient's electronic health record, which may ensure continuation of care after the initial ED visit. Further research should be conducted on the feasibility of offering HPV vaccination or referring patients to outpatient providers from the ED for further vaccination and screening.

When evaluating the feasibility of influenza and pneumococcal vaccination in the ED, barriers consistent with current HPV vaccine administration were found, including: lack of insurance, young age, and low perceived need for vaccine administration [32]. A cross-sectional study performed in an inner-city ED found that vaccinating in the ED gave uninsured patients and adolescent patients access to vaccinations they would otherwise be unable to obtain [32].

When considering vaccine administration to adolescents in the ED, there are some concerns because parents can give inaccurate immunization histories, with some data showing approximately 45 % inaccurate vaccination history given to providers [33]. This provides a potential barrier to the emergency department's ability to administer required immunizations to their patients. ED access to pediatric electronic medical records (EMRs) could assist and alleviate physician concerns.

Administration of influenza and pneumococcal vaccine to the elderly in the ED has been considered feasible when immunization protocols are in place [31]. Creating and incorporating protocols specific to immunization in the ED could benefit the populations without access to primary medical and preventive care needs [34].

Methods to Promote Immunization in the Emergency Department

Wait times in the ED have continued to increase over the past few decades [35]. Some hospitals have started using these long wait times as an educational opportunity for their patients' preventive health-care concerns. Some academic centers have utilized medical students, while other areas utilize public health advocates and their nursing staff for education in the waiting room [25, 35]. Furthermore, the information offered in the ED waiting room would not be limited to registered patients, as staff could reach out to all visitors [35].

Conclusion

In summary, cervical cancer is an important cause of morbidity and mortality worldwide. Effective preventive measures exist for this devastating disease; however, access to care remains an important barrier. Early work demonstrated the feasibility of conducting Pap tests in the ED, although follow-up was poor. Administration of HPV vaccine is feasible, although linkage to aftercare is needed for this three-vaccine series. The ED could serve as a site for education and screening for HPV. The potential for vaccination in the ED remains yet to be seen.

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Radiological and Nuclear Terrorism: The Oncologic Emergency Response

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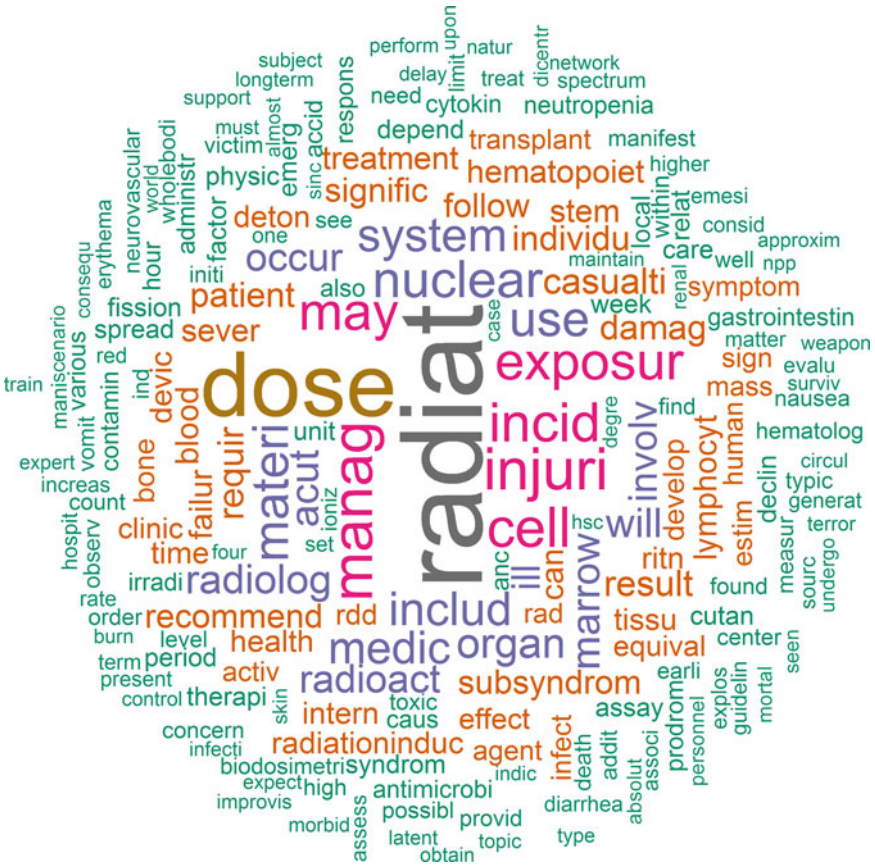

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Introduction

A rudimentary understanding of radiation physics and the hazards associated with exposure to radiation in various scenarios is essential. Basic formal education in medical school is limited, and most physicians have never managed a casualty from a radiological incident. An introduction to the vocabulary of radiation physics, instrumentation, and illnesses is required to provide the basis for understanding radiation-induced pathophysiology and medical management.

The term "radiological event" refers to incidents or effects that involve exposure to materials that are radioactive. The term "nuclear event" refers to any radioactive material resulting from fission. Radiological materials can be relatively innocuous, or they can be extremely dangerous, depending upon their inherent physical structure, the nature of the radiation they emit, and the amount of material involved in an incident. Nuclear materials, on the other hand, present almost no significant hazard to humans in their natural form. If they undergo fission, however, newly generated radionuclides may present a significant hazard to humans and the environment from either the fission process itself or the by-products of nuclear fission. Nuclear fission is required for the detonation of improvised nuclear device (IND) and more sophisticated nuclear weapons (NW). Fission is also required to generate heat for the production of electricity in nuclear power plants (NPPs). In fission reactors, steam generated from the nuclear process is used to turn a turbine which in turn rotates a generator [1].

Measurement of radioactivity. Radioactivity (sometimes called the activity of a radiation source) is the term used for measurement of radioactive material. Radioactivity or activity is measured in curies (Ci) in the English measurement system or the becquerel (Bq) in the SI system (SI = International System of Units or Système International). A Bq is equivalent to one disintegration of an atomic nucleus per second. A Ci is equivalent to 3.7×10^{10} disintegrations per second (dps). A Bq is so small that it is much more common to see units in multiples of Bq such as megabecquerels (MBq), gigabecquerels (GBq), etc. Likewise, a curie is so large that it is much more common to see units in fractions of Ci such as millicuries (mCi), microcuries (μCi), etc.

Units of dose measurement. The unit rad is often used in the English system to describe the amount of ionizing radiation that is absorbed in a cell, tissue, organ, or the body (rad = radiation absorbed dose). It is equivalent to 100 ergs of energy deposited in 1 g of tissue. The gray (Gy) is equivalent to 1 J of energy deposited in 1 kg of tissue. One Gy is equivalent to 100 rad. The rem (rad equivalent man) is a unit of equivalent dose which is used to measure the long-term biological risk related to ionizing radiation exposure (in the USA). The sievert (Sv) is the international unit (SI) for equivalent dose. One Sv is equivalent to 100 rem. The terms Gy and Sv will be used henceforth.

Radiological and Nuclear Scenarios of Concern

Key to understanding radiological and nuclear incidents are the types of injuries and illnesses that they can cause.

The following radiation scenarios are of concern for emergency care responders:

- Radiological exposure device (RED)
- Radiological dispersal device (RDD)
- Improvised nuclear device (IND)
- Nuclear weapon detonation (NWD)
- Nuclear power plant (NPP) incident

RED. An RED is a radiation source that might be surreptitiously placed in a location that will allow unsuspecting individuals to come in contact with it or be exposed to it. The radiation-induced injuries and illnesses that result from exposure or touching the source vary depending upon the nature of the source, the radiation emitted, and the energy of the radiation emitted. It is possible for an RED to cause severe damage up to and including ARS subsyndromes as well as acute local radiation injuries (LRI) or damage to the skin and deeper tissues/organs.

RDD. An RDD is any device that can be used to spread radioactive material. "Dirty bombs" are a common topic of discussion in an age of increasing terrorism. Many believe that an RDD is equivalent to a dirty bomb. This is not necessarily the case because an RDD does not need to explode. An RDD is any device that can be used to spread radioactive materials. A dirty bomb or explosive RDD is any device that uses conventional explosives that when detonated will pulverize and spread particles or larger pieces of radioactive materials into the environment. Improvised explosive devices (IEDs) are detonated on a daily basis in parts of the world to cause physical harm to people or structures. The manufacture of an explosive RDD requires an IED to which is added some amount of radioactive material. An RDD could also involve the use of a device that could spread, for example, liquid radioactive materials. The consequences of an explosive RDD could involve radiation-induced injuries and illnesses, however, could also involve physical trauma and/or thermal burns.

IND and NWs. The main differences between an IND and an NW are the activity of the fissile materials used for a detonation and the sophistication required for manufacture of such a device. The NWs detonated over Japan to bring about the end of World War II in the Pacific Theater were on the order of 10–15 kilotons (KT) of TNT and involved the use of only a few pounds of U-235 or Pu-238. Weapons developed

later during the Cold War were on the order of megatons. When discussing nuclear weapons (NW), it is important to realize that they are designed and manufactured with very sophisticated nuclear, chemical, and electrical engineering skills and techniques maintained only by the international nuclear powers. In either case, the detonation of an IND or an NW could be devastating with massive infrastructure damage and mass human casualties. The fallout of radioactive material descending to the ground after being blown into the atmosphere by the detonation can result in significant human radiation exposures. The acute and subacute consequences of such detonations will involve physical trauma, thermal burns, as well as radiation-induced illnesses/injuries.

NPP incidents. NPP incidents are exceedingly rare, and when they do occur, the results can be highly variable. The Chernobyl (1986) and Fukushima (2011) incidents resulted in multiple human health effects primarily related to exposures to and contaminations with radioactive materials. At Chernobyl, there were 28 acute deaths attributed to acute radiation syndrome that were from ARS [2]. There were no reported casualties specifically related to acute radiation effects from the Fukushima incident. The Three Mile Island incident in 1976 also had no associated adverse human health effects from radiation.

The most common NPP incident relates to control of heat that is generated by a mass of fissile material undergoing fission. If there is a failure anywhere along the path of cool water provision, the reactor may overheat, may melt (thus the term meltdown), or even catch fire. This kind of incident is called a loss-of-coolant accident (LOCA). The results of environmental release of radioactive materials could be a significant source of adverse human health effects.

Radiation-Induced Injuries and Illnesses

Radiation-induced injuries and illnesses occur in a spectrum from minor to severe involving various cells, tissues, and organs. Minor injuries can merely involve exposures to the hematopoietic and cutaneous systems that require no significant medical intervention at below about 1 Gy (100 rad). Severe injuries/illnesses can result in amputations, disruption, and/or loss of vital bodily functions, up to and including death. All of these serious conditions will require timely and aggressive medical care. The systems of greatest concern are the hematopoietic, cutaneous, gastrointestinal, and the neurovascular (cerebrovascular) systems.

Radiation injuries/illnesses, unlike infectious agent exposures and chemical insults, are curious in that they usually have a prodromal period during which one may see only nonspecific symptoms and signs of injury or illness. The prodrome is often followed by a latent period during which the patient may appear relatively well, but injury to various tissues is progressing. The manifest illness phase of ARS occurs when the damage to particular cell types, tissues, and organs appear. At the end of the manifest illness phase, the cell, tissue, organ, or human either lives or dies. The prodrome begins earlier with higher doses; the latent period becomes shorter as the dose becomes higher; the manifest illness period begins earlier with higher doses. The absence of the latent period may be an ominous sign of a higher dose and ultimately significant morbidity and mortality.

Any radiation injury or illness should result in engagement of radiation health and protection experts in these matters. These personnel might include health physicists (HP), medical physicists (MP), diagnostic radiologists (including those with nuclear medicine training), radiation oncologists, hematologists, and/or medical oncologists. Key is that these personnel have experience with radiation dose extent and magnitude estimation. Early dose magnitude estimations will help guide emergency department triage and medical management before more precise dosimetric estimations are available.

Early Diagnostic Evaluation of Acute Radiation Injury

The Clinical History and Laboratory Findings

Proper application of a well-structured interview technique can lead to a diagnosis of radiation injury. Clinicians should consider radiation toxicity as part of their differential diagnosis in individuals presenting with the prodromal symptoms of nausea, vomiting, and diarrhea in the setting of a radiological incident. If acute radiation injury is not considered, a prompt diagnosis will be missed. Early in the patient workup, an initial CBC (complete blood count) with differential should be obtained and repeated every 4–6 h to monitor for a decline in the absolute lymphocyte and neutrophil counts. Blood for individual radiation dose estimates (e.g., radiation biodosimetry) should be obtained at this time.

In the delayed evaluation of patients in terrorism cases where the incident occurred 2–4 weeks previously, the treating medical team may see a patient with some or many aspects of the acute radiation syndrome with or without the cutaneous subsyndrome. Clinical signs and symptoms may include:

(1) Pancytopenia, immune dysfunction, sepsis, impaired wound healing, and GI bleeding (hematopoietic subsyndrome)
(2) Malabsorption, ileus, fluid and electrolyte imbalance, acute renal failure, and cardiovascular failure (gastrointestinal subsyndrome)
(3) Confusion, disorientation, hypotension, cerebral edema, ataxia, convulsions, and coma (neurovascular subsyndrome)

Various authors have suggested that the presence of nausea, vomiting, diarrhea, and fever may correlate with the general range of exposure dose. Zhang has noted that approximately 100 % of patients with whole-body dose greater than the LD_{50} or the dose required to cause mortality in 50 % of the population (approximately 3.5–4.0 Gy without treatment), will have early nausea and vomiting, and many will exhibit altered deep tendon reflexes [3]. In addition, Hartmann et al. have noted an increased body temperature for effective whole-body dose >2.5 Gy and acute diarrhea for dose >9 Gy [4].

Time to Emesis

Two clinical parameters are relatively quickly available for quantitative analysis of radiation injury after a severe incident: (1) the time to emesis and (2) lymphocyte depletion kinetics. In work performed at Oak Ridge Associated Universities 1964–1975, with patients undergoing long-term radiation therapy at a relatively low-dose rate ($n=502$ patients, 0.8–90 R/h), 50 percentile frequency doses were obtained as follows: $ED_{50}=1.08$ Gy for anorexia, $ED_{50}=1.58$ Gy for nausea, and $ED_{50}=2.40$ Gy for emesis. A trend is noted whereby the time to emesis decreases with increasing dose [5, 6] though there is much variability among individuals and circumstances using this as a sole biodosimeter.

Lymphocyte Depletion Kinetics

In papers by Goans et al., a simple prediction algorithm was presented to estimate effective whole-body dose within 8–12 h after moderate and high-level gamma accidents and after criticality accidents [7–9]. The algorithm is based on the observation that lymphocyte depletion follows first-order kinetics after high-level gamma accidents. Using historical data from both gamma and criticality accidents, lymphocytes are observed to follow approximately an exponential decline in time within the first 24–48 h. This algorithm has been incorporated into the Armed Forces Radiobiology Research Institute (AFRRI) Biodosimetry Assessment Tool (BAT) program [10] (Table 1).

Table 1 Absolute lymphocyte count decrease and approximate estimate of absorbed dose

Absolute count 8–12 h post event	*Rough estimate of absorbed dose*
1700–2500/mm^3	0–4 Gy
1200–1700/mm^3	4–8 Gy
<1000/mm^3	>8 Gy
Absolute lymphocyte count 48 h postexposure	*Absorbed dose estimate*
1000–1500/mm^3	1–2 Gy
500–1000/mm^3	2–4 Gy
100–500/mm^3	4–8 Gy
<100/mm^3	>8 Gy

A whole-body dose of 1 Gy or less should not noticeably depress the lymphocyte count below the normal range taken as 1500–3500/mm^3 (from Goans [11])

Cytogenetic Biodosimetry

In the historical evolution of the medical management of radiation incidents, prior to 1960, determination of dose relied on the history of the event, health physics studies, time and motion simulation, and analysis of any dosimetry that might have been present. Additionally, medical management was heavily weighted toward clinical response to the evolution of various syndrome characteristics of the ARS or of acute local cutaneous injury. Since the period 1960–1970, the dicentric chromosome assay has been extensively developed, harmonized to international standards, and is now considered worldwide to be the gold standard for biodosimetry [12].

Researchers at AFRRI and REAC/TS have established the conventional lymphocyte metaphase-spread dicentric assay and have applied it to the clinical management of several overexposure accidents. The dicentric assay is also performed at Yale University School of Medicine and other select medical institutions to determine whole-body dose in victims of radiation incidents. In addition, the premature chromosome condensation (PCC) assay has been found useful at various dose levels. Conventional metaphase-spread chromosome-aberration biodosimetry techniques are robust, but they are laborious and time-consuming. In addition, for potential high-dose irradiation above the median lethal dose, it is expected that radiation-induced cell death and delay in cell cycle progression into mitosis will interfere with dose estimation. In order to overcome this limitation, quantitative analysis of radiation-induced damage may be performed using resting peripheral lymphocytes in lieu of metaphase spreads. The use of interphase cytological assays, such as the PCC assay, can eliminate these inherent problems associated with the use of metaphase-spread cytogenetic assays.

Recently, it was suggested that the dicentric assay may be adapted for the triage of mass casualties [13–15]. Lloyd et al. described an in vivo simulation of an accident with mass casualties receiving whole- or partial-body irradiation in the 0- to 8-Gy range [13]. Faced with an urgent need for rapid results, clinical triage was accomplished by scoring as low as 20 metaphase spreads per subject, compared with the typical 500–1000 spreads scored in routine analyses for estimating dose. However, Lloyd et al. suggested increasing the analyses to 50 metaphase spreads when there is disagreement with the initial assessment or when there is evidence of significant inhomogeneous exposure [13, 16] (Table 2).

Table 2 Proposed biodosimetry technique as a function of expected dose

Dose range (Gy)	Proposed validated dosimetry method	Prodromal effects	Manifest symptoms	Survival expectancy
0.1–1	Dicentric/PCC	None to mild (1–48 h)	None to slight decrease in blood count	Almost certain
1.0–3.5	Lymphocyte depletion kinetics/ dicentrics/PCC	Mild to moderate (1–48 h)	Mild to severe bone marrow damage	0–10 % death
3.5–7.5	Lymphocyte depletion kinetics/PCC	Severe (1–48 h)	Pancytopenia, mild to moderate GI damage	10–100 % death within 2–6 weeks
7.5–10.0	Lymphocyte depletion kinetics/PCC	Severe (<1–48 h)	Combined BM and GI damage	90–100 % death within 1–3 weeks
>10.0	PCC	Severe (minutes to <48 h)	GI, neurological, cardiovascular damage	100 % death (within 2–12 days)

Reprinted with permission from Prasanna et al. [16]

Table 3 Levels of hematopoietic toxicity

Symptom or sign	Degree 1	Degree 2	Degree 3	Degree 4
Lymphocyte changes[a]	1.5×10^9 cells/L	$1–1.5 \times 10^9$ cells/L	$0.5–1 \times 10^9$ cells/L	$<0.5 \times 10^9$ cells/L
Granulocyte changes[b]	2×10^9 cells/L	$1–2 \times 10^9$ cells/L	$0.5–1 \times 10^9$ cells/L	$<0.5 \times 10^9$ cells/L
Thrombocyte changes[c]	100×10^9 cells/L	$50–100 \times 10^9$ cells/L	$20–50 \times 10^9$ cells/L	$<20 \times 10^9$ cells/L
Blood loss	Petechiae, easy bruising, normal hemoglobin level	Mild blood loss with <10 % decrease in hemoglobin level	Gross blood loss with 10–20 % decrease in hemoglobin level	Spontaneous bleeding or blood loss with >20 % decrease in hemoglobin level

See Table 3 of Dainiak et al. [28] (reprinted with permission from Dainiak et al. [28])
[a]Reference value $1.4–3.5 \times 10^9$ cells/L
[b]Reference value $4–9 \times 10^9$ cells/L
[c]Reference value $140–400 \times 10^9$ cells/L

Acute Radiation Syndrome (ARS)

ARS (or acute radiation sickness) consists of a spectrum of diverse clinical signs and symptoms that develop after a whole-body or significant partial-body irradiation of >1 Gy delivered at a relatively high-dose rate. In 2000, an international group of subject matter experts that assembled in Ulm, Germany, categorized these findings into four organ systems (e.g., the hematopoietic, gastrointestinal, cutaneous, and neurovascular systems), each of which occurs individually or in combination [17]. ARS is best thought of as a Venn diagram with four overlapping circles, each representing a subsyndrome that corresponds to an affected organ system. Depending on radiation dose, clinical findings assigned to an organ system may occur concurrently or sequentially with those assigned to the other systems. The signs and symptoms of each of the resulting four subsyndromes of ARS are summarized in Tables 3 (hematopoietic subsyndrome) and 4 (gastrointestinal, cutaneous, and neurovascular subsyndromes). The severity of signs and symptoms for each organ system is quantified as "degrees" of toxicity (degree 1, 2, 3, or 4). The "response category" (grade 1, 2, 3 or 4) correlates with overall severity of ARS and is determined by the highest degree of toxicity within any of the organ systems.

Hematopoietic subsyndrome (HS). Radiation-induced damage is determined in part by the radio sensitivity of the affected cells with the most rapidly dividing cells (e.g., cells in the bone marrow, intestinal crypts, and testes) having the greatest sensitivity. Hematopoietic stem/progenitor cells in the bone marrow and circulation are particularly sensitive to ionizing radiation with a dose (D_0) of approximately 1 Gy at a dose rate of 0.8 Gy/min [18]. At doses of 2–3 Gy, hematopoietic stem/progenitor cells exhibit reduced capacity to divide. Morphological changes in interphase cells of the bone marrow include nuclear karyorrhexis, cytoplasmic fragments, nuclear and intercellular bridging, multinuclearity, and pseudo-Pelger-Huet anomaly [19]. Chromosomal bridges and fragments are seen in actively dividing cells of the marrow. Bone marrow hypoplasia and/or aplasia may develop at doses >5–7 Gy, resulting in severe pancytopenia weeks to months after exposure [20]. The pathophysiologic mechanisms underlying these radiation-induced effects on the bone marrow involve dose-dependent, clonal elimination of stem/progenitor cell populations and their progeny [21, 22]. Depending on dose, dose rate, and radiation quality factor, various degrees of pancytopenia develop several weeks after exposure [23, 24].

Lymphocytes are the most radiosensitive of the circulating blood cells in spite of their being terminally differentiated and largely mitotically inactive. Enhanced radiosensitivity may be explained in part by the observations that radiation alters recirculation properties and surface antigen expression of lymphocytes [25, 26]. The rate of decline in lymphocytes is exquisitely dependent on the absorbed radiation dose

Table 4 Grading system for response based on clinical signs and symptoms

Symptom	Degree			
	1	2	3	4
Gastrointestinal system				
Diarrhea				
Frequency, stools/d	2–3	4–6	7–9	10
Consistency	Bulky	Loose	Loose	Watery
Bleeding	Occult	Intermittent	Persistent	Persistent, large amount
Abdominal cramps or pain	Minimal	Moderate	Intense	Excruciating
Cutaneous system				
Erythema[a]	Minimal transient	Moderate (<10 % BSA)	Marked (10–40 % BSA)	Severe (>40 % BSA)
Sensation or itching	Pruritus	Slight, intermittent pain	Moderate, persistent pain	Severe, persistent pain
Swelling or edema	Present, asymptomatic	Symptomatic, tension	Secondary dysfunction	Total dysfunction
Blistering	Rare, sterile fluid	Rare, hemorrhage	Bullae, sterile fluid	Bullae, hemorrhage
Desquamation	Absent	Patchy, dry	Patchy, moist	Confluent, moist
Ulcer or necrosis	Epidermal only	Dermal	Subcutaneous	Muscle or bone involvement
Hair loss	Thinning, not striking	Patchy, visible	Complete, reversible	Complete, irreversible
Onycholysis	Absent	Partial	Partial	Complete
Neurovascular system				
Nausea	Mild	Moderate	Intense	Excruciating
Vomiting	Occasional (1 time/day)	Intermittent (2–5 times/day)	Persistent (6–10 times/day)	Refractory (>10 times/day)
Anorexia	Able to eat	Intake decreased	Intake minimal	Parenteral nutrition
Fatigue syndrome	Able to work	Impaired work ability	Needs assistance for ADLS	Cannot perform ADLS
Temperature, °C	<38	38–40	>40 for <24 h	>40 for >24 h
Headache	Minimal	Moderate	Intense	Excruciating
Hypotension	Heart rate >100 bpm, blood pressure >100/70 mm/Hg	Blood pressure <100/70 mmHg	Blood pressure <90/60 mmHg, transient	Blood pressure <80/? mmHg, persistent
Neurologic deficits[b]	Barely detectable	Easily detectable	Prominent	Life-threatening, loss of consciousness
Cognitive deficits[c]	Minor loss	Moderate loss	Major impairment	Complete impairment

See Table 3 of Dainiak et al. [43] (reprinted with permission from Dainiak et al. [43])
BSA body surface area, *ADLS* activities of daily living
[a]The extent of involvement is decisive and should be documented for all skin changes
[b]Reflex status (including corneal reflexes), papilledema, seizures, ataxia, and other motor signs or sensory signs
[c]Impaired memory, reasoning, or judgment

(see above discussion of the decline in absolute lymphocyte count (ALC) as an individual radiobiodosimeter).

Other hematological findings include a decline in the absolute neutrophil count (ANC) and the platelet count. The ANC may briefly increase within hours after exposure, a phenomenon first described by Fliedner as an "abortive rise" [17]. The abortive rise is believed to be due to migration of preformed myeloid elements across the marrow-blood barrier into the circulation, although demargination cannot be excluded as a mechanism for this transient effect. Thereafter, the ANC declines over several days to weeks, depending on radiation dose. The abortive rise is typically seen with HS-1 and HS-2 and appears to indicate reversible marrow damage from a survivable exposure. The absence of an abortive rise in ANC is observed in HS-3 and HS-4 and is felt to auger irreversible bone marrow damage. Neutropenia and thrombocytopenia reach a nadir at 1–2 weeks after exposure to >3–4 Gy. Anemia follows due to impaired erythropoiesis and hemorrhage from the gastrointestinal tract and other organs as a consequence of thrombocytopenia.

The most significant consequences of lymphopenia and neutropenia are disruption of immune defenses and predisposition to life-threatening infections. ANCs of <500–1000 cells/mm^3 (HS-3 and HS-4) are associated with bacterial, viral, and fungal infections, similar to what occurs in the setting of neutropenia and lymphopenia from any other cause. Management of febrile neutropenia and attendant infections should follow guidelines recommended by the Infectious Diseases Society of America (IDSA), using broad-spectrum prophylactic and therapeutic antimicrobial agents [27]. Prophylaxis may include amoxicillin plus clavulanate or a fluoroquinolone with streptococcal coverage, an antiviral agent (such as acyclovir or valacyclovir) for patients who are positive for herpes simplex virus (HSV) or cytomegalovirus

(CMV), and an antifungal agent (such as fluconazole or posaconazole for mucosal and invasive infections with drug-sensitive *Candida* species). Whenever possible, prophylactic antimicrobial agents should be administered before the onset of critical leukoneutropenia (HS-4). Additional antimicrobials should be added to broaden coverage as clinically indicated based on clinical course, culture and sensitivity results, and laboratory findings.

Management of the HS includes administration of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) when the dose is expected to be >2 Gy and/or when it is anticipated that the ANC will decline to <500 cells/mm^3 for 7 days or longer [28]. A strong recommendation for cytokine therapy was made by a panel of subject matter experts that was convened at the World Health Organization in 2009 to evaluate the quality of published evidence and develop recommendations for treatment of ARS in a hypothetical scenario involving hospitalization of 100–200 victims [28]. The Food and Drug Administration (FDA) has approved these myeloid colony-stimulating factors for use in a radiological incident. Cytokine therapy should be initiated with 24 h of exposure and should continue until the ANC reaches and maintains a level of >1000 cells/mm^3 in the absence of active infection. For individuals with active infection, cytokines should be continued together with antimicrobial agents, according to guidelines of the IDSA [27].

Erythroid-stimulating agents (ESAs) should be administered to individuals with prolonged anemia and/or a significant decline in hemoglobin level [28]. The rationale for ESA therapy is to avoid the need for red blood cell infusion. The lowest dosage that induces a hemoglobin level of >9–10 g/dL should be used. Oral iron supplementation should be considered in conjunction with ESA therapy.

Although other growth factors (including stem cell factor, interleukin-3, and the pegylated form of erythropoietin and G-CSF) have been administered sequentially or concomitantly with G-CSF and/or GM-CSF to victims of a radiological incident [28], their limited use and lack of documentation of response to the specific growth factor preclude recommendation of their use in a radiological incident at this time.

Because radiation injury to the bone marrow is typically heterogeneous, leaving areas of unirradiated or minimally irradiated/damaged marrow that are capable of reconstituting lymphohematopoiesis over time, a watch-and-wait approach is recommended after initiating myeloid growth factor therapy. Administration of hematopoietic stem cells (HSCs) should be considered only after failure of a 2–3-week trial of cytokine treatment has been demonstrated [28]. A review of 31 patients undergoing HSC transplantation for accidental radiation injury found that 27 patients died, and the remaining four patients survived with a rejected allograft [29]. Causes of death after therapeutic HSC transplantation include burns (55 %), hemorrhage (41 %), infection (15 %), and acute respiratory distress syndrome (ARDS) (15 %) [30]. Since survival outcomes are poor among HSC transplant recipients with radiation burns, GS, renal failure, and/or adult ARDS, HSC transplantation should not be performed in individuals with nonhematopoietic organ failure and/or active infection [28, 31–33]. In the case of a large radiological incident, the Radiation Injury Treatment Network (RITN), a voluntary consortium consisting of >70 transplant centers, donor centers, and umbilical cord blood banks, will be activated [34, 35].

When transfusion is indicated for severe cytopenia, blood products should be irradiated (25 Gy) to prevent transfusion-associated graft-versus-host disease (TA-GVHD). Since TA-GVHD is almost universally fatal in this population, its prevention by prior irradiation of blood products is mandatory. Leukoreduction may lessen febrile reactions and the immunosuppressive effects of blood transfusion, limit platelet alloimmunization, and reduce CMV infection [36, 37]. Leukoreduction is recommended whenever feasible.

National Network for Management of Mass Radiation Casualties

In the USA, a network has been developed of transplant centers, hospitals, blood donation centers, and stem cell banks to provide resource-intense medical management of mass casualties from a radiological event. The Radiation Injury Treatment Network (RITN) provides comprehensive evaluation and treatment for victims of radiation exposure or other marrow toxic injuries (like those caused by mustard agent). Many of the casualties with radiation injury will be salvageable but require specialized outpatient and/or inpatient care. Recognizing this need, the US National Marrow Donor Program/Be The Match Marrow Registry, the US Navy, and the American Society for Blood and Marrow Transplantation collaboratively organized RITN, which provides expertise in the management of bone marrow failure, blood component therapy, stem cell collection, and umbilical cord blood banking across the USA.

The RITN is preparing for the resulting medical surge of radiation only casualties from the detonation of an improvised nuclear device.

The goals of RITN are:

- To develop treatment guidelines for managing hematologic toxicity among victims of radiation exposure
- To educate health-care professionals about pertinent aspects of radiation exposure management through training and exercises
- To help coordinate the medical response to radiation events
- To provide comprehensive evaluation and treatment for victims at participating centers

The RITN collaborates with the Department of Health and Human Services and the Assistant Secretary for Preparedness and Response to ensure coordination following a mass casualty marrow toxic incident that would require their involvement in a national response. The RITN has developed ARS Treatment Guidelines and Referral Guidelines for local hospitals that receive individuals who show early signs of ARS [38]. In addition, the RITN has, in collaboration with staff managing the Radiation Emergency Medical Management (REMM) website, developed treatment orders for adults and children [33].

The RITN estimates that of survivors from an IND detonation, only 1 % of radiation only casualties will be candidates for hematopoietic stem cell transplantation. Approximately 30 % of casualties are expected to require specialized supportive care in an inpatient setting that involves isolation to protect individuals with febrile neutropenia. Finally, nearly 70 % of casualties are expected to require ambulatory care for treatments such as administration of cytokines and antimicrobials, serial assessment of the CBC, and calculation of the absolute lymphocyte count [39].

RITN medical staff are specialists in hematology and oncology who have daily experience in treating patients with hematologic signs and symptoms that characterize HS. Hospitals that participate in RITN have established standard operating procedures (SOPs) for managing mass casualties. They coordinate locally with emergency management personnel and public health officials and conduct annual training and exercises to constantly improve their level of preparedness.

Cutaneous subsyndrome (CS). Injury to the skin and subcutaneous tissues is highly dependent on localized radiation dose [40–42]. At 3–4 Gy, transient epilation occurs (CS-1). At 6–10 Gy, persistent erythema (CS-2) may occur. The degree of erythema may wax and wane and must be distinguished from an early or prodromal erythema that disappears during the latent period. This prodromal erythema should not be confused with the persistent erythema found in the manifest illness phase of the CS at doses of 10–15 Gy. At higher doses, moist desquamation and ulceration (localized dose of 20–25 Gy) and blisters and bullae (CS-3, localized dose of >30 Gy) are observed. Damage to subcutaneous tissues (CS-4) is highly dependent upon the type and energy of the radiation as well as the duration of irradiation.

Management of CS includes topical steroids, topical antihistamines, and topical antibiotics [43]. Systemic steroids are not recommended, unless there is another indication for their use. Ulcers, necrosis, and intractable pain require surgical excision, skin grafts, and skin flaps [44]. Intractable pain from compression of cutaneous nerve bundles has been successfully treated by local infusion of mesenchymal stem cells [45]. Adipose-derived and bone marrow-derived stem cells are showing promise as treatment for radiation-induced tissue injuries but still lack long-term follow-up for possibilities of genomic instability and malignant transformation [45–47].

Gastrointestinal subsyndrome (GS). The GS may be seen at doses as low as 1 Gy (100 rad). Only the prodromal phase of mild anorexia, nausea, vomiting, and diarrhea is seen at doses of <1.5 Gy (100–150 rad, GS-1 and GS-2) [48]. At doses of >5 Gy (500 rad), damage occurs to stem cells of the small intestine that are found in crypts at the base of microvilli. The GS is manifest by severe nausea and vomiting within 30–60 min of exposure at these doses (GS-3 and GS-4) [23, 24]. These findings may be accompanied over time by hematemesis, hematochezia, fluid and electrolyte shifts, hypovolemia with eventual renal failure, and cardiovascular collapse.

Sloughing of the lining of the GI tract removes the barrier to bacterial translocation from the intestinal lumen to the bloodstream. Bacterial translocation occurs at a time of immunocompromise from neutropenia and lymphopenia, predisposing to sepsis [49]. If the HS is not appropriately treated, death will almost certainly ensue from the GS.

Management of the GS includes antimicrobial prophylaxis and therapy to achieve therapeutic drug levels (rather than bowel decontamination), replacement of fluids and electrolytes, bowel decontamination (with concomitant systemic antibiotics), loperamide to control diarrhea, and a serotonin receptor antagonist to control emesis [43].

Neurovascular subsyndrome (NS). Also known as the cerebrovascular syndrome, the NS typically occurs at radiation doses that are not compatible with life. Acute, irreversible neurotoxicity occurs at whole-body doses of >10 Gy (1000 rad) (NS-2, NS-3, and NS-4). Signs and symptoms include disorientation, fever, ataxia, headache, neurologic deficits, seizures, and coma. At lower doses (3–4 Gy), a milder form of NS consisting of mild headache, limited vomiting (once daily) and tachycardia without fever, hypotension, or neurological deficits (NS-1) may occur as well. Management of typical NS includes symptom control and supportive care for the patient and family. Administration of a serotonin receptor antagonist, mannitol, furosemide, antiseizure medications, and analgesics is recommended, as needed on an individual basis [43].

Other considerations. Involvement of the tracheobronchial tree and lungs is observed at 1–6 months following exposure to a high radiation dose [50]. Edema and leukocyte infiltration of the lung parenchyma occur during the initial day to week after exposure. An acute exudate occurs after 1–3 months, followed by collagen deposition and fibrosis after months to years. Delayed pulmonary involvement may simulate acute respiratory distress syndrome (ARDS) from any cause

with similar morbidity and mortality approaching 100 %. Interstitial pneumonitis accompanied by a restrictive ventilatory defect may lead to death. Management of respiratory failure includes ventilator support with a lung protection strategy, using the lowest possible inhaled oxygen concentration to maintain an arterial oxygen saturation of >90 % [43]. Radiation damage may occur in other organ systems, including the renal, vascular, and cardiac systems. Multiorgan failure (MOF) can be an intermediate- to long-term complication of radiation exposure with significant morbidity and mortality. Vigilance for damage to other organ systems must be maintained throughout medical care. The pathophysiology of MOF is likely complex and remains poorly understood [51]. Its management includes prolonged mechanical ventilation and hemodynamic monitoring [52].

Internal contamination. Internal contamination with radioactive materials is a medical toxicology issue, that is, the management of a poisoning, which is extremely complex. The potential for possible internal contamination with radioactive materials is a matter of emergency, or at least urgent, concern because treatment for internal contamination may need to be initiated *within hours* after the contaminating incident. Following an R/N incident, medical toxicologists and/or the Radiation Emergency Assistance Center/Training Site (REAC/TS; 24/7 emergency phone, 865-576-1005) to assist with management of internal contamination with radioactive materials should be involved.

Summary

A myriad of specialists, especially those well versed in hematologic abnormalities, will be required for any significant ionizing radiation to the whole body or a significant portion thereof because of the potential for injury to circulating WBCs or the bone marrow. In fact, inappropriate management of the HS will almost certainly result in elevated morbidity, if not mortality from the HS itself or damage to other organ systems. The manifestations of immunologic incompetence including the spectrum of infectious diseases must be treated properly in order to improve patient survival. Practitioners must be also vigilant for multiple organ dysfunction/failure secondary to ionizing radiation exposure.

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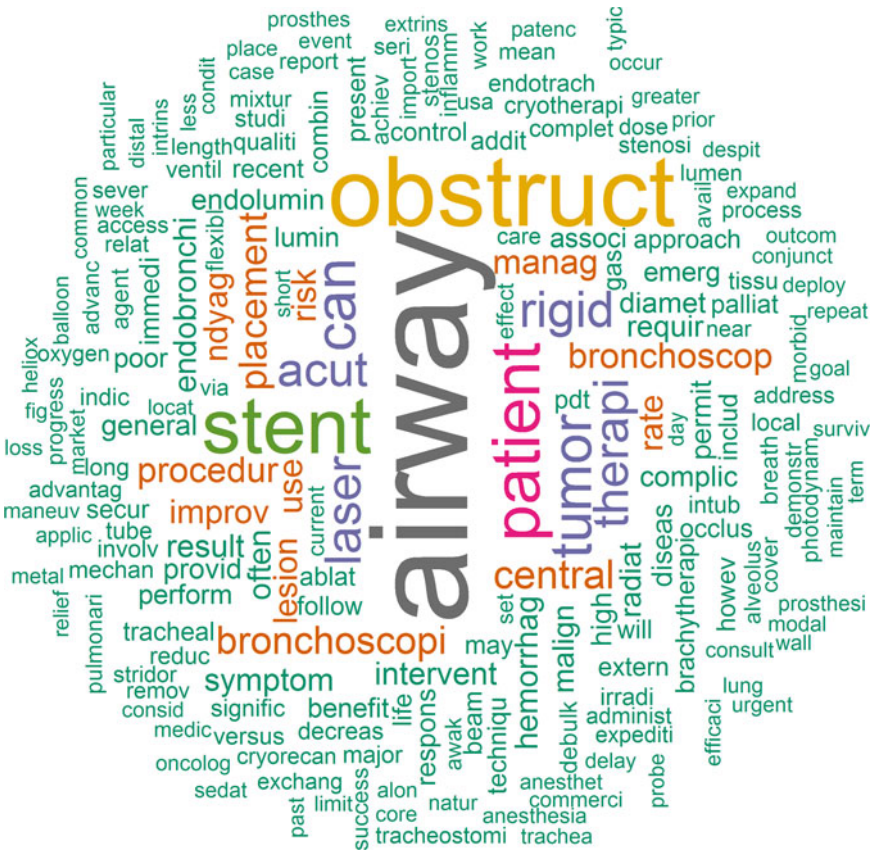
Part III

Evaluation and Treatment

Emergent Management of Acute Airway Obstruction from Malignant Disease

Brittany L. Powell and Pierre R. Theodore



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Introduction

Acute obstruction of the airway in the emergent situation results from a wide variety of malignant and benign disease processes. However the acute management of obstructive conditions of the airway can be summarized as establishing a secure and patent route for adequate gas exchange. The most expeditious means to this end is a function of the location of the obstruction and the nature of the obstruction. Difficult anatomy, hemorrhage, dense secretions, or inflammation can significantly complicate the task of clearing the airway. Obstruction of the central airways by the tumor is associated with poor prognosis. For the patient and clinician alike, the presentation can be frightening, and advanced interventional pulmonary/endobronchial techniques may be required to achieve prompt palliation. The alleviation of central airway obstruction by the tumor is generally palliative, with the principle goal of improving quality of life rather than cure, and thus a thorough discussion of risks and benefits of intervention and individual patient goals of care should occur whenever possible. This chapter will cover an approach to the patient with airway obstruction that results from malignancy involving the trachea or proximal bronchial tree, affecting gas exchange.

Of the roughly 200,000 new cases of lung cancer per year in the United States, an estimated 30 % will develop clinically evident endoluminal disease. A fraction of these patients develop central airway obstruction [1, 2].

Central airway obstruction is often separated into divisions of endoluminal versus extraluminal versus mixed obstructions (see Fig. 1). The nature of the obstruction governs the use of stent versus endobronchial tumor resection or a combination of both approaches. Generally the diagnosis of intrinsic versus extrinsic obstruction can only be made via expert bronchoscopy, though high-resolution CT scans often suggest endoluminal disease. Biopsy of critically narrowed airway processes is to be undertaken with great caution as inflammation or hemorrhage can result in complete luminal compromise (see Fig. 2).

Symptoms of Airway Obstruction

Shortness of breath is often a chronic symptom associated with tumors of the lung. However, in greater than 50 % of patients with central airway stenosis, stridor and tachypnea often result. A tracheal diameter reduced to 8 mm by obstruction will usually cause exertional symptoms, progressing to

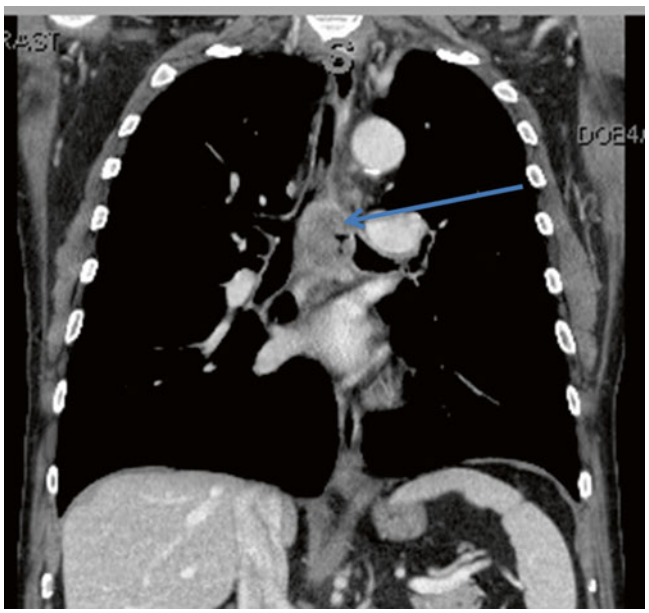


Fig. 2 Coronal image of mixed intrinsic-extrinsic central airway obstruction from mid-esophageal squamous cell carcinoma (arrow marks obstruction)

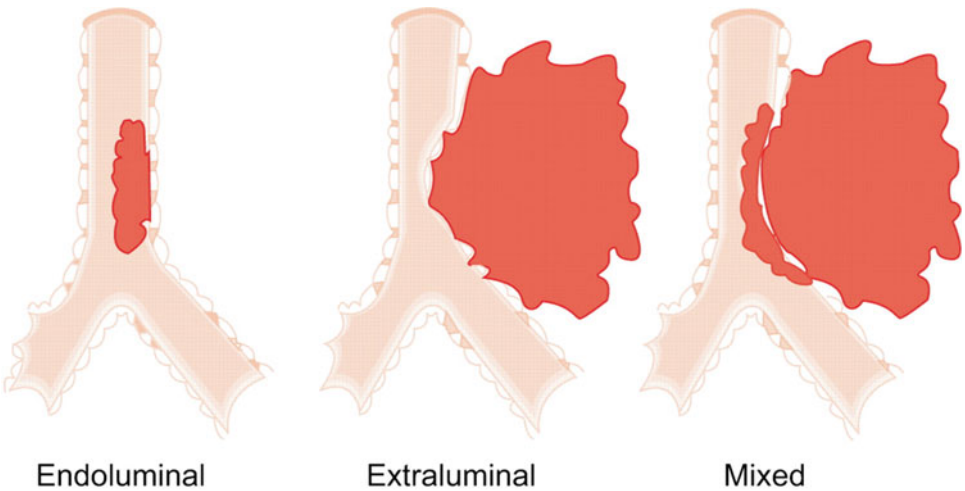


Fig. 1 Categories of central airway obstruction: endoluminal (1), extraluminal (2), and mixed (3) obstruction of the trachea and proximal bronchi. [This material has not been reviewed by the European Respiratory Society prior to release; therefore, the European Respiratory Society may not be responsible for any errors, omissions, or inaccuracies or for any consequences arising therefrom, in the content. Reproduced with permission of the European Respiratory Society ©: European Respiratory Journal Jun 2006, 27 (6) 1258–1271; doi:10.1183/09031936.06.00013906]

stridor when the lumen is reduced to 5 mm [2]. Stridor occurs when erratic air currents pass through the obstructed tracheobronchial tree resulting in high-pitched breath sounds. The effect is generally most marked on inspiration and can progress to near complete obstruction as a result of infection, inflammation, or aspiration event. Additionally malignant central airway obstruction can produce dyspnea, hemorrhage, or obstructive pneumonia or a combination of all the above and is considered a medical emergency.

When the specialized care required for stent placement is unavailable and the patient is in jeopardy of progression to complete obstruction, fiber-optic awake intubation with a smaller diameter (5-0 or 6-0 French) wire-reinforced endotracheal tube is the most expeditious means of securing the airway. Repeated attempts of direct laryngoscopy and orotracheal intubation are to be discouraged due to the risk of inflammation and hemorrhage. Awake endotracheal intubation permits image-guided access to the airway with minimized trauma to the upper airway. Once access beyond the obstruction is gained, the patient may be sedated by inhalational or intravenous anesthetic agents. Urgent transfer to a center with interventional pulmonary and thoracic oncology services or consultation follows.

Heliox

Helium-oxygen ("Heliox") mixtures have been used in upper airway obstruction, primarily as a bridge to obstruction removal without adverse associated events. Administering this gas mixture works to decrease the work of breathing, decrease airway resistance, and increase delivery of oxygen to the lungs [3, 4]. The lower density of helium gas contributes to these ends, and the recommended mixture, administered by face mask, is dependent on the predominant problem, hypoxia or hypercarbia. If the patient is primarily suffering from hypercarbia, an 80 % helium mixture should be used. For hypoxia, oxygen delivery should be maximized by using 100 % oxygen [5]. Heliox can be used as an alternative to invasive procedures when they are too dangerous or impossible to perform due to characteristics of the obstruction, for example, higher-grade blockage, involvement of neck soft tissue, distance to obstruction, and tracheal deviation [4].

Rigid Bronchoscopy

Rigid bronchoscopy is an indispensable tool of the surgeon or advanced interventional pulmonologist for the management of acute airway obstructive phenomena that result from tumors, foreign body, or hemoptysis. The rigid instrumentation required for access to the trachea and proximal airways is not well tolerated by the awake patient and requires general anesthesia. Furthermore, the hemodynamic alterations in heart rate and blood pressure reflecting the autonomic response to rigid bronchoscopy mandate close monitoring and management. Gas exchange with the rigid bronchoscope despite high-pressure "jet" ventilation can be poor. For these reasons, most surgeons prefer to perform rigid bronchoscopy in an operating room or dedicated bronchoscopy suite with an attentive anesthesia staff. Our preference is for muscle relaxant to be provided to the patient to facilitate placement of the rigid bronchoscope into the airway. Generally a standard endotracheal tube $\geq$7.5 French is advanced into the airway and secured to the skin to permit an unpressured evaluation of the lesion or obstructive process with flexible bronchoscopy. Rarely, the rigid bronchoscope is required to establish a patent airway as the first maneuver.

Generally after induction of anesthesia with an IV agent coupled with a muscle relaxant, the patient is maintained on an IV sedative infusion (i.e., propofol) as the seal of the cuffless rigid bronchoscope is poor and loss of inhaled anesthetic is common.

As a practical measure, connections, light sources, and compatibility between the rigid bronchoscope and the jet ventilator should be assured before commencing the procedure.

Atlantoaxial (C1–C2) subluxation is a concern in patients with inflammatory conditions of the spine (rheumatoid arthritis) or congenital atlantoaxial ligamentous laxity (e.g., in trisomy 21). In patients considered at high risk for cervical spine dislocation, particular caution should be exercised in introducing the rigid scope to the airway and during manipulations during the procedure, and patients and families should be apprised of the risk of spinal cord trauma.

At the conclusion of the procedure (laser ablation, mechanical coring out of lesions, or stent placement), the patient is typically reintubated with a standard endotracheal tube and weaned from the ventilator as tolerated. Several recent series have demonstrated the safety and efficacy of rigid bronchoscopy in the management of central airway occlusion from malignant disease, which is at present our strategy of choice for acute and emergent management. Despite the lack of level I evidence in support of the practice, patients are typically administered 30 mg/kg of methylprednisolone (Solu-Medrol) steroid IV to help mitigate inflammation in the airway as a consequence of the abrasive rigid bronchoscope manipulations.

Nd:YAG Laser Therapy

Several large series have convincingly demonstrated the safety and efficacy of neodymium-yttrium-aluminum-garnet (Nd:YAG) laser photoradiation since introduction in the 1980s [6]. With a principal aim of palliation, Nd:YAG laser is capable of both vaporization of obstructing tissue and

maintaining hemostasis. With the laser set at between 20 and 50 W with 2–4 s of pulses applied to the tumor bulk, the luminal diameter can be restored following removal of any chunks of tumor remaining in airway after laser application is complete. We have chosen to perform laser ablation in conjunction with rigid bronchoscopy. The rigid bronchoscope gives ready access for manual tumor debulking or tamponade of bleeding. A flexible bronchoscope can be placed through the RB permitting precise guidance of the laser tip. Major morbidity and mortality associated with the use of the laser are infrequent. Perforation of the airway, hemorrhage, and respiratory failure with inability to wean from the ventilator have been described [7]. The immediate results are generally gratifying with the majority of patients describing improvement [8]. In cases in which urgent clearance of the airway is required, Nd:YAG laser in combination with rigid bronchoscopy provides the most immediate reestablishment of sufficient airway luminal diameter.

Airway Stenting

Indications for acute placement of an airway stent are summarized below.

Airway stents can provide significant benefits beyond laser fulguration alone. For central airway obstructions from intrinsic (intraluminal) lesions, an airway stent is most commonly deployed in concert with Nd:YAG sessions [9]. Stents are classified as metallic or silicon based and covered or non-covered (see Fig. 3). Virtually all current commercially available airway stents are self-expanding. However endoluminal balloons can be of benefit in expanding tightly stenosed airways prior to stent deployment.

The US Food and Drug Administration (FDA) has approved the synthetic polymer Polyflex™ stent (Rüsch, Kernen, Germany). Additionally, Nitinol composite stents, Ultraflex stents (Boston Scientific), and Alveolus stents (Alveolus Inc, Charlotte, NC, USA) have garnered the market's largest share (see Fig. 4). The latter-generation covered wall stents provide considerable advantages over previous uncovered stents including less rapid in-stent stenosis and application in smaller airways [11]. Polyflex™ stents do not have studs outside, so they are more prone to migration. Thin, self-expanding wall stents currently marketed include Ultraflex stents (Boston Scientific) and Alveolus stents (Alveolus Inc, Charlotte, NC, USA), which both have thin polymer membranes. Recent reports support the concept that airway stenting for obstructive airway lesions results in improved quality of life with acceptable rates of morbidity. 80–90 % of patients with tumor-related airway stenoses reported relief of symptoms with stent placement [12].

Airway stenting generates no consistent improvement in pulmonary function tests (PFTs), but patients report improved symptoms and decreased work of breathing. These outcomes are most pronounced with treatment of tracheal lesions, with decreased benefit from addressing stenoses of main stem bronchi [13, 14]. If postobstructive atelectasis has persisted greater than 2 weeks, it is unlikely that stenting will achieve significant re-expansion. If the obstruction is acute, or there is greater than 50 % stenosis, airway loss can be life-threatening; in these cases it is often more prudent to intubate distal to the lesion and perform therapeutic pulmonary toilet before addressing the principal stenosis (Table 1).

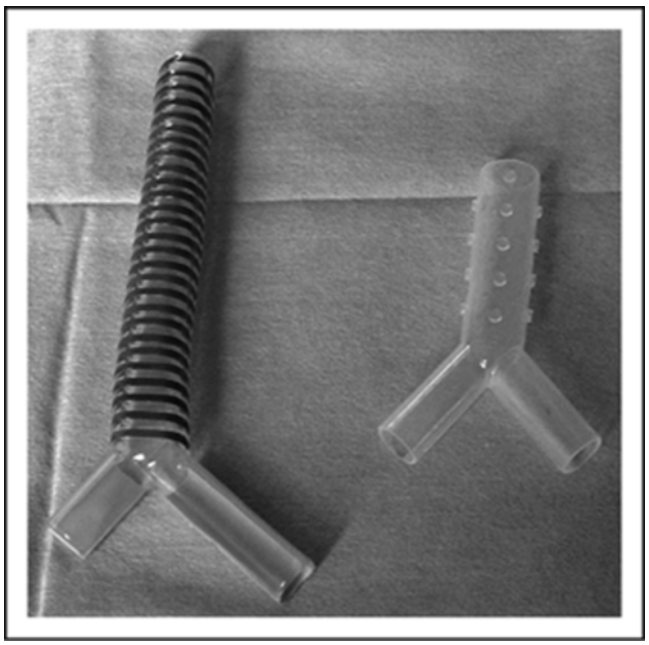


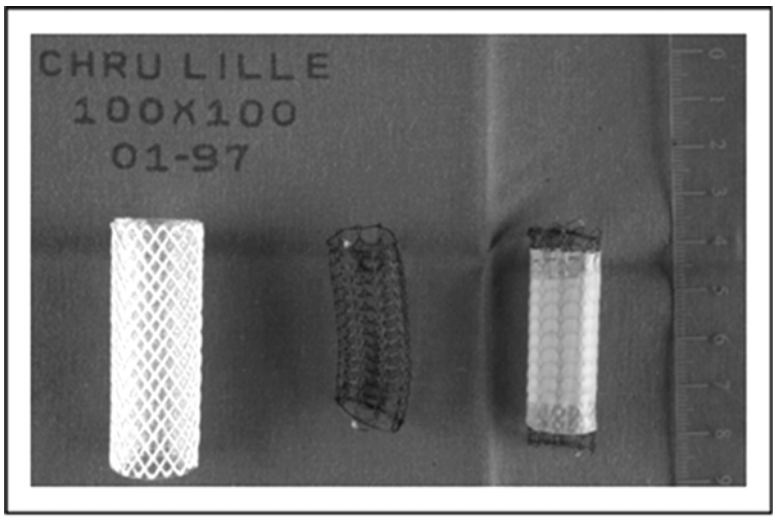
Fig. 3 Hybrid and silicone (Dumon)-based stents [10]. [Reprinted from Ref. 10 with permission from Elsevier]

Lesions that are at risk for acute restenosis after debulking or extrinsic lesions not associated with transmucosal endoluminal disease are often well managed with stent placement. Stents of decreasing diameter have recently been approved by the US Food and Drug Administration, but the role of more distally placed airway stents is not clear.

Stents are classified as metallic or silicon based and covered or non-covered. Virtually all current commercially available airway stents are self-expanding. However endoluminal balloons can be of benefit in expanding tightly stenosed airways prior to stent deployment.

The only absolute contraindication to stent placement is extrinsic compression from an aneurysmal vessel as stent placement is associated with an unacceptable risk of erosion into the adjacent vessel with catastrophic hemorrhage.

Complications of stent placement are encountered in the acute and long-term setting. The overall mortality from acute stent placement is very low and typically related to acute loss of airway control from hemorrhage or rarely from an acute



From left to right: totally covered nitinol stent, uncovered and covered ultraflex stent.

Fig. 4 Nitinol and Ultraflex stents. [Reprinted from Ref. 10 with permission from Elsevier]

Table 1 Indications for central airway stents [15]

• Airway obstruction from intrinsic or extrinsic compression in patients with disease or comorbid ailments precluding surgery
• Tumor in growth despite frequent laser treatments
• Adjunct to laser or photodynamic therapy to maintain lumen patency after treatment
• Loss of cartilaginous support
• Treatment of tracheoesophageal fistula
• Relief of postobstructive pneumonia for better cancer staging; may permit parenchyma-sparing surgery
• Relief of postobstructive pneumonia in septic patient allowing for inclusion in chemotherapy protocols

Table 2 Complications from stent placement

Procedural	Immediate	Long term	Related to metallic stent removal
Malpositioning	Bleeding	Migration	Retained stent pieces
Perforation of tracheobronchial wall	Migration	Retention of secretions	Mucosal tear
Surgical emphysema	Retention of secretions	Infection	Reobstruction requiring silicone stent
Tension pneumothorax	Infection	Granulation tissue	Need for postoperative mechanical ventilation
	Obstruction of bronchial orifices	Metal fatigue	Tension pneumothorax
	Pneumoperitoneum	Halitosis	

tear of the airway resulting in an inability to ventilate the patient [16]. Laser ablation and coring out of lesions via rigid bronchoscope prior to stent placement can be associated with hemorrhage in the short term. By contrast over the longer term, complications from stent placement are quite common as outlined in Table 2 and include migration, infection, or granulomatous tissue further compromising the luminal diameter. Mechanical insufficiencies of the stents have been reported. Granulation tissue encroaching on the lumen can often be managed with repeated laser ablation and balloon dilation.

Tracheostomy with Wire-Reinforced Long-Length Prosthesis

Several commercially marketed tracheotomy prostheses are available (Smiths Medical, St. Paul, MN, USA; Cook Medical, Bloomington, IN, USA) which are of long or adjustable length permitting passage of a secure airway past tracheal obstructions and can be indispensable in urgent situations. The prostheses (i.e., "Bivona tubes") are often wire reinforced to resist the radial compressive force of luminal tumor or paratracheal mass. The long segment tubes can be placed even in awake, sedated

patients with adequate local anesthetic followed by tracheostomy and expeditious bronchoscopic guidance past tracheal obstruction. Adjustable prostheses are particularly useful as the length can be tailored to terminate just above the carina. This approach provides adequate luminal diameter (6–8 F) until more definitive therapy such as external-beam irradiation or indwelling tracheal stent placement can be performed. Such long tracheostomy prosthetics are limited in application to stenoses of the trachea and can permit emergent stabilization of an impending airway occlusion. Conditions such as anaplastic thyroid cancer with airway involvement in which prognosis is poor can often be addressed with this palliative maneuver.

External-Beam Radiation Therapy (EBRT), High-Dose Endobronchial Brachytherapy, and Photodynamic Therapy (PDT)

Several less invasive modalities have been adopted recently for management of tumors obstructing the central airways.

High-dose endobronchial brachytherapy in conjunction with other modalities may provide an important adjunct to endoluminal laser ablative therapies. Speiser and Spratling have presented their series of over 250 patients treated with endobronchial radiation therapy with a 60–90 % rate of response. The response rate, however, comes at a cost of a near 15 % risk of major complication including radiation-induced pneumonitis and major hemorrhage [17].

Endobronchial brachytherapy iridium 192 via remote afterloading as introduced by Henschke has shown promise in reducing the complications of direct interstitial implantation of radioactive seeds [18, 19]. The response rate is high with good symptomatic improvement and radiographic resolution of postobstructive atelectasis. The response is durable with low recurrence rates within 6 months after completion of therapy. While the response rate is high, the use of endobronchial radiation therapy alone fails to address the acute mechanical obstructive symptoms, and therefore as a monotherapy it is inadequate. Combination of laser fulguration of tumor followed by endobronchial irradiation permits immediate relief of obstruction in addition to a measure of local control of tumor.

PDT

Photodynamic therapy uses a photosensitizing agent (Photofrin®) which when administered intravenously is selectively retained within tumor cells. The agents are activated upon exposure to a light of proper wavelength generating cytotoxic oxygen radicals which lead to tumor necrosis. PDT has been used for obstructing lesions of the central airways that are not at immediate risk of airway occlusion. The advantage of PDT is that for submucosal isolated tumors of the airway in patients who are poor candidates for operation, satisfactory local control can be achieved. In addition to laser and rigid bronchoscopic relief of airway obstruction, PDT as an adjunct can prevent or delay reocclusion.

External-Beam Radiation Therapy and Multimodal Therapy

Two older studies [20, 21] of external-beam irradiation or brachytherapy in conjunction with Nd:YAG laser for patients with central airway occlusion from malignancy demonstrate improved median survival versus Nd:YAG therapy alone. More recent work with modern techniques demonstrates response rates to external-beam radiotherapy of nearly 80 % [22]. It is important to note that patients with airway obstruction may present with acute symptoms that require near immediate intervention and thereby not be good candidates for delay in therapy required for consultation, planning CT scans, and elective radiotherapy. These data suggest that combination therapy at a center experienced in both endobronchial techniques and thoracic radiation oncology can achieve improved rates of local control and survival. Tumor debulking or "coring out" of tumor can be carried out mechanically by the blade of the rigid bronchoscope in combination with Nd-YAG laser for hemostasis. Brachytherapy is delayed for 2–4 weeks after laser debulking, and three afterloading sessions at weekly intervals are performed with an endobronchial irradiation dose of 5 Gy per session. While procedural morbidity was low, an extension of survival in patients with a central invasive tumor may partially explain an increased risk of fatal hemoptysis with this approach.

Cryotherapy and Cryorecanalization

Cryotherapy involves the use of extreme cold on the tip of a rigid or flexible probe to induce tumor necrosis (see Fig. 5). Often a repeat procedure is indicated for later retrieval and removal of the tumor from the airway. Retrieval of tumor tissue is performed 5–10 days post-cryotherapy, so this procedure may not achieve immediate lumen recanalization. The technique utilizes nitrous oxide as the freezing agent, delivered to the tip of the probe via a fiber-optic bronchoscope [24].

Cryotherapy has the advantages of being technically less complex than some of the other tumor debulking methods, with a reduced risk of wall perforation, thus eliminating some more serious complications of other techniques. However, in the acute airway emergency, cryotherapy is not favorable because it requires a series of procedures [25]. Generally for tumors that have progressed in obstruction but do not present as an acute emergency, or for maintenance of airway patency, cryoablation provides an additional effective option.

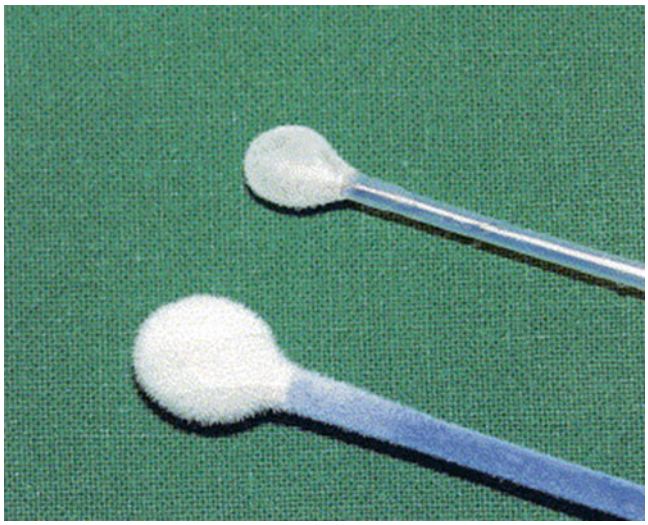


Fig. 5 Cryotherapy probe (*back*) and cryorecanalization probe (*front*) [23]

A relatively new advent to the repertoire of tools for alleviating acute airway obstruction is cryorecanalization, which is an effective solution to the acute airway obstruction. This method uses an updated probe designed to cryogenically freeze the tumor in the airway and subsequently remove the mass in the same procedure. Advancements in cryoprobes over the past decade have lowered the burden of second "cleanup" procedures following cryorecanalization [23]. Efficacy of cryorecanalization is related to many factors, which should guide patient selection for this type of intervention. In a recent retrospective study of 40 cryorecanalization procedures, distal involvement and obstruction age (from the first day of obstruction to the day of intervention) were shown to be indications for success [26]. 72.5 % of the procedures were successful. Notably, this study and another study [23] from 2003 found that location of the tumor was not identified as a predictor of success, as success rates for the Nd-YAG laser modality have been.

Complications in cryorecanalization include hemorrhage and bronchial wall damage [23, 26]. While immediate airway patency is a purported advantage and cryorecanalization is an alternative to heat ablative therapies, few outcomes studies have been published in comparison to other therapies for central airway obstruction [2, 4, 6, 7, 10, 14, 16, 17, 24, 26–45].

Conclusion

Central airway occlusion, occurring in roughly one-third of all patients with intrathoracic malignancies, is a significant source of morbidity and poor quality of life. The symptoms of stridor, shortness of breath, and limitation of physical exertion are indications for palliative maneuvers and procedures. The urgency of the clinical scenario dictates the approach to the disease. In patients with stable airways, CT scanning and MRI permit careful planning such as type and length of stent or the feasibility of external-beam irradiation. Flexible bronchoscopy can permit the most careful evaluation of the airway, but definitive therapy should be planned to limit the number of manipulations of the tenuous airway. For patients presenting with acute life-threatening central airway occlusion, obtaining a secure airway expeditiously remains the cornerstone of management. Such patients should be offered intubation in a controlled setting (the OR being ideal) with available rigid bronchoscopy. Mechanical coring out of the airway lesion and placement of a secure endotracheal tube is the most rapid means of restoring a satisfactory lumen. In patients that have a sufficient luminal diameter and intrinsic tumor, Nd:YAG laser is the approach of choice to vaporize and reduce the obstruction. For incompletely resolved airway obstructions or those at high risk for recurrence, stent placement, particularly self-expanding metal stents, is an effective means of maintaining patency despite the adverse events sometimes encountered. Endoluminal high-dose radiation therapy and brachytherapy have the additional benefit of treatment of tumor with potential longer-term local control and should be considered in consultation with radiation oncology colleagues. While long-term outcomes of patients with malignancy-related airway obstruction are poor, the majority (80 %) will have symptoms significantly improved by surgery. This improvement related to quality of life provides the rationale for thorough thoughtful management of central airway obstruction.

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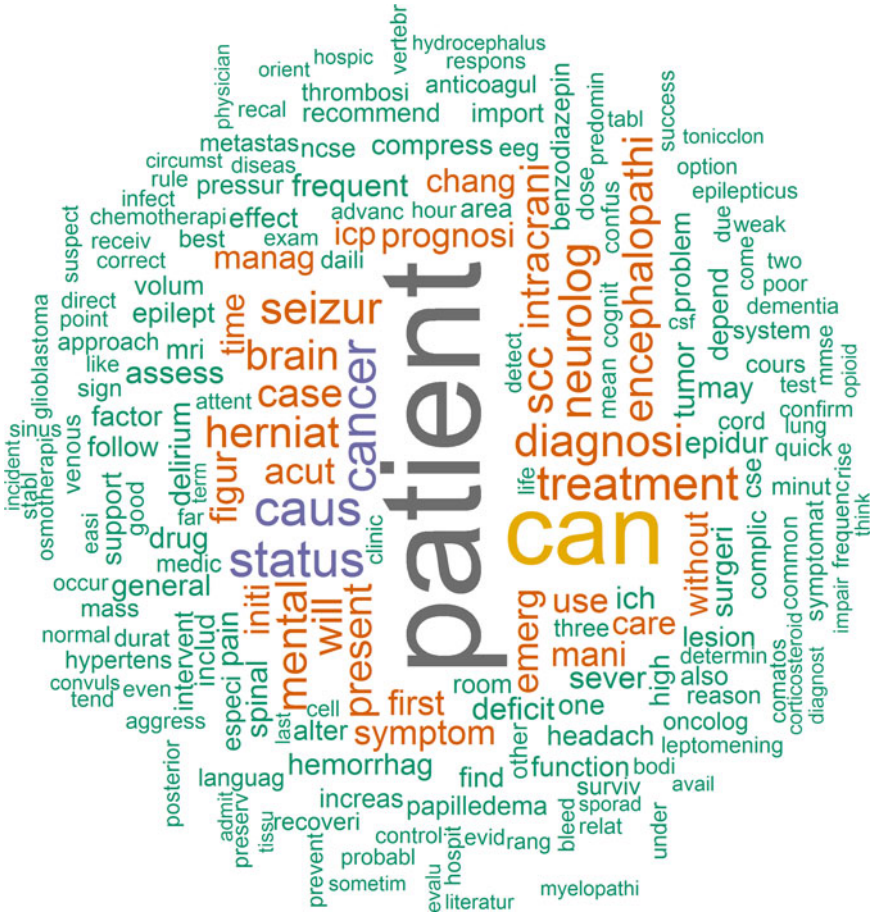
Oncologic Emergencies of the Central Nervous System (CNS)

Ivo W. Tremont-Lukats and Sudhakar Tummala



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Approach to the Patient with Acute Change in Mental Status

Background and Terminology

The term *mental status* applies here to a state of wakefulness in alert persons. Changes in this mental status can also affect cognition, including orientation to self, place, and time; the ability to register and recall objects (memory registration and recall after minutes); the ability to understand and execute more complex commands such as backward spelling or arithmetic operations (attention/concentration), and language. Changes in mental status can occur in a patient with a mental function considered as normal or within a range of normality or can appear against the backdrop of a more chronic cognitive disorder such as dementia or mental retardation. In the medical literature and in our daily medical jargon, altered mental status (AMS); changes in mental status; confusion; encephalopathy, and delirium are used interchangeably. The first three predominate in daily spoken and written language and in general highlight the symptom. Encephalopathy and delirium are more relevant as diagnostic keywords, with delirium being in use far more frequently in the medical literature. For the rest of this chapter, we will use **delirium or encephalopathy to designate any acute change in arousal and mental function in a patient with cancer**.

Frequency

Altered mental status is a powerful driver to use emergency services. Of 154 patients admitted to the emergency department (ED) at the University of Texas M.D. Anderson Cancer Center (UT-MDACC), altered mentation was the chief complaint in 22 of them (14 %), after pain, nausea/vomiting, and dyspnea [1]. It was also the fourth chief complaint among 283 patients with cancer who died in the emergency departments, accounting for 14 % of these deaths [2]. In institutions with advanced cancer patients, up to 84 % of patients can be encephalopathic [3]. AMS was the second most frequent reason for a neurology consultation at the Memorial Sloan Kettering Cancer Center (MSKCC) [4], and it has been from 2009 to 2015 the most frequent reason at UT-MDACC.

Causes

Most patients with cancer have more than one reason to have encephalopathy. The most relevant causes to bear in mind in the ED assessment are in Fig. 1. The first three suspects to think about and investigate are **drugs, infection, and organ failure** [5]. Opioids and benzodiazepines are by far the most common drugs responsible for a toxic encephalopathy in the ED, in the recovery rooms, and in hospitalization areas. Obviously the relative effect of drugs cannot be quantified since many patients have renal or liver impairment and other contributory factors. Chemotherapy can also cause acute encephalopathy (Table 1), and some of these drugs have been linked to the posterior reversible encephalopathy syndrome (PRES) [6]. Physicians caring for cancer patients in the emergency departments should think about PRES if symptoms and findings (confusion, headaches, cortical blindness, seizures, and hypertension) point to that diagnosis [7] and especially if patients are on chemotherapy and immunosuppressive drugs, notably cyclosporine, tacrolimus, or sirolimus [7–9].

Assessment

Two elements are key in the diagnosis of encephalopathy: the first is the acute onset, in terms of minutes or hours; the second is the *fluctuating* course in attention levels. Thus, the clinical diagnosis is easy in most cases. There are several instruments to assess the mental status well suited to cancer patients [10–15]. The mini-mental state examination (MMSE) [16] is easy to learn and to use and can quickly detect a patient with encephalopathy, especially when assessing orientation, recall, and attention/concentration. We quickly screen patients using only these domains of the MMSE to diagnose most patients with encephalopathy. The language domain is useful to evaluate the language function as part of the neurologic exam, but it is generally preserved in encephalopathic patients. For patients with suspected or confirmed dementia or another cognitive impairment, the MMSE cannot sort out what is chronic or acute, and we rely on information by others if available to determine a baseline cognitive function. Our recommendation is not to evaluate dementia in these patients when they are acutely ill or delirious.

Management

Not all patients need all the tests in Fig. 2, but the essential laboratory data and procedures for an adequate diagnosis of encephalopathy and its cause(s) are shown in the two upper dots. The treatment of delirium is supportive, and its resolution depends on the underlying problems; if these complications are controlled or resolved, the encephalopathy may improve and completely disappear. Figure 3 depicts the principles of treatment as outlined elsewhere [17].

Brain Herniation

Principles

The intracranial volume is the result of the sum of the volumes of brain tissue, cerebrospinal fluid (CSF), and blood within a compartment that is rigid (skull) [18, 19].

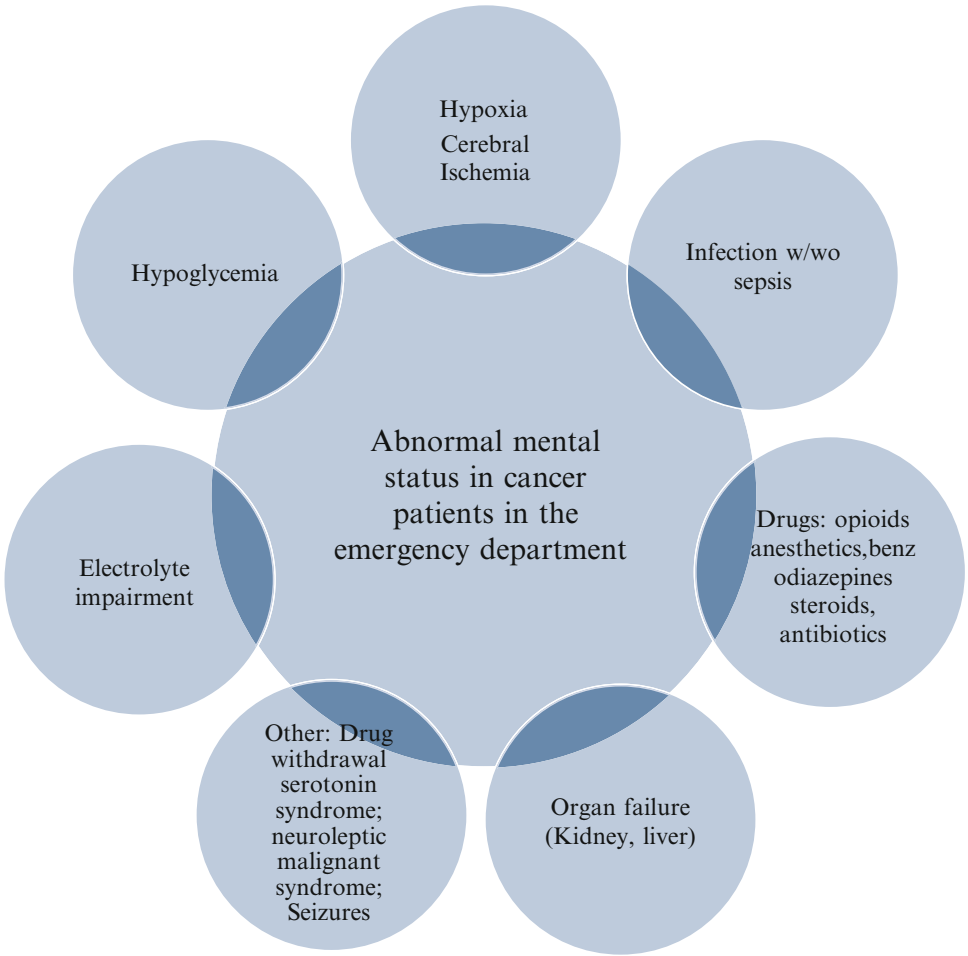


Fig. 1 Differential diagnosis of altered mental status

Table 1 Chemotherapy drugs that can cause acute encephalopathy [8]

Drug	Comment
Methotrexate (high dose, IV or IT)	
Cisplatin	Associated with PRES
l-asparaginase	May also cause acute cerebral ischemia and venous thrombosis
	Associated to PRES
Ifosfamde	Encephalopathy may be similar to PRES
Gemcitabine	Associated with PRES
Cytarabine	Associated with PRES
Bevacizumab	Associated with PRES

PRES posterior reversible encephalopathy syndrome, *IV* intravenous, *IT* intrathecal

This means that changes in relative volumes will not alter the total intracranial volume (Monro-Kellie doctrine). Figure 4a and b illustrate the interplay of these compartments and how an increase in intracranial pressure (ICP) can lead to brain herniation. An increase in ICP is compensated by a shift of CSF into the spinal subarachnoid space and a reduction of blood volume by the cerebral venous system. If the cause of high ICP supersedes these compensatory mechanisms, the intracranial pressure rises and the brain parenchyma can herniate in three directions following a gradient pressure: under the falx (subfalcine herniation), past the tentorium cerebellum (uncal or transtentorial herniation), and past the foramen magnum (tonsillar herniation). Impending brain herniation needs also to be recognized so treatment can be initiated early (Fig. 5a and b).

Causes

In oncologic practice, cerebral edema and an intracranial mass are the main causes of brain herniation syndromes [20]. Any intracranial hemorrhage can behave like a mass and precipitate brain herniation.

Assessment

It is important to bear in mind that not all patients with intracranial hypertension present with the same symptoms and

Fig. 2 Evaluation of altered mental status

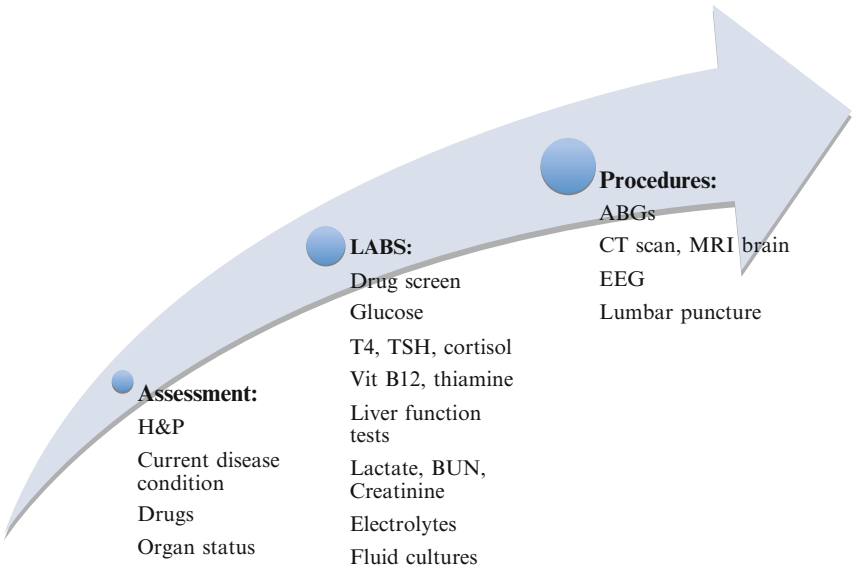
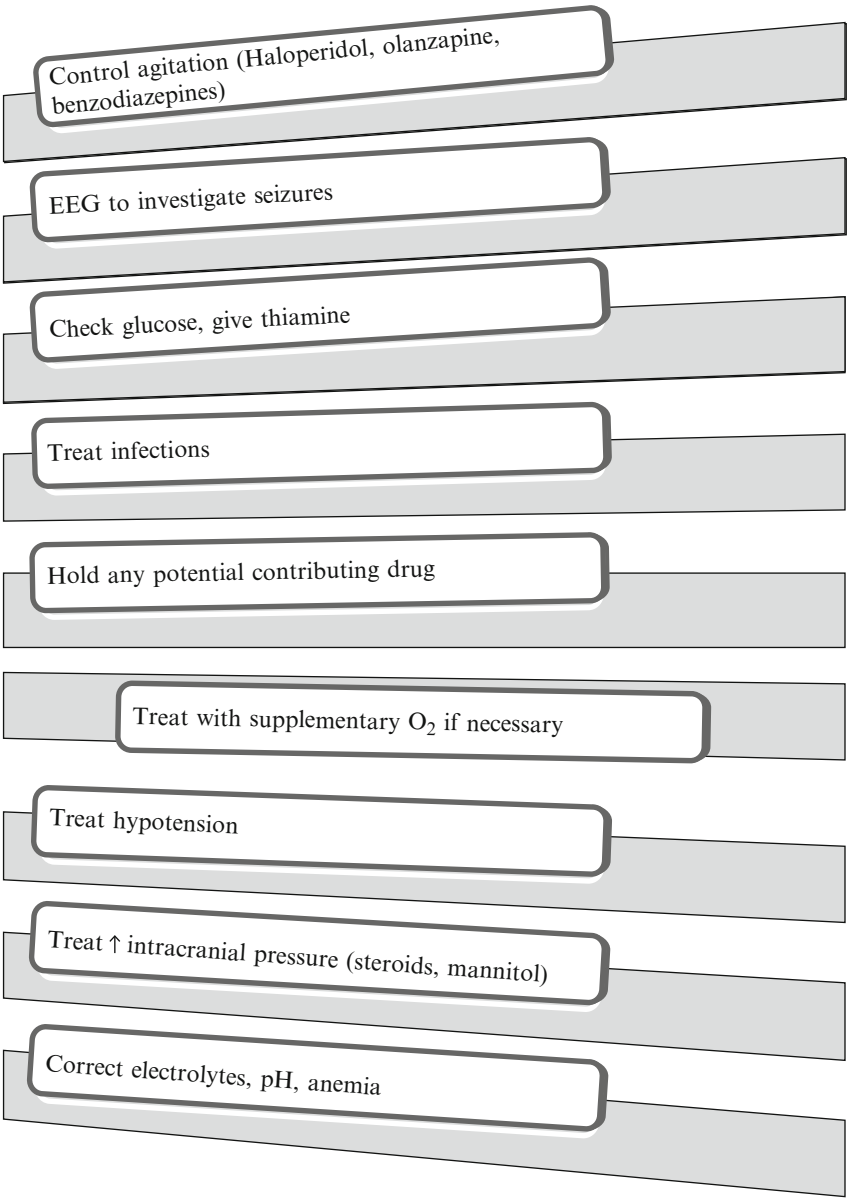


Fig. 3 Treatment of altered mental status



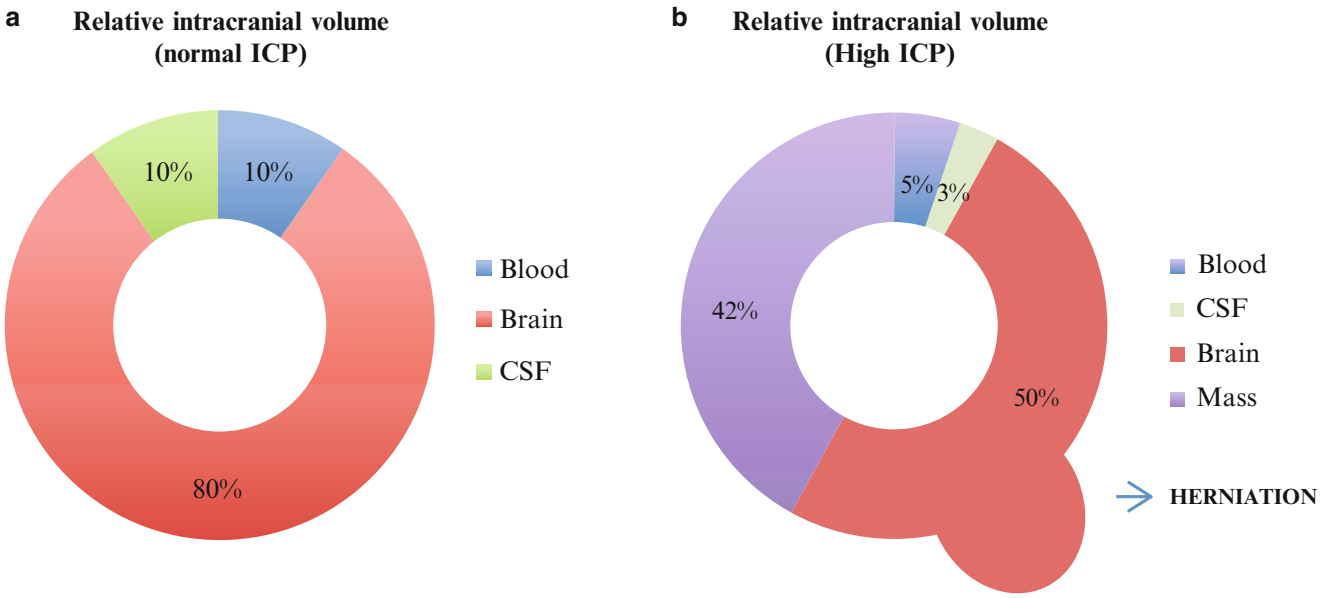
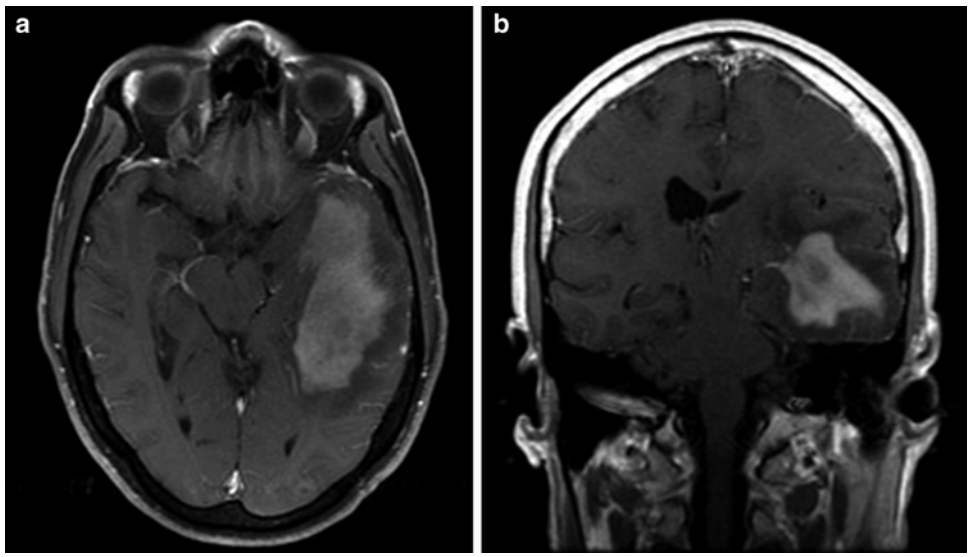


Fig. 4 (**a**, **b**) Relationship between ICP and volumes of brain tissue, CSF, and blood

Fig. 5 (**a**, **b**) Brain herniation



findings; we have seen patients with radiographic evidence of herniation without focal signs, without papilledema, and who are not comatose or even obtunded, as described elsewhere [21]. Others do not have herniation but have mass effect, neurologic deficits, and changes in mental status. In general, **headache, neck pain, altered mental status, or seizures** can be the symptom or symptoms indicating intracranial hypertension. Papilledema is a very useful sign, but not all patients have it, and sadly, very few physicians other than ophthalmologists have funduscopy skills to find papilledema in the ED (Fig. 6). Other patients can present with episodic, acute bursts of neurologic dysfunction that tend to be mistaken for epileptic seizures; many of them have mass lesions or hydrocephalus from leptomeningeal involvement. Such episodes are due to sudden rises in intracranial pressure (*plateau waves*) and last from 1 to 20 min [17, 20] (Table 2).

Management and Prognosis

After a rapid assessment in the ED, the team diagnosis is high ICP with or without brain herniation. The patient may or may not have signs of brain herniation on exam. The specific circumstance will dictate the urgency of interventions.

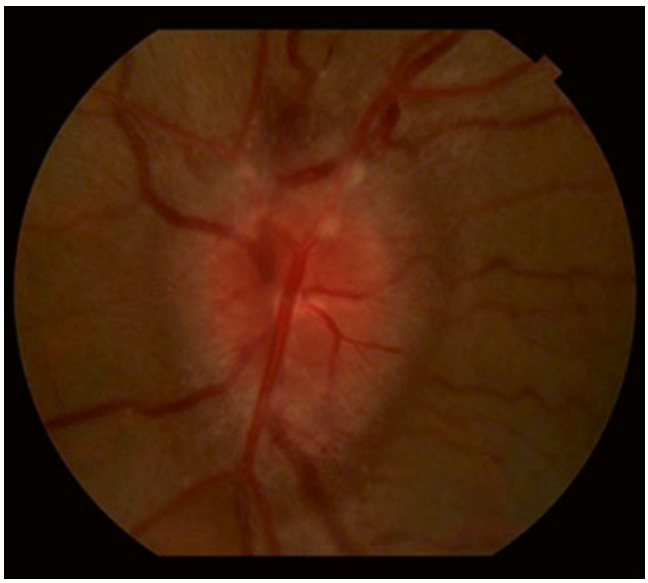


Fig. 6 Papilledema

Table 2 Signs and symptoms associated with plateau waves

Altered consciousness (delirium, stupor or coma)
"Spells" of blank stare (confused with partial complex seizures)
Spontaneous, wide oscillations of blood pressure, respiration, or heart rate
Headache, pain in neck or shoulders
Nasal pruritus
Nausea/vomiting
Facial flushing
Shivering, goose bumps, sweating
Temperature increase
Yawning or hiccups
Opisthotonus
Mydriasis
Weakness of CN III or VI
Nuchal rigidity
Clonic movements of extremities
Decorticate or decerebrate posturing
Bilateral Babinski signs

These episodes are paroxysmal, may last minutes, and frequently are triggered by stimuli such as touch, pain, suction, and positioning (adapted from Ref. [37])
CN cranial nerve

The medical interventions effective in controlling or decreasing ICP in cancer patients depend on the injury responsible for the high ICP and include hyperventilation, osmotherapy, and corticosteroids (Table 3). Hyperventilation most times can be safely done in the intensive care units, although it can be initiated in the ED. Mannitol and corticosteroids can be administered in the ED and in the patient ward. The prognosis of **symptomatic, acute brain herniation in our cancer patients is bad**, with most dying in minutes or hours regardless of cause. If they are resuscitated in the hospital and survive resuscitation efforts, they eventually are unresponsive and comatose in the ICU, and the family later has to withdraw advanced life support. Patients with metastatic or primary tumors and gradual progressive increased ICP have a higher probability to be treated successfully with osmotherapy only, especially steroids, and debulking surgery in the appropriate circumstances [17, 20, 22, 23].

Status Epilepticus (SE)

Definition and Classification

Convulsive status epilepticus (CSE) is a life-threatening emergency [20, 23–25]. Patients have ongoing or intermittent generalized seizures without recovery to baseline. Various convulsive body movements include partial tonic-clonic, generalized tonic-clonic, or predominant tonic posturing or clonic movements. Partial convulsive status epilepticus (*epilepsia partialis continua*) and nonconvulsive status epilepticus (NCSE) should be treated promptly. These later conditions might not have overt clinical manifestations and would require bedside EEG for prompt diagnosis. In neuro-oncology, SE means ongoing or intermittent generalized seizures *without recovery of consciousness* to baseline. SE can be convulsive (CSE) or nonconvulsive (NCSE), and patients can have one or the other or both in the ED. CSE is easily recognizable; the seizures can be partial tonic-clonic or generalized tonic-clonic, with predominance of tonic posturing, clonic movements, or no predominance at all.

Causes

Epileptic seizures are a frequent symptom of brain metastases (leptomeningeal, dural, or parenchymal), primary brain tumors (meningiomas, astrocytomas, oligodendrogliomas), metabolic disorders (hyponatremia, hypoglycemia, hypoxia, hypercalcemia), CNS infections, intracranial hemorrhage, ischemic infarctions, and treatment-related factors.

Assessment

Tumors can give rise to localized seizures or generalized seizures. In some cases, the seizures are hardly visible and subtle; **nystagmus and sporadic facial, finger, or toe twitching can be the only manifestation of CSE**. NCSE can be challenging as it can present with varied manifestations ranging from being awake and confused to overt coma. Diagnosis is confirmed by electroencephalogram (EEG). As for any diagnostic test, the EEG has its limitations, especially

Table 3 Emergency medical treatment of patients with de facto or impending cerebral herniation (adapted from Ref. [37])

Intervention	Dose	Onset/duration	Advantage(s)	Disadvantage(s)
Hyperventilation	Goal: lower pCO2 to 25–30 mmHg by increasing respiratory rate with same tidal volume	Seconds/minutes	Fastest onset Effective for high ICP regardless of cause	Very short duration, with effect lost after several hours Will require endotracheal intubation May be more harmful to an already injured brain
Osmotherapy (mannitol, 20 % solution)	1 g/kg iv initial dose; next doses are tapered to 0.5 g/kg and 0.25 g/kg q6h	Within 15–20 min/Max effect is in 60 m Keep osmolality between 210 and 320 mOsm/L	Longer duration May be effective regardless of cause Note: still is the standard of care in cancer patients	Rebound effect is possible Hyperosmolality and acute renal failure
Osmotherapy (hypertonic saline solutions)	3 %: 50 mL in 10 m; 7.5 %: 250 mL; 23.4 %: 30–60 mL	Onset is within minutes	Effective when mannitol is not 23.4 % Needs central line for administration –could be considered for rapidly evolving herniation	Very little experience in brain tumors Presented as safer than mannitol but it may have adverse effects: CHF, hyperchloremic acidemia, hypernatremia, seizures
Corticosteroids (dexamethasone most used)	We use on initial dose 10 mg, followed by 4–6 mg iv q4-6 h. Decrease as soon as possible	24–36 h/days	Reliable and steady effect in vasogenic edema from metastatic or primary brain tumors	Not effective in anoxic-ischemic or toxic edema AE: hyperglycemia, mood changes, insomnia, immunosuppression, cushing syndrome, skin frailty, accelerated bone resorption Myopathy can be disabling

ICP intracranial pressure, *CHF* congestive heart failure, *AE* adverse effects

when the seizures occur intermittently. Prolonged EEG or repeat EEG might be needed. Nondiagnostic EEG *does not* rule out a seizure. Clinical judgment should prevail, and if there is high suspicion (patients with brain tumors, meningitis, brain hemorrhage, CNS infections), it is clinically and ethically justified to start treatment with benzodiazepines and anticonvulsant drugs [26].

Management and Prognosis

The management is based on ventilatory and circulatory support and early use of benzodiazepines, phenytoin, levetiracetam, sodium valproate, phenobarbital, propofol or midazolam, and, in some cases, pentobarbital. Time is of essence and quick administration of abortive (benzodiazepines), and intravenous antiepileptics may prevent evolution to refractory status epilepticus. For practical purposes, we recommend urgent and aggressive treatment of any seizure lasting more than 2 min (if duration can be estimated). If the duration is uncertain, the treatment has to be equally aggressive, even though the probability of success ("breaking" the SE) is less if the patient has been in status for hours or for days. The prognosis depends on the duration of status, underlying causes, and presence of additional complications. CSE and partial status epilepticus can contribute to additional neurological worsening in brain tumor patients due to cytotoxic edema and intracranial hypertension.

ICH

Importance

Under ICH we find parenchymal, subarachnoid, subdural, and epidural hemorrhages [27]. Although nontraumatic, these hemorrhages can occur as an adverse effect of anticoagulation or are due to thrombocytopenia, disseminated intravascular coagulation (DIC) associated to the disease (leukemia) or sepsis, and to leukostasis in leukemia. In many other cases, the hemorrhage is spontaneous without external factors other than the neovascularization of the tumor (melanoma, glioblastoma). The use of therapies against the vascular endothelial growth factor (VEGF) like bevacizumab can also cause ICH, and we see more patients with glioblastoma with this complication in the ED [28].

Presentation

Patients with ICH can arrive to the ED with the classic picture of sudden headache, altered mental status including stupor and coma, focal deficits, and epileptic seizures. However, many other come with a more subtle and longer time course, mostly subacute, of headaches, delirium, or sporadic epileptic seizures. This is true especially of patients with intratumoral bleeding (melanoma, renal cell carcinoma, lung cancer, and glioblastomas). In community hospitals, a few

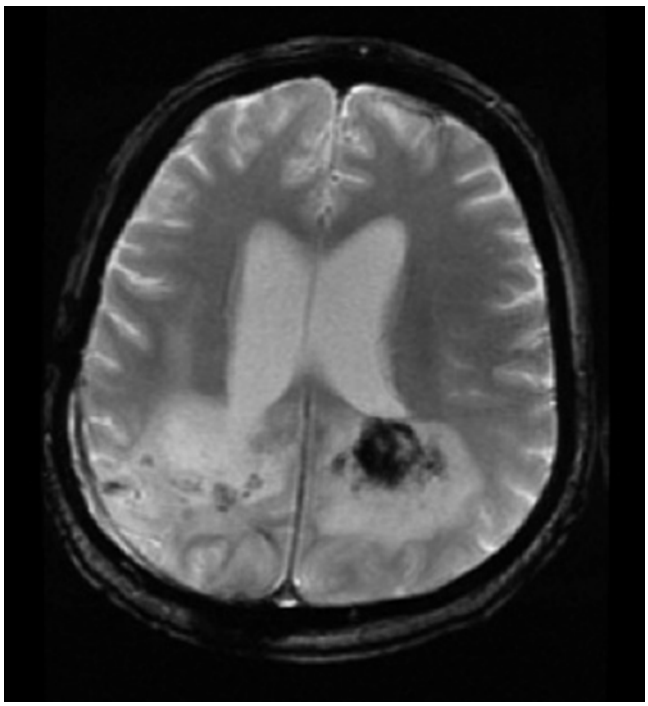


Fig. 7 Intracranial hemorrhage

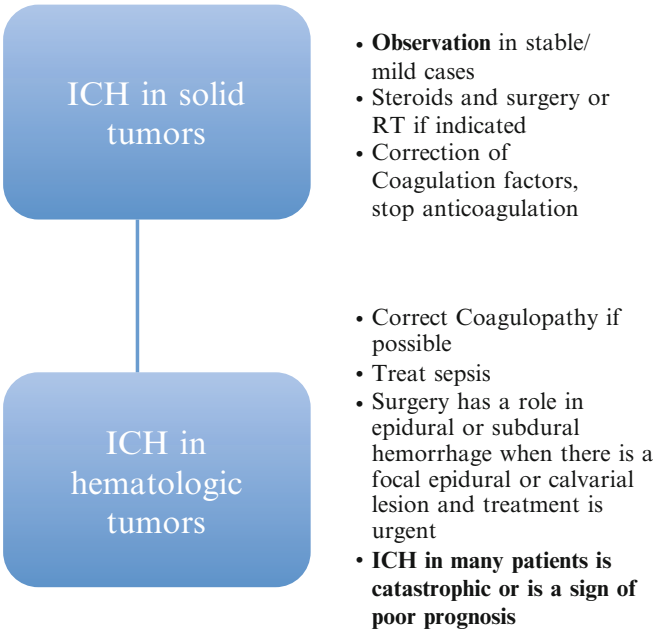


Fig. 8 Treatment of intracranial hemorrhage

patients without history of cancer are admitted with an ICH as the initial manifestation of neoplasm.

Diagnosis

The diagnosis is straightforward. A CT scan confirms the ICH in most cases. Occasionally, calcifications can confuse the diagnosis but the MRI solves the issue. We have found that T1 with and without gadolinium and gradient echo or T2* (star) sequences are most helpful (Fig. 7). Bleeding in venous angiomas, cavernomas, incidental aneurysms, and in elderly patients with amyloid angiopathy can sometimes pose a problem. In most cases, a careful analysis of the MRI sequences correctly identifies the cause.

Treatment and Prognosis

The treatment of ICH may vary according to the location of bleeding and the status of the underlying cancer at the time of hemorrhage (Fig. 8). In our experience, most patients with solid tumors and ICH that are symptomatic but stable can be managed conservatively. Unstable patients usually arrive after a cardiac arrest or are stuporous or comatose. These patients, if they survive, have severe and irreversible neurological deficits that will exclude them from any further oncologic interventions, and supportive care will be the best option [27, 29].

Venous Sinus Thrombosis

Frequency

Venous sinus thrombosis is a rare cause of stroke in Western countries (0.5–1 % of all strokes), but the frequency is higher in cancer; approximately 8 % of adults with dural and sinus thrombosis had malignancy, and prognosis for survival or recovery in this group was independently worse than in non-cancer patients [30].

Presentation

Headache, confusion, and seizures are common presentations [31, 32]. As in other emergencies, there is variation of severity. **Younger** patients tend to present with headache and papill-edema (increased ICP), whereas **older patients (>50 years)** have more encephalopathy [33]. Sometimes the thrombosis is an incidental finding in patients with prothrombotic factors, including the factor V mutation and the presence of lupus anticoagulant or antiphospholipid antibodies.

Diagnosis

Venogram by CT or MRI is the most direct means of noninvasive diagnosis [34]. The regular MRI of the brain can point to the suspect area before the angiogram is done.

Treatment and Prognosis

As others have concluded, the treatment of this condition in the cancer patient is not clear. In asymptomatic patients, we tend to treat with anticoagulation, but there is no evidence that this approach is better than no treatment at all. In symptomatic, stable patients, supportive measures (analgesia, osmotherapy for high ICP) are the first steps, followed by anticoagulation with subcutaneous low-molecular weight heparin (LMWH) or intravenous unfractionated heparin. The optimal duration has not been established, but many patients receive treatment for 3 months, 6 months, and some permanently, reflecting how little we know about treatment outcomes for lack of well-controlled studies. There is initial evidence, but not definitive, that thrombectomy and lysis with the tissue plasminogen activator (tPA) are effective interventions in selected cases [35]. We have no experience with these agents as most of our patients have contraindications or their prognosis is poor. For asymptomatic and stable, symptomatic patients, the prognosis for survival and neurologic function is good. For patients with acute presentation with brain herniation and CSE, the outlook is not good, with a high mortality rate.

Spinal Cord Compression (SCC)

Importance and Extent of the Problem

The vast majority of cases of SCC are from epidural metastases originating from vertebral bodies, and the neurological symptoms result from extrinsic compression of the spinal cord, not from infiltration. **Back pain** is the most frequent symptom that anticipates SCC, and detection of epidural lesions at this stage is key, because treatment can be successful in preventing spinal cord damage [36]. **Once the neurological deficits follow, recovery is more difficult, and the consequences can be devastating**: a patient with paraplegia, with loss of sphincter control, will become totally dependent for care now, and the quality of life and treatment perspectives will radically change.

Causes

As a rule of thumb, about two-third of SCC cases are due to breast, lung, lymphoma, and multiple myeloma. In prostate cancer, about 90 % of patients with bone metastases have vertebral lesions that can spread to the epidural space and cause SCC.

Assessment

1. **Pain** is by far the most frequent symptom at presentation, roughly in 90 % of patients with SCC. Its time course is mostly progressive, in crescendo, and will be invariably followed by weakness, sensory loss, and dysautonomia. This is the time when diagnosis and treatment are precious, because they will prevent the onset of a neurological deterioration that will be irreversible. The pain can range in severity from mild to severe. Gentle percussion of the posterior vertebral bodies will help localize the area where the source of problems is. Nevertheless, about one in ten patients can have painless SCC.
2. **Patients can have a normal neurologic exam** (the best case scenario), whereas others already have weakness in lower extremities, paresthesias, or bladder/bowel incontinence. In SCC, a sensory level is characteristic, and the deep tendon reflexes below the lesion will be hyperactive. Despite being an upper motor neuron lesion, the weakness can be flaccid or spastic (depending on the acuteness of compression), and the extensor plantar response (Babinski sign) may or not be present initially. Preservation of light touch in the buttocks, perineum, and posterior thighs (sacral sparing) is possible in about one of every five patients [37].
3. **Gait ataxia is a common finding in SCC** [38]. With back pain, the diagnosis of SCC can be relatively easy, but it is important to remember that some cases can present with isolated ataxia.
4. Rarely, patients with SCC can present oddly, with Lhermitte phenomenon, hydrocephalus with papilledema, spinal myoclonus, tongue numbness, and facial pain or numbness [37].

Management

MRI of the whole spine with and without contrast is the best imaging test to diagnose SCC (Fig. 9). Occasionally, a patient will require a computed tomography (CT) instead because of pacemaker or any MRI-incompatible hardware or foreign body. Because of its accuracy, MRI will distinguish other spinal cord lesions [39] such as epidural abscess, epidural lipomas, spinal stenosis, transverse myelitis, acute ischemia, and leptomeningeal metastases.

Dexamethasone is the cornerstone of initial treatment. Different authors have recommended doses that range from 10 mg initially [23] to 96–100 mg as a loading dose [37]. There is no optimal dose for subsequent doses after the initial administration and no consensus guidelines.

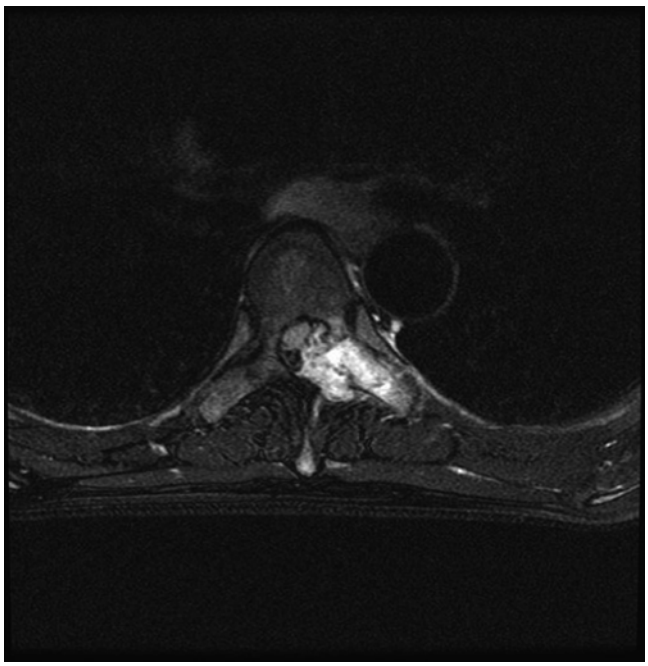


Fig. 9 Spinal cord compression

We recommend 10 mg IV initially, followed by 4 mg IV two to four times daily, depending on the severity of compression and neurologic deficits. In patients with no compression or with no deficits, dexamethasone 4 mg orally twice daily is enough. The next step is to determine whether radiation therapy, surgery, or both will be performed. There is consensus [36, 37, 40, 41] that:

1. Patients with epidural metastasis, **no SCC, or SCC without myelopathy** can receive RT first. If the tumor is radioresistant and there is no contraindication, surgery follows.
2. **Patients with SCC and myelopathy or neurological deficits**: RT first if tumor is sensitive. If not (e.g., non-small cell lung cancer, squamous cell carcinomas), surgery is the first option.
3. **Patients can be reirradiated** if they responded well initially but relapsed in the same area. If the SCC is causing deficits, surgery may be the first.
4. If there is **mechanical instability, surgery comes first** regardless of any neurological compromise. Kyphoplasty and vertebroplasty are good options for compression fractures.
5. For patients with **extensive systemic disease**, RT is the recommended approach. Some with good performance status (PS) could have surgery, but this decision is taken individually. Most patients in this group and with poor PS could receive RT. Hospice care is an acceptable and reasonable at this point.

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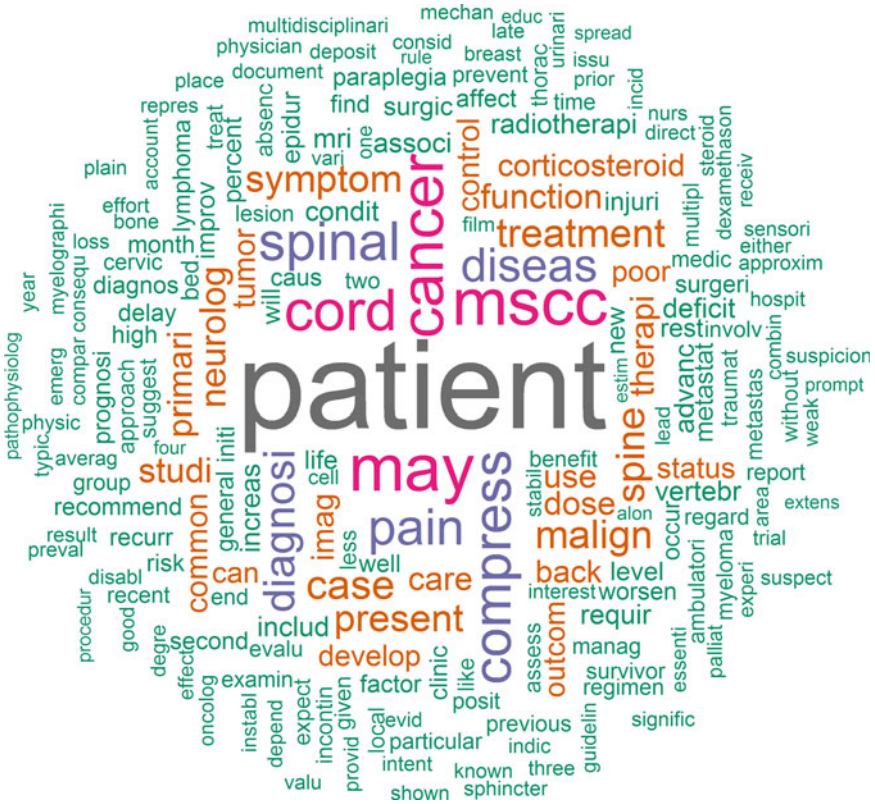
Malignant Spinal Cord Compression

Jayne M. Viets-Upchurch



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Introduction

Traumatic spinal cord injury is a well-documented, devastating injury leading to sensory loss, paralysis, sphincter dysfunction, and protracted pain. The Centers for Disease Control and Prevention estimates that there are 12,000–20,000 such cases annually. Malignant spinal cord compression (MSCC) occurs at a similar rate to traumatic spinal cord injury. It is less well understood but equally devastating.

Cancer is the most common systemic disease affecting the spine [1] and MSCC can represent a true oncologic emergency. It results from tumor-related compression of the thecal sac and spinal cord [2, 3]. Like traumatic injury, untreated MSCC leads to paraplegia, incontinence, and permanent disability. It presents clinically in approximately 3–10 % of cancer-related deaths [4, 5]. Cancer patients have a median survival of 3–6 months from diagnosis of MSCC [4, 6, 7]. Once treated, 10–14 % of patients experience recurrent compression either locally or at another vertebral level.

The past several years have yielded significant advances in the diagnosis and treatment of this condition. Nevertheless, prompt recognition and treatment is essential to maintain mobility and neurological function. Any former or active cancer patient presenting with new or worsening back pain, even in the absence of neurological deficit, merits evaluation for spinal cord compression [8]. Individual risk assessment is necessary [9].

Epidemiology

Postmortem studies suggest that MSCC affects 5–36 % of cancer patients [10, 11]. In a US nationwide study of 15,367 cases of MSCC [5], the mean age at hospitalization was 62 years. Men outnumber women nearly two to one, with only 37 % of cases occurring in women. In approximately 20 % of cases, MSCC was the initial presentation of cancer [7, 12]. With increasing cancer prevalence and prolonged life expectancy of diagnosed patients, the incidence of malignant spinal cord compression is expected to increase.

Prevalence of MSCC varies depending on tumor type. Cancers of the breast, lung, and prostate each account for 15–20 % of cases. Renal cell carcinoma accounts for an additional 5–10 %. Multiple myeloma and lymphoma are the most frequent liquid tumors associated with MSCC, each contributing 5–10 % of cases [3, 5, 13]. It may affect 7.9–15 % of myelomas [4, 5] and 13 % of lymphomas [5]. Interestingly, 5.5 % of patients with prostate cancer develop MSCC [5]. In contrast, it occurs in only 0.2 % of pancreatic cancers [4]. In children the most commonly associated malignancies are sarcoma, neuroblastoma, germ-cell tumor, and Hodgkin's disease [3, 13].

The most common location of MSCC is the thoracic spine (69 % of cases); 29 % of cases occur at the lumbosacral level and 10 % at the cervical area [3, 14]. It is hypothesized that this pattern represents the primary tumor's lymphatic drainage. Accordingly, metastases from breast and lung cancers tend to be found in the thoracic spine. Pelvic and intra-abdominal malignancies most commonly migrate to the lumbar spine.

Spinal cord compression may happen at any level. Multiple, noncontiguous spinal epidural metastases were noted in 31 % of patients who underwent complete imaging of the spine [14]. Among those, up to two-thirds may have multicentric disease affecting with lesions in more than one region (cervical, thoracic, and lumbar) of the spine [15].

Historical factors that predispose the patient to MSCC include known metastatic disease at the time of cancer diagnosis and known vertebral metastases. Pain in the thoracic spine and abnormal gait are suggestive of cord compression [16]. The absence of these findings is not sufficient to rule out the disease.

Pathophysiology

Most cases of MSCC are epidural in origin, arising from the vertebral column in 85 % of patients [3]. Epidural spread is caused mainly by hematogenous mechanism through the Batson venous plexus [17]. Progressive bone involvement debilitates the bone cortex eventually leading to vertebral collapse with compression of the spinal canal. Epidural spread is less likely caused by direct tumor extension (i.e., erosion through the bone) or by direct deposition of tumor cells into the epidural space [13].

Ultimate neuronal injury is thought to involve vasogenic edema [18], leading to ischemia [17] presumably through venous infarction, but there has been debate regarding this last phenomenon [19]. In cases of paralysis, demyelination is evident [19].

Clinical Presentation

History

The primary complaint is pain in 83–96 % of malignant spinal cord compression [20, 21], though this is a nonspecific sign. Pain can be referred, local, radicular, or a combination of all three [22]. Symptoms in MSCC at presentation can be motor (weakness, paraplegia), sensory (numbness, neuropathic pain), and/or autonomic (incontinence). While symptoms may vary based on the location of the metastatic lesion, they are a poor indicator of the level of the involvement [15].

Back pain is present for a median of 62 days prior to treatment of MSCC, highlighting the historical delay in diagnosis and treatment [23]; patients presenting with radiculopathy are symptomatic on average of 9 weeks prior to diagnosis [24]. Because cord compression is an evolving condition, a patient with previously stable back pain may present with recently worsening symptoms.

Patients may report the pain in a band-like distribution. It is generally described as sharp, shooting, or deep [8]. As with mechanical back pain, pain associated with MSCC may worsen with weight-bearing loads, which bring pressure to bear on the vertebral column [25]. Other common precipitating factors include coughing, bending, and sneezing [8]. Twenty percent of patients report that rest in a supine position exacerbates symptoms often disrupting sleep [1, 8]. These patients may sleep in an upright position.

Weakness follows pain with an estimated 35–85 % of patients endorsing the symptom [26]. Previous studies have shown that 40–64 % of patients were not ambulatory at the time of diagnosis [20, 27]. Recent case series report an increased number of ambulatory patients—possibly due to increased clinician awareness [28]. In other studies, only 9 % of patients were able to walk independently [29]. Loss of sensation, dense paraplegia, and incontinence are late findings and likely signal some degree of permanent disability [20].

Misdiagnosis is a common issue in the emergency department setting. In an interesting retrospective study of 63 patients with spinal cord compression (not necessarily malignant), 18 (29 %) were misdiagnosed [30]. Consequently, there was a significant delay in diagnosis despite obvious neurological deficits at presentation.

An important clinical inquiry is to determine whether back pain in an established cancer patient can be ruled out without extensive imaging. Unfortunately, clinical examination alone cannot exclude MSCC. Because of the high specificity (0.98), any cancer patient with new back pain should be considered to have metastasis until proven otherwise [1].

Physical Examination

A detailed physical examination is essential to diagnosing MSCC. Spinal tenderness may be present overlying the level of metastatic deposit. A thorough neurological examination, including sensation, strength, and reflexes, should be carefully documented. If spinal instability is suspected, range-of-motion testing is contraindicated and the patient should be immobilized. Hyperreflexia and upward going Babinski reflex are common findings [16]. Weakness and paraplegia are late findings. Decreased rectal sphincter tone and urinary incontinence are indicators of poor outcome. A bedside bladder scan may be useful for documenting post void residual to assess for evidence of urinary retention.

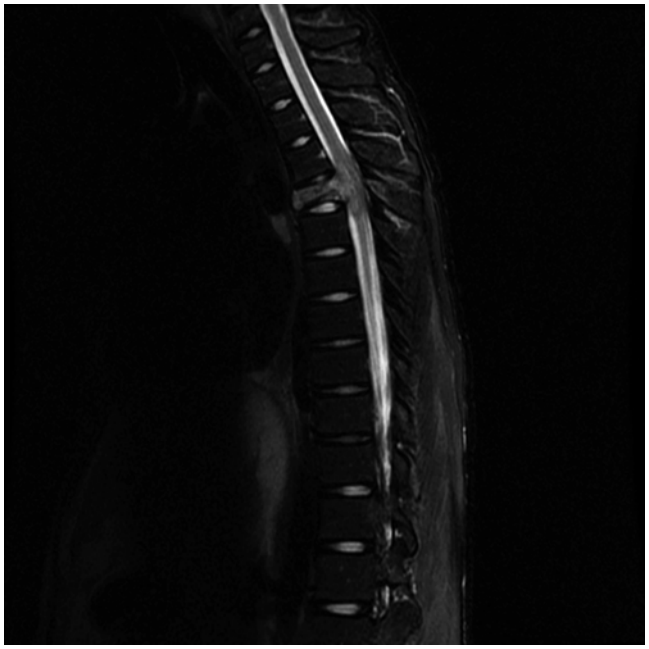

Fig. 1 A 16-year-old female with ovarian cancer and spinal cord compression at the level of the third thoracic vertebra

Patients with cervical spine tenderness or symptomatology should be immobilized and placed in a Philadelphia collar until stability of the area can be assessed. The modified Frankel classification [31], adapted from the traumatic spine cord injury work by Frankel et al. [32], may be used to assess the degree of disability.

Imaging

Incidental discovery of MSCC on imaging in the absence of neurological findings is rare. By themselves, plain films of the spine are of little value in diagnosing the condition. Approximately 26–29 % of total metastatic deposits are occult and not visible on X-ray [7, 11]. Furthermore, given the prevalence of osteoarthritic changes of the spine in adult patients, such plain films may offer false reassurance as to the nature of the pain.

Advanced imaging is essential to delineate the extent of disease. Prior to the 1990s, spinal cord compression was diagnosed by myelography [33]. Fortunately, this invasive and uncomfortable procedure has largely been supplanted by magnetic resonance imaging (MRI) (Fig. 1) [15]. While gadolinium-enhanced MRI can help to determine intradural tumor or leptomeningeal disease, it is not required for cord compression studies. Unenhanced MRI is equal to myelography in detecting epidural disease and is more sensitive at detecting vertebral metastasis [34], justifying its use and reducing procedure time compared to gadolinium-enhanced studies.

Computer-assisted tomography (CT)-guided myelography is of value for patients unable to tolerate MRI [35]. If both CT and MRI are unavailable, bone scintigraphy in combination with plain films may be of use [33].

Imaging studies should include the entire spine, not just the perceived area of interest. Up to 31 % of patients have multilevel disease [14]. Sensory deficits and mechanical pain may be present 2–4 vertebral levels away from the actual lesion [16]. If MRI suggests cord compression, severity can be graded using the MSCC scale [36].

Management

The goal of therapy is symptom control and preservation of function. This requires a multidisciplinary approach and may involve radiation therapy, surgery, and medical efforts.

Nursing Efforts

Upon diagnosis and initiation of therapy, serial neurological evaluation should be undertaken. Neurovital signs should be scheduled to coincide with other nursing efforts to ease the burden of care and minimize patient discomfort. Strict bed rest (including logroll and bedpan use) should be instituted if there is suspicion of spinal cord instability. Patients with involvement of the cervical spine should have a Philadelphia collar placed until spinal stability has been confirmed. In the United Kingdom, the National Institutes for Health Care Excellence guidelines recommend all patients with suspected cord compression be nursed in a flat position [24]. Other authors do not believe that strict bed rest is necessary. Proponents of this theory believe that MSCC is inherently different from that caused by trauma. Authors supporting this position contend that the increased incidence of deep vein thrombosis, infection (particularly from the respiratory and urinary tracts), and decubitus ulcers outweighs the benefit of bed rest. Patient performance status and preference should be taken into consideration as those with good functional status may be quite resistant to bed rest, particularly if it worsens their symptoms. In cases where cord compression is strongly suspected, these patients should be educated on proper bed rest.

Radiotherapy

Whether for therapeutic or palliative intent, radiotherapy is provided to virtually all patients. Issues regarding duration and dosing depend on intent of therapy and must be individualized to the patient. Guidelines have been recommended, but in spite of widespread use, there is a paucity of randomized controlled trials to clarify the role of specific regimens [37].

While single-dose regimens provide similar symptom control as fractionated regimens, there is an increased incidence of local recurrence [28, 38]. Patients who experience local recurrence may be candidates for re-irradiation [39, 40]. Generally speaking, patients with a favorable prognosis will benefit from longer courses of therapy [41, 42]. End-of-life patients with a poor prognosis are typically treated with a single-dose regimen [38, 41]. One study in neurologically intact patients suggested that radiotherapy alone may be sufficient therapy in this select group [43]. However, this is not considered standard of care.

Surgical Therapy

Surgery is indicated in 10–15 % of MSCC cases [39]. Previously, laminectomy was the primary surgical option available. It provided suboptimal results. Over the past two decades, significant improvements have been made. New surgical techniques including circumferential decompression of the spine with anterior posterior surgery stabilization have advanced the care of these patients [44]. These advances in combination of surgery with radiotherapy have improved outcomes [45].

Patients with a good functional status, limited disease, and a life expectancy greater than 3–6 months may benefit from surgery [46]. Those patients with paraplegia of less than 48 h duration may experience a degree of functional restoration. Surgical evaluation is required in cases of spinal instability, direct cord compression due to a bony fragment, and impending sphincter dysfunction. Unknown primary tumors will require biopsy even if full resection is not possible. Patients not responding to radiotherapy or those who have previously received radiotherapy may benefit from surgical intervention [18].

Medical Therapy

The mainstay of medical therapy is treatment with corticosteroids [47]. Unless contraindicated, it is recommended for all patients, particularly those with neurologic deficits. Initial trials demonstrated that corticosteroids improve functional status as well as symptoms in MSCC. Controversy exists regarding the effective dose. In a randomized, controlled trial by Sorensen et al. [48], which sought to evaluate functional outcomes of high-dose corticosteroids as an adjunct to radiotherapy, 57 patients received either high-dose dexamethasone or no corticosteroid therapy. Fifty-nine percent of patients in the dexamethasone group were ambulatory

6 months after treatment compared to 39 % in the group who did not receive steroids [48]. More recent studies have shown no improvement in outcome compared to lower-dose corticosteroids [49].

National guidelines in both Canada and England now recommend more moderate dosing. A common recommendation is a loading dose of 10 mg dexamethasone followed by 16 mg per day in 2–4 divided doses [2, 4, 50]. In patients with recent-onset neurologic deficits, higher doses may be considered [2].

High-dose corticosteroids are associated with psychosis, gastric ulceration and perforation, rectal bleeding, and hyperglycemia. Care should be taken to mitigate against these effects. Steroids should be weaned as tolerated. Gastrointestinal (GI) prophylaxis should be initiated. Special attention should be given to glucose control (particularly in patients with preexisting diabetes).

While not typically of use in the emergency department, chemotherapy may be of value. Seminomas and lymphomas may show dramatic response to treatment [51].

Special Considerations

A patient without a biopsy-confirmed cancer diagnosis in need of corticosteroid treatment presents a dilemma. In spite of improved surveillance and diagnostic practices, 20 % of malignant spinal cord compression occurs in patients without a known malignancy. If there is any question regarding the nature of the lesion, tissue diagnosis must be obtained without delay.

Steroids are used with curative intent in treatment of plasmacytomas, thymomas, lymphomas, multiple myeloma, and germ-cell tumors [51]. In these circumstances, corticosteroids given before tissue samples are obtained may cause regression of disease, hindering diagnosis and complicating delivery of definitive chemotherapy [52, 53]. In the absence of neurological deficit, corticosteroids may be withheld pending consultation with neurosurgery and oncology.

Cancer patients are at increased risk of recurrent malignancy. Overall, cancer survivors have a 14 % higher risk of developing new malignancy than the general population [54]. In fact, second primary malignancy accounts for 16 % of new cancer diagnoses [55].

The etiology of second primary malignancy varies. Treatment-related secondary cancers are well-documented complications of chemotherapeutic, hormonal, and radiation modalities. Familial cancer syndromes result in multiple primary cancer sites. Shared risk factors and lifestyle choices such as tobacco and alcohol use and sun exposure contribute to development of second primaries. Cancer survivors who are thought to have no evidence of disease may be experiencing either recurrent disease or the initial manifestations of a second primary process.

Prevention

Bisphosphonates have been shown to be effective in controlling symptoms from and prevention of skeletal metastases in breast cancer. As such, they may play a role in prevention of MSCC.

Patient education is of primary importance. Lu et al. [16] found that only 54 % of patients were aware that back pain should be reported to their physician. Delays in diagnosis and treatment are common and well described in the literature [23]. Patients should be instructed to call their physician within 24 h from the development of any new or worsening back pain and should be advised to seek immediate care if they develop any neurological symptoms.

To facilitate appropriate and prompt management of MSCC, hospitals and treating physicians should develop diagnostic algorithms to minimize delays in referral to a comprehensive center for further treatment.

Prognosis

MSCC can be treated successfully; nonetheless it is associated with a poor outcome in most patients. It is evidence of an uncontrolled and aggressive disease process.

The greatest predictors of outcome are ambulatory and functional status at the time of diagnosis (generally based on an Eastern Cooperative Oncology Group scale).

Although lymphoma and myeloma patients fare better than other patients, the average lifespan after development of MSCC is less than 6 months [4, 6, 7]. However, patients with limited disease and good functional status may survive for years [44]. Patients with poor functional status and those with end- or late-stage disease should be referred to palliative care for the management of symptoms [56].

Given the poor prognosis of MSCC in general, end-of-life discussions are warranted. In a retrospective study of 88 patients with MSCC [57], "do not resuscitate" orders were in place in only 9 % of the patients during their hospital admission. Improved doctor-patient communication in the ED setting will facilitate the patient's coping with future losses.

Conclusion

Metastatic spinal cord compression is an uncommon but well-established consequence of advanced cancer. It affects both survivors and patients with active disease. Patient education is a key factor in early diagnosis. It may represent the first manifestation of cancer (or a second primary cancer in the case of long-term survivors.) The primary complaint is typically back pain. Neurologic deficits are associated with a poor outcome. Diagnosis requires a high index of suspicion.

Unenhanced, non-contrasted MRI is the imaging modality of choice. Definitive treatment requires a multidisciplinary approach including medical, surgical, and radiotherapeutic approaches. Symptom control and maintaining (or regaining) functional status are of paramount importance. MSCC is associated with a poor prognosis and palliative care, and end-of-life issues should be addressed with all patients who develop the condition.

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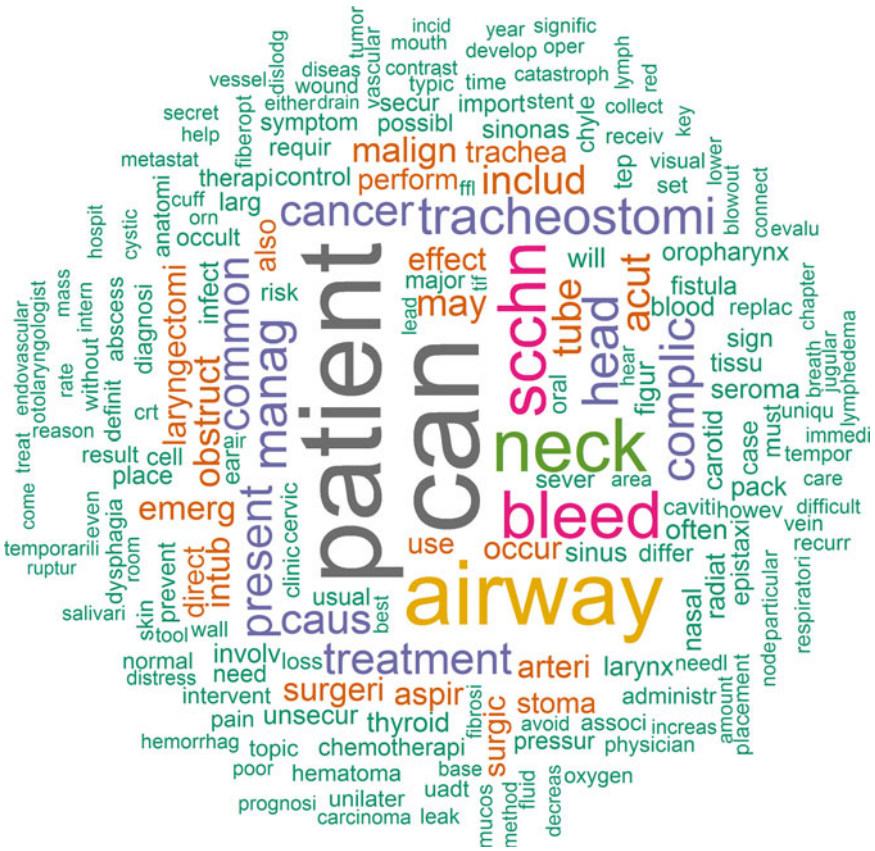
Head and Neck Oncologic Emergencies

Eugene Son, C. David Fuller, and Neil D. Gross



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Introduction

Head and neck cancer is the fifth most common cancer worldwide with almost 53,000 people diagnosed each year in the United States [1]. These include malignancies of the upper aerodigestive tract (UADT) which begins at the lips and nose and extends to the mucosal surfaces of the cervical trachea and esophagus. The UADT includes the oral cavity, oropharynx, hypopharynx, larynx, nasal cavities, and paranasal sinuses. The most common malignancy of the UADT is squamous cell carcinoma of the head and neck (SCCHN), making up over 97 % [2]. For simplicity, SCCHN will be the focus of this chapter. Other pathologies in the head and neck including carcinoma of the major and minor salivary glands, thyroid, and skin will not be covered.

Uncontrolled SCCHN can result in life-threatening emergencies, principally from compromise of the airway and/or bleeding. Patients with undiagnosed SCCHN may present to the emergency department (ED) in distress because SCC of the base of the tongue and larynx can grow to be large with relatively few symptoms [3]. In this chapter, we will discuss acute management of the airway in patients with SCCHN. We will also review management of emergent bleeding in patients with SCCHN. Finally, we will cover common complications from treatment of SCCHN and end with clinical pearls for acute management of SCCHN in the ED.

Airway Management

Airway obstruction due to malignancy of the UADT affects up to 80,000 patients annually, with most patients presenting to the ED for acute care [4]. Ideally, discussions about airway management in patients with SCCHN should occur well before an emergency. This may include prophylactic tracheostomy. In addition to acute airway obstruction, SCCHN patients have increased rates of aspiration pneumonia because of dysphagia and difficulty handling even normal oral secretions [5]. The 1-year and 5-year incidence of clinically meaningful aspiration in SCCHN patients is 15.8 % and 23.8 %, respectively, with 84 % of these patients being hospitalized [6]. For the purposes of this chapter, we have divided the airway into unsecure and secure.

Unsecured Airway

Undiagnosed SCCHN can lead to signs of obstruction before causing other symptoms such as pain [7]. Metastatic cervical adenopathy can also cause obstructive lymphedema and direct extrinsic compression of the airway. Patients with undiagnosed SCCHN may present with orthopnea, hoarseness, dysphagia, odynophagia, and hemoptysis [7]. Stridor and/or drooling can be signs of an unsecured airway.

In stable patients, a contrasted computed tomography (CT) of the head, neck, and chest can be performed quickly to assess the location and extent of the obstruction [7]. This imaging study provides important staging information if malignancy is confirmed. Flexible fiber-optic laryngoscopy (FFL) is a critical tool for assessing the airway and is the most direct method to evaluate for impending obstruction (Fig. 1). Skilled management of the FFL is important for evaluating a potentially tenuous airway. Topical administration of lidocaine and oxymetazoline or phenylephrine to the nasal cavities makes FFL more tolerable and safe (Fig. 1). The management of a suspected unsecure airway starts with optimal position to make the patient as comfortable as possible. Administration of supplemental oxygen may be helpful but should be used with caution in patients with uncompensated chronic obstructive pulmonary disease (COPD). Administrating nebulizers and steroids is unlikely to improve the airway but may temporarily help palliate the patient. The use of Heliox, a mixture of helium and oxygen, has been described in the acute management of patients with an unsecure airway. The decreased viscosity of Heliox can temporarily improve airflow and reduce stridor. Because it is an inert gas, it can assist in temporizing an unsecure airway but may not be readily available in the ED [8].

Don't see labels on Figure 1.

SCCHN patients with acute respiratory failure from an unsecure airway should be managed expeditiously. Transoral intubation is preferred if FFL predicts that direct visualization of the endolarynx can be achieved safely. The use of laryngeal mask anesthesia (LMA) is not recommended in these cases because of likely distortion of the normal anat-

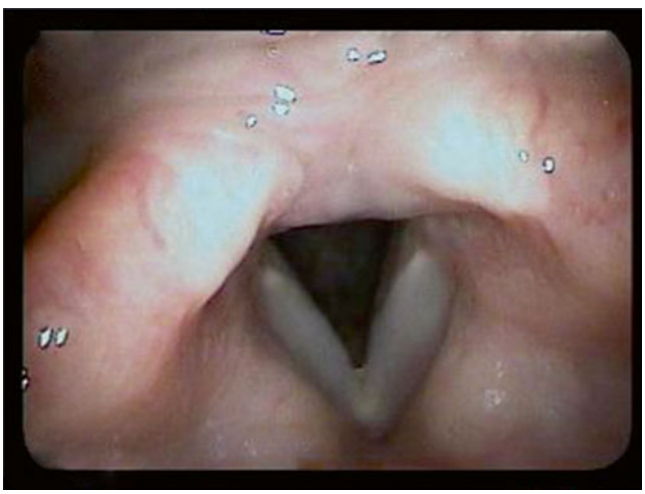

Fig. 1 Flexible fiber-optic laryngoscopy demonstrating normal larynx. *A* airway; *VC* vocal cord

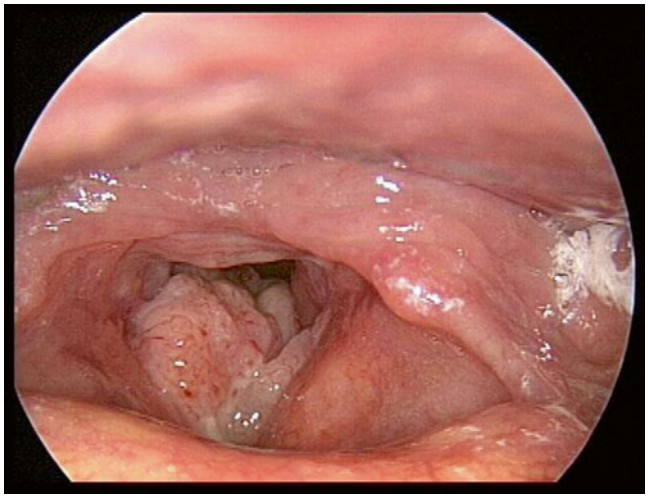

Fig. 2 Flexible fiber-optic laryngoscopy demonstrating obstructing mass of the larynx. Note loss of visualization of the vocal cords and the markedly decreased diameter of the airway (A)

omy. In cases where oral intubation is not possible (e.g., obstructing mass, trismus), awake fiber-optic transoral or nasotracheal intubation is an option. Nasotracheal intubation is preferred over awake fiber-optic oral intubation to decrease patient gagging but requires a unique skill set and is probably best performed by experienced anesthesiologists or otolaryngologists. Successful intubation can avoid an emergent surgical airway and allow a controlled environment for formal tracheostomy [3]. SCCHN involving the larynx is most likely to result in an unsecured airway (Fig. 2). Intubation of a patient with locally advanced SCC of the larynx can be hazardous because of the distorted anatomy and risk of bleeding during laryngoscopy. In these cases, the airway is best managed in the operating room by an experienced anesthesiologist and/or otolaryngologist.

If attempted intubation is unsafe or unsuccessful, then a surgical airway via cricothyroidotomy or tracheostomy should be performed. Awake tracheostomy can be performed under local anesthesia in select SCCHN patients with an unsecure airway. This is best performed in the operating room. If an urgent airway is needed (e.g., acute obstruction), then a "slash" cricothyroidotomy should be performed. A vertical incision is usually advised in this setting as a midline dissection is critical to minimize bleeding and allowing for identification of the airway across a vertical range. In cases where the trachea is deviated, a needle on a saline-filled syringe with negative pressure can be used to locate the trachea by visualization of air bubbles [9]. Transtracheal catheterization has also been described if cricothyroidotomy or tracheostomy cannot be performed [10].

Some head and neck cancers, particularly thyroid cancers, can cause paralysis to one or both of the vocal cords via direct involvement of the recurrent laryngeal nerves (Fig. 3).

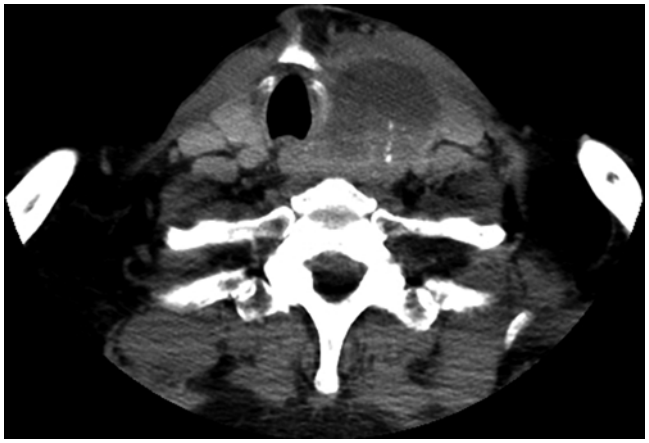

Fig. 3 Axial computed tomography (CT) of the neck demonstrating a left-sided thyroid mass with invasion into the cricoid cartilage. This patient presented with a paralyzed ipsilateral vocal cord secondary to involvement of the recurrent laryngeal nerve

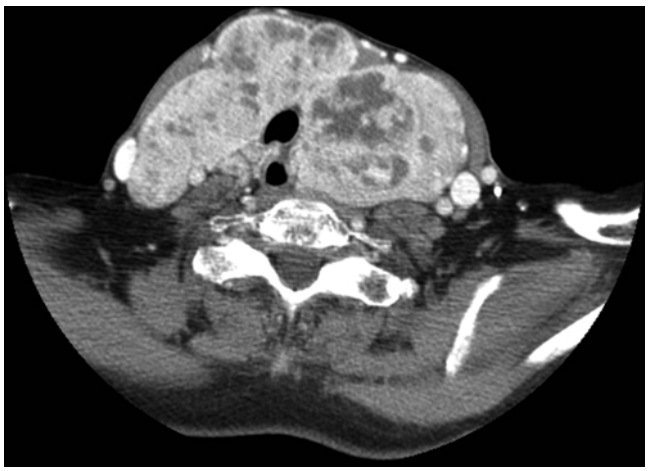

Fig. 4 Axial computed tomography (CT) of the neck demonstrating a large goiter with narrowing of the airway (A) but no obstruction

This is in contrast to large goiters that can distort the airway over time but rarely cause respiratory distress (Fig. 4). Acute bilateral vocal fold paralysis, either by direct tumor involvement or iatrogenic after thyroid surgery, can cause respiratory distress marked by stridor. These patients typically require intubation and subsequent tracheostomy if possible. Anaplastic thyroid cancer is the prototypic malignancy to cause acute airway obstruction by direct tracheal involvement, recurrent laryngeal nerve involvement, or both. Fortunately, anaplastic thyroid carcinoma comprises only 1.7 % of all thyroid cancers [11]. The management of the airway in patients with anaplastic thyroid cancer is complex and controversial particularly given the dismal prognosis associated with the disease [12]. For this reason, current American Thyroid Association guidelines recommend against elective tracheostomy [11].

Secured Airway

The airway management of SCCHN patients with a tracheostomy or laryngectomy stoma requires some familiarity with changes to the anatomy with these procedures. Most clinicians are familiar with tracheostomy patients whereby the oral cavity, oropharynx, and larynx are bypassed by a tube directly into the trachea. In contrast, laryngectomy patients are obligate "neck breathers" with no remaining connection between the mouth and trachea.

As with all patients presenting with respiratory distress, conservative measures should always be initiated including oxygen administration. However, nasal cannula or facemask administration may have no effect if the patient breathes through a surgically created stoma in the neck. Oxygen can be applied to both the face and stoma for tracheostomy patients but only the stoma for laryngectomy patients. Fiberoptic tracheoscopy can be a valuable tool to rule out a proximal obstruction. The scope can be introduced inside the stoma or tube in place to visualize the carina and proximal main stem bronchi.

SCCHN patients with a tracheostomy are at risk of life-threatening complications, including bleeding, tube dislodgement with airway obstruction, and death [13]. There are known late complications of tracheostomy in up to 65 % of patients that are possible including granulation tissue formation, tracheomalacia, tracheoinnominate fistula (TIF), tracheoesophageal fistula, pneumonia, and aspiration [14]. These potential complications from tracheostomy tubes are important to recognize in the acute setting.

Patients can present to the ED with airway obstruction despite having a tracheostomy tube. If a tracheostomy tube dislodges, then every effort should be made to replace the tube as the stoma can close substantially in a matter of hours. If the original tracheostomy tube is too large for the tracheostomy stoma at the time of replacement, then the tract can be dilated with a nasal speculum or a smaller tube can be inserted. An endotracheal tube can even be used temporarily to secure the airway if needed. However, it is important to keep the cuff visible near the stoma to avoid a main stem bronchus intubation.

Mucous p lugging of a tracheostomy tube can cause acute airway obstruction and death. For this reason, most commercially available tracheostomy tubes have an interchangeable inner cannula. Patients need appropriate humidification of air and also frequent suctioning of the tube to prevent mucous buildup. Applying small amounts of saline bullets and suctioning with a soft flexible catheter can soften and remove hardened mucous.

There are special considerations regarding emergency management of laryngectomy patients. A survey of members of the National Association of Laryngectomy Clubs in the United Kingdom underscored concerns regarding the quality of care they receive in the emergency setting [15]. So it is incumbent upon ED physicians to be familiar with the anatomy of patients after laryngectomy and common complications that can occur. For example, it is important to realize that either a standard tracheostomy tube or more customized laryngectomy tube may be used for comfort or to stent the stoma. In the superior posterior wall of the trachea, a tracheoesophageal puncture (TEP) device may be present which provides a one-way valve for air to flow from the trachea into the esophagus for speech (Fig. 5). If a patient needs to be mask ventilated, then the laryngectomy patient should be intubated through the stoma either with a cuffed endotracheal or tracheostomy tube past the TEP if present. The rate of 30-day unplanned readmission independent of complications following laryngectomy ranges from 26.5 % to 42 % [16]. Most of these patients present for stomal or TEP complications [16]. Non-humidified air entering the proximal trachea can cause thickened respiratory secretions that are difficult to clear. These secretions can dry into dense circumferentially crusts which can obstruct the airway. Post-laryngectomy patients also frequently come to the ED for TEP dislodgement. When this happens, a chest film must be taken to rule out aspiration of the device as aspiration has been reported to occur in up to 13 % of patients [17]. If the patient comes with a dislodged TEP device in hand, replacement can be difficult without extensive experience and specialized tools. Replacement of the TEP is usually done by a speech and language pathologist or otolaryngologist. If replacement is not an immediate option, then placement of a temporary red rubber catheter through the TEP site can help prevent closure of the puncture itself and aspiration.

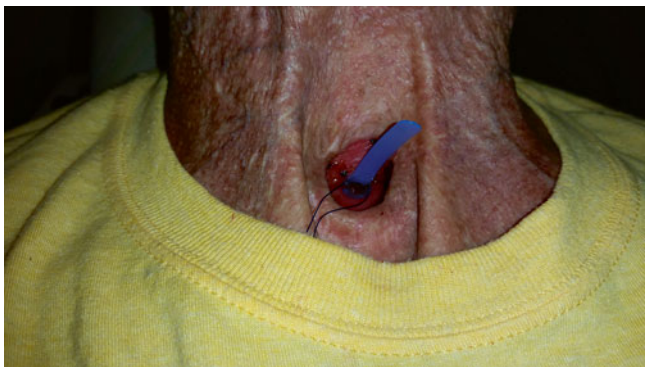

Fig. 5 Laryngectomy stoma with blue tracheoesophageal puncture (TEP) voice prosthesis in place

Bleeding Management

Patients with head and neck cancer, most notably SCCHN, can develop life-threatening bleeding. There is a rich vascular supply to the head and neck region. Bleeding can occur

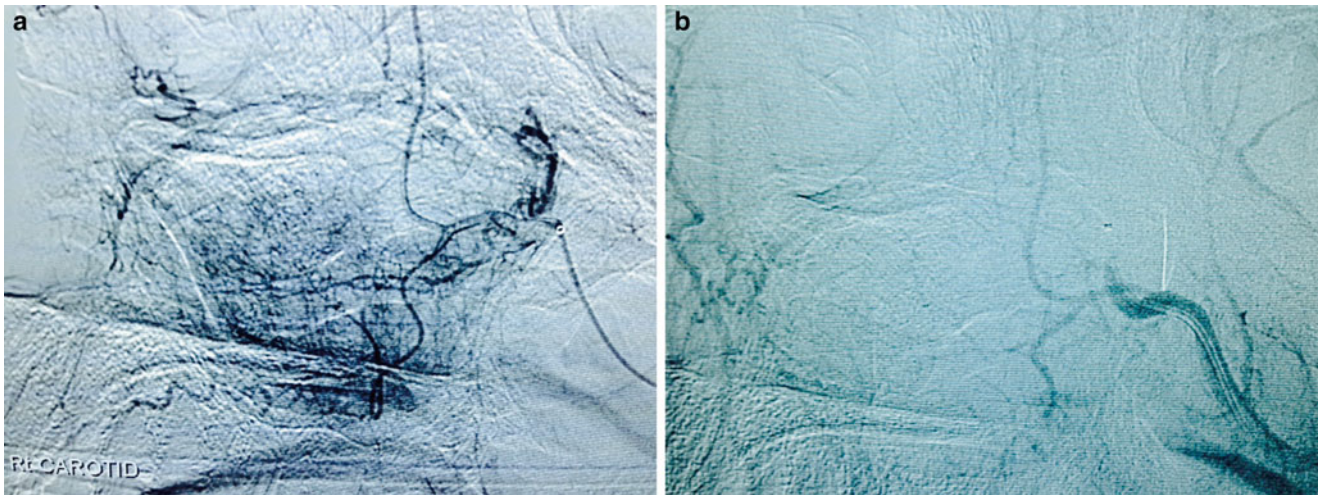

Fig. 6 Angiogram of the right internal maxillary artery in a patient with epistaxis from a sinonasal cancer before (**a**) and after (**b**) embolization

from direct tumor involvement and/or as a side effect of treatments [18]. The most common cause of bleeding is poor wound healing after surgery or radiation. The initial management of bleeding in head and neck cancer patients is no different than the general population. The patient must first be stabilized. The ABCs (airway, breathing, and circulation) of shock trauma should be addressed. Two large-bore intravenous lines should be obtained. Warmed isotonic electrolyte solutions such as lactated Ringer's solution or normal saline should be administered in bolus fashion. Transfusion of packed red blood cells (pRBC) should be considered. When administering large amounts of pRBC, calcium supplementation should be considered as there are chelating agents of calcium in these blood products [19]. Laboratory studies including complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (aPTT), and other coagulation labs should be performed and corrected as needed to assist in hemostasis.

Acute Arterial Bleeding

Acute arterial bleeding from the mouth or neck can occur after treatment of SCCHN. Surgery can strip the vascular supply of the arterial wall. Radiation therapy can cause obliteration of the vasa vasorum, premature atherosclerosis, adventitial fibrosis, and fragmentation of tunica media elastic fibers leading to weakening of the arterial wall [20]. Patients with head and neck cancer have other factors that contribute to poor wound healing including poor tissue perfusion, soft tissue exposure to salivary enzymes, and infections [21].

Major arterial bleeding is often preceded by a sentinel bleed, usually from a pseudoaneurysm, that can be profuse but self-limited [21]. A spontaneous cessation of brisk bleeding in a patient with SCCHN can give the emergency physician a false sense of safety. Immediate diagnostic work-up followed by treatment should be obtained to prevent a catastrophic bleed. CT imaging may show irregular thickening of the arterial wall of major vessels [7]. If the patient is stabilized, CT angiography (CTA) can be an effective screening tool for locating site of hemorrhage and can also assist in procedures performed by the intervention neuroradiologist [21]. Prophylactic treatment of the diseased vessel can prevent catastrophic events (Fig. 6a, b).

Direct pressure is key to temporarily controlling any acute bleeding. In the head and neck, there is the additional challenge of managing the airway. So if the bleeding is coming from the mouth, then the airway must be secured before effective pressure can be applied. With the airway secured, bleeding from the mouth can generally be stopped with a throat pack. If a tracheostomy tube is present, the cuff should be immediately inflated to prevent aspiration of blood into the lower airway and lungs. If the tracheostomy tube does not have a cuff, then it should be replaced with a cuffed tracheostomy tube. If a significant amount of blood becomes static in the trachea and the bronchial tree, then clots will cause total obstruction of the airway. This risk is much lower in laryngectomy patients since the oral cavity and oropharynx have no connection to the airway. Even so, it is advisable to intubate the trachea for protection in these patients during any significant bleeding episode. Once the airway is secure, the underlying cause of bleeding can be investigated and managed by a head and neck surgeon and/or interventional neuroradiologist.

Carotid Blowout

The most feared bleeding complication from SCCHN is carotid rupture (aka carotid blowout). Without immediate, aggressive intervention, carotid blowout is uniformly fatal.

Before interventional angiography, hemostasis for carotid artery rupture was obtained via an open surgical approach. This was associated with 60 % neurological morbidity and 40 % mortality. More recently, endovascular stenting of a carotid artery rupture has shown >80 % survival and far fewer neurological events. However, endovascular stent placement without further treatment has a recurrent bleeding up to 26 % [21]. So, the patients who are successfully resuscitated and stented should undergo subsequent definitive surgical management (e.g., overlying soft tissue flap reconstruction) to prevent further bleeding episodes [22]. In dire cases, the ipsilateral carotid artery can be permanently occluded, albeit with at least a 15–20 % risk of delayed cerebral complications [23].

Internal Jugular Vein Bleeding

Internal jugular vein bleeding, although rarer than carotid artery bleeding, can occur after treatment of SCCHN. These are typically less severe, characterized by multiple episodes, and aggravated by coughing [24]. Internal jugular vein bleeding is almost uniformly associated with a pharyngocutaneous fistula [24]. The treatment is surgical exploration of the wound and ligation.

Tracheoinnominate Fistula

A tracheoinnominate fistula (TIF) is a connection from the trachea to the innominate artery. It is a rare complication after tracheostomy placement ranging from 0.1 to 1 % in incidence and usually occurring between postoperative days 7 and 14 [23]. There a number of factors that can predispose a tracheostomy patient to this complication including lower placed tracheotomies, overinflated cuffs causing erosion of the trachea, and anomalies of the innominate or other large-caliber arteries [25]. Before this catastrophic event, there may be an ominous sign of milder pulsating bleeding from the tracheostomy (sentinel bleed) [25].

TIF has a high rate of mortality as it causes rapid exsanguination in combination with aspiration of large amounts of blood. The mortality rate approaches 100 %, even when surgical intervention is taken [26]. Definitive management of a TIF requires a sternotomy and vascular repair in the operating room. Placing direct pressure against the anterior tracheal wall can temporize the bleeding. This can be done either digitally with a finger or placing a cuffed tube, creating a temporary tamponade [25]. Endovascular embolization or placement of a stent graft of the innominate artery has also been described[23].

Epistaxis

Epistaxis is a common reason for presentation to the ED. Management of epistaxis from head and neck malignancy or after surgery is different from ordinary epistaxis and merits special considerations. A typical case of epistaxis can usually be watched and stopped with digital pressure and lubrication of the nasal mucosa with nasal saline spray and antibiotic ointment. Epistaxis in the setting of a sinonasal cancer can be more serious and should be handled more aggressively.

With active epistaxis, visualization with anterior rhinoscopy or endoscopy may not be possible depending on the volume of bleeding. The patient should be sitting up and positioned leaning forward to allow the bleeding to exit the nares and not down the airway. If the bleeding is severe, the airway may need to be secured with intubation. Packing if often required to tamponade uncontrolled epistaxis. There are dissolvable packing materials, such as cellulose polymers (Surgicel) and porcine skin gelatin (Gelfoam), and non-dissolvable packing materials, such as cross-linked polyvinyl alcohol (Merocel) and balloon packs (Rapid Rhino). A headlight, nasal speculum, and bayonet forceps should be used for the placement of packing. Other products such as topical thrombin components (Floseal) can be topically placed inside the nose to aid in hemostasis.

Management of Treatment Complications

Surgical Complications

There are risks of complications after surgery for SCCHN beyond those already covered in this chapter (airway and bleeding). The most common complications after surgery are edema and seroma formation.

After neck dissection (cervical lymphadenectomy), it is common for patients to develop lymphedema of the lower face and neck. Patients who receive adjuvant treatment including radiation therapy and chemotherapy can have profound lymphedema during after treatment. This most commonly presents in the neck and submental region with pitting and non-pitting edema [27]. Seroma is a collection of sterile, straw-colored serous fluid in a dead space of the surgical field and most commonly happens after neck dissection and thyroidectomy. A seroma can easily be mistaken for an abscess if the skin is red and tender. A white blood cell (WBC) may not be helpful as this can be elevated after surgery without infection. A key difference is that there are typically no clinical signs of severe infection (e.g., fever, sepsis) with seroma. If there is uncertainty, then sterile

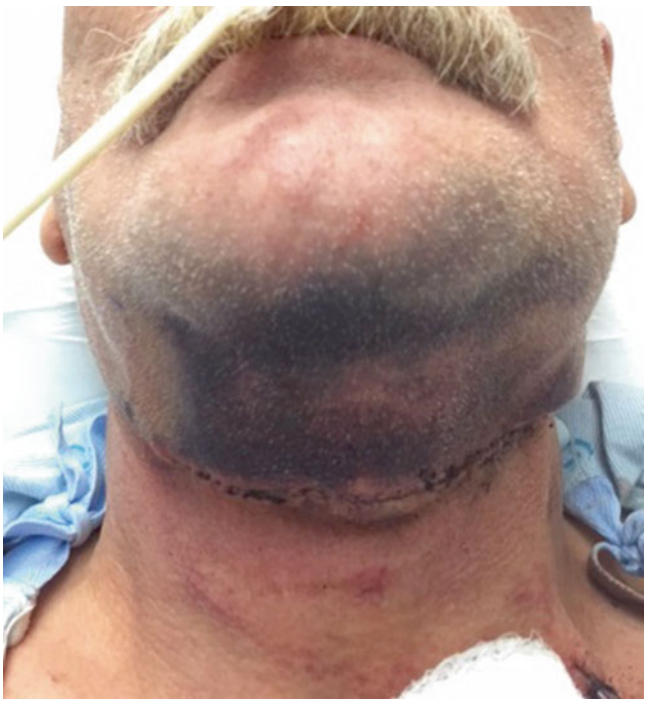

Fig. 7 Hematoma of the upper neck 24 h after neck dissection. Note ecchymosis of the overlying skin

needle aspiration of the fluid can be diagnostic. Seromas do not require emergent treatment.

In contrast to seroma, a hematoma is a collection of blood within the surgical bed and can occur in up to 4 % of all major head and neck cancer surgeries [28]. A hematoma can be distinguished from seroma by the presence of bruising and turgor of the overlying skin (Fig. 7). An expanding hematoma of the neck should be recognized as an emergency because of the potential for airway compression. The treatment of an expanding hematoma is evacuation of the hematoma and control of any bleeding vessels. This is best performed sterilely in the operating room to reduce the risk of infection but may be necessary at the bedside if the patient develops an unstable airway.

A chyle leak is an uncommon complication that can occur after surgery in the low neck. A chyle least can present in a similar manner to a seroma. The defining difference is that chyle has a characteristic milky color and can have inflammatory effects. Chyle leaks present soon after major neck surgery often when drains are still in place. Most chyle leaks occur on the left due to the presence of the thoracic duct emptying in the left subclavian vein near the internal jugular vein. Needle aspiration of a suspected chyle leak will be unproductive. Most chyle leaks can be managed conservatively with a no-fat diet and continuation of drain.

Salivary fistula is a complication distinct to surgery of the head and neck. A salivary fistula can present like a seroma but is treated differently. There may be other signs of infection including erythema, turbid fluid in the drain, purulence, or wound breakdown. Needle aspiration can be performed but the fluid should be tested for amylase which would be unique to saliva. Pharyngocutaneous fistula, when there is a connection from the pharynx to the skin, can occur after major head and neck surgery particularly in patients who have had prior treatment with radiation [29]. Treatment typically includes incision, drainage, and packing of the wound.

Radiation Therapy Complications

Radiation therapy (RT) is a commonly used method of treatment for head and neck cancer, particularly SCCHN. RT-related toxicities in the head and neck include erythema, ulceration, xerostomia, lymphedema, fibrosis, and osteoradionecrosis (ORN). RT has early and late effects on normal tissue. The early effects are caused by DNA damage and reactive oxygen species formation with resultant cell death to ciliated epithelium, blood vessels, and secretory glands [30]. The late effects are caused by ischemia from microvascular damage and fibrosis, which cause tissue edema, erythema, hemorrhage, and thickened secretions [30]. The combination of chemotherapy and radiation therapy (CRT) in the head and neck causes a synergistic effect on cancer cells but also has this effect on normal cells causing increased and more severe toxicities [31]. A large population-based study showed that 62 % of head and neck cancer patients receiving CRT and 46 % of patients receiving RT alone had a hospitalization or ED visit for an acute adverse effect [1]. The most prominent side effect of RT or CRT is dysphagia. Dysphagia is the result of tissue fibrosis, mucositis, laryngopharyngeal dysmotility, and xerostomia [32]. Severe dysphagia can lead to malnutrition, aspiration, and pneumonia.

A complication unique to RT of the head and neck is osteoradionecrosis (ORN) of the jaw. ORN of the jaw is a result of direct and indirect (loss of saliva) tissue effects that culminate in poor bone healing [33]. The patient can present with recurrent or chronic pain, mandible fracture, and exposed bone in the oral cavity. ORN of the jaw after RT is often precipitated by a dental procedure. Radiation-induced necrosis of cartilage is also a well-known complication of RT. For example, radiation-induced necrosis of the larynx can occur even years after treatment [34]. Differentiating radionecrosis of the larynx from recurrent cancer can be difficult. Diagnosis is based on examination and clinical suspicion.

Chemotherapy Complications

Patients receiving chemotherapy can manifest complications in the head and neck. For primary SCCHN, chemotherapy is often used in combination with RT for definitive treatment or

alone a palliative therapy. Some common agents used for SCCHN include cisplatin, carboplatin, 5-fluorouracil, docetaxel, and cetuximab. These drugs can cause nausea and vomiting, renal failure, myelosuppression, thrombocytopenia, mucositis, and neuropathy. The majority of patients treated with CRT experience severe mucositis [35]. This can lead to decreased quality of life, weight loss, gastrostomy dependence, and increased ED visits and hospitalizations [36]. When symptoms are severe enough, up to one-third of SCCHN patients will require hospitalization [37]. The most common reason for presentation to the ED during or after CRT is dehydration and malnutrition. Symptoms can be ameliorated with topical lidocaine or "magic mouthwash," which usually includes topical lidocaine, steroid, antifungal, and antibiotic. Finally, acute hearing loss can occur from the administration of chemotherapy, most notably cisplatin. Sudden-onset tinnitus may be an early sign of acute hearing loss. Steroids and discontinuation of cisplatin may limit the loss of hearing. However, cisplatin-induced hearing loss is generally permanent.

Common Pitfalls

Neck Abscess Versus Occult SCCHN Cystic Cervical Lymph Node Metastasis

The work-up of a patient presenting to the ED with a neck mass often includes a contrast-enhanced CT of the neck. It is common that the only abnormality observed is a fluid-filled collection with peripheral rim enhancement (Fig. 8a, b). In an adult, this almost invariably represents occult SCCHN metastatic to a cystic or necrotic lymph node in the neck. It can unfortunately be misinterpreted as an abscess, particularly if there is redness of the skin and tenderness [38]. Unlike an abscess, these patients will usually lack the cardinal findings of infection, fever, and elevated WBC. Fine-needle aspiration (FNA) biopsy is the most appropriate diagnostic test of any persistent neck mass >2 cm in an adult patient. Incision and drainage is strongly discouraged without a definitive diagnosis of abscess as it can substantially alter the management of a patient with occult SCCHN metastatic to a cervical lymph node.

Sinusitis Versus Occult Sinonasal Malignancy

Acute bacterial sinusitis is a common diagnosis for patients presenting to the ED. Sinonasal cancer, on the other hand, is exceptionally rare. However, patients with cancer involving the sinuses are often treated unsuccessfully for sinusitis for weeks or months before an alternative diagnosis is entertained. The result is a delay in diagnosis that can impact the stage of disease, treatment options, and prognosis.

There are a few key differences between patients with sinusitis and sinonasal malignancy. First, the clinical presentation is strikingly different. Patients with sinonasal cancer most often present with unilateral, rather than bilateral symptoms. Unilateral nasal obstruction, persistent nasal bleeding, facial pain or pressure, facial numbness, visual changes, and/or epiphora should be carefully evaluated for a possible sinonasal malignancy. This could most readily be accomplished with a sinus CT. Any unilateral opacification of the sinuses should prompt timely referral to an otolaryngologist (Fig. 9).

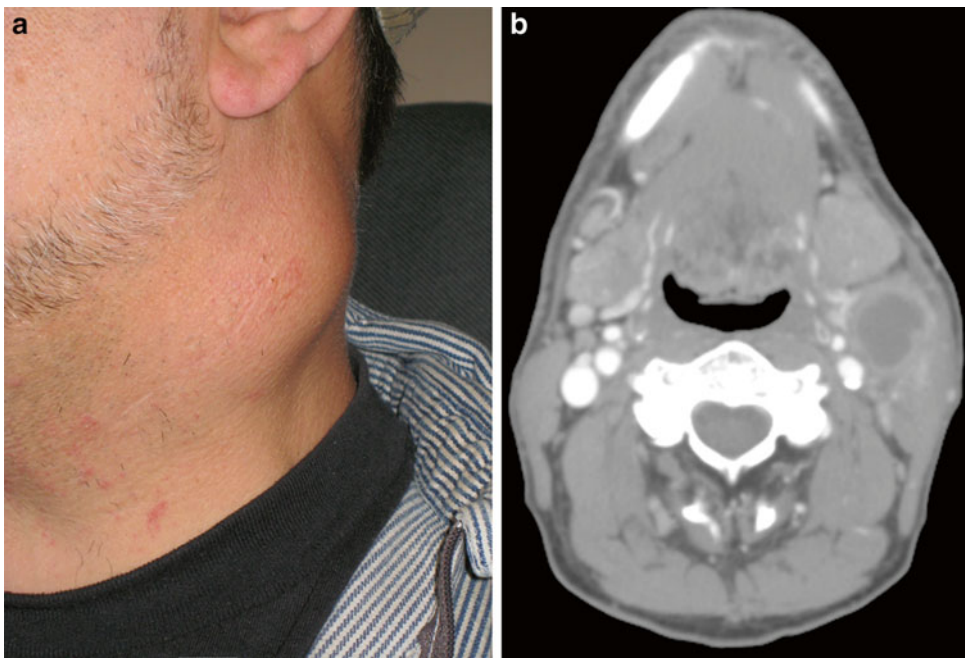

Fig. 8 Patient presenting with a non-tender left-sided neck mass (**a**) which appears cystic on axial computed tomography (CT) imaging (**b**). Any lateral neck mass in an adult should be considered cancer until proven otherwise, regardless of smoking status or other risk factors

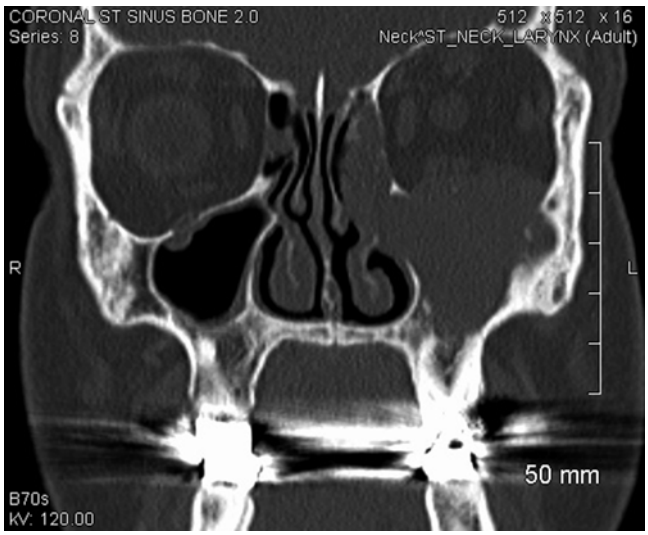

Fig. 9 Coronal computed tomography (CT) of the sinuses demonstrating a left-sided nasal cavity mass with opacification of the left maxillary sinus and ethmoid sinuses and invasion into the ipsilateral orbit. Any unilateral opacification of the sinuses is concerning for malignancy

Ear Infection Versus Occult SCCHN of the Oropharynx

Unilateral otalgia is a common presenting symptom of SCCHN involving the oropharynx, including the tonsil or base of the tongue. Other common causes of ear pain are infection and temporal mandibular joint (TMJ) disorder. It is important for medical practitioners in the ED to be able to distinguish between benign and malignant causes of ear pain. Similar to occult sinonasal malignancy, a delay in diagnosis is common for patients with SCCHN of the oropharynx.

The incidence of SCCHN involving the oropharynx (tonsil or base of the tongue) continues to increase dramatically [39]. This has been attributed to the human papillomavirus (HPV) which is now associated with >70%of these cases. Patients with HPV-associated SCCHN tend to be younger and are more often nonsmokers [40]. So they are often not thought to be at risk of head and neck cancer. However, unilateral otalgia without clinical findings of an ear infection (e.g., ear drainage, middle ear effusion, painful ear canal) should prompt a thorough evaluation of the oropharynx by a specialist to rule out occult malignancy.

Summary

The UADT is a complex area where functions of breathing and eating take place in a highly vascularized area. Patients with SCCHN will present to the ED with difficult airways. The initial physician must have a preconceived plan for airway control in these patients. Anatomy and physiology of the surgically altered airway in patients with tracheostomies and laryngectomies are essential topics to know for appropriate acute care of neck breathers. Bleeding related to treatment of SCCHN can be catastrophic. Therefore, control of the airway along with methods to temporize the patient is important. The use of pressure to tamponade a hemorrhage along with shock trauma principles can be employed before definitive management by the head and neck surgeon. There are other complications of treatment related to surgery, radiation therapy, and chemotherapy that must be recognized to prevent further complications. To avoid common pitfalls of SCCHN management, the ED physician must also be aware of distinctions between signs of malignancy and common otolaryngologic symptoms, as improper treatment can significantly decrease a patient's prognosis.

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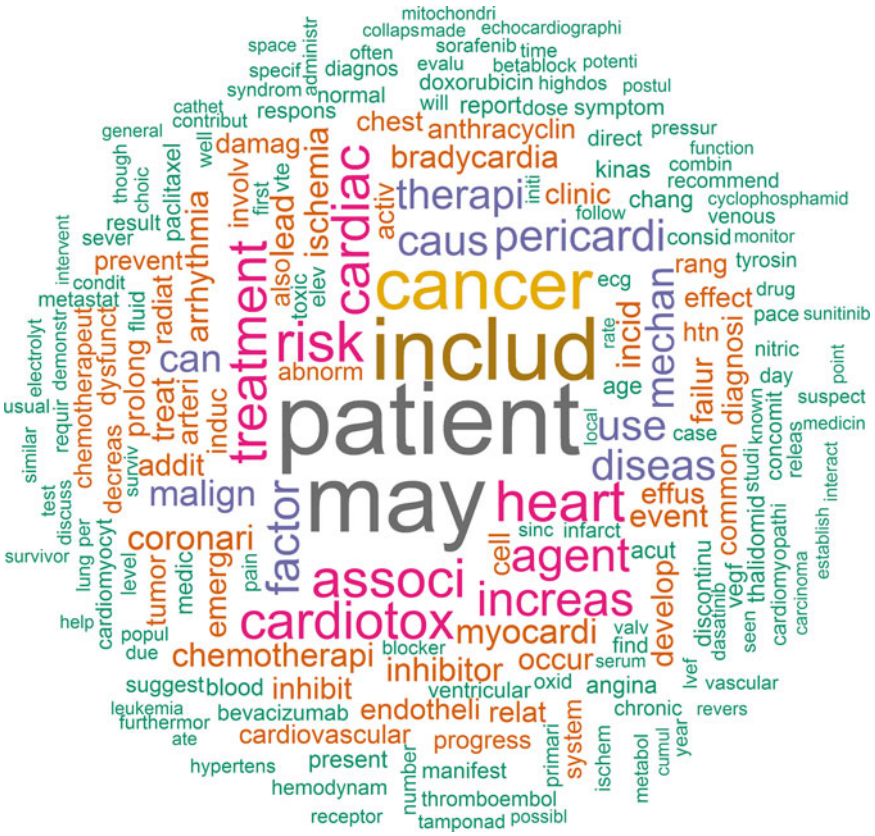
Cardiovascular Emergencies

Adam H. Miller



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Introduction

In this chapter we will explore, in some detail, cardiovascular conditions encountered in oncologic emergency medicine and discuss chemotherapy and radiotherapy contributions to their etiology. The chapter will discuss potential and known mechanisms of action for commonly used cancer therapies. Furthermore, comprehensive diagnosis and treatment discussions will provide emergency physicians with the tools to manage oncology-related cardiovascular emergencies encountered in clinical practice.

The most common oncocardiologic emergencies involve (1) arrhythmias, (2) ischemic heart disease, (3) heart failure, (4) thromboembolic disease, (5) hypertension, and (6) malignant pericardial effusion.

Arrhythmias

Arrhythmias often require patients to seek emergency department (ED) attention. Arrhythmias may be related to a patient's malignancy and cancer treatment or may be the result of an unrelated medical problem. Milder symptoms include "palpitations" or "fluttering in the chest," while more serious sequelae include near syncope or syncope. Patients may present after experiencing transient or permanent neurologic deficits, peripheral embolization, or acute claudication as the result of clot migration.

(a) Primary arrhythmias are disturbances that arise from cardiac and pericardial structures. These can be caused by focal (involving one or more localized areas of the myocardium) or diffuse abnormalities. These can occur in cancer and non-cancer patients and may be related to ischemia; increased intracardiac pressure and wall stress; congestive, hypertrophic, and infiltrative cardiomyopathy (CMP); and fibrosis related to age. Several other abnormalities may be more common in the cancer patient including intracardiac thrombi, primary (benign myxomas, malignant sarcomas) and metastatic malignant intracardiac tumors (carcinoma of the lung, breast, malignant melanoma, lymphoma, and leukemia), amyloid infiltration, myopericarditis, pericardial constriction, and cardiomyopathy related to antitumor agents.

(b) Secondary arrhythmias arise from unidentifiable structural or localized metabolic abnormalities including general toxic reactions to drugs or chemicals; increased sympathetic states related to anxiety; mediator release, i.e., pheochromocytoma, carcinoid tumors, or hyperthyroidism; and derangements of metabolism, i.e., fluid and electrolyte abnormalities. Additionally in cancer, tumor lysis may create an environment that is arrhythmogenic [109].

Table 1 Incidence of QT prolongation in patients associated with specific chemotherapeutic agents including arsenic trioxide, dasatinib, lapatinib, nilotinib, and vorinostat

Chemotherapeutic agent	Incidence of QT prolongation
Arsenic trioxide	26–93 % (may persist from 1 to 5 weeks after infusion) [14, 87, 88]
Dasatinib	<1–3 % (FDA website) [14]
Lapatinib	Up to 16 % [14]
Nilotinib	1–10 % [14, 89, 90]
Vorinostat	3.5–6 % [14]

1. *QT prolongation* may lead to ventricular arrhythmias (Table 1). Cancer patients are at increased risk of QT prolongation since 16–36 % have baseline ECG abnormalities [79, 86]. The cancer patient is commonly treated with QT-prolonging medications other than the chemotherapy, including antiemetics, antifungals, and quinolone antibiotics. Other comorbidities that may be arrhythmogenic include structural heart disease, renal or hepatic dysfunction, and electrolyte abnormalities resulting from vomiting, diarrhea, and decreased oral intake.

   Mechanism: the mechanism by which these chemotherapeutic agents cause QT prolongation is in part blockage of delayed rectifier potassium current [91].

   Diagnosis of QT prolongation is made by ECG interpretation. The ECG-QTc interval is considered normal when ≤440 ms and prolonged in men and women if longer than >450 and >470 ms, respectively. Increases of ≥60 ms from baseline or >500 ms after administration of a medication raise the risk of an arrhythmia. Predisposing factors include female gender, heart failure (HF), elderly age, myocardial infarct (MI)/ischemia, electrolyte imbalances, bradycardia, and chemotherapeutic medications mentioned above [91].

   Treatment includes periodic ECG monitoring and assessment for other agents and conditions that increase the risk of QT prolongation, i.e., electrolyte abnormalities (secondary arrhythmia), congenital long QT syndrome, concomitant antiarrhythmic medicines or other drugs known to cause QT prolongation, and cumulative high-dose anthracycline therapy. Dosage adjustment and/or discontinuation of predisposing agents may be required [14]. Emergency complications of QT prolongation include ventricular arrhythmias, particularly torsade de pointes.

   Treatment of torsades de pointes (polymorphic ventricular tachycardia) includes intravenous magnesium sulfate 2 g initially regardless of the serum magnesium level. Nonsynchronized defibrillation may be appropriate if sustained, hemodynamically unstable polymorphic ventricular tachycardia or fibrillation develops. Overdrive transcutaneous pacing may be indicated to shorten the QTc. Pacing is effective in preventing recurrence and may be useful in cases refractory to magnesium or when

torsades de pointes is precipitated by bradycardia. If overdrive pacing is initiated, short-term pacing rates of 90–110 beats per minute should be used. Isoproterenol titrated to a heart rate of ≥90 beats per minute is another option and is useful when temporary pacing is unavailable or while preparing for intravenous catheter insertion. Remember to always maintain serum potassium levels in the high-normal range and discontinue any QT-prolonging medications and drugs interfering with patients' metabolism [93]. The goal in the emergency setting must be directed toward hemodynamic stabilization, discovery of correctable pathologies, and control of symptoms.

2. *Bradycardia and heart block* in cancer patients may be caused by fibrosis due to old age or radiation therapy, amyloidosis, and primary cardiac tumors (primary arrhythmia) as these are conditions that potentially affect the cardiac conduction system [79]. Additionally, bradycardia and heart block have been associated with the chemotherapeutic agents paclitaxel and thalidomide.
   (a) Paclitaxel cardiotoxicity manifests with an asymptomatic bradycardia that is reversible [67, 80, 81], and the incidence of this manifestation ranges from between <0.1 and 31 % [14, 66, 67, 80, 81].

   Mechanism postulated for paclitaxel to cause arrhythmias is via its effects on the Purkinje system or extracardiac autonomic control [80]. Additionally, the vehicle Cremophor EL that paclitaxel is formulated in may cause cardiac disturbances. In the case of hypersensitivity reactions, Cremophor EL is known to induce histamine release [66]. Histamine release in the cardiac tissue can increase myocardial oxygen demand as well as coronary vasoconstriction and chronotropic effects [67].

   (b) Thalidomide-induce bradycardia is reported to occur in 0.12–55 % of patients treated [82–84].

   Mechanism of this induced bradycardia has been postulated to be due to central sedative effects or an activation of the vasovagal pathway. Thalidomide reduces tumor necrosis factor-alpha levels causing rapid and complete inhibition of the dorsal motor neurons (part of the nucleus of the vagus nerve). This could lead to over-reactivity of the parasympathetic nervous system resulting in bradycardia. Additionally, thalidomide-induced hypothyroidism may cause bradycardia [83, 85].

   Diagnosis of bradycardia is typically defined as a heart rate <60 beats per minute. Thyroid disease or electrolyte abnormalities should be considered for these cases.

   Treatment for bradycardia associated with paclitaxel can range from monitoring only to pacemaker implantation. Cardiac monitoring for the first hour of paclitaxel infusion is recommended [14]. Bradycardia associated with thalidomide use depends on the severity of clinical symptoms. Certainly if symptoms are clinically significant, the agent should be discontinued. If third-degree heart block is present, a permanent pacemaker is indicated. All concomitant medication inducing bradycardia including beta-blockers, calcium-channel blockers, and digoxin should be discontinued.

Ischemic Heart Disease

When a cancer patient presents to the ED experiencing chest pain [50], they often require a workup and treatment for myocardial ischemia. Chest pain can be a manifestation of unstable angina and acute coronary syndrome both of which refer to more serious cardiac etiologies of ischemic heart disease. Unstable angina includes new-onset angina, angina at rest, acceleration of angina, and post-infarct angina. Acute coronary syndrome encompasses unstable angina but additionally includes non-ST elevation and ST-elevation myocardial infarction [110]. Therapies to combat cancer that may be associated with increased risk of coronary artery disease and/or acute coronary syndrome (ACS) include radiation and chemotherapy. Some of the chemotherapeutic agents implicated include:

1. Alkylating agents including cyclophosphamide: These have been postulated to cause intracapillary microemboli and resultant ischemic myocardial damage [13, 27]. Furthermore, coronary vasospasm has been proposed as a mechanism by which cyclophosphamide cause ischemia [10].
2. Antimetabolites include capecitabine (Xeloda) and 5-Fluorouracil (Adrucil). The most common symptom of 5-Fluorouracil (5-FU) cardiotoxicity is angina-like chest pain. It is less commonly associated with myocardial infarction (MI), arrhythmias, heart failure (HF), cardiogenic shock, and sudden death [51, 52]. The incidence of cardiotoxicity associated with 5-FU ranges in the literature between 1 and 68 % [10, 51–58]. Cardiac events occur within 2–5 days after initiation of therapy and may last up to 48 h [51]. Ischemic electrocardiogram (ECG) changes have been reported in 68 % of patients; however, only 43 % have elevations of serum cardiac markers [59]. Mortality is estimated to be 2.2–13 % [54, 57]. High doses (>800 mg/m^2) and continuous infusions are associated with increased risk for cardiotoxicity (7.6 %) as compared to bolus injections (2 %) [51, 54, 59]. Other risk factors for cardiotoxicity include history of cardiovascular disease, prior mediastinal radiation, and concurrent use of chemotherapy [52–55, 57, 58]. Capecitabine-induced cardiotoxicity (including myocardial ischemia/infarct) incidence is between 3 and 9 % [52, 55, 60, 61]. Typical anginal

symptoms appear 3–4 h after therapy with dosages ranging from 1500 to 2500 mg/m^2/day [51–60]. ECG changes including ST-segment elevations are noted in many cases while serum cardiac markers are normal [51–60]. Furthermore, echocardiography and coronary angiograms are often normal, and previous cardiac disease is not a consistent risk factor [51–65]. Coronary artery thrombosis, arteritis, or vasospasm has been suggested though unproven as the pathogenesis of cardiotoxicity associated with 5-FU and capecitabine [55]. Other mechanisms may include direct myocardial toxicity, interaction with the coagulation system, and autoimmune responses [55, 62].

3. Antimicrotubule agents, including paclitaxel (Taxol), have been described in cases of myocardial ischemia/infarct. Several clinical trials report cardiac ischemia in 5 % of patients [66], though others have reported a lower incidence [67]. In the case of docetaxel (Taxotere) administration, the incidence of MI is 1.7 % [14, 68]. Myocardial ischemia associated with paclitaxel is thought to be augmented by underlying heart disease though the Cremophor EL vehicle in which it is formulated is perhaps responsible for toxicity related to its induction of histamine release [66].
4. Monoclonal antibody-based tyrosine kinase inhibitors, including bevacizumab (Avastin), cause arterial thrombotic events (ATEs) more frequently in cancer patients treated with combination chemotherapy rather than as a single agent [14]. In a pooled analysis of five trials treating metastatic colorectal cancer, non-small cell lung cancer, and metastatic breast cancer, the overall ATE incidence was 3.8 % [69]. MI/angina is reported to occur in 0.6 % of bevacizumab-treated patients [69]. ATEs may occur at any time during therapy, with the median time to event being approximately 3 months. These events are not associated with dose or cumulative exposure. Age >65 and a previous ATE are risk factors [69, 70]. The *mechanism* associated with bevacizumab-induced arterial thrombosis is thought to involve VEGF. VEGF stimulates endothelial cell proliferation, promotes endothelial cell survival, and helps maintain vascular integrity [71]. Thus, anti-VEGF therapy may decrease the regenerative capability of endothelial cells in response to trauma, leading to endothelial cell dysfunction and defects in the interior vascular lining, exposing subendothelial collagen. This exposure to collagen-activated tissue factor increases the risk for thromboembolic events [71, 72]. Additionally, inhibiting VEGF causes a reduction in nitric oxide and prostacyclin and increases hematocrit and blood viscosity via overproduction of erythropoietin, predisposing the patient to thromboembolism [72].
5. Small-molecule tyrosine kinase inhibitors, including erlotinib (Tarceva) and sorafenib (Nexavar), are associated with MI/ischemia in 2.3 % of patients receiving 100 mg/day erlotinib with gemcitabine compared with 1.2 % when receiving gemcitabine alone for the treatment of pancreatic cancer [14, 73]. With regard to sorafenib, approximately 3 % of patients in clinical trials experience myocardial ischemia. Sorafenib is associated with a higher incidence of MI/ischemia compared to placebo among patients treated for renal cell carcinoma (3 % vs. <1 %) [74].

Diagnosis of ACS is made based on the patient's clinical presentation, ECG changes, and the elevation of cardiac enzymes [75, 76].

Treatment of patients with cancer and suspected ACS should follow established ACC and AHA guidelines [77]. Caveats to consider in the cancer patient with chest pain and suspected ACS are that coronary artery occlusion due to arterial embolism [111, 112] and coronary artery vasospasm that may or may not be related to anticancer therapy are considerably more common in the cancer patient than the general population. Treatment guidelines [77] include percutaneous coronary intervention, antiplatelet, and anticoagulant therapy, all of which can be complicated when treating an emergency cancer patient due to concomitant thrombocytopenia or recent surgery. The only data-driven intervention, albeit derived from a retrospective study, is that aspirin use improves 7-day survival in cancer patients with thrombocytopenia and ACS without increasing bleeding risk [78]. Also, beta-blockers use leads to improved 7-day survival in cancer patients with ACS [78]. When patients develop chest pain concurrent with 5-FU and capecitabine therapy, immediate cessation of the agent and antianginal therapy should be employed and an ischemia workup initiated. The use of vasodilators including nitrates and calcium-channel blockers is also advised. Decisions to restart the offending agent should be made by the treating oncology team. Sorafenib should be discontinued when patients develop cardiac ischemia, and bevacizumab should be discontinued if severe ATEs occur. In the emergent evaluation of cancer patients with suspected ACS, potentially correctable exacerbating factors (anemia, hyperthyroidism, or shunting of blood through a vascular tumor) and the increased risk of thrombolysis or revascularization (owing to increased bleeding or intracranial metastasis) should be considered prior to the initiation of a treatment plan. Thrombolytic agents are absolutely contraindicated in the presence of primary or metastatic brain lesions.

Heart Failure (HF)

Heart failure (HF) is newly diagnosed in 700,000 people each year in the United States. HF in cancer patients may be related to the malignancy or its treatment (Table 2). Several different coexisting factors may contribute to cardiac dysfunction. This cardiac dysfunction may remain subclinical until the systolic

Table 2 Clinically relevant findings to diagnose heart failure per the Framingham criteria [103] and the American College of Cardiology/American Heart Association classification [104]

Criteria source	Criteria/classification	Clinical findings/symptoms manifested in heart failure
Framingham criteria	Major criteria	Jugular vein distension
		Rales
		Paroxysmal nocturnal dyspnea or orthopnea
		Cardiomegaly
		Acute pulmonary edema
		S3 gallop
		Hepatojugular reflex
		Increased venous pressure >16 cm of water
	Minor criteria	Ankle edema
		Dyspnea on exertion
		Pleural effusion
		Tachycardia (>120 bpm)
		Hepatomegaly
		Night cough
		Vital capacity reduction of 1/3 from maximum
	Major or minor criteria	Weight loss of 4.5 kg or more in 5 days in response to treatment
American College of Cardiology/American Heart Association	Class I	Asymptomatic
	Class II	Mild symptoms with moderate exertion
	Class III	Symptoms with minimal activity
	Class IV	Symptoms at rest

function deteriorates below some trigger value. The clinically relevant findings to diagnosis HF are established as per the Framingham Criteria when either two major or one major and two minor criterion are present [103].

Patient with Class I and II heart failure can often be managed in the outpatient setting, while patients with Class III and IV heart failure often need admission to the hospital for symptomatic treatment.

The following discussion involves chemotherapy-associated left ventricular dysfunction (LVD) and/or heart failure (HF) [2, 3, 4] (Table 2).

1. Anthracycline agents, including doxorubicin (Adriamycin), epirubicin (Ellence), and idarubicin (Idamycin), can lead to acute, early-onset chronic progressive, and late-onset chronic progressive cardiotoxicity [6, 7]. Acute cardiotoxicity occurs in <1 % of patients immediately after anthracycline infusion and manifests with acute, transient decline in myocardial contractility. This is usually reversible [8]. The early-onset chronic progressive occurs in 1.6–2.1 % of patients during the first year [8] and the late-onset chronic progressive in 1.6–5 %. The late-onset chronic progressive form typically presents as a dilated cardiomyopathy in adults [7]. Late-occurring cardiotoxicity may not manifest clinically until 10–20 years after treatment. The risk of clinical toxicity increases with the cumulative dose of anthracycline, bolus administration, history of prior radiation, the use of other concomitant agents known to have cardiotoxicity, female gender, underlying cardiovascular disease, age (young and old), and an increased length of time since anthracycline completion [6, 7, 9]. These agents are more toxic in cancer patients with existing cardiac disease, particularly coronary artery disease. Pathophysiologic mechanisms of anthracycline cardiotoxicity, including doxorubicin, are dose dependent and involve redox cycling and the generation of reactive oxygen species (ROS). Zhang et al. demonstrated that cardiomyocyte-specific deletion of Top2b (encoding topoisomerase-IIb) protects cardiomyocytes from doxorubicin-induced DNA double-strand breaks and transcriptome changes responsible for defective mitochondrial biogenesis and ROS formation. In mice, cardiomyocyte-specific deletion of Top2b protects them from the development of doxorubicin-induced progressive heart failure, thus suggesting that doxorubicin-induced cardiotoxicity is mediated by topoisomerase-II beta [5]. Recent single-center studies suggest that ACE inhibitors and beta-blockers are efficacious in the treatment of chemotherapy-induced cardiomyopathy.
2. Alkylating agents including cyclophosphamide (Cytoxan) and ifosfamide (Ifex) have been associated with heart failure in 7–28 % of patients [10–13]. This cardiotoxicity may range from asymptomatic pericardial effusions to HF and myopericarditis [11, 13]. The risk of cardiotoxicity appears to be dose related and occurs within 1–10 days after administration of the first dose [10]. Additional risk factors include prior anthracycline or mitoxantrone therapy and mediastinal radiation [10, 12]. The pathophysiologic mechanism of cyclophosphamide cardiotoxicity is hypothesized to involve direct endothelial injury, followed by extravasation of toxic metabolites resulting in damage to cardiomyocytes, interstitial hemorrhage, and edema [10–13, 27]. Ifosfamide similarly may induce HF.
3. Antimetabolites including clofarabine may cause transient left ventricular dysfunction in up to 27 % of pediatric patients with acute lymphoblastic leukemia [14].
4. Antimicrotubule agents including docetaxel (Taxotere) are associated with HF incidence between 2.3 and 8 % [15, 16].
5. Proteasome inhibitors including bortezomib in the treatment of multiple myeloma are associated with the development of HF [17].
6. Monoclonal antibody-based tyrosine kinase inhibitors including bevacizumab and trastuzumab have been associated with the development of HF. In the former, the incidence is between 1.7 and 3 % [18, 19] and the later between 2 and 28 % [20, 21]. The mechanism of bevacizumab-induced HF may be related to uncontrolled

hypertension and inhibition of vascular endothelial growth factor (VEGF)/VEGF receptor signaling [28]. Trastuzumab and lapatinib may cause cardiotoxicity secondary to inhibition of cardiomyocyte human epidermal growth factor receptor 2 (ErbB2 signaling) by interfering with normal growth, repair, and survival of the cardiomyocytes [29–31]. Binding to ErbB2 may regulate mitochondrial integrity through the BCL-X proteins, leading to ATP depletion and contractility dysfunction [32, 33].

7. Small-molecule tyrosine kinase inhibitors including dasatinib, lapatinib, imatinib mesylate, and sunitinib have been associated with various cardiotoxicities. Dasatinib is associated with HF in 2 and 4 % of patients treated for leukemia [14]. Lapatinib is associated with LVD in 1.6 % [22]. Imatinib mesylate cardiotoxicity has been reported to be between 0.5 and 1.7 % [23, 24]. Sunitinib treatment of gastrointestinal stromal tumor and metastatic renal cell cancer is associated with LVD in 4–11 % of patients [25]. Dasatinib toxicity mechanisms may be similar to imatinib since they are both inhibitors of Abl. Dasatinib also inhibits Src and a number of other kinases that may be involved in the development of cardiotoxicity [28]. The mechanism of imatinib cardiotoxicity may be through inhibition of c-Abl [32, 34]. The possible mechanism of sunitinib cardiotoxicity, postulated from animal studies, points to its induction of mitochondrial damage in cardiomyocytes, but no apoptosis [26]. A hypothesized mechanism is that HTN may play an important role, since it may inhibit a receptor tyrosine kinase that helps regulate the response of cardiomyocytes in HTN. Additionally, it may inhibit ribosomal S6 kinase, leading to the activation of the intrinsic apoptotic pathway and ATP depletion [25]. Furthermore, coronary artery disease may be a risk factor associated with the development of HF [26].

Diagnosing to detect cardiac dysfunction during chemotherapy, regular monitoring of heart function is important. A baseline evaluation of LVEF should be obtained. Alexander et al. [35] first demonstrated serial assessment of LVEF to be useful in clinical practice. Furthermore, HF and cardiomyopathy should be defined utilizing a thorough clinical history and physical exam of the patient, combined with diagnostic testing including electrocardiograms, chest radiography, routine blood testing, and in the patient with suspected or known HF, to obtain noninvasive imaging, e.g., contrast echocardiography, and multi-gated acquisition scan [MUGA] to evaluate cardiac function [36]. Still, endocardial biopsy remains the gold standard for diagnosis of CMP. It is the most sensitive and specific; however, the invasiveness of the procedure limits its use.

Biochemical markers may be used to detect changes in LVEF. One study of troponin I demonstrated elevation soon after high-dose chemotherapy predicted the future development of LVEF depression [37], and another study demonstrated that troponin I elevation identifies patients at higher risks of future cardiac events [38]. Additionally, B-type natriuretic peptide is positively correlated with cardiac events and subclinical cardiotoxicity, more specifically to diastolic than systolic dysfunction [39, 40]. Preventive measures to minimize the risk of anthracycline-induced CMP relate to the cumulative lifetime dose of the drug [8]. Other measures recommended to decrease anthracycline-induced cardiotoxicity include continuous rather than bolus administration; use of anthracycline analogs including idarubicin, epirubicin, and mitoxantrone, or liposomal anthracyclines; and the addition of cardioprotectants including dexrazoxane. Dexrazoxane may cause cardiomyocyte-specific deletion of Top2b (encoding topoisomerase-IIb) that protects cardiomyocytes from doxorubicin-induced DNA double-stranded breaks and transcriptome changes that are responsible for defective mitochondrial biogenesis and reactive oxygen species (ROS) formation [5].

Treatment of anthracycline-induced HF includes beta-blockers and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker [41]. These interventions have been shown to reverse cardiac remodeling and improve survival. Advanced HF usually requires additional measures including diuretics, digoxin, or aldosterone antagonists. End-stage HF patients without cancer recurrence could be considered for synchronized pacing, ventricular assist devices, or cardiac transplant [41]. Enalapril has been shown to prevent a decline in LVEF as well as cardiac events in cancer patients treated with high-dose chemotherapy [42]. Other studies of angiotensin-converting enzyme inhibitors demonstrated that they do not prevent progressive cardiac dysfunction in all patients [43, 44]. Beta-blockers have also emerged as standard-recommended treatment [41] in anthracycline-induced CMP [45, 46]. Carvedilol may have some therapeutic advantages as it may possess some antioxidant properties [47, 48]. Trastuzumab-induced cardiotoxicity generally reverses over a mean time period of 1.5 months after discontinuation of the agent [49].

Venous Thromboembolism (VTE)

Cancer is a prothrombotic state. The risk of VTE appears to be highest in metastatic disease and in those with established risk factors. Risk factors include the use of central venous catheters and associated comorbidities including immobility, HF, atrial fibrillation, dehydration, and concurrent chemotherapy [79]. The following discussion will elaborate on several chemotherapeutic agents shown to induce VTE disease:

1. Cisplatin is a platinum-based therapy that increases the risk of thrombotic events. The incidence is between 8.5 and 12.9 % in those treated for urothelial transitional cell carcinoma [94]. Seventy-four percent of these events,

including DVT and PE, occurred within the first two cycles of treatment [94].
2. Vorinostat-associated TE incidence ranges from 4.7 to 8 % [14, 95, 96].
3. Thalidomide-associated TE incidence ranges from <5–58 %, depending on whether it is used in newly diagnosed patients or whether it is used in combination with dexamethasone or other chemotherapy, specifically doxorubicin [97–102]. The median time to an event is 3 months [99].
4. Lenalidomide-associated TE incidence ranges from 3 to 75 % 144–149. Similar to thalidomide, lenalidomide TE incidence rates vary based on whether it is used in combination with dexamethasone or other chemotherapy, including doxorubicin [102] and erythropoietin (75 %), in newly diagnosed patients [99, 102].
5. Erlotinib-associated TE events have been reported in 1.2 and 11 % of patients [14, 73].

The pathophysiology of VTE involved the baseline hypercoagulable state seen in cancer. The contributory factors include high levels of inflammatory cytokines with activation of the clotting system and inhibition of natural anticoagulant mechanisms, particularly the activated protein C system, impaired fibrin polymerization and reduced fibrinolysis, as well as alteration of endothelial surfaces.

Anticancer treatments contribute to thrombogenesis by the release of procoagulants and cytokines through chemotherapy-induced tumor cell damage, direct endothelial damage, as well as hepatotoxicity, leading to decreased production of normally produced anticoagulants [94]. With respect to the mechanism of cisplatin-associated TE, some evidence suggests that it induces platelet activation and aggregation, possibly involving monocyte procoagulant activity. Cisplatin-based therapies may also alter endothelial cell integrity [94]. Additionally, cisplatin may elevate von Willebrand factor levels, cause hypomagnesemia-induced vasospasm, and have antiangiogenic activity [131, 132]. With regard to thalidomide- and lenalidomide-associated TE, the mechanism may involve direct action on endothelial cells previously damaged by doxorubicin [98]. It may also involve interactions between platelets and the endothelium [100, 133]. Increased platelet aggregation and von Willebrand factor have been found in patients treated with thalidomide.

Diagnosis: The test of choice for DVT is compression ultrasonography, as it is both sensitive and specific. When PE is suspected, spiral computed tomography angiography is the diagnostic test of choice. Nuclear medicine techniques, e.g., ventilation/perfusion scan, can also be utilized. Magnetic resonance pulmonary angiography may be considered in patients who have contraindications to iodinated contrast media [99].

Prevention of TE associated with thalidomide and lenalidomide has been investigated by the International Myeloma Working Group who recommend tailoring the choice of thromboprophylaxis based on individual risk factors including age, obesity, previous VTE, central venous catheter, immobility, comorbidities, concomitant medications, surgery, inherited thrombophilia, myeloma-related risk factors (diagnosis and hyperviscosity), and myeloma therapy-related risk factors (concomitant steroids, doxorubicin). When using thalidomide and lenalidomide alone, no therapy is recommended. Otherwise, aspirin (81–325 mg) may be used in patients with no risk factors or ≤1 risk factor for VTE. Low-molecular-weight heparin (LMWH) equivalent to 40 mg enoxaparin or full-dose warfarin is recommended for those with two or more individual/melanoma-related risk factors or those receiving concomitant high-dose dexamethasone or doxorubicin [99].

Treatment of TE is to relieve symptoms and prevent embolization and recurrence. Treatment should adhere to guidelines put forth by the American College of Chest Physicians. Treatment of patients with TE and cancer should consist of low-molecular-weight heparin (LMWH) for the first 3–6 months, followed by either warfarin or LMWH indefinitely or until the cancer is resolved [134].

Hypertension (HTN)

Hypertension (HTN) and cancer are common (37 %) [92, 113]. The prevalence before chemotherapy is similar to that in the general population (29 %) [114]. The chemotherapeutic agents given these patients to treat their cancer disrupt angiogenesis, thereby inducing the development of HTN [92] (Table 3). The mechanism of antiangiogenic therapy-related HTN is thought to be related to VEGF inhibition. VEGF inhibition decreases nitric oxide production in the wall of the arterioles and other resistant vessels [71]. As nitric oxide is a vasodilator, its inhibition promotes vasoconstriction, increased peripheral vascular resistance, and blood pressure [71].

Bevacizumab decreases endothelial nitric oxide synthetase activity which may stimulate plasminogen activator inhibitor-1 expression, leading to an increased risk of HTN [120]. Other hypotheses include that VEGF inhibition may affect the renin–angiotensin system [121] and may also be

Table 3 Common chemotherapeutic agents and their associated incidence of hypertension

Chemotherapeutic agent	Associated incidence of hypertension
Bevacizumab	The incidence is 4–35 % [18, 19, 115–117]. Treat with antihypertensive agents while bevacizumab is continued [14]
Sorafenib	17–43 % of those treated [74] [118, 119],
Sunitinib	Ranges from 2 to 8 % [124, 125]. HTN is seen within the first 4 weeks of therapy [26]

responsible for cholesterol emboli syndrome leading to bevacizumab-induced complications [122, 123].

Diagnosis of HTN is defined by the Seventh Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure as blood pressure ≥140/90 mmHg.

Treatment of antiangiogenic therapy-induced HTN requires standard antihypertensives. Bevacizumab-, sorafenib-, and sunitinib-induced HTN may require combination antihypertensives, and the question of chemotherapy discontinuation is controversial. ACE inhibitors may be preferred as first-line therapy due to their ability to prevent proteinuria and plasminogen activator inhibitor-1 expression [120] and their potential to reduce microcirculatory changes, decrease the catabolism of bradykinin, and increase release of endothelial nitric oxide [116]. Consideration of drug–drug interactions is advised in sorafenib-treated patients. Sorafenib is metabolized via the cytochrome p450 system, mainly by CYP3A4. Dihydropyridine calcium-channel blockers, e.g., diltiazem and verapamil, should not be used as they are similarly metabolized. Amlodipine or nifedipine is preferred. Phosphodiesterase inhibitors or nitrates to increase nitric oxide levels have been suggested, though not proven, to be effective [126]. As HTN is a risk factor for HF, it may be beneficial to deploy medications that prevent morbidity and mortality of HF including carvedilol, metoprolol succinate, ACE inhibitors, and angiotensin receptor blockers.

Malignant Pericardial Effusion

Malignant pericardial effusion occurs when there is excess fluid collection in the pericardial space (sac) caused by malignancy. This condition usually occurs because of obstruction of lymphatic drainage or an excess of fluid secretion from tumor nodules on the pericardial surface. Normally, the pericardial sac contains a small amount of pericardial fluid (25–35 ml), and it has a very limited ability to distend. When larger amounts of pericardial fluid develop rapidly, a pericardial effusion may progress to tamponade. Patients may present with fatigue, dyspnea, orthopnea, pleuritic chest pain, syncope, or arrhythmia. Physical exam findings range from normal sinus to sinus tachycardia, jugular venous distention, organomegaly, pulsus paradoxus (>10 mmHg drop in systolic blood pressure during inspiration), lower extremities edema, hypotension, and, eventually, circulatory collapse. Pulsus paradoxus can be seen in the absence of tamponade in patients with lung cancer or other conditions accompanied by significant lung disease or cor pulmonale. In patients with chest malignancies, a finding of pulsus paradoxus suggests effusion, but not necessarily, tamponade.

Diagnosis includes EKG findings of low QRS voltage, electrical alternans, and nonspecific ST-T wave changes. Chest radiographs may reveal cardiomegaly ("water-bottle" silhouette). Computed tomography and magnetic resonance imaging frequently detect pericardial effusion as an incidental finding. These modalities have limited ability to quantify the effusion. Two-dimensional echocardiography is the diagnostic test of choice since it can help with establishing diagnosis and also guide management. Size of the pericardial effusion is typically graded as minimal, small, moderate (<2 cm), or large (>2 cm). Fibrous strands are frequently seen in the pericardial space by echocardiography but are difficult to differentiate from the occasional tumor mass invading the pericardial space. Echocardiographic signs of cardiac tamponade include right atrial compression and diastolic collapse of the right ventricle as well as cardiac "rocking" (a side-to-side or front-to-back movement of the heart) [106]. Alterations in the respiratory variation of Doppler flow patterns across the mitral valve can be helpful in evaluating the hemodynamic effects of pericardial effusion. Inferior vena cava dilatation that does not collapse with inspiration ("sniffing") and (occasionally) left atrial collapse in late diastole and early systole may be seen. Doppler criteria for cardiac tamponade include a 25 % decrease in E-flow velocity amplitude during inspiration seen on the flow pattern of the mitral valve and/or a 25 % decrease in flow velocity across the tricuspid valve with expiration.

Common neoplasms associated with malignant pericardial disease are carcinomas of the lung and breast. Malignant melanoma is the tumor most likely to metastasize to the heart. Lymphomas (both Hodgkin's and non-Hodgkin's), leukemias, and gastrointestinal neoplasms are also associated with pericardial effusions [105]. Although malignant pericardial effusion can occur as an early manifestation, they are usually a late finding in patients with metastases. The majority of patients are asymptomatic, and the effusion is discovered incidentally on cardiac ultrasound ordered for other reasons during their treatment.

Treatment depends on the patient's hemodynamic stability. Echocardiography-guided pericardiocentesis with the placement of a drainage catheter into the pericardial space is the treatment of choice in patients with hemodynamic compromise [108]. Complications are infrequent though pericardial bleeding can result when a coronary artery is damaged, and pneumothorax is especially common in patients with coexisting emphysema.

A surgical pleuropericardial window can be made to obviate the need for repetitive pericardiocentesis. This is usually achieved in the operating room setting; however, it is possible to perform under local anesthesia in the ED or intensive care unit.

For patients with hemodynamic compromise and a rapid accumulation of fluid, the pleuropericardial window offers the most definitive therapy. The use of local chemotherapeutic agents or agents given to sclerose the pericardium will prevent fluid reaccumulation in many patients [107].

Cardiovascular Effects of Radiotherapy

Radiation therapy to the chest area can cause heart damage by four mechanisms. Radiation heart damage can (1) produce direct muscle fiber damage leading to progressive loss of heart function, (2) injure vessels supplying the heart muscle with blood leading to ischemia and possible myocardial infarction, (3) cause pericardial inflammation leading to compression and constriction of the heart muscle, and (4) cause valve damage leading to valve narrowing or leakage [129]. Evidence suggests that mean radiation doses of ≤20 Gy to the heart increase the risk of cardiotoxicity [127, 128] and that interactions of radiation and other drug treatments, i.e., anthracyclines and tyrosine kinase inhibitors, and conventional cardiovascular risk factors, i.e., smoking and hypertension, can compound cardiotoxicity risk.

Because cancer is one of the two most common causes of mortality and morbidity worldwide [1, 130], we have provided you with the most relevant data concerning the cardiovascular side effects of chemo- and radiation therapy. As medicine becomes more able to treat malignancy and the number of survivors in the adult population increases, so does the likelihood of encountering a patient complaining of manifestations of these antineoplastic interventions [1].

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Pulmonary Complications in Cancer Patients

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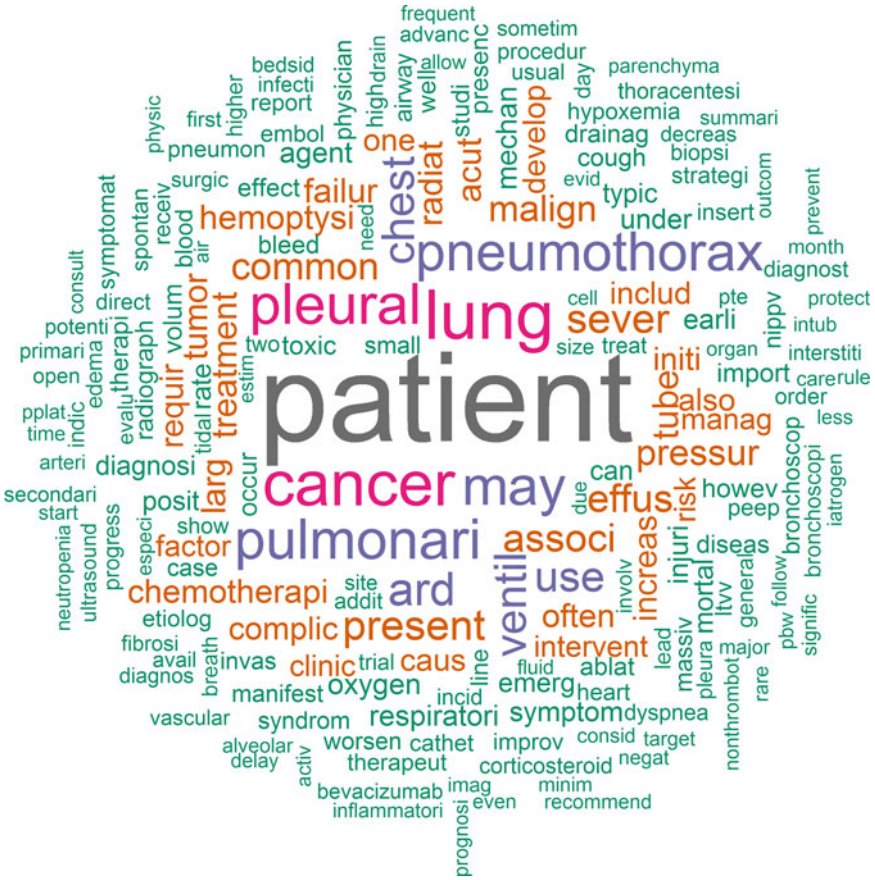

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Introduction

The number of patients alive with cancer has been increasing steadily [1]. This is directly linked to an aging population, improved diagnostic and screening tools for cancer, more advanced therapy, and decrease in cancer-related mortality. The age-adjusted invasive cancer incidence rate in the United States is 533.8 per 100,000 population [2]. More than 1.4 million people were projected to be diagnosed with cancer in the United States in 2009. In Europe, there were an estimated 3,191,600 cancer cases diagnosed and 1,703,000 deaths from cancer in 2006 [3]. Intensive chemotherapy regimens and the use of new and more targeted therapeutic drugs have resulted in high cancer cure rates. However, the treatment often leads to repeated invasive procedures, drug-related organ toxicities, and increased susceptibility to infection. As a consequence, emergency department (ED) physicians and intensivists are increasingly managing cancer patients presenting with one or multi-organ dysfunction. Pulmonary complications include respiratory failure, including acute respiratory distress syndrome (ARDS), pleural diseases (such as pleural effusion or pneumothorax) chemotherapy, or radiation-induced pulmonary toxicity, hemoptysis, and pulmonary embolism.

Respiratory Failure, ARDS, and Ventilator Management

Respiratory Failure

The most common life-threatening condition patients with cancer is acute respiratory failure (ARF) [4]. In fact ARF occurs in up to half of patients being treated for malignancies [5]. It is often associated with high mortality, especially in those who require mechanical ventilation [6]. Etiologies of respiratory failure in cancer patients are many. The most frequent include pneumonia, cardiogenic pulmonary edema, ARDS, chemotherapy or radiation-induced lung injury, pneumothorax and bronchopleural fistula, large pleural effusions, hemoptysis, and thrombotic/non-thrombotic embolus [7–9].

Acute Respiratory Distress Syndrome (ARDS)

ARDS represents an acute and diffuse inflammatory lung injury. It leads to increased pulmonary vascular permeability, acute inflammation of the alveolar walls, and diffuse alveolar damage [10]. Clinical hallmarks of ARDS are hypoxemia and bilateral radiographic opacities in the absence of heart failure. The hypoxemia is profound as defined by a ratio of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) of 300 or less. ARDS is further subdivided into mild (300–201 ratio), moderate (200–100 ratio), and severe ($\leq$100 ratio) [11].

ARDS in patients with malignancies is not well studied, as often these patients were excluded from ARDS trials. Few studies are available, especially in patients with neutropenia. Higher mortality was noted overall in retrospective assessment of ARDS network trials and was attributed to a more severe presentation and an advanced age [12, 13]. The mortality of cancer patients with ARDS in these trials was 54 % compared to 24 % in non-cancer patients [12]. The presence of neutropenia is one important contributing factor; whether a manifestation of the underlying cancer or secondary to chemotherapy. Severe pulmonary infections are more common. Also lung injury due to chemotherapy agents or radiation may worsen ARDS in patients with cancer [12]. One study of ARDS in neutropenic patients with cancer identified several prognostic factors [13]. Mokart et al. showed a mortality of 63 % at 28 days which was associated with organ dysfunction, the absence of neutropenia recovery, and the use of vasopressors. On the other hand, factors associated with a good prognosis were use of initial antibiotic active against difficult-to-treat bacteria, receiving first-line chemotherapy cycle, or early stage of cancer [14]. The course of ARDS in patients with neutropenia was different from that of the general population. In general, the outcome of ARDS is determined in the first 10 days [15], by which time half of patients either have died or weaned off treatments. In patients with neutropenia, more than 85 % of ICU survivors were still hospitalized after 10 days [14]. One recent study evaluated the various etiologies of ARDS in patients with malignancies [16]. Infectious etiologies were found in 88.3 % of patients.

Also in the same study, noninvasive positive-pressure ventilation (NIPPV) was used in more than a third of cancer patients with ARDS. Ultimately the majority (71 %) of patients on NIPPV required endotracheal intubation in correlation with severity of ARDS. Failure of NIPPV ventilation was associated with worse outcome. Also, this study looked at prognostic predictors and showed that two factors are associated with lower hospital mortality: solid tumor and primary ARDS (caused by direct lung insult including infectious or noninfectious causes). Factors associated with higher mortality are allogenic bone marrow transplant, higher admission Sequential Organ Failure Assessment scores (SOFA) [17], presence of invasive fungal infection, and failure of NIPPV [16].

Ventilator Management

Early recognition in the emergency department and initiation of supportive therapy including mechanical ventilation are mainstay in the management of ARDS patients.

With the increasing demand for care in the ED as well as ICU beds [18], ED physicians are expected to manage many patients on mechanical ventilation in the ED. When invasive mechanical ventilation is initiated and initially managed in

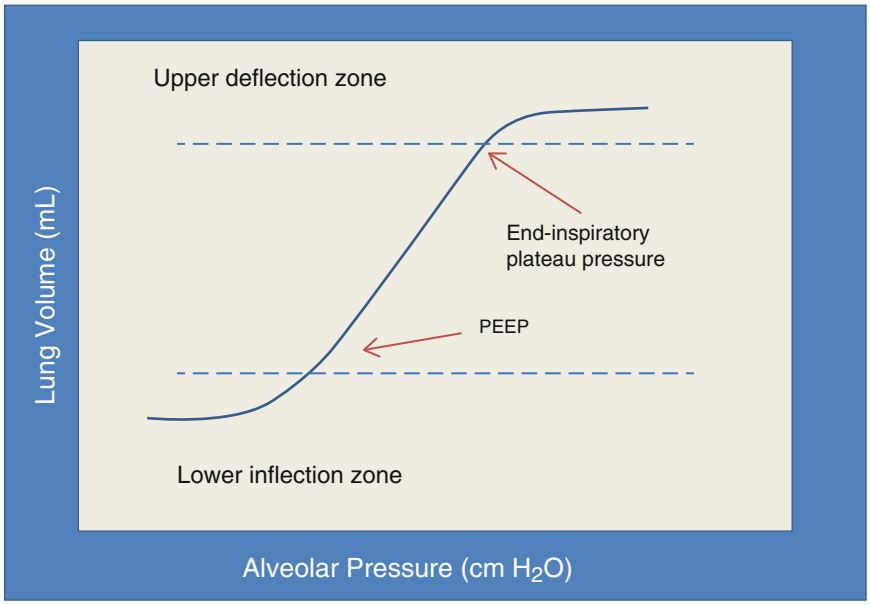

Fig. 1 The inspiration limb of a pressure-volume curve in an ARDS patient without PEEP application. Initial pressure application produces very little lung inflation as the pressure is applied against wet boggy lung. As lung begins to inflate, compliance improves, and the curve assumes a steeper slope. As tidal volumes become too large for that patient's lung that is questionable for ventilation (overinflation), the curve flattens. Low tidal volume strategy in ARDS should target avoiding moving into the flattening portion of curve (upper deflection zone, *upper arrow*). The goal of PEEP application is to avoid collapse of lung at end inspiration and a repeated cycle of lung collapse and reopening with each delivered ventilation breath (with production of shear force injury or atelectrauma). Therefore optimal PEEP would be applied at the lower end of the upslope of the curve (lower arrow, lower inflation point)

the ED, the ED physician should have an understanding of open-lung ventilation and the associated low tidal volume ventilation (LTVV) or lung-protective positive-pressure ventilation.

NIPPV is delivered to select patients obviating the need for an endotracheal tube. The ventilator is connected to the patient via a facemask. The mask is attached firmly to the patient's face using straps in order to prevent air leak. Most clinicians prefer the use of invasive intermittent positive-pressure ventilation (IPPV) over NIPPV in patients carrying the diagnosis of ARDS considering the potential for hypoxemia to worsen in these patients and the risk for rapid deterioration. However, one prospective randomized study evaluated the early use of NIPPV versus high concentration of oxygen in a less severe group of patients with mild ARDS [19]. Despite a historical high rate of intubation in patients with ARDS initiated on NIPPV, this study showed a significant decrease of the respiratory rate, improved PaO_2/FiO_2 ratio, and lower incidence of subsequent organ failures. However, this study had a very selective young group of patients who were able to tolerate and cooperate with the use of this mode of ventilation.

When using IPPV, it is very important to consider the following issues: (a) alveolar involvement in ARDS is heterogeneous and (b) damage caused by adjustments in ventilation to maintain adequate blood gases may result in delayed additive iatrogenic lung injury. Therefore, LPPPV or LTVV is the preferred mode of ventilation for patients with ARDS. The rationale for this mode is that overdistension of the alveoli is a major reason for ventilator-induced lung injury (Fig. 1). The majority of evidence suggests that LTVV improves mortality as well as other meaningful outcomes in patients with ARDS. The multicenter ARMA trial [20] compared LTVV (initial tidal volume 6 ml/kg predicted body weight, PBW) versus conventional ventilation (initial tidal volume 12 ml/kg/PBW). The benefits of LTVV were lower mortality rate (31 vs 40 %) and more ventilator-free days (12 vs 10 days). As expected, LTVV may be associated with hypercapnia, which is generally well tolerated and may be associated with beneficial effects not directly related to LTVV [21, 22]. In permissive hypercapnia, the accepted and managed rise of $PaCO_2$ and subsequent acidosis increases arterial and tissue oxygenation by a right shift of the oxygen-hemoglobin dissociation curve and possibly by increasing cardiac output and circulating catecholamines. However, the rise of the $PaCO_2$ should occur gradually. Rapid rise should be avoided as the negative effects may exceed the beneficial ones (increased heart rate/blood pressure, arrhythmias, and pulmonary vasoconstriction/worsening hypoxemia). A typical approach for enacting a low tidal volume strategy in ARDS would be as follows: (a) set tidal volume initially to 8 ml/kg/PBW; (b) then titrate down to 7 and then 6 ml/kg/PBW; (c) then measure the airway plateau pressure (Pplat), and if $\leq$30 cmH_2O, no other adjustment is required; and (d)

Table 1 ARDSnet PEEP table [69]

Lower PEEP/higher FiO_2								
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
FiO_2	0.7	0.8	0.9	0.9	1.9	1.0		
PEEP	14	14	14	16	18	18–24		
Higher PEEP/lower FiO_2								
FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16
FiO_2	0.5	0.5–0.8	0.8	0.9	1.0	1.0		
PEEP	18	20	22	22	22	24		

Use a minimum PEEP of 5 cmH_2O. Consider use of incremental FiO_2/PEEP combinations such as shown below to achieve goal. Consider the higher PEEP table in the presence of more severe hypoxemia. [Reprinted with permission from: Hough CL, Kallet RH, Ranieri VM, Rubenfeld GD, Luce JM, Hudson LD. Intrinsic positive end-expiratory pressure in Acute Respiratory Distress Syndrome (ARDS) Network subjects. Critical care medicine. 2005;33(3):527–32]

if Pplat is >30 cmH_2O, then further decrease tidal volume to as low as 4 ml/kg/PBW to achieve target. Higher Pplat may be allowed in the presence of obesity or anasarca.

Open-lung ventilation represents the addition of positive end-expiratory pressure (PEEP) to the LTVV strategy, targeting to prevent collapse of edematous lung at end expiration. PEEP is believed to maximize alveolar recruitment and prevent cyclic atelectasis. According to several meta-analyses, the use of open-lung ventilation has been associated with improved oxygenation. However, the effect on mortality has not been well established [23–25]. The ARMA trial used a type of open-lung strategy in both arms, increasing PEEP levels with increasing severity of hypoxemia. Open-lung strategy has repeatedly shown improved oxygenation and perhaps more importantly, improved lung compliance. The titration of PEEP is typically based on oxygenation deficit or pressure-volume curves (see discussion below). When guided by oxygenation, start with the lowest PEEP possible to maintain an adequate PaO_2 55–80 mmHg with an FiO_2 of less than 60 % and then titrate PEEP according to the ARDS net PEEP/FiO_2 table (Table 1). When pressure-volume curves are used, it is important to calculate lung compliance and use a PEEP level that moves the end-expiratory P/V point onto the steep part of the pressure-volume curve (Fig. 1).

One additional, non-ventilation-related strategy is worthy of mention in the early management of ARDS patients, i.e., the use of neuromuscular blockade. There is some evidence that early use of neuromuscular blockade agents in patients with ARDS is associated with better outcomes including mortality [26, 27]. Decreased patient-ventilator asynchrony, chest wall elastance, work of breathing, and oxygen consumption may have been the underlying mechanisms for this beneficial effect, but a more intriguing hypothesis relates to an effect on transalveolar pressure. Overinflation injury correlates best with transpulmonary (TP) pressure at end inspiration. In the paralyzed patient, both the Pplat, as an estimate of end-inspiratory pressure, and the pleural pressure Ppl are positive; therefore, the TP pressure estimate is Pplat – Ppl. In the spontaneous breathing patient, the pleural pressure may be negative at end inspiration, and this negative pressure will increase transpulmonary pressure with the delivery of the same tidal volume. Paralysis, by eliminating inspiratory effort, would be expected to decrease TP pressure in the presence of overinflation, thereby decreasing the risk of ventilator-induced lung injury.

Summary

Acute respiratory failure and ARDS are common in patients with malignancies. Infectious etiologies are most common. Early recognition and intervention are crucial and should be initiated in the emergency department upon presentation. A trial of NIPPV is acceptable initially in stable and cooperative patients. Lung-protective and open-lung ventilation strategies are keys to improve outcomes and survival.

Pneumothorax and Pleural Effusion

Pleural manifestations are not uncommon in patients with malignancies. The pleura is often a metastasis site from local or distant cancers, presenting more commonly as pleural effusions rather than solid masses. Also the pleura can be involved with spontaneous or iatrogenic pneumothoraces in patients with malignancies.

Pneumothorax

Definitions, Etiologies, and Diagnostic Modalities

Pneumothorax refers to the presence of air in the pleural space. The classification of pneumothorax includes spontaneous, traumatic, or iatrogenic. Spontaneous pneumothorax occurs without obvious cause, either primary without evidence of underlying lung disease or secondary with apparent underlying lung disease, often COPD. Traumatic pneumothorax occurs after a blunt or penetrating trauma to the chest. Iatrogenic pneumothorax occurs after a diagnostic or therapeutic intervention such as transthoracic lung biopsy, central line placement, or barotrauma due to mechanical ventilation. The incidence of pneumothorax, in patients receiving mechanical ventilation, ranges between 7 and 14 % [28]. Patients with acute lung injury or ARDS are at increased risk.

Clinical manifestations range from asymptomatic to respiratory failure to prolonged bronchopleural fistulas (BPFs).

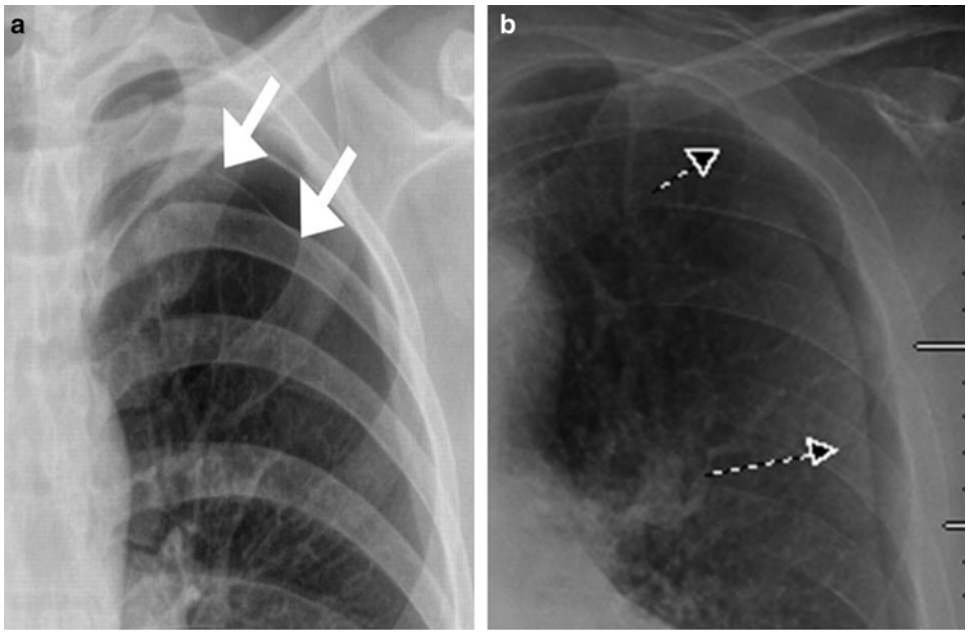

Fig. 2 (**a**) White visceral pleural line in pneumothorax. (**b**) Black Mach band in skin fold

Prompt diagnosis and management are crucial especially in symptomatic patients with underlying lung diseases or critically ill patients requiring mechanical ventilation.

Clinical manifestations and presentations of pneumothorax are widely variable. Sometimes incidentally found on routine chest imaging, the presence of a pneumothorax is clinically suspected in the appropriate clinical setting. A small pneumothorax can be asymptomatic and self-limited, whereas a large pneumothorax can cause hypoventilation, hypoxemia, and/or hemodynamic instability.

Tension pneumothorax represents a surgical emergency and requires emergent intervention. It may lead to respiratory failure requiring mechanical ventilation. It may also complicate preexisting respiratory failure on positive-pressure ventilation.

In intubated and sedated patients, a pneumothorax should be suspected with sudden and unexplained worsening respiratory failure, increased oxygen requirements, hemodynamic instability, and sudden rise in peak and plateau pressures. It is frequently diagnosed based on clinical presentation, risk factors, and physical exam (not by imaging), followed by immediate emergent decompression in hemodynamically unstable patients. However, the increasing availability of bedside ultrasonography by ED physicians has made emergent imaging confirmation of pneumothoraces possible prior to emergent decompression.

The current first-line imaging modality used to identify a pneumothorax is chest radiography, although bedside ultrasonography has great potential to compete for the diagnostic method of choice in the future. The typical finding is displacement of the white visceral pleural line from the chest wall on an upright chest radiograph. The underlying lung parenchyma should be examined for the presence of lung disease that would suggest a pneumothorax. In bedridden or ICU patients, care should be exercised in order to differentiate visceral pleural line from skin folds. Skin folds frequently extend beyond the rib cage; blood vessels and lung parenchyma often extend beyond the skin fold. Their attenuation profile is also different, forming a negative black Mach band instead of the white visceral pleural line (Fig. 2).

Computed tomography (CT) diagnosis is best utilized for complicated or unclear situations. However, CT scans are more accurate in determining size of pneumothorax when compared to chest radiography [29].

As briefly mentioned above, ultrasound may also be a value to diagnose or rule out a pneumothorax [30], particularly in patients where it is needed emergently at the bedside, such as in ICU, ED, or a trauma patients [31]. The use of bedside ultrasonography has emerged in the past several years as the modality of choice in intensive care units where ultrasonography trained physicians are available. Beside ultrasonography offers several advantages over chest radiography or CT scans including rapid availability, lack of radiation, real-time interpretation, and lower cost. It also offers the ability to immediately rule out a pneumothorax after an invasive procedure or in the midst of a clinical deterioration.

Clinical Scenarios in Cancer Patients

The common clinical scenarios facing ED physicians with cancer patient presenting with a pneumothorax would be:

1. Secondary spontaneous pneumothorax in patients with underlying lung disease, such as emphysema and concomitant diagnosis of cancer. In fact most cancer patients

presenting with a secondary spontaneous pneumothorax had lung cancer (20 %) underlying chronic obstructive pulmonary disease (COPD or emphysema) (50 %) [32]. The mechanisms could be due to bronchopleural fistula within a necrotic tumor, tumor-induced rupture of subpleural bleb, or direct invasion of the pleura. These patients require hospitalization for observation and potentially chest tube suction. Surgical interventions such as pleurodesis or wedge resection may be required. The group of patients with active cancer have a significantly worse survival compared to those without active cancers (3 vs 31 months) [32].

2. Iatrogenic pneumothorax following diagnostic procedures: CT-guided or bronchoscopic lung biopsies as well as therapeutic procedures such as thoracentesis, bronchoscopic endobronchial tumor ablations, or percutaneous radiofrequency ablation may produce pneumothorax. CT-guided biopsy is often considered when the abnormality is not easily accessible with a bronchoscope but is associated with higher rate of pneumothorax, average 10–15 % [33]. A high level of suspicion should exist in patients who undergo CT-guided biopsy and present with worsening dyspnea, cough, chest pressure, or pain. Usually symptoms occur within 3 h after the procedure; however, onset can be delayed in a small percentage (4 %) of patients [34]. Approximately 20 % of patients with this complication require chest tube insertion, depending on the size of the pneumothorax and associated symptoms. Predisposing factors include distance of the target to the pleura, number of needle passes traversing normal lung, and presence of underlying lung diseases [34].
3. Treatment-related pneumothorax secondary to thoracentesis, bronchoscopic ablation of central airway obstruction, percutaneous radiofrequency ablation, or chemo-induced tumor necrosis. With the use of ultrasound, the rate of pneumothorax post-thoracentesis has dropped significantly to less than 2 % [35]. When a pneumothorax occurs, it is usually small and only a third of patients require chest tube insertion, considered if the pneumothorax is large or progressive and the patient is symptomatic or requiring mechanical ventilation.

Central airway malignant obstruction is currently aggressively treated with several minimally invasive bronchoscopic interventions. One-third of patients with advanced lung cancer develop central airway obstruction, and several other malignancies may metastasize to the airway. Pneumothorax after an ablative bronchoscopy, although rare, is usually immediate and treated in the bronchoscopy laboratory. It is most often related to supportive care such as jet ventilation during rigid bronchoscopy. Nevertheless, pneumothorax must be ruled out in symptomatic patients presenting after any ablative bronchoscopy.

Image-guided percutaneous therapies became popular over the last two decades for the treatment in pulmonary malignancies, especially in nonsurgical candidate patients. They include radiofrequency or microwave ablation. Pneumothorax is the most common periprocedural complication after these two ablative techniques, 40 % and 16 %, respectively [36, 37]. Risk factors are similar to CT-guided biopsies. In addition, the number of tumor ablations during a single procedure and lack of prior lung surgery were risk factors as well.

It was observed that patients with a background diagnosis of emphysema have an almost doubled pneumothorax rate of 68 % [36]. However only 10 % of patients with pneumothorax require chest tube drainage, and only 0.6 % develop bronchopleural fistula after chest tube insertion.

Treatment

Simple manual aspiration using an intercostal needle or small catheter is indicated in noncomplicated patients presenting with first episode of a large or symptomatic secondary spontaneous pneumothorax. Treatment consists of inserting a needle or catheter in the pleural space, aspirating the pleural air followed by removal of the needle or catheter. Resolution rate is high [38]. When simple aspiration is unsuccessful to keep the lung inflated or when air leak is large or persistent, then a tube thoracostomy is indicated. There is no evidence that large tubes (20–24 F) are any better than small tubes (10–16 F) in the management of pneumothoraces. The initial use of large (20–24 F) intercostal tubes is not recommended, although it may become necessary to replace a small chest tube with a larger one if there is a large air leak preventing complete reinflation of the lung [39].

The most common position for chest tube insertion is in the mid-axillary line. This position minimizes the risk of injury to underlying structures such as the viscera and internal mammary artery. For apical and large pneumothoraces extending to the apex, an antero-apical approach is favored. It requires minimal positioning and rotation of a critically ill patient. The second intercostal space in the mid-clavicular line is often chosen; two finger breath from the lateral sternal border. The internal mammary vessels are at risk but bedside ultrasound may be very helpful in choosing the optimal location while avoiding vascular structures.

Pleural Effusion

Patients with cancer frequently develop pleural effusions, and 25 % of all pleural effusions in a general hospital are due to cancer, and up to 50 % of patients with a variety of metastatic malignancies develop a paramalignant or malignant pleural

effusion [40]. In addition 30–70 % of all exudative pleural effusions are malignant pleural effusions [41]. Paramalignant pleural effusions are caused by tumor effect on surrounding structures; pleural fluid cytology and pleural biopsy are usually free of cancer cells. Malignant pleural effusions are caused by direct invasion of the pleura, and the fluid cytology or pleural biopsies may be positive for malignant cells.

Nearly all malignant or paramalignant pleural effusions become symptomatic. It is advisable to treat these effusions upon presentation especially if moderate to large in size since the recurrence may hinder and delay therapy for underlying malignancy. Several important questions face the ED physician when evaluating patients with malignant pleural effusions. Does the effusion need to be drained? What is the volume of fluid that can be drained safely at one time? What is the appropriate size of the chest tube?

Drainage

Since symptoms are frequent in patients with cancer and pleural effusion, drainage is recommended. For patients who do not need to be admitted after drainage, a simple therapeutic thoracentesis is recommended. We advocate the use of an 8-f French pleural drainage catheter, inserted in the posterior axillary line under ultrasound guidance with gravity drainage. We prefer gravity drainage to repeated manual aspirations as it avoids the steep fluctuations in negative pleural pressure, allows for slower re-expansion of the lung, and allows for pleural pressure monitoring.

Amount of Drainage

Initial thoracentesis is a simple way for symptomatic relief of acute presentation as well as to assess degree of lung re-expansion, which may be important to determine future management strategies. It has been advocated to drain only 1.5 l during therapeutic thoracentesis, the rationale being to minimize the risk of re-expansion pulmonary edema (REPE) [42]. We believe in draining the majority of pleural effusion as much as tolerated by the patient for several reasons: One, the incidence of REPE is extremely rare and typically patients develop early mild symptoms (cough, chest pressure) allowing termination of the procedure [42]. Two, in order to assess if patient is candidate for future pleurodesis with post-thoracentesis chest radiograph, one would need to document the juxtaposition of visceral and parietal pleura. Three, draining the majority of pleural effusion provides the optimal and longest symptomatic relief in between recurrences. The common side effects from large-volume thoracentesis are cough and chest discomfort [42]. Therapeutic thoracentesis should be interrupted in case of development of symptoms, as they may precede more severe complications such as REPE if drainage continues. Once symptoms develop, patients should limit deep breathing and refrain from talking with long sentences as further stretching the lung may lead to worsening symptoms. These symptoms typically resolve spontaneously.

Chest Tube Size

If presenting with recurrent large malignant pleural effusion, we recommend small-bore (8–16 Fr) chest tube insertion in posterior axillary line, with connection to pleurovac system without wall suction or gravity drainage bag. We also advocate early pulmonary consult in order to plan for long-term fluid management strategies. We do not see any advantages to large bore chest tube insertion, as documented in a previous study [43].

Some special situations may face ED physicians with patients carrying tunneled pleural catheters presenting for worsening symptoms due to inability to drain or clog catheters. Pulmonary consult is suggested in these situations, as an evaluation of the pleural space with chest radiograph or thoracic ultrasound is required to evaluate for residual pleural fluid. If this is the case, intrapleural catheter instillation of alteplase may be indicated to unclog the tube [44].

Summary

Pleural effusion and pneumothorax are common pulmonary manifestations in patients with cancer, most commonly occurring after required interventions treating the primary malignancy. Early recognition and intervention are indicated as delays may interfere with cancer treatment. Small-bore chest tubes are as good as the large bores and should be used primarily. The use of bedside ultrasound has improved the diagnostic accuracy and minimized complications.

Hemoptysis

Etiologies

One of the most common causes of hemoptysis is lung cancer, along with inflammatory and infectious etiologies such as bronchiectasis, bronchitis, and tuberculosis [45]. During their lifespan, 20 % of patients with lung cancer develop hemoptysis. Non-small cell lung cancer patients have a higher incidence than small cell. Other malignant causes include endobronchial metastatic carcinoma (melanoma, breast, colon, or renal cancer), bronchial carcinoid in young patients, and Kaposi sarcomas in AIDS patients. Hemoptysis could

also be chemotherapy induced caused by necrosis of large tumors or potential medication side effect. With the development of several antiangiogenic agents inhibiting vascular endothelial growth factor for the treatment of advanced lung cancer, more patients are started on those agents as they progress with their disease. One of the reported side effects of these agents, e.g., bevacizumab, is hemoptysis. When hemoptysis from bevacizumab occurs, it is often massive. In fact life-threatening hemoptysis has been reported up to 9 % in patients receiving bevacizumab [46], and most of the hemorrhages were fatal and occurred during first initial cycles of treatment [47]. It is therefore important to recognize and attribute hemoptysis in patients receiving bevacizumab and realize that most often it is fatal. Early critical care and interventional pulmonary or radiology consults are crucial in patients receiving bevacizumab presenting with hemoptysis even if mild.

Massive Hemoptysis

Several definitions have been proposed for massive hemoptysis and they were all initially based on volume of blood per 24 h. The volumes used for the definition are variable and range between 100 and 1000 ml per 24 h period [48]. In our opinion a massive hemoptysis is present when a patient is coughing more than 100 ml/24 h and raises concerns as to airway protection issues or gas exchange impairment. Massive hemoptysis is the cause of death in 3 % of patients with lung cancer. Urgent diagnostic and therapeutic intervention is advised in patients with massive hemoptysis. Several initial steps are important upon presentation. First is to localize, position, protect the airway, optimize gas exchange, and then control the bleeding [49].

Clinical suspicion, previous history, and available previous imaging are important in localizing or estimating the location of the bleeding. The suspected bleeding site should be placed in a dependent position in order to prevent spillage or formation of large blood clots into the non-bleeding lung. In case massive bleeding is associated with symptoms, endotracheal intubation should be performed using at least an 8.0 mm endotracheal tube (ETT). A large ETT tube facilitates in and out access for the therapeutic bronchoscope and provides a route for laser coagulation or cryoprobe-assisted removal of large blood clots. An additional feature to the presence of an ETT is the ability to push the tip deep into the non-bleeding main bronchus and further protect the non-bleeding side from blood contamination. This maneuver obviously needs bronchoscopic guidance. After intubation, mechanical ventilation may be started with optimized settings to achieve adequate oxygenation and ventilation. Also, correction of underlying coagulopathy is warranted.

Bronchoscopy with instillation of epinephrine or ice-cold saline is a temporary measure to potentially control bleeding until laser ablation equipment is available for more permanent control. Bronchoscopic measures are effective for bleeding sites within the reach of the bronchoscope. Otherwise, arteriographic localization of a bleeding site and embolization is the method of choice to control bleeding from peripheral sites not easily reached through the airways [50]. Surgical evaluation and possible intervention is indicated in case of an uncontrollable bleeding site. Surgical intervention in bleeding patients is associated with significant morbidity and mortality [51].

Summary

Hemoptysis in cancer patients is a serious manifestation of airway involvement or chemotherapy side effect. Hemoptysis is often massive and potentially fatal in patients receiving bevacizumab. Early intervention and consultation of specialized services are crucial steps in the management of this massive hemoptysis.

Chemotherapy and Radiation-Related Pulmonary Toxicities

Chemotherapy-Related Pulmonary Toxicity

Acute Complications

Pulmonary toxicity from antineoplastic agents is common. It is estimated that 10–20 % of patients receiving chemotherapy develop some form of lung toxicity [52, 53]. Pulmonary injury can vary from mild to severe and is divided into acute and delayed onset [54]. The acute onset syndromes include inflammatory interstitial pneumonitis, pulmonary edema, bronchospasm, pleurisy, or pleural effusion, typically presenting after the first one or two cycles of the administered agent.

The inflammatory interstitial pneumonitis syndrome is a hypersensitivity-like reaction. It is the most common chemotherapy-associated lung injury [55]. It has an acute to subacute presentation with productive cough, worsening dyspnea associated with low-grade fevers, and fine crackles on physical exam. A chest radiograph shows either an interstitial or mixed interstitial and alveolar pattern. The most common agents associated with this syndrome are methotrexate, bleomycin, procarbazine, and carmustine. It can mimic an atypical pneumonia or hypersensitivity pneumonitis. The prognosis is generally favorable with discontinuation of the offending agent and treatment with corticosteroids in more severe cases.

The pulmonary edema syndrome, less common than interstitial pneumonitis syndrome, has a more acute presentation. Caused by endothelial inflammation and vascular leak, it leads to non-cardiogenic pulmonary edema (NCPE).

Patients may present with severe dyspnea. Cough, fatigue, and increased work of breathing may also be present, sometimes associated with profound hypoxemia and crackles on physical exam [55]. Chest radiograph shows similar findings to those found in patients with pulmonary edema but with normal size heart. It is typically an exclusion diagnosis after establishing a normal heart function in a clinical picture of congestive heart failure. Chemotherapeutic agents most commonly associated with NCPE are by order of frequency cytarabine, interleukin 2, trans-retinoic acids, and gemcitabine. A higher incidence of NCPE has been reported in patients undergoing allogenic and autologous bone marrow transplant, beginning with induction chemotherapy [56, 57].

Bronchospasm- and asthmatic-like reactions can also occur with chemotherapy agents. They have been reported upon exposure to the first cycle. Two mechanisms are responsible, IgE- and non-IgE-related. The chemotherapy agents causing IgE-related bronchospasm are platinum compounds such as cisplatin, carboplatin, and oxaliplatin. The ones causing non-IgE-related bronchospasm are taxanes (paclitaxel, docetaxel), asparaginase, and epipodophyllotoxins (etoposide and teniposide). In the acute setting, anaphylactoid reactions in the absence of hypotension should be treated with intramuscular injections of epinephrine 1:1000, 0.5 mg per single dose. In the presence of severe hypotension or shock, continuous intravenous infusion of epinephrine is recommended. Antihistamines, corticosteroids, as well as bronchodilators and supplemental oxygen (with lung symptomatology) are also indicated.

Pleurisy or pleural effusion can be a manifestation of chemotherapy-induced side effects with methotrexate. When administered in high doses, it may cause chest pain, sometimes 2–5 days later, in 2–4 % of patients. Thirty percent of those may progress and develop pleural effusion [58]. Pain typically subsides 3–5 days after discontinuation of the drug and may relapse if the offending agent is restarted [59].

Late Complications

The late-onset chemotherapy-related pulmonary complications usually present 2 months after completion of therapy [54]. The most common manifestation is pulmonary fibrosis. The agents most commonly associated with this complication are bleomycin, busulfan, carmustine, and mitomycin-C. The common risk factors to this toxicity are advanced age, concomitant radiation treatment, or combination chemotherapy. The use of supplemental oxygen even at low flow rates amplifies bleomycin toxicity and may play a role in the development of pulmonary fibrosis even years after treatment [60].

Patients typically present with insidious onset of dyspnea associated with nonproductive cough. Physical examination reveals crackles and chest radiograph shows bibasilar reticular interstitial markings. Pulmonary function tests may show restrictive disease. History and physical examination along with elimination of other underlying issues such as congestive heart failure are essential to make the diagnosis. Bronchoscopy may be useful in ruling out lymphangitic spread as well as infectious etiologies. Definitive diagnosis may require video-assisted thoracoscopic surgery. Supportive treatments along with a trial of corticosteroids are mainstay of therapy; however, use of oxygen in patients who have bleomycin lung toxicity should only be used in case of severe hypoxemia.

Radiation-Related Pulmonary Toxicity

Radiation-induced lung injury results from the combination of direct radiation cytotoxicity in addition to radiation-induced cellular signal transduction. This cellular activation initiates a repair process that involves cytokines and growth factors such as basic fibroblast growth factor, interleukin-1, and transforming growth factor-beta, leading to the development of fibrosis. Radiation pneumonitis develops in about 5–15 % of patients receiving high-dose external beam radiation as treatment for lung cancer. Several risk factors have been described including volume of lung irradiated, total dose of radiation >60 Gy, number of fractions delivered, concomitant chemotherapy, previous radiation treatment, and weaning of systemic steroids. Age is not a risk factor but radiation pneumonitis seems to be worse in elderly patients [61]. Patients usually become symptomatic 2–3 months after completion of treatment. If symptoms start earlier, patients suffer from a more severe course. The most common symptom is dyspnea, which may be associated with pinkish productive cough. Most patients evolve to develop progressive fibrosis. The diagnosis is usually clinical and based on the timing of radiation treatment and typical chest radiograph findings corresponding to the field of radiation [54]. Bronchoscopy is rarely helpful and serves only to rule out infectious or recurrent malignant process. Corticosteroid therapy is a common clinical practice, although its efficacy is controversial in the literature. Prednisone (1 mg/kg. or equivalent doses of other corticosteroids) is indicated for acute radiation pneumonitis but not in fibrosis. Therapy should be continued for several months and tapered down slowly as there is some evidence that rapid tapering may lead to relapse [62].

Another reported and more acute form of radiation-induced lung injury is radiation-related bronchiolitis obliterans with organizing pneumonia (BOOP) [63]. Most of the reported cases are patients irradiated for breast cancer. Common manifestations include cough and fever and, to a lesser degree, dyspnea. The radiographic findings start in the radiation field but may progress even to the contralateral lung in 40 % of the cases. Patients respond dramatically to corticosteroids but also carry the risk of significant relapse if tapered in a short period of time.

Summary

Radiation pneumonitis often progresses to lung fibrosis and is typically limited to the radiation field. Clinical and radiographic suspicions are important in establishing the diagnosis. Radiation-induced BOOP is a more acute form that often involves the contralateral lung. Treatment with corticosteroids should be tapered slowly in order to avoid the risk of a relapse.

Non-thrombotic Pulmonary Embolism NTPE

NTPE is the embolization on non-thrombotic tumor material into the pulmonary circulation, blocking it either entirely or partially [64]. The non-thrombotic tumor material in patients with cancer includes macro- or microembolism. It is called pulmonary tumor embolism (PTE). These emboli are distinct from true metastasis as they remain intravascular and rarely invade the pulmonary parenchyma. With complete occlusion, necrosis of the dependent pulmonary parenchyma similar to thrombotic events follows. When partially occluding the vascular lumen, inflammatory reaction, vascular intimal proliferation, and activation of the coagulation cascade may develop. The reported incidence of PTE is very variable 0.19–26 % [65–67]. This variability is a reflection of the difficulty in diagnosing this syndrome. There is predominance of digestive system and liver tumors associated with PTE; breast cancer and cardiac lymphomas have also been reported but at a lesser rate. The risk of tumor embolization is increased with patients undergoing chemotherapy, radiation, or surgical intervention (fragmentation and embolization of tumor fragments or cells). The presentation is often insidious, progressing over several weeks to months. In rare instances it can be acute 10–20 % [68]. In patients with proximal and large tumor emboli, the presentation could be dramatic and acute with signs of right heart failure. Patients typically present with worsening dyspnea, cough, and increased work of breathing, sometimes associated with ascites and peripheral edema reflecting the increased right heart pressure. The gold standard test is pulmonary artery blood cytology, obtained through a pulmonary artery catheter. Even though PTE are not considered to be metastasis, the prognosis is still poor. Treatment is supportive and should be directed to the primary tumor. Chemotherapy does not generally affect the prognosis of patients with PTE unless the primary tumor is very chemotherapy responsive such as trophoblastic or Wilms tumors.

Summary

PTE syndrome is often the result of tumor destruction whether with medications or surgical intervention. Symptoms are insidious, however may mimic thrombotic events. Diagnosis is often clinical but sometimes can be made with pulmonary artery blood cytology. Prognosis is generally poor.

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Venous Thromboembolism

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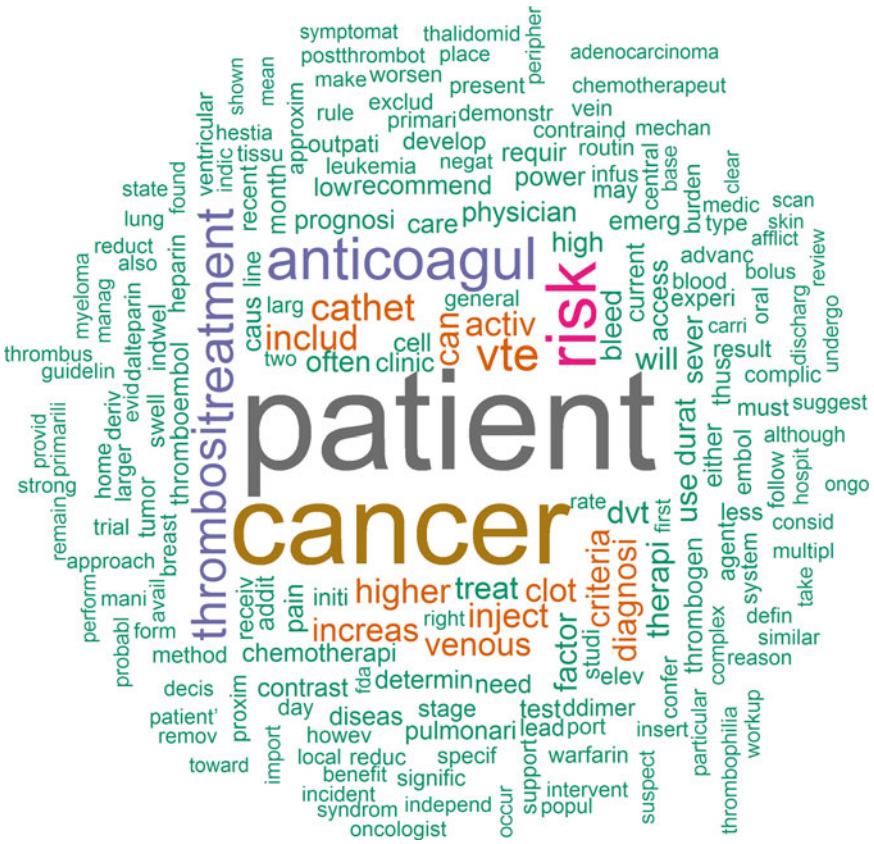

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Pathophysiology of Thromboembolism in Cancer

Annually, 1.5 million patients will receive a new diagnosis of cancer in the USA, of whom 5 % or 75,000 patients will go on to be afflicted with an additional diagnosis of venous thromboembolic disease (VTE). The risk of VTE is 53-fold higher than baseline in the first 3 months after diagnosis of cancer and remains approximately fourfold higher until 15 years after initial cancer diagnosis [1]. Carrying a dual diagnosis of both cancer and pulmonary embolism is associated with worsened prognosis, increased recurrence rates, longer duration of anticoagulation, and worsened bleeding risks.

In healthy patients, the vessel endothelium prevents thrombus formation by acting as a barrier to the underlying subendothelium, which contains tissue factor (TF). When TF is exposed through vessel wall damage, it complexes with circulating Factor VIIa and initiates the extrinsic pathway, the primary driver behind the entire coagulation cascade. To initiate a clot, tissue factor (TF) must bind with circulating factor VIIa. This results in a complex capable of converting factor X to Xa, which cleaves prothrombin to thrombin, which in turn cleaves fibrinogen to fibrin, leading to generating a cross-linked fibrin clot after the action of factor 13, itself activated by thrombin. Cancer increases the exposure of tissue factor to the blood by several mechanisms, including the surface characteristics of cancer cells, their production of TF-bearing microparticles, and by direct damage as a result of tumor spread. As an example, pancreatic cancer, which is a highly thrombogenic cancer, causes significant elevations in microparticle-associated tissue factor, leading rates of VTE of 45 % in some series [2, 3]. In addition to increased production of TF, cancers can also release various proinflammatory cytokines, interleukins, and procoagulants [4].

Cancer patients undergo a variety of procedures and treatments that further increase their risk of thrombosis. Surgery, chemotherapy, and radiation therapy cause a proinflammatory state and some chemotherapeutic agents produce a prothrombotic state that independently increases clotting risk, notably fluoropyrimidines, L-asparaginase, and thalidomide derivatives. The chemotherapeutic agents Ara C and 5-fluorocytosine alter the metabolism of coumarins and complicate the ability to achieve stable anticoagulation. Cancer patients frequently have other risk factors for VTE including indwelling catheters, immobility, and folate deficiency.

Thrombogenic Cancers

Emergency physicians will often consider the need to test for VTE while treating patients with cancer. However, thrombogenicity varies with host factors, tumor stage, and type. In general, the more undifferentiated the cell type, and the larger the tumor burden, the higher the risk. Cancers that appear to confer no or minimal risk of VTE include localized breast, cervical, prostate, and non-melanomatous skin cancers such as squamous cell carcinoma and basal cell carcinoma. However, advanced stage breast cancer patients, or breast cancer patients undergoing chemotherapy, may have a thrombosis risk of up to 10 % during treatment [5]. Similarly, treatment of leukemias, particularly acute lymphocytic leukemia treated with L-asparaginase and acute promyelocytic leukemias treated with all-trans-retinoic acid, has each been associated approximately with a 10 % incidence of VTE throughout the course of therapy. Other cancers that are particularly thrombogenic include adenocarcinoma, glioblastoma, melanoma (in contrast to other skin cancers), lymphoma, and multiple myeloma [6]. Pancreatic, stomach, ovarian, and renal cell cancers carry notoriously high risk.

Clinicians should be especially vigilant for VTE during the induction phase of chemotherapy, as this is the most thrombogenic period [7]. L-Asparaginase and bolus fluorouracil treatment confer particularly high thrombosis risks, probably by reducing antithrombin concentrations [8]. While localized breast cancer has a relatively low thrombogenic potential, risk approximately doubles with tamoxifen treatment, whereas aromatase inhibitors do not appear to increase risk. Concomitant treatment with red cell growth factors such as erythropoietin clearly increases the risk of thrombosis, regardless of tumor type or stage [9]. Any patient who presents with extremity swelling or chest pain during their initial treatment phase with these drugs should undergo criteria outlined in Table 1 to exclude thromboembolism. Similarly, multiple myeloma patients treated with lenalidomide or thalidomide are at risk, although one large Japanese cohort study found this to be 1.4 % and at baseline for their cancer [10]. Bevacizumab presents a complex picture, with some studies suggesting a high risk and a more recent systematic review showing no increase compared with matched patients receiving other forms of chemotherapy for similar tumors [11]. A clinical prediction rule has been developed by Khorana et al. [9] to determine which cancer patients are at highest risk for future thrombosis (Table 2). In this model, patients with $\geq$3 points are found to have VTE risks of approximately 7 %.

What Does VTE Mean for the Cancer Patient?

Cancer patients who develop VTE have a higher risk of morbidity and mortality than both patients with cancer and patients with VTE. This risk represents the synergistic effect between the two disease entities. Diagnosis of VTE in cancer confers several independent, negative consequences. These include a reduced overall probability of survival, indication of more aggressive cancer, and a higher risk of bleeding from anticoagulation than non-cancer patients with VTE [12]. In

Table 1 Diagnostic criteria required to exclude venous thromboembolism in cancer patients

DVT	PE
Negative full-leg duplex ultrasonography[a]	Adequate quality negative CTPA
Negative (<500 ng/μL) D-dimer plus negative proximal ultrasound	Negative homogenous perfusion scan
Two negative proximal ultrasounds 2–7 days apart[b]	Low probability V/Q scan and a single negative bilateral whole-leg lower extremity duplex ultrasonography or two negative proximal ultrasounds 2–7 days apart

[a]Full-leg ultrasound includes spectral and B-mode compression imaging of the proximal and distal femoral vein and the popliteal, posterior tibial, peroneal, and greater saphenous veins
[b]Proximal ultrasound includes spectral and B-mode compression imaging of the proximal and distal femoral vein and the popliteal vein

Table 2 Risk tool of Khorana for prediction of which patients undergoing chemotherapy will develop VTE

Site of cancer	Risk score
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecological, bladder, testicular)	1
Prechemotherapy platelet count >350,000/μL	1
Hemoglobin <10 g/dL or red cell growth factors	1
Prechemotherapy white blood count >11,000/μL	1
Body mass index >35 kg/m^2	1

addition, medications are more difficult to take due to ongoing nausea. Pill fatigue can impair adherence to anticoagulation therapy, as these patients are often on multiple additional medications, and in patients taking vitamin K antagonists such as warfarin, the additional needle sticks for INR checks can be onerous. Finally, cancer patients tend to experience higher severity of clot burden than patients without cancer. In the authors' experience, these thrombi are both larger and more extensive in both the extremities and in the lung, leading to more devastating disease and increased incidence of postthrombotic syndrome.

Special Considerations For Diagnosis

The diagnostic approach to a cancer patient with suspected VTE mirrors that of other moderate- to high-risk patients with suspected PE (Table 1). Unfortunately, while being at higher risk for thrombosis, cancer patients are also at higher risk for complications from diagnosis. There is an increased risk of contrast-induced nephropathy in these patients, which already is 11 % in the general population [13, 14].

The D-dimer, which normally can be used to reliably exclude VTE because of its high sensitivity, becomes markedly less specific in the cancer population. Many cancer patients will have positive D-dimer results in the absence of clot, meaning that the test is less useful in patients with active cancer. These patients experience system-wide activation of the clotting network, and thus elevated D-dimer levels may herald poor cancer prognosis but not thrombosis [15]. While a negative D-dimer still helps rule out VTE, it does so in a smaller proportion of patients with active cancer.

IV access is often more difficult in this population, reducing the changes of having a peripheral IV large enough to allow mechanical bolus injection of radiological contrast material for CT angiography. The indwelling port or catheter that is used for chemotherapy delivery is often not approved for contrast injection, and typically the accepted access is a 20-gauge peripheral IV or larger required at or proximal to the antecubital fossa. To use indwelling central venous catheters or ports for contrast injection, the device must specify a power injectable line. These lines are capable of withstanding 300 psi injections or greater, compared to most central access which can only withstand 25 psi. Currently, three common catheter brands that do not support power injections are Hickman, Broviac, and Vascath. Some examples of catheters supporting power injection are the Bard Power Port®, Power PICC®, Power Hickman®, Power Line®, and the PFM CT Port.

Risk Stratification and Management

In the era of target-specific anticoagulants (TSAs, formerly referred to as novel oral anticoagulants or NOACs) such as rivaroxaban, apixaban, and dabigatran, the need to hospitalize all patients with thromboembolic event, including PE, is being called into question. It has been long held that many patients with DVT can be safely discharged home [16].

Box 1 The Hestia criteria

Patient fails criteria if any of the below are true
Hemodynamically unstable
Requires thrombolysis or embolectomy
Active bleeding or high risk for bleeding
More than 24 h supplemental O_2 required to maintain O_2 saturation >90 %
PE diagnosed while currently under active anticoagulant therapy
Severe pain requiring >24 h intravenous analgesic therapy
Medical or social reason for hospitalization >24 h (infection, malignancy, no support system, etc.)
Creatinine clearance <30 mL/min
Severe liver impairment
Pregnancy
Documented history of heparin-induced thrombocytopenia (HIT)

Box 2 The POMPE-C criteria (used in an online calculator for overall risk of death at 30 days)

If all criteria shown are absent, the patient's risk of death is sufficiently low to justify home treatment for the patient with active cancer
Absence of a Do Not Resuscitate order
No respiratory distress (defined by the patient showing fear, anxiety, or dyspnea)
No unilateral leg swelling
No altered mental status
Heart rate <100 beats/min
Respiratory rate <28 breaths/min
Pulse oximetry >94 % on room air
Weight >140 pounds

However, several assurances must be made, chief among them a low-risk status. Low-risk status with cancer primarily refers to the lack of a reason why the patient would need hospital care in the next 30 days. The primary determinant of success of outpatient treatment will be access to anticoagulant and ability to administer it. The preferred method of treatment for both DVT and PE in active cancer remains injected low molecular weight heparins [17]. Thus, it is the first objective with home treatment to determine if the patient and caretakers have the capacity and competence to administer twice daily subcutaneous injections. Other determinants of return to the hospital are pain control, decompensation of other disease processes, need for oxygen, or hemodynamic and respiratory effects of concomitant PE, which occurs in over 1/3 of patients [18, 19]. Patients with significant iliofemoral clot burden may require admission for catheter-based therapy in view of evidence that this approach significantly decreases postthrombotic syndrome and leg ulceration, which are the major complications of these proximal, occlusive DVTs [20].

Patients with PE are increasingly being treated at home, starting the same day of diagnosis, provided that these patients meet low-risk criteria [20–23]. Several criteria have been validated, including the Hestia criteria and the PESI and sPESI scores [24–27]. However, the sPESI score excludes discharge of patients with cancer. The Hestia criteria do not exclude patients with cancer, but we suggest that cancer patients with VTE must also meet a separate set of rules, of which two have currently been published: POMPE-C and criteria derived from the RIETE (Registro Informatizado de Enfermedad Tromboembolica) database by den Exter et al. These criteria include additional predictors such as metastases, immobilization, and low body weight and stratify cancer patients into percentage risk and low, medium, high, and very high risk, respectively [24, 28].

Thus, to deem a patient with either DVT or PE and with active cancer (which has been defined as under the current care of an oncologist or receiving palliative therapy, any patient with metastasis) as low risk for home treatment, we recommend a two-step approach. First, apply the Hestia criteria (Box 1), and second, for patients with confirmed PE, or patients with DVT and strongly suspected PE, apply either the POMPE-C criteria or the den Exter criteria (Box 2) [24, 29, 30].

Treatment

At present, the recommended method of treatment for VTE in cancer is injections of 200 IU/kg body weight once daily of dalteparin, a LMWH, as opposed to warfarin [31]. The CLOT trial in 2003 demonstrated that dalteparin was superior to warfarin with a 52 % risk reduction profile for recurrence of clot [31]. It is important to recognize that there is a

widespread assumption that enoxaparin 1 mg/kg body weight (Lovenox®) is equivalent to dalteparin (Fragmin®), although this has never been demonstrated in a clinical trial.

Despite the knowledge of a risk reduction from dalteparin, patients often request oral therapy, as injections are expensive, onerous, and painful and cause bruising that patients see as disfiguring [26]. In general, the authors strongly believe that physicians underestimate the negative perceptions that patients have toward injections [26]. Given the difficulty of self-injection and cost of the injectable LMWHs, many emergency departments have access to case managers or social workers who will help with the transition to outpatient therapy.

In 2013, rivaroxaban (Xarelto®) 15 mg BID for 21 days, followed by 20 mg qday thereafter, was approved for outpatient therapy of VTE. Dabigatran (Pradaxa®) recently received FDA clearance, and apixaban (Eliquis®) is currently under review by the FDA for this indication. As these target-specific anticoagulant (TSA) medications are significantly easier to take and less invasive for patients, they will likely be rapidly adapted for this indication if demonstrated to be noninferior to LMWH.

Available data support a shift toward the use of orally available TSAs for treatment of patients with active cancer and VTE. The basis for this statement comes from a pooled subgroup analysis of patients with cancer at the time of enrollment in the EINSTEIN-DVT and PE studies [27]. Together, these studies randomized 430 patients with active cancer, resulting in a reduction in relative risk of both VTE and bleeding, producing a net clinical benefit (hazard ratio, 0.60; 95 % CI, 0.36–0.99) that favored rivaroxaban-treated patients over patients treated with oral vitamin K antagonists.

Duration of need for anticoagulation sometimes emerges as a concern in the emergency department, particularly for patients who present with bleeding. Although several stopping criteria have been derived [32], none is adequately validated to provide clear, binary decision-making for cancer patients. A general rule of thumb is to anticoagulate for the duration of cancer treatment and then for several months thereafter. At minimum, cancer patients with any venous thrombosis, even if distal or superficial, should have 3 months' duration of anticoagulation and patients with proximal DVT or any PE should have 6 months' duration of anticoagulation [32]. There is some evidence that men who develop pulmonary embolism during cancer should be on lifelong anticoagulation. Thus, the prudent emergency practitioner would be wise to consider thrombosis as a cause for disease in patients recently in remission. Patients with a history of cancer that is inactive and who develop thrombosis should be treated in accordance with guidelines recommended for a patient with unprovoked DVT (3–6 months) and PE (minimum of 6 months).

Incidental Diagnosis and Thrombophilia Work-Up

Patients will occasionally be diagnosed with PE, discovered incidentally during routine imaging. This is often because of a CT scan of the chest performed with iodinated contrast for other reasons, such as staging of lung cancer or routine surveillance. The prognosis and treatment for these emboli are unchanged and confer the same risk to the patient as does symptomatic embolism [25]. All cancer patients, with any confirmed venous thrombosis (including calf, saphenous, brachial, axillary, or jugular) or any PE, including subsegmental PE, require systemic anticoagulation if they have no contraindications. Often patients and family are unaware of the worsened prognosis.

The thrombophilia work-up adds only unnecessary cost to the care of the cancer patient [33–35]. In terms of treatment choices and duration, cancer dominates as the driver of decision-making regarding the type and duration of anticoagulation, regardless of the patient's other genetic predisposition to thrombosis. Current guidelines do not support the testing of patients or their families for thrombophilia in the setting of a cancer-associated thrombus, including the "Choose Wisely" points issued by the American Society of Hematology [36].

Catheter-Associated Thrombosis

Extraluminal thromboses occur in 7 % of cancer patients with indwelling central venous catheters [37]. Intraluminal occlusions are best treated by interventional radiologist or other specialists with access to and experience using fibrinolytic agents (e.g., Cathflo®) for this purpose. Extraluminal venous thrombosis (which is a form of DVT) can be treated by either removal of the catheter or anticoagulation with the catheter in place. In contrast to other sites of deep venous thrombosis, symptomatic PE occurs less often in <5 % of patients, but more than half experience total venous obstruction which can lead to postthrombotic syndrome and venous scarring that causes permanent stenosis [37, 38]. Moreover, peripherally inserted central catheters (PICC lines) present a higher risk of thrombosis in cancer patients [37]. Thus, the decision to leave or remove the thrombosed catheter should be based primarily on the degree of swelling and pain, balanced against the need for the catheter and availability of alternative source of venous access, as determined in conjunction with the patient's oncologist.

For indwelling lines used for active chemotherapy or other ongoing treatment, anticoagulation is often the best route. If the catheter can be removed, and the patient has trivial swelling and no pain, the author's preference for

Table 3 Findings that suggest a worsened prognosis and may serve as indications for thrombolysis

Vital sign and physical examination abnormalities	Lab and imaging abnormalities
Systolic blood pressure <90 mmHg or a 40 mmHg drop from a known baseline blood pressure	Elevated cardiac BNP (>90 pg/mL) or pro-BNP (>900 pg/mL)
Hypoxemia (<92 % at or near sea level) with respiratory distress	Elevated troponin or CK-MB
Altered mental status or delirium, usually seen as agitation, panic, and inattention	Right ventricular dilation with or without hypokinesis on echocardiography, a tricuspid annular plane systolic excursion (TAPSE) distance <16 mm, lobar or larger clot burden on CT together with RV>LV and evidence of contrast reflux

subsequent treatment is a 7-day course of anticoagulation. Patients with visible swelling or pain should have 3 months of anticoagulation [17]. Prophylactic anticoagulation has shown disappointing results in both adults and children for prevention of catheter-associated thrombosis [39, 40].

Advanced Treatment

For all patients with massive PE, defined by either hypotension (systolic blood pressure <90 mmHg) or a 40 mmHg drop in systolic blood pressure, observed in the ED, clinical guidelines are aligned to recommend systemic fibrinolysis in the absence of contraindications (Table 3) [41, 42]. We recommend infusion of 15 mg of alteplase followed by 85 mg over 2 h. All patients should receive full-dose heparin anticoagulation (e.g., 5000 U unfractionated heparin bolus, followed by 16–18 U/kg/h infusion and PTT monitoring).

Patients with cancer have higher risk of bleeding with standard anticoagulation and probably have higher bleeding risk with administration of fibrinolytic agents [43, 44]. Recent work has suggested that a subpopulation of patients with DVT and PE (with <20 % having malignancy) will benefit from advanced therapies such as thrombolysis or catheter-based treatment [20, 45]. These patients fall primarily into two categories: DVT patients, with large iliofemoral clot burden causing pain and leg swelling, and PE patients, with right ventricular dysfunction, evidenced by an elevated troponin measurement (>99 percentile at a precision of 10 % coefficient of variability), or an elevated brain natriuretic peptide (BNP >90 pg/mL) or an elevated pro-BNP (>900 pg/mL), or an echocardiogram that demonstrates right ventricular hypokinesis or dilation, often defined as the right ventricular diameter larger than the left ventricular diameter [41]. No specific studies have been performed for catheter-based treatment of either PE or DVT in cancer patients. Regarding inferior vena cava filters in patients with PE who can be anticoagulated, no evidence has shown a clinically important net benefit for their insertion, and we do not recommend their use in any patient with PE who can be anticoagulated.

Patients with Absolute Contraindications to Anticoagulation

The treatment options are limited. An important intervention for these patients is to insert a vena cava filter as soon as possible [46]. With limited options for the patient in the presence of a strong contraindication to anticoagulation, such as active gastrointestinal bleeding, or recent glioblastoma surgery, physicians may be forced to consider treatments based upon case reports or hypothetical reasoning. These include inhaled nitric oxide (35 ppm by face mask or 50 ppm by nasal cannula) to reduce pulmonary vascular resistance and inhaled heparin which may localize anticoagulation in the lung vasculature [47]. Under fluoroscopic guidance, an interventional radiologist can place an infusion catheter through the body of the thrombus lodged in a proximal pulmonary artery and infuse 0.5 mg/h of alteplase with or without adjunctive ultrasonic (e.g., Ekosonic®), hydraulic (e.g., Angiojet®), or mechanical (e.g., rotating pigtail) catheter disruption. No clinical trials have tested this method and the risk of hemorrhage remains unknown. Methods of clot extraction, including the use of the large-bore Angiovac® device, or open surgical thrombectomy, require that the patient be placed on an extracorporeal perfusion circuit with systemic anticoagulation.

Follow-Up

Discharge of patients for outpatient follow-up must be done in conjunction with an outpatient physician. This may either be the patient's primary care physician or oncologist. As stated earlier, with the development of the target-specific anticoagulants, routine anticoagulation monitoring in the form of "coumadin clinics" will become less prevalent, especially in view of the fact that warfarin is not recommended to treat active cancer. Thus, the role of the physician in evaluating and caring for the patient with blood clots will shift away from simple INR management and dosage adjustment and instead focus on duration of therapy, prognosis, and quality

of life. These skills are well within the purview of primary care physicians. Stopping criteria, while imperfect, can be used in a shared decision-making model to determine individual duration of anticoagulation [32].

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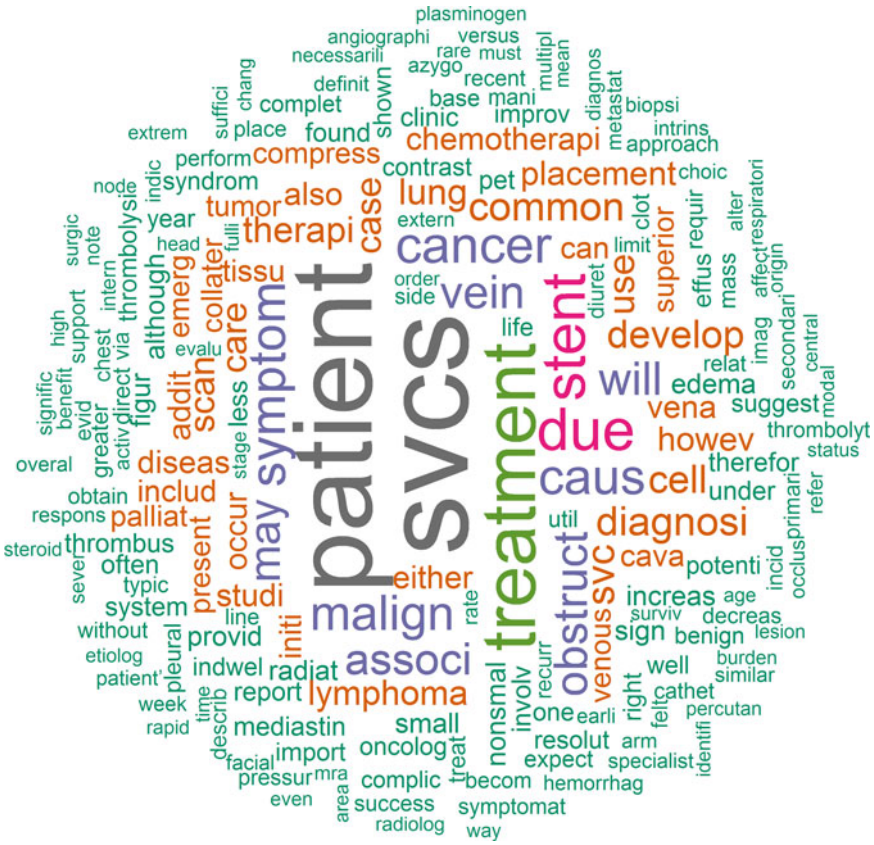
Superior Vena Cava Syndrome (SVCS)

David E. Manthey and Leslie R. Ellis



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Superior Vena Cava Syndrome Etiology/Epidemiology

Superior vena cava syndrome (SVCS) was first described by the Scottish physician William Hunter in 1757 in a case involving syphilitic infection of the aorta [1]. The epidemiology of the disease is that it currently affects about 15,000 people per year in the USA, occurring most commonly in patients between the ages of 50–70 years old [2]. It is commonly thought that 85 % or more of SVCS is due to malignant disease. However, a recent review of the cause of SVCS in 2006 showed that although malignancy was still the most common etiology, it only accounted for 60 % of the cases of SVCS [3]. When malignancy is the cause, it is most commonly associated with non-small cell lung cancer (50 %), small-cell lung cancer (25 %), lymphoma (10 %), and metastatic lesions (10 %), typically from breast cancer (Fig. 1). SVCS is actually found in a greater percentage of patients who have small-cell lung cancer (10 %) versus non-small cell lung cancer (less than 2 %), but because of the greater incidence of non-small cell lung cancer, the majority of cases of SVCS seen will be in that population [4]. The lymphomas associated with SVCS are overwhelmingly non-Hodgkin lymphomas, despite the fact that Hodgkin lymphomas typically present with mediastinal lymphadenopathy. Common subtypes of non-Hodgkin lymphomas associated with SVCS include the diffuse large B cell and lymphoblastic lymphoma subtypes. A type of lymphoma called primary mediastinal large B cell lymphoma with sclerosis, although more rare, has a greater likelihood of being associated with SVCS when present, with up to 57 % of patients having SVCS as presentation and over 80 % having some radiographic evidence for the potential for SVCS [5, 6]. Obstruction of the superior vena cava in these situations is typically due to external compression from either the primary mass or an involved lymph node, although tumors less likely to be associated with SVCS can cause SVCS via intravascular extension and occlusion, such as intravascular large cell lymphoma or thymoma, to name a few [7, 8]. Approximately 2 % of all cancer patients will develop some degree of SVCS [2, 9].

Surprisingly, according to a recent study, up to 40 % of the cases are now caused by indwelling lines secondary to an intrinsic thrombus associated with the line. This is felt to be due to not only compromised intraluminal laminar flow due to the presence of the indwelling line but also from alteration of the integrity of the vessel wall due to irritation of the endothelium by the catheter tip or wire lead [10]. However, only 1–3 % of patients with central venous catheters will become symptomatic [11]. This is commonly referred to as "benign" SVCS as it is not due to malignancy or alternatively because it is caused by intrinsic clot rather than external compression. A patient with benign SVCS tends to be in the 30–40-year age range. Approximately 25 % of pacemaker insertions are associated with obstruction or stenosis of the central venous system. It is reportedly less in patients with implanted pacemakers at an incidence of 0.2–3.3 % [12]. Other causes of SVCS include mediastinal fibrosis, vascular diseases (atherosclerotic), infection (histoplasmosis, tuberculosis, syphilis, actinomycosis), goiter, benign mediastinal tumors (cystic hygroma, thymoma, teratoma), pericardial constriction, and nephritic syndrome. In pediatric patients, the cause of SVCS is most commonly iatrogenic secondary to indwelling central lines, ventriculoperitoneal shunts, or due to complications of cardiovascular surgery rather than caused by a cancer.

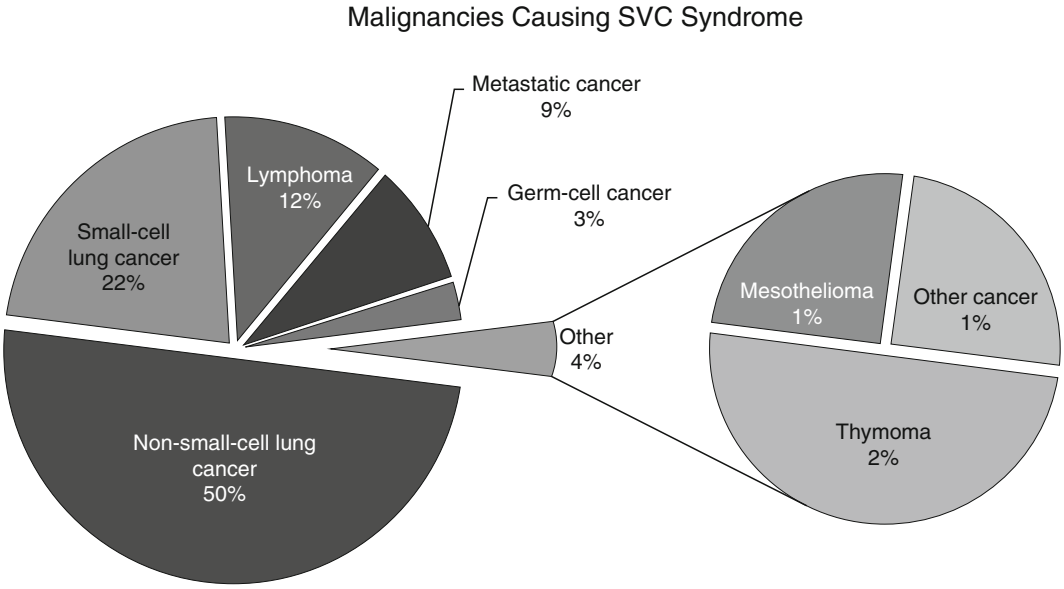

Fig. 1 Distribution of malignancies causing superior vena cava syndrome. [Reproduced from McCurdy, M.T. and C.B. Shanholtz, *Oncologic emergencies*. Crit Care Med, 2012. 40(7): p. 2212–22, with permission from Wolters Kluwer Health]

Anatomy

To fully understand the signs and symptoms of SVCS, the corresponding anatomy should be reviewed. The superior vena cava is 4–6 cm in length and 1.5–2 cm in width in an adult. It originates from the left and right innominate veins and terminates into the right atrium. The SVC does not contain any venous valves. The vein itself is thin walled and therefore easily compressible. It is surrounded by lymph nodes that may become enlarged and cause external compression. It is joined just above the right atrium by the azygos vein, which drains the veins from posterior aspect of the abdominal to chest cavities. The azygos vein can become an alternative drainage system for the upper extremity through collateral veins if it is not obstructed (Fig. 2). Therefore, the position of the SVC obstruction above and therefore not including the azygos vein may alter the severity and rapidity of onset of SVCS symptoms. Other potential sites for collateral development include the internal mammary veins, lateral thoracic veins, paraspinal veins, and esophageal veins, although the ability of these systems to fully compensate for SVC obstruction is more limited than the azygos vein system. The development of these collaterals usually occurs over a period of weeks; therefore SVCS due to rapid tumor growth may not be associated with sufficient collateral development and symptoms may be more severe. When the vena cava is obstructed, the venous pressure in the cervical veins increases to 20–40 mmHg which is significantly more than the normal range of 2–10 mmHg [13]. Development of collaterals and the rapidity of the obstruction will affect the actual values.

Clinical Features (Signs/Symptoms)

The clinical features of SVCS align with what you would expect to encounter due to an obstruction of the major venous drainage of the head, neck, and upper extremities (Fig. 3, panel a). The most common sign of SVCS is facial edema (82 %) which may be most noticeable in the morning after being in a recumbent position or with bending forward. Even in the presence of marked physical changes due to facial edema, this is rarely of clinical consequence [14]. Additional signs include distended neck veins (63 %), distended chest veins (53 %), arm edema (46 %), and facial plethora, also referred to as a red ruddy complexion (20 %) [15]. An interesting sign is the Pemberton sign which is the exaggeration of the edema and flushing of the face due to the placement of the patient's arms over the head [16].

Most patients have symptoms for 2–4 weeks before a diagnosis is made. The development of collaterals may delay the onset of symptoms and signs. The most common symptoms of SVCS are cough (54 %) and dyspnea (54 %). The latter is commonly due to an associated pleural effusion and is seen more often in malignancy-associated SVCS. Additional symptoms include hoarseness (17 %), syncope (10 %),

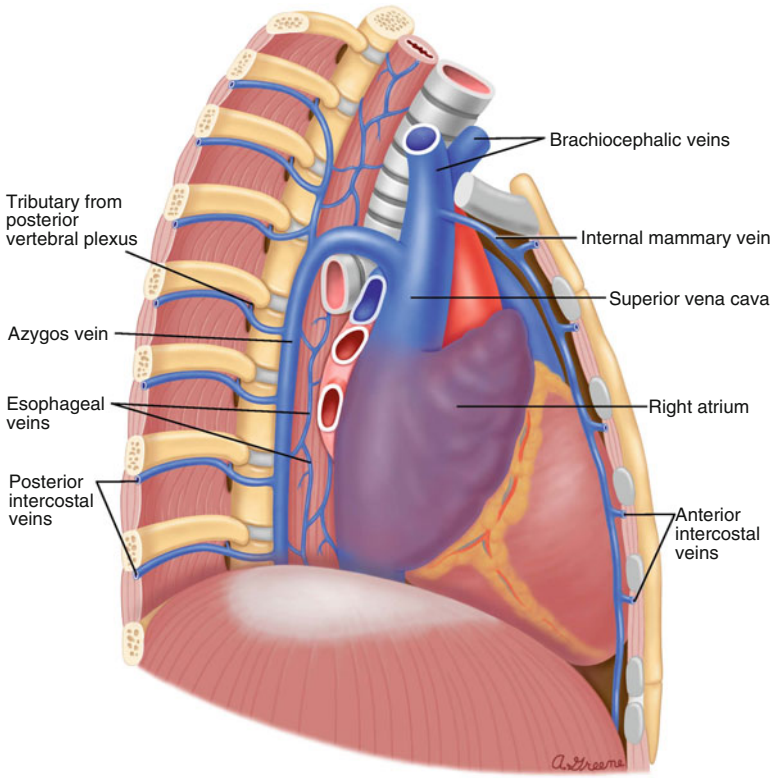

Fig. 2 Anatomy of the superior vena cava and veins of the mediastinum. [Reproduced with permission from: Drews R. Malignancy-related superior vena cava syndrome. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Copyright © 2014 UpToDate, Inc. For more information visit www.uptodate.com]

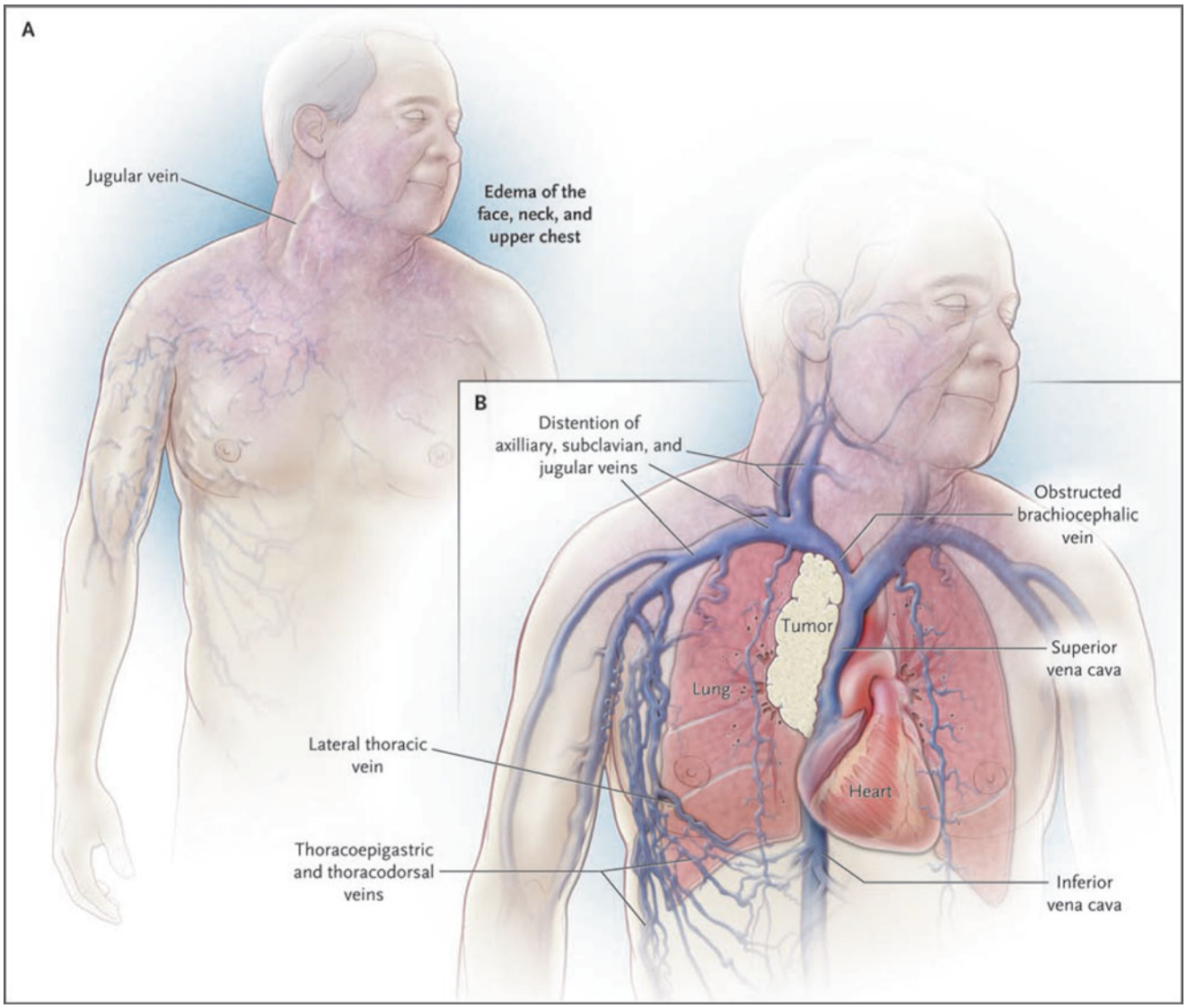

Fig. 3 (**a**, **b**) Clinical manifestations in a patient with superior vena cava syndrome including facial edema, plethora, jugular venous distention, and prominent superficial vascularity of the upper chest and neck are shown in *panel a*. The vascular anatomy of the upper chest, including the heart, superior vena cava, inferior vena cava, and subclavian vessels, is shown in *panel b*. The SVC is being compressed by tumor. [From The New England Journal of Medicine, Wilson LD, Detterbeck FC, Yahalom Y, Superior Vena Cava Syndrome with Malignant Causes, 356: 18 ©2007 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society]

headaches (9 %), and dizziness (6 %). Stridor may occur in 4 % of patients due to swelling around the trachea. Confusion (4 %) and obtundation (2 %) may also be present if cerebral edema is occurring but are unlikely to be the only complaint. Visual symptoms (2 %) are also rarely encountered. It is important to note that improvement in these symptoms does not necessarily represent resolution of SVCS but instead may reflect the development of an adequate venous collateral system. Additionally, symptoms may not be due solely to SVCS but due to direct compression of additional structures by the primary or metastatic mass. This pearl is especially important when considering altered mental status or neurological findings which may be due to increased venous pressure in the cranial vault or due to brain metastases from the primary tumor [17]. The most concerning signs and symptoms are those suggesting respiratory compromise or cerebral edema, as this may be life threatening. Because over 70 % of the malignancies associated with SVCS are either small-cell or non-small cell lung cancer, an accurate history as to tobacco use is important. Additionally, a thorough lymph node exam may be able to highlight palpable supraclavicular lymphadenopathy or multiple areas of lymphadenopathy, both of which have a high likelihood of being associated with malignancy [18].

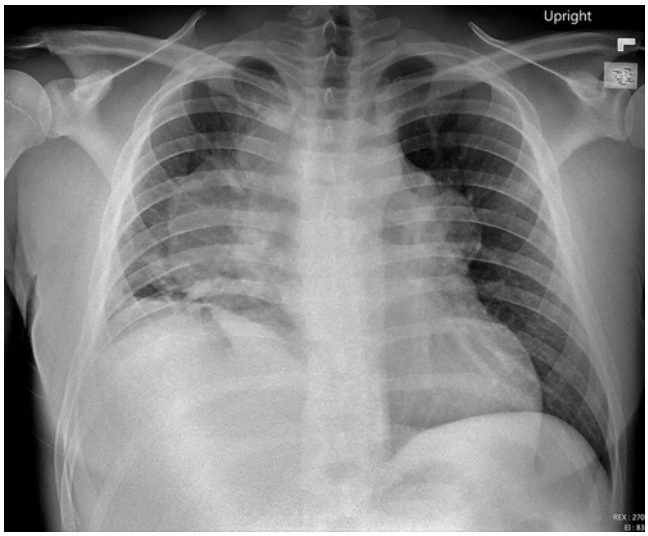

Fig. 4 Radiographic evidence of mediastinal mass (lymphoma) with right-sided pleural effusion

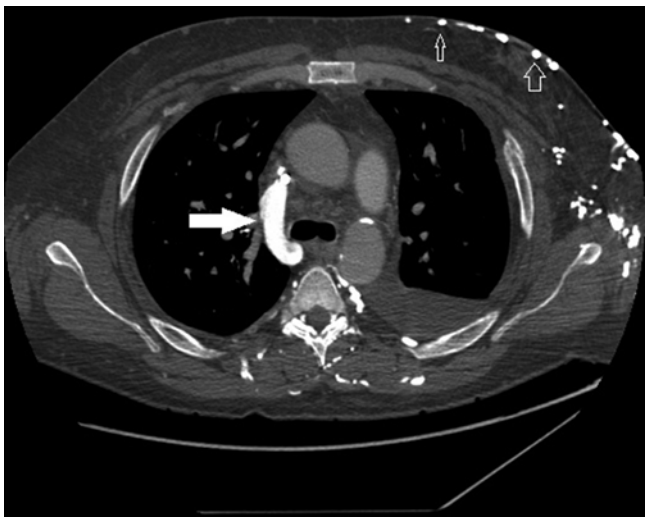

Fig. 5 Superior vena cava syndrome with blood returning via collaterals draining to the azygos vein. *White open arrows* pointing to collaterals. *White solid arrow* pointing to azygos vein

Radiographic Evaluation

Although the diagnosis is suspected on a clinical basis, it is confirmed by radiologic studies. The chest radiograph (CXR) is abnormal in 84 % of patients with SVCS, reflecting the malignancy that is causing the obstruction [2]. The findings on CXR include mediastinal widening (64 %) and superior mediastinal mass, 75 % of which occur on the right side, as expected with the SVC anatomy (Fig. 4). Pleural effusions are found in 25 % of patients and, in older radiologic literature, are purported to be found mostly on the right side.

For definitive diagnosis, computed tomography (CT) of the chest with intravenous contrast is the modality of choice. CT angiography (CTA) can identify the location of the obstruction as above or below the azygos vein. At the same time, it will identify the development of collateral vessels (Fig. 5). It will differentiate between intrinsic clot and mass versus extrinsic compression of the superior vena cava with or without a superimposed thrombus [19] (Fig. 6). In addition a chest CT may give information about structures such as the vocal cords/airway as well as where best to perform a biopsy (via mediastinoscopy, bronchoscopy, or percutaneous fine needle aspirate). CTAs have been found to have sensitivities of 96 % [20]. However, this modality and magnetic resonance angiography (MRA) both require the patient to lie flat, which may increase their dyspnea and therefore cause movement on the scan.

One epidemiologic study found pleural effusions on CT which occurred in 70 % of cases when associated with malignant causes and in only 58 % of cases associated with benign causes [21]. Most effusions are small, with the majority filling less than 25 % of the hemithorax. Contrary to the expected, pleural effusions occur on either side with equal

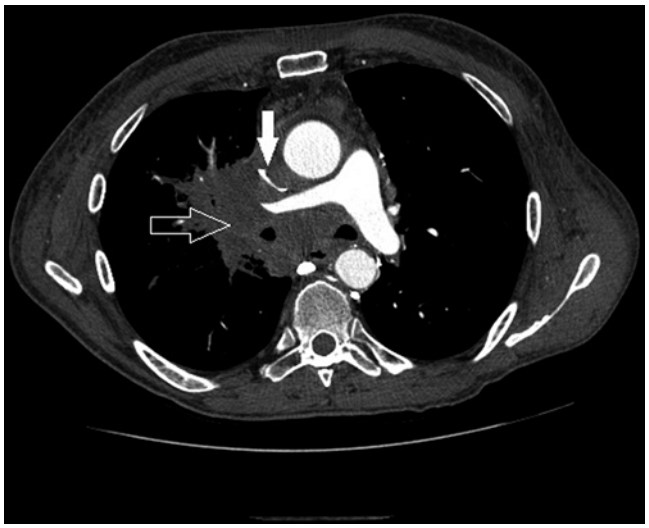

Fig. 6 Superior vena cava syndrome caused by lung cancer. *White open arrow* pointing to mass obliterating the right main stem bronchus. *White closed arrow* pointing to collapsed superior vena cava

incidence. The effusions, when sampled, were found to be either chylous in origin or exudative. This is different from the classic thinking that the fluid was transudative due to hydrostatic pressure differences. The chylous origin may be due to obstruction of the thoracic duct or due to impedance of lymphatic flow.

As indwelling devices are also a common cause of SVCS, those patients presenting with unilateral arm swelling in the setting of having an indwelling device will often undergo a Doppler ultrasound of the upper extremity to rule out a thrombus in the subclavian, axillary, and brachiocephalic veins. It is important to note, however, that the SVC cannot

be directly imaged by a Doppler ultrasound (due to its encasement by the ribs) and therefore additional imaging such as CT is required. Some texts suggest that the patency of the SVC can be indirectly determined by normal waveforms in distal veins such as the subclavian or brachiocephalic, but there is no definitive evidence to back this approach. Transesophageal echocardiography would allow for imaging of the SVC and the right atrium but is more invasive.

Contrast venography can also diagnose SVCS, but it uses a significant load of iodinated contrast and radiation exposure. Venous cannulation of the affected arm may be difficult as well, and if completely obstructed, limited visualization will occur. Finally, extrinsic compression versus internal clot cannot be distinguished. Venography is commonly done before stenting by interventional radiology and will provide information about the patency of the vena cava, as well as the extent of collateral circulation.

Magnetic resonance angiography (MRA) is also relatively sensitive (92–96 %) and may be used in those patients who are allergic to contrast dye. However, MRA carries the risk of gadolinium-induced nephrogenic systemic fibrosis in patients with renal failure. It provides much greater detailed imaging of the mediastinal structures and can be viewed in multiple planes. Disadvantages include cost and duration of scanning in a dyspneic patient.

Positron emission tomography (PET) scans, either with or without CT scans, are commonly used in oncology to assist in the staging of disease both before and after treatment. However, the benefit to diagnosing SVCS with a PET scan is still dependent upon the CT portion of the scan. Specifically, a PET scan without a CT scan will have the ability to show a PET-avid mass in the area of the SVC but will not be able to provide a clear picture of SVC compression or obstruction. Similarly, a PET/CT, with the CT scan performed without IV contrast, will provide better images of the mediastinal area, but diagnosis of SVCS will still be limited. The only way to definitively diagnose SVCS with a PET scan would be to obtain a PET scan followed by a CT scan with IV contrast. Due to the increased costs associated with PET scans and the relative decreased availability, PET scans remain a method of staging prior to initiation of treatment as opposed to a fast or accurate way to diagnose a patient with SVCS.

Histologic Diagnosis

Sixty percent of patients with SVCS will have this to be the presenting symptom of their cancer [22]. Malignancy must be confirmed by a tissue diagnosis, although this does not necessarily require a biopsy of the mass that is causing the SVCS. An individualized approach is needed to see if less-invasive means can be utilized to obtain a tissue diagnosis before proceeding to mediastinoscopy. Less-invasive means of obtaining a tissue diagnosis of malignancy are diagnostic in 87 % of cases. Cytological analysis of the sputum is diagnostic in 68 % of cases [23]. Thoracentesis of the pleural fluid yields a diagnosis in only about 50 % of patients with SVCS and an associated pleural effusion. Bronchoscopy and transthoracic needle aspiration biopsy may each provide a diagnosis in up to 70 % of cases and are associated with minimal complications in this patient population, with only 0.5 % of patients each developing hemorrhage or worsening of respiratory symptoms [24]. However, a mediastinoscopy or mediastinotomy can provide a diagnosis in greater than 90 % of the cases, with little increase in complications, as only 3 % of patients developed significant hemorrhage with the procedure [25, 26]. Whenever a lymphoma is on the differential, an excisional biopsy is preferred in order to allow the pathologist to determine tumor architecture and have sufficient tissue to perform immunohistochemical staining, both of which aid in an accurate diagnosis of the particular subtype of lymphoma. Suffice it to say, the importance of having a tissue diagnosis in a newly presenting malignancy should not be understated.

Treatment

Historically, treatment for SVCS consisted of emergent radiation, steroids, and diuretics. Importantly, SVCS was described in textbooks as an oncologic emergency, but recent evidence has shown that not all SVCS cases require emergent therapy [22]. In order to attempt to distinguish which patients with SVCS would require aggressive therapy, a proposed staging system has been developed [14]. This algorithm proposes a different treatment approach based on the severity of disease as graded (Table 1).

As can be noted from the treatment algorithm (Fig. 7), emergent treatment is only indicated if altered mental status,

Table 1 Grading of symptoms associated with SVCS

Grade	Definition	Estimated incidence (%)
0	Asymptomatic; radiographic evidence	10
1	Edema in head /neck, plethora	25
2	Functional impairment of voice, facial muscle by edema (dysphagia, cough, visual disturbance)	50
3	Mild/Moderate cerebral edema; Mild/Moderate laryngeal edema; Poor venous return with orthostatic syncope	10
4	Confusion, Obtundation; Stridor Significant hemodynamic compromise	5
5	Fatal	<1

From: Yu, J.B., L.D. Wilson, and F.C. Detterbeck, Superior vena cava syndrome--a proposed classification system and algorithm for management. J Thorac Oncol, 2008. 3(8): p. 811–4, with permission from Wolters Kluwer Health (14)

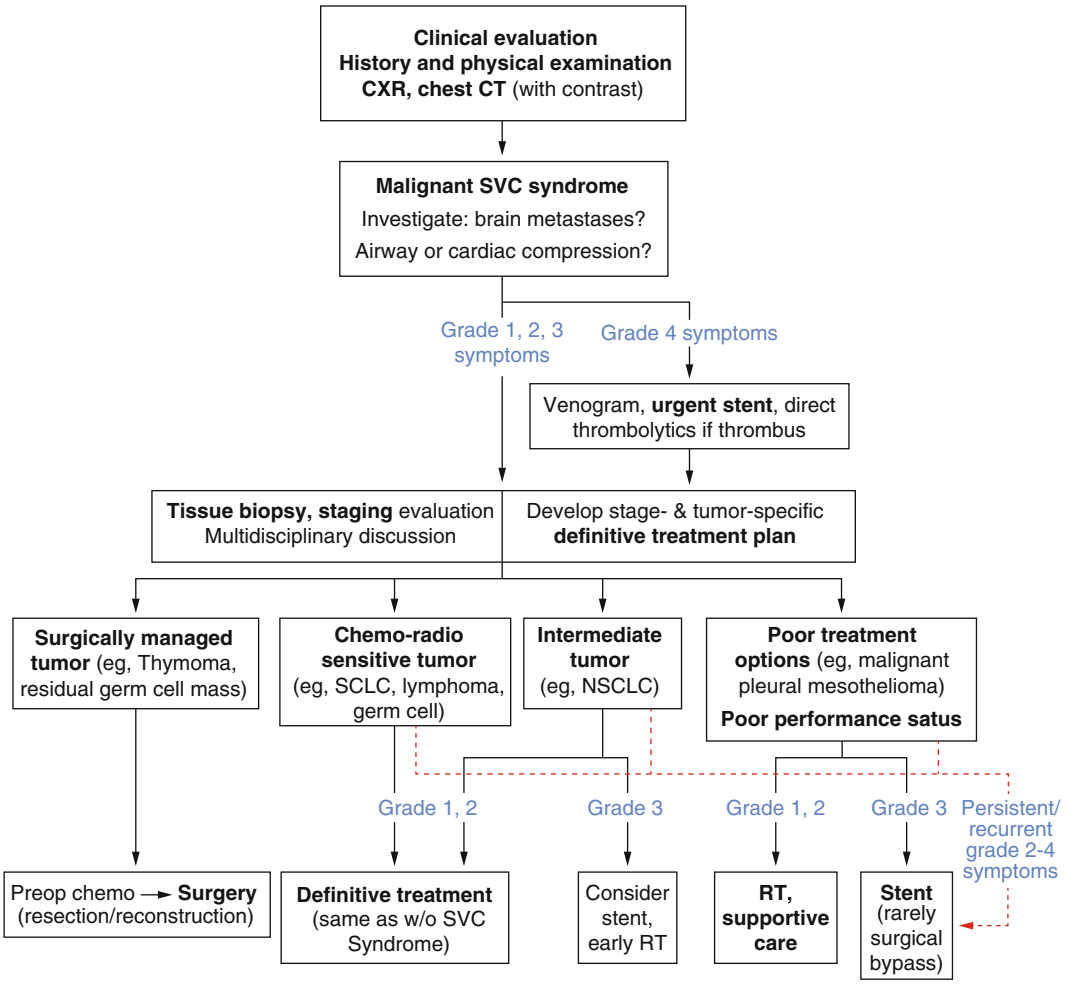

Fig. 7 Proposed algorithm for treatment of SVCS based on the severity of symptoms and etiology. [Reproduced from Yu, J.B., L.D. Wilson, and F.C. Detterbeck, Superior vena cava syndrome—a proposed classification system and algorithm for management. J Thorac Oncol, 2008. 3(8): p. 811–4, with permission from Wolters Kluwer Health]

respiratory distress, or hemodynamic instability has occurred. The emergent treatment in these cases would be either thrombolytic for thrombus or stent placement for extrinsic compression and/or thrombus. If not emergent, therapy is supportive or directed at the underlying cause.

Supportive Therapy

In the recent past, glucocorticoids have been utilized based on case reports suggesting benefit. However there is no good evidence to support their use. They have been suggested in lymphoma or thymoma as they reduce the tumor burden or if they are indicated in the treatment of the underlying malignancy [4]. However, in a previously undiagnosed patient, this potential benefit will have to be weighed against the potential risk of eliminating a tissue diagnosis. Along the same vein, diuretics have been used, based again on anecdotal evidence. Since the disease is based on limited flow return to the heart and not on volume overload, it does not make intrinsic sense to utilize diuretics. In one study randomizing patients to glucocorticoids, diuretics, or neither therapy, the incidence of improvement clinically was similar among all three groups [22].

Elevation of the head of the bed to theoretically decrease the hydrostatic pressure increase in the brain secondary to the elevated cervical venous pressures has been suggested and has little to no downside.

Treatment of Malignant Causes of SVCS

For patients with SVCS due to malignant causes, the treatment goals are twofold, relieving the obstruction as well as treating the underlying malignancy. Initiation of treatment with chemotherapy and/or radiation therapy before a diagnosis is obtained not only exposes to the patient to the side effects of the treatment without guarantee of response but also

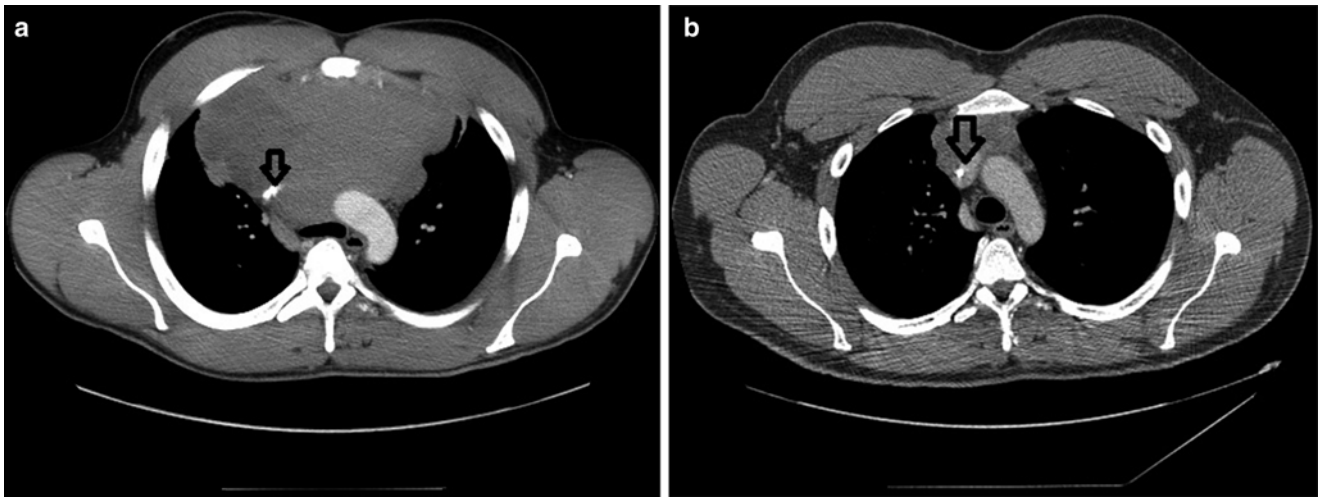

Fig. 8 (**a**) Superior vena cava syndrome caused by mediastinal tumor (lymphoma). *Black open arrow* pointing to collapsed vena cava with central line in place. (**b**) Same patient s/p induction chemotherapy with marked reduction in tumor burden. *Black open arrow* pointing to open vena cava with central line in place

decreases the yield for an exact tissue diagnosis, with one study reporting only one of six patients (16.7 %) having a histologic diagnosis obtained after chemoradiation therapy was initiated [27].

Chemotherapy

Chemotherapy is often the initial treatment of choice for SVCS in a symptomatic patient if the tumor causing the SVC compression is felt to be chemotherapy sensitive. Small-cell lung cancer, non-Hodgkin lymphomas, and germ cell tumors are all felt to be chemosensitive and even symptomatic patients with SVCS will have chemotherapy initiated first. This is in contrast to non-small lung cancer, which traditionally is felt to be less chemosensitive and for whom radiation therapy is often the initial treatment of choice [28]. Multiple studies have shown that prompt initiation of chemotherapy in patients with small-cell lung cancer is an effective way (77 % response rate) to alleviate the symptoms due to SVCS within 1–2 weeks of beginning treatment, although a small percentage of patients will have their obstructive symptoms recur (17 %) [4, 29–33]. Similarly, for lymphomas, prompt initiation of treatment with chemotherapy is usually sufficient to prevent worsening of symptoms and ultimately alleviate the obstruction due to disease (Fig. 8).

With the advent of a greater understanding of molecular pathways involved in malignancies, and the development of treatments that specifically target these pathways, more novel agents are being utilized to treat patients with SVCS due to malignancy. For example, the BRAF inhibitor vemurafenib has been shown to successfully treat SVCS in a patient with melanoma, with resolution of his symptoms by 72 h [34].

Radiotherapy

Again, almost 50 % of malignancies causing SVCS are non-small lung cancer. This tumor is more radiosensitive than it is chemosensitive, and therefore radiation therapy is the modality of choice for a patient presenting with symptomatic SVCS due to non-small cell lung cancer. Symptom improvement may begin as soon as 72 h after initiation of treatment with complete resolution of symptoms two weeks into treatment in anywhere from 63 % to 80 % of patients, with about 20 % of patients developing recurrence of SVCS after treatment was complete [4]. This is compared to response rates of 59 % for chemotherapy alone and 31 % for concomitant chemoradiation in patients with non-small lung cancer.

However, it is difficult to note how much of the improvement in symptoms is from the radiation therapy alone versus the development of a collateral vasculature that finally becomes sufficient to compensate for the obstruction. In an interesting study evaluating patients being treated with radiation therapy for SVCS, 85 % of the patients reported improvement in symptoms, yet consecutive venograms showed that only 31 % of patients had complete resolution of their SVC obstruction, and only 23 % had partial resolution of the SVC obstruction. Evaluation during autopsy revealed even lower numbers, with only 24 % of patients with either complete or partial resolution of the SVC obstruction [17].

Stents

Percutaneous transluminal stents have emerged on the treatment realm for SVCS. Stents are indicated as an emergent treatment or for cancer that is not responsive to treatment. Intravascular stents provide symptomatic relief secondary to edema within 48–72 h. Only 17 % of patients had complete

relief with the stent suggesting that the edema is multifactorial beyond the vena cava obstruction [35]. Tissue diagnosis will not be adversely affected by stent placement. Stents do not interfere with treatment of the cancer with either radio or chemotherapy and, most importantly, remain an additional treatment option for those patients who have recurrence of their SVCS after initially responding to either chemotherapy or radiation therapy [35].

In one study of patients with malignancy-associated SVCS, the treatment was clinically successful in 95 % of cases (156 out of 164 patients) with an early mortality rate of 2.4 %. Relapse occurred in 22 % (36 patients), but re-stenting was successful in 75 % of these patients. Recurrence was associated with occlusion, initial associated thrombosis, or steel stents. Complications occurred more commonly if the stent was >16 mm in diameter [36]. Some have suggested using stents for indwelling catheters or primary treatment of benign SVCS [37].

Complications of stent placement include migration of the stent, hematoma at the site, perforation of the SVC, bleeding, infection, and pulmonary embolism. These have been reported in 2–7 % of patients treated with stent placement.

Anticoagulation is often recommended after stent placement or for the treatment of coagulation associated with SVCS, but there are no evidence-based protocols to support this practice. It is based upon use of other stents and the treatment of other venous clotting. Use of thrombolytic therapy as an additional therapy to stent placement is associated with an increased morbidity.

Surgical Bypass Grafting

Surgical bypass grafting from the innominate or jugular veins to the right atrial appendage or distal SVC has been described for many years. Over the last 5 years, the practice has shifted from an open surgical technique to endovascular stenting.

Treatment of Benign (Non-malignant Causes) of SVCS

Medical treatment with steroids or diuretics has not been shown to be useful, especially in treating SVCS of benign origin. If an indwelling line is present, and the SVC was due to a clot, then anticoagulation is often utilized, although the effectiveness of this approach has not been shown either in the short- or long-term setting.

Stent

Stents can be placed across the occlusive lesion. Catheters are introduced from above via the internal jugular vein or below the diaphragm via the common femoral vein (Fig. 9). A wire is placed across the obstructive lesion. If recombinant tissue plasminogen activator is to be used, it is often delivered via a catheter with multiple side ports. Then a percutaneous balloon angioplasty is performed with a 10–16 mm angioplasty balloon. After the angioplasty, a stent is placed. The incidence of early re-intervention for thrombus in one study was 4 % [37]. Patency at 30 days was 96 %.

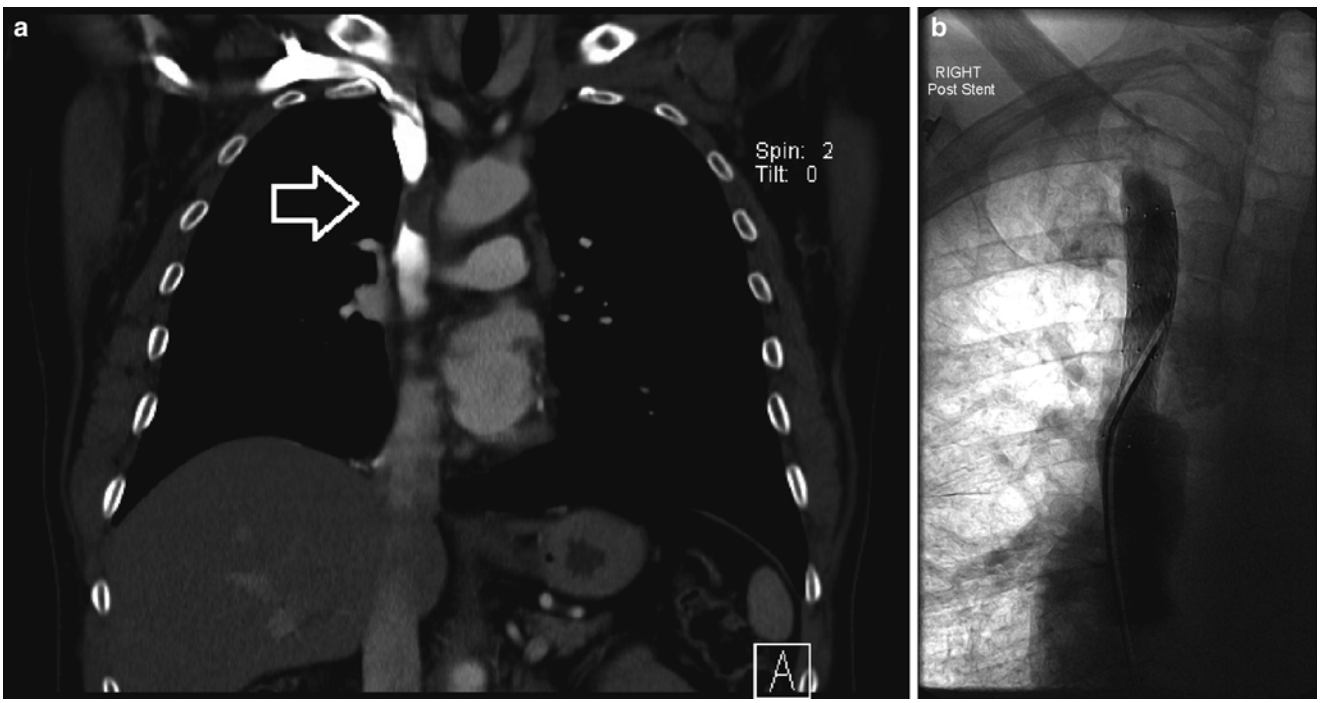

Fig. 9 (**a**) CT coronal view superior vena cava syndrome. *White open arrow* indicates area of narrowing on contrasted study. (**b**) Deployment of a stent across the superior vena cava

Thrombolytics

Patients who have developed SVCS due to intraluminal thrombus may benefit from thrombolysis, often in combination with stent placement. The use of thrombolytics (typically tissue plasminogen activator or urokinase) before stents are placed has been shown to decrease the length of blockage due to thrombus and therefore the number of stents placed [35, 38–42]. It is also felt that thrombolysis prior to stent placement decreases the burden of material that has the potential to embolize during stent placement. Adverse events, however, are increased as well when thrombolytics are used, with complications such as gastrointestinal hemorrhage, hemoptysis, and intracranial hemorrhage documented. This does have to be balanced with the relative success rate of thrombolysis, which has been reported to be as high as 88 % [43]. Although typically thrombolysis occurs by pharmacological means, new advances in technology have provided additional methods of clot dissolution, primarily through the use of ultrasound accelerated catheter-directed thrombolysis, which utilizes high-frequency sound waves in combination with tissue plasminogen activator [44]. This relatively new technology will require time to see if becomes as widely accepted as traditional chemical thrombolysis.

Prognosis

The outcomes of patients with malignant SVCS are directly related to the underlying malignancy and do not necessarily portend a lower overall survival compared to patients with similar tumor types who do not have SVCS [2]. Within the literature for small-cell lung cancer alone, studies have shown either no change or an improvement in overall survival for those patients who presented with SVCS when compared to patients who did not develop SVCS [29, 31–33, 45].

However, many studies will describe the median life expectancy for a patient that develops SVCS as being only 6 months, yet many patients have survived over 2 years with treatment [14]. In some patients, treatment of the underlying malignant disease will result in cure of the disease and resolution of the SVCS.

In addition to the underlying etiology, poor prognostic factors for SVCS in patients with malignant cause include advanced age (>50), history of smoking, and use of steroids [46].

Recurrence (Durability of Treatment)

Almost 32 % of patients with SVCS secondary to small-cell lung cancer after treatment, with chemotherapy, radiotherapy, or indeed both, had a recurrence of the SVCS syndrome, but this data is from 1983 and treatment has invariably changed since then [30]. Relapse after placement of a SVC stent is reported at around 11 % (various reported values of 9–20 %). Most of these are successfully intervened upon by a second stent placement.

Palliative Care Discussions

As with any potentially life-threatening illness, the consideration of involving palliative care specialists is a must. There are many definitions of palliative care, but most involve the concepts of preventing and minimizing suffering, optimizing one's quality of life, and aligning the healthcare team's values with those of the patient. In the field of oncology, organizations such as the Institute of Medicine and the World Health Organization have recognized that palliative care specialists can play a special role in the care of cancer patients [47]. This is supported by a study that identified an improved quality of life for patients with metastatic non-small cell lung cancer who had an early intervention with palliative care while also receiving standard oncologic care [48]. This was also the basis for the American Society of Clinical Oncology's provisional clinical opinion to extend this recommendation for early involvement of palliative care specialists to any patient with metastatic cancer or a significant burden of disease, again in combination with chemotherapy and/or radiation therapy [49].

Many have used the concept of estimated life expectancy as a surrogate marker for when to more fully involve the palliative care team in a patient's care. In fact, the National Comprehensive Cancer Network's Guidelines for Palliative Care references a life expectancy of less than 6 months as a trigger to more actively engage palliative care, for which SVCS is one indicator [50]. However, additional factors must be taken into account, including the underlying malignancy that has caused the SVCS, the patient's performance status, and the patient's wishes. It is crucial that an oncologic specialist be involved in the conversations with the patient and other members of the healthcare team in order to provide an overall perspective of the disease course and potential outcomes.

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Neutropenic Fever

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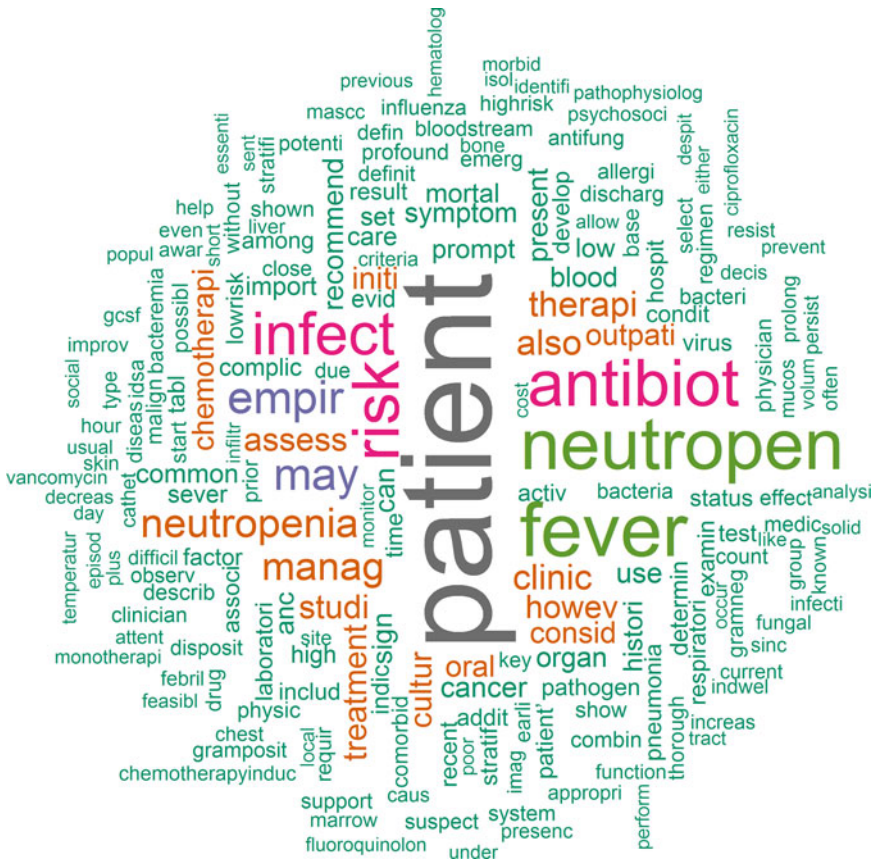

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Introduction

Neutropenic fever is a common but potentially life-threatening cancer complication that affects 10–50 % of patients with solid tumors and more than 80 % of patients with hematologic malignancies [1]. Population-based data surveillance indicates mortality from neutropenic fever to be as high as 6.8 % [2]. However, a study has shown that mortality varies according to comorbidities and it can reach to 50.6 % among those who have five comorbidities [3]. Due to either myelosuppression or disrupted integrity of the anatomy from chemotherapy or inherent part of the malignancy, cancer patients are at risk of infection. However, because signs and symptoms of inflammation are often attenuated among such population, fever may be the earliest and the only indication of infection. Therefore, it could be difficult to assess the severity of the infection among these populations [4, 5]. To prevent progression to severe sepsis and possible mortality, early recognition and intervention is essential among these patients [3, 4]. To improve the overall management of patients, emergency physicians should be aware of the importance of prompt assessment and rapid initiation of treatment of cancer patients with neutropenic fever.

Definition

Neutropenic fever results from profound bone marrow suppression (usually from chemotherapeutic treatment regimens) with resultant significant reduction of the absolute neutrophil count (ANC) that renders cancer patients susceptible to serious infections, often with fever as the only clinical finding [6–8]. Specific definitions of fever and neutropenia can vary by institution or organization. For example, the American Society of Clinical Oncology (ASCO) defines fever as a temperature of ≥38.3 °C by oral or tympanic thermometry, but the Infectious Diseases Society of America (IDSA) defines fever as a single oral temperature of ≥38.3 °C or a temperature of ≥38.0 °C lasting for 1 h [9]. For the classification of neutropenia, ASCO defines neutropenia as an ANC <1000 μL^{-1}, severe neutropenia as ANC <500 μL^{-1}, and profound neutropenia as ANC <100 μL [4, 9], whereas IDSA defines neutropenia as an ANC <500 μL^{-1} or expected ANC in the next 48 h <500 μL^{-1}. IDSA also defines profound ANC as <100 μL^{-1} [4].

Pathophysiology

Pathophysiology of Neutropenia

Neutropenia can result from poor hematopoiesis either in hematologic malignancy or bone marrow suppression by metastatic infiltration. However, the most common cause of neutropenia is cytotoxic chemotherapy. The ANC nadir usually occurs 5–10 days following chemotherapy [10]. Exposure to prior chemotherapy, immunosuppressive status, laboratory abnormality, such as elevated alkaline phosphatase, bilirubin, or aspartate aminotransferase, low glomerular filtration rate, and cardiovascular comorbidities are risk factors of rapid ANC decrease. Chemotherapy drugs such as anthracyclines, taxanes, topoisomerase inhibitors, platinums, gemcitabine, vinorelbine, cyclophosphamide, and ifosfamide are also known to induce neutropenia [11].

Infection in Neutropenic Fever

Infection is known to be accountable for half of neutropenic fever cases [12]. However, because of poor inflammatory reaction, the patient may not show localized signs or symptoms to suggest infectious source other the fever. Erythema, induration, or abscess formation may be minimal or absent due to a low number of pus-generating neutrophils. For the same mechanism, pulmonary infiltration may not present physically audible or radiologically visible evidence [10]. Clinical evidence of infection can be shown in only 20–30 % of febrile episodes, and commonly infected sites are the intestinal tract, lung, and skin [4]. Bacteremia can be documented in 10–25 % of neutropenic fever patients, and most episodes occur in patients with prolonged or profound neutropenic status [4, 6]. Besides immunosuppressive effect of chemotherapy, chemotherapy-induced mucositis may also contribute to infection among febrile neutropenic patients. An intact mucosal barrier defends the system from infection [13]. Disruption of the integrity of the mucous membrane allows colonizing microorganisms to become disseminated, especially when the ANC declines [14–16].

Common Infections and Related Microorganisms

Recent studies show that gram-positive organisms are more common bloodstream isolates, while gram-negative pathogens were more prevalent in the past. It is thought because of increased incidence of chemotherapy-induced mucositis, indwelling catheter use, and the use of prophylactic antibiotics against gram-negative bacteria [4, 17–20]. Coagulase-negative staphylococci are known to be the most common blood isolates. Table 1 shows common bacterial organisms in neutropenic patients [4].

Fungi are less often documented as responsible pathogens in the early stage of neutropenia. They are rather encountered in the setting of prolonged neutropenia or after empirical antibiotic

Table 1 Common bacterial organisms in neutropenic patients[a] [4]

Gram-positive bacteria	Gram-negative bacteria
Coagulase-negative staphylococci	*Escherichia coli*
Staphylococcus aureus[b]	*Klebsiella* species
Enterococcus species[c]	*Enterobacter* species
Viridans group streptococci	*Pseudomonas aeruginosa*
Streptococcus pneumonia	*Citrobacter* species
Streptococcus pyogenes	*Acinetobacter* species
	Stenotrophomonas maltophilia

[a]Table is adapted from IDSA guidelines (Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America)
[b]Including methicillin-resistant strains
[c]Including vancomycin-resistant strains

therapy [4]. *Candida* is known to be found most commonly and may cause bloodstream infection or invasive disease in the setting of indwelling intravascular catheters, previous use of broad-spectrum antibiotics, use of mechanical ventilation, immunocompromised conditions such as leukemia or bone marrow transplant, and parenteral nutrition [20–22]. Chemotherapy-induced mucositis may allow locally colonized *Candida* to enter the bloodstream, predisposing the patient to invasive candidemia [17]. Molds such as *Aspergillus* can cause fatal infection to sinuses or lungs but typically occurs among patients with prolonged and profound neutropenia [4, 20].

Initial Assessment

All patients with fever and suspected neutropenia should promptly undergo a detailed history, physical examination, laboratory assessment, microbiology, and imaging studies. Additionally, patients with abnormal vital signs, such as tachycardia and hypotension, should be treated promptly, as it carries a high mortality if not treated as an emergency.

History

The following key elements should be included:

- Age—age >65 years has been shown to be an independent risk factor for the development of neutropenia [23].
- Type and stage of underlying malignancy—patients with hematologic malignancies are five times more likely to develop neutropenic fever compared with patients with solid tumors [2]. In addition, advanced stage of underlying malignancy itself is a risk factor for neutropenic fever [24, 25].
- Nature of chemotherapy given—initial identification of the patients who are on chemotherapy, timing of the most recent chemotherapy given, he type of drugs used, and the intensity of treatment predict the risk for neutropenic fever [26, 27].
- Prior prophylactic antibiotics—may guide selection of the empiric antibiotic therapy; also, this group of patients may be at higher risk for *C. difficile* infections, fungal infections, and infections with resistant pathogens.
- Combined chemoradiation—patients on combined chemoradiation have an increased risk of neutropenic fever [28].
- History of prior neutropenia or neutropenic fever—prior episodes predict recurrent neutropenia and neutropenic fever [28].
- Comorbidities, such as heart, liver, and kidney disease—associated with increased risk of developing neutropenic fever during chemotherapy [25, 26, 29].
- Drug allergies—will guide choice of antibiotics.

Physical Examination

Patients presenting with neutropenic fever may not have localizing signs and symptoms other than fever due to the inability to mount an adequate inflammatory response. Hence, a thorough physical examination should be performed with emphasis on potential foci of infection, including careful attention to vital signs, the entire skin, and all bodily orifices, such as the sinuses, oropharynx, lungs, abdomen, genitalia, and perianal area. Deliberate exam to the site of previous procedures, such catheter insertion, biopsy, and bone marrow aspirate sites, is also important.

These patients may have urinary tract infection in the absence of dysuria or pyuria, cellulitis without evidence of pain and swelling, or pneumonia without clinical sign or symptoms. Inflammation or ulceration of the oral and anal mucosa should be also addressed. However, digital rectal examination can allow the bacteria to enter the bloodstream and should be avoided among neutropenic patients.

Laboratory and Radiology Investigations

Initial laboratory evaluation should consist of complete blood cell count with differential, blood urea nitrogen, serum creatinine, electrolytes, liver function tests, urine analysis, blood cultures, urine cultures, and other cultures as indicated. Chest X-ray should be also obtained.

- CBC with differential count and platelet count will determine the presence of neutropenia.
- Blood urea nitrogen and creatinine—Renal dysfunction has been associated with increased risk of complications from neutropenia [24, 25]. Renal function tests also help in risk-stratifying patients.

- Liver function tests—Elevated hepatic transaminase enzymes may be due to chemotherapy toxicity, other drug side effect, or disease progression. Hypoalbuminemia is also an independent risk factor for the development of complications related to neutropenic fever [24, 25]. Liver function tests also help in risk-stratifying patients.
- Cultures—Concomitant blood cultures should be drawn peripherally and from all lumens of the central line if present. In patients without a central venous catheter (CVC), two separate samples should be obtained from each of two venipuncture sites [4]. One study showed that the total volume of blood cultured is a crucial determinant of detecting a bloodstream infection. IDSA recommends each set should have a blood volume of 20 mL (no more than 1 % of estimated patient total blood volume in children) [4, 30]. Urine cultures are indicated as dysuria and pyuria are often absent (89 % of the time) despite infection [31]. Sputum for bacterial and fungal stains and cultures and assays for respiratory viruses should be sent, if present [32]. *C. difficile* colitis is a frequent GI infection seen in patients with neutropenic fever; therefore, stool analysis for *C. difficile* should be performed in the presence of diarrhea. Patients who present with signs and symptoms of meningitis should have CSF analysis for cell count, protein, glucose, and bacterial cultures. Skin lesions should be biopsied or aspirated if the lesion is suspected for infection. Sputum, if collectible, should be sent for bacterial culture, and lower respiratory tract specimens by bronchoalveolar lavage (BAL) could be considered if an infiltration on chest imaging is uncertain. Nasal wash and BAL specimens should be sent for detection of adenovirus, influenza A and B viruses, respiratory syncytial virus (RSV), and parainfluenza virus if the patient presents with symptoms of respiratory virus infection during influenza seasons or outbreaks [4].
- Imaging—A chest X-ray (CXR) should be ordered as part of initial evaluation in neutropenic patients with respiratory symptoms [4]. Since neutropenic patients may have pneumonia without cough or shortness of breath, a CXR can assist in diagnosis of pneumonia. However, the physician should be aware that even with definite infectious pneumonia, the CXR can be negative on presentation [33]. One study supports that high-resolution CT demonstrated pneumonia in more than one-half of persistently febrile neutropenic patients who had normal findings on routine chest radiograph [34].

Management

Risk Assessment and Disposition

Clinical Risk Assessment

The modern management of neutropenic fever began about 50 years ago when several landmark studies demonstrated superior mortality and morbidity outcomes associated with the empiric treatment of broad-spectrum antibiotics prior to isolation of bacterial organisms [35–39]. Since then, extensive clinical and research efforts have focused on developing the most effective antibiotic treatment regimens for patients with neutropenic fever based on individual risk stratification and identification of the causative infectious organism [40–42]. Risk stratification is based on past medical history, related cancer history, and thorough physical examination, and laboratory assessment should be initiated in order to provide optimal treatment for each patient. Stratifying patients at presentation of neutropenic fever not only helps physicians to make a decision of type of antibiotics and timing of hospital discharge but also reduces the overuse of resources [4, 25, 43, 44]. Clinical studies have proven safety and feasibility of new approaches such as outpatient treatment or early hospital discharge for low-risk neutropenic fever patients compared to traditional inpatient care [25, 43, 45–47].

"High-risk" patients have a greater risk for severe infection, prolonged and profound neutropenia, and medical comorbidities. Patients with certain types of cancer, such as acute leukemia and/or under intense chemotherapy such as induction chemotherapy or stem cell transplantation, may also be considered as high risk. Table 2 provides the IDSA definition of high-risk patients. "Low-risk" patients are those who are expected to have neutropenia for less than 7 days and are in clinically stable condition without significant comorbidities. Usually, they are the patients with solid tumors but not exclusively [4].

Additionally, for more objective risk stratification, a multinational scoring system is also available. In 2000, Klastersky et al. introduced the Multinational Association for Supportive Care in Cancer (MASCC) Risk Index, a scoring system of weighted risk factors to identify low-risk neutropenic fever cancer patients [25]. MASCC was subsequently validated by several studies and is widely accepted for stratifying low- to high-risk subgroups of neutropenic fever patients [1, 4, 48] (Table 3).

Once a patient with neutropenic fever is identified at the emergency department, the clinician should start risk assessment, since the decision of the antibiotic choice and final disposition will be partially made based on the risk assessment. High-risk patients should be admitted to the hospital with prompt IV empirical antibiotics, while oral antibiotics and outpatient management with close follow-up could be considered for low-risk patients [4, 9, 10]. Before making a decision for outpatient management, the presence of other underlying conditions should be considered. Studies have shown that serious complications have developed up to 11 % of patients who are classified as low risk by MASCC. Thus, ASCO published exclusion criteria for outpatient management with low-risk neutropenic fever patients (Table 4) [9]. Inpatient management is recommended for the low-risk patients with any of the exclusion criteria.

Table 2 IDSA definition of high-risk patients of febrile neutropenia [4]

• Profound neutropenia (ANC ≤100 cells/mm^3)
• Presence of any comorbid medical problems including but not limited to:
– Hemodynamic instability
– Oral or gastrointestinal mucositis that interferes with swallowing or causes severe diarrhea
– Gastrointestinal symptoms, including abdominal pain, nausea and vomiting, or diarrhea
– Neurologic or mental status changes of new onset
– Intravascular catheter infection, especially catheter tunnel infection
– New pulmonary infiltrate or hypoxemia or underlying chronic lung disease
• Evidence of hepatic insufficiency (defined as aminotransferase level >5 × normal value) or renal insufficiency (defined as a creatinine clearance of <30 mL/min)

Table 3 The multinational association for supportive care in cancer risk index score [25]

Characteristic	Weight
Burden of illness: no or mild symptoms[a]	5
No hypotension	5
No chronic obstructive pulmonary disease[b]	4
Solid tumor or no previous fungal infection[c]	4
No dehydration	3
Burden of illness: moderate symptoms[a]	3
Outpatient status	3
Age <60 years	2

Maximum score is 26; low-risk patients are identified by a cumulative score ≥21 points, and high-risk patients are those whose score is <21

[a]Burden of illness refers to the general clinical status of the patients as influenced by the febrile neutropenic episode (no or mild symptoms, score of 5; moderate symptoms, score of 3; and severe symptoms or moribund, score of 0). Scores of 3 and 5 are not cumulative

[b]Chronic obstructive pulmonary disease refers to active chronic bronchitis, emphysema, decrease in forced expiratory volumes, or need for oxygen therapy and/or steroids and/or bronchodilators requiring treatment at the presentation of the febrile neutropenic episode

[c]Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection

A critically important aspect of the management of neutropenic fever is the prompt initiation of empiric antibiotic therapy at the earliest possible time (within 30–60 min) after the presentation to the emergency medical setting [4, 9, 42, 49–54]. Studies have indicated that early initiation of empiric antibiotic treatment in patients with neutropenic fever may improve morbidity and mortality from this complication [55–58]. In addition, several small studies in different clinical settings have indicated that administrative interventions with quality improvement measures can substantially reduce initial time to antibiotics for both pediatric and adult patients with neutropenic fever [59–62].

Psychosocial and Logistic Requirements

Even if the patient is determined to be in low-risk group, using clinical risk assessment tools, outpatient management may not suitable because of the patient's social status. There is no strong evidence that supports psychosocial risk assessment criteria described below, but experts recommend including only patients who meet the psychosocial and logistic requirements for outpatient management (Table 5) [9]. These requirements help the clinician to determine whether it is safe to discharge the patient home with oral antibiotics. The patient's social conditions, such as supporting system, and the primary oncologist's accessibility for close monitoring, are included in these requirements. If there is clinical doubt about the feasibility to closely monitor the patient, it is reasonable to admit the patient for inpatient management. It is also important to assess the primary oncologist's availability or the institution's capability to monitor the patient closely by phone or any other modality.

Antibiotic Therapy

General Consideration

Prompt empirical antibiotic therapy is the key of the treatment for neutropenic fever, as it prevents serious morbidity and mortality. As a recent large observational study showed that 23 % of neutropenic fever patients have documented bacteremia, empirical antibiotics are critical to cover possible occult infections until the blood culture results are available [4, 63].

Despite of the higher frequency of gram-positive bacteremia, because gram-negative bacteremia was associated with greater mortality, empiric coverage of gram-negative bacteria is mandatory [20]. In particular, empiric coverage for *P. aeruginosa* is essential considering its high mortality rate associated with this infection [4]. However, it is also important for the clinicians to be aware of their own institution's current microbiology surveillance to have a better idea about possible pathogens [64].

No single empirical antibiotic regimen has been found to be superior to others [65]. All of the recommended regimens are similar in their bactericidal activity, antipseudomonal activity, and minimal toxicity. The goal of empirical antibiotic therapy for patients with neutropenic fever is to cover the most likely and most virulent pathogens to prevent life-threatening infections. However, the final selection of a particular antibiotic regimen should be made considering the patient's risk status, presenting sign and symptoms, and disposition. A patient care algorithm combined with the recommended empirical antibiotic regimen based on the risk status is depicted at Fig. 1.

Table 4 Additional clinical exclusion criteria of initial outpatient care with MASCC score ≥21 [9]

Category	Criteria
Cardiovascular	Presyncope/witnessed syncope Accelerated hypertension New onset or worsening of hypotension Uncontrolled heart failure, arrhythmias, or angina Clinically relevant bleeding Pericardial effusion
Hematologic	Severe thrombocytopenia (platelets <10,000 μL^{-1}) Anemia (Hb <7 g/dL or Hct <21 %) ANC <100 μL^{-1} of expected duration ≥7 days Deep venous thrombosis or pulmonary embolism
Gastrointestinal	Unable to swallow oral medications Intractable nausea and/or vomiting New onset or clinically relevant worsening of diarrhea Melena, hematochezia (nonhemorrhoidal), or hematemesis Abdominal pain Ascites
Hepatic	Impaired hepatic function (aminotransferase values >5× ULN) or clinically relevant worsening of aminotransferase values Bilirubin >2.0 or clinically relevant increase in bilirubin
Infectious	Presence of a clear anatomic site of infection (e.g., symptoms of pneumonia, cellulitis, abdominal infection, positive imaging, or microbial laboratory findings)[a] Any evidence of severe sepsis[b] Allergies to antimicrobials used for outpatients Antibiotics ≤72 h before presentation Intravascular catheter infection
Neurologic	Altered mental status/sensorium or seizures Presence of or concern for CNS infection or noninfectious meningitis Presence of or concern for spinal cord compression New or worsening neurologic deficit
Pulmonary/thoracic	Tachypnea or hypopnea Hypoxemia, hypercarbia Pneumothorax or pleural effusion Presence of cavitary lung nodule or imaging findings suggestive of an active intrathoracic process
Renal	Impaired renal function (creatinine clearance ≤30 mL/min) or oliguria or clinically relevant worsening renal function (as determined by the treating physician) New onset of gross hematuria Urinary obstruction or nephrolithiasis Clinically relevant dehydration Clinically relevant electrolyte abnormalities, acidosis or alkalosis (requiring medical intervention)
Other significant comorbidities	Presence of a major abnormality in regard to: organ dysfunction, comorbid conditions, vital signs, clinical signs or symptoms, laboratory data, or imaging data Any relevant clinical worsening (as determined by the treating physician) of organ dysfunction, comorbid conditions, vital signs, clinical signs or symptoms, laboratory data, or imaging data Pregnant or nursing Need for IV pain control Fractures, injuries, or need for emergent radiation therapy

ULN upper limit of normal

[a]New onset of minimal symptoms of urinary tract infection and sinusitis may be excluded from this requirement in most settings with neutropenia <7 days and absence of fungal infection

[b]Severe sepsis is a syndrome defined by the presence of evidence for SIRS (systemic inflammatory response syndrome), defined by ≥2 of the following criteria: body temperature >38 °C or <36 °C, heart rate >90 beats/min, respiratory rate >20 min^{-1}, $PaCO_2$ <32 mmHg, an alteration in the total leukocyte count to $>12\times10^9$ or $<4\times10^9$ L^{-1}, or the presence of >10 % band neutrophils in the leukocyte differential, plus evidence of infection, plus evidence of end-organ dysfunction (altered mental status, hypoperfusion defined by hypotension, by an elevated serum lactate >4 mmol/L, or by oliguria, and/or hypoxia)

Before selecting antibiotics, it is important to review the following: recent culture and antibiotic susceptibility results; history of infection or colonization with vancomycin-resistant Enterococcus (VRE), methicillin-resistant Staphylococcus aureus (MRSA), or other antibiotic-resistant organisms; presence of an indwelling catheter; antibiotic history; current antibiotic prophylaxis; and clinical evidence for a source of infection; allergies; and organ dysfunction.

Table 5 Psychosocial and logistic requirements for outpatient management

• Residence ≤1 h or ≤30 miles (48 km) from clinic or hospital
• Patient's primary care physician or oncologist agrees to outpatient management
• Able to comply with logistic requirements, including frequent clinic visits
• Family member or caregiver at home 24 h a day
• Access to a telephone and transportation 24 h a day
• No history of noncompliance with treatment protocols

High-Risk Patients

Patients in the high-risk category require admission to the hospital with initiation of IV antibiotics. Antibiotics with antipseudomonal activity (such as cefepime, meropenem, imipenem-cilastatin, and piperacillin-tazobactam) may be used as monotherapy. Ceftazidime is no longer considered reliable at many institutions because of its decreasing potency against gram-negative organisms and poor activity against gram-positive pathogens [66, 67]. Other antibiotics, such as aminoglycosides, fluoroquinolones, and/or vancomycin, may be added if there is any sign of complications, focal infections, or suspected antimicrobial resistance [4]. However, recent studies have shown that there is no evidence that combination therapy is superior to monotherapy [68].

Vancomycin or other antimicrobials with activity against gram-positive pathogens (e.g., daptomycin and linezolid) are not a standard part of initial antibiotic therapy, due to concern of its overuse and the development of drug resistance in *Enterococcus* species and *S. aureus* [69, 70]. However, it should be considered for suspected catheter-related infection, skin/soft tissue infection, pneumonia, or hemodynamic

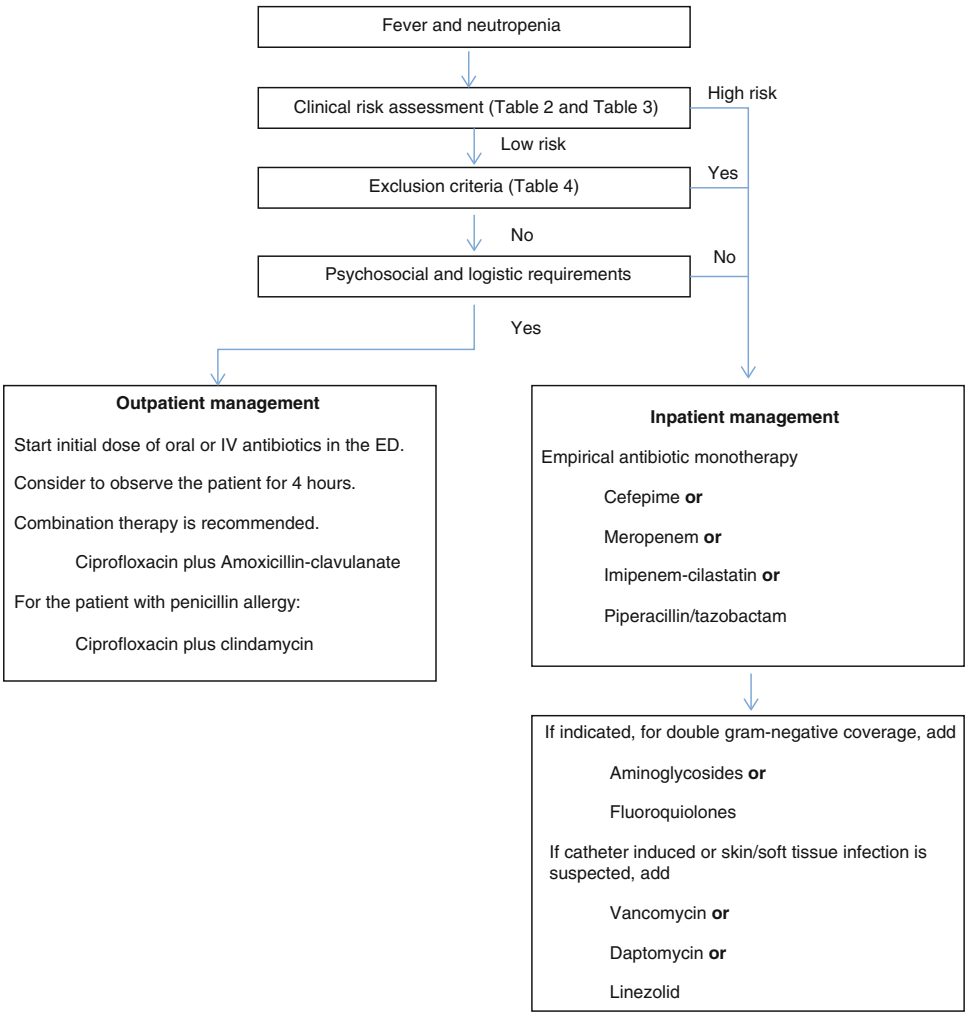

Fig. 1 Proposed algorithm for febrile neutropenia

Table 6 Indications for addition of antibiotics active against gram-positive organisms to the empirical regimen for fever and neutropenia [4]

• Hemodynamic instability or other evidence of severe sepsis
• Pneumonia documented radiographically
• Positive blood culture for gram-positive bacteria, before final identification and susceptibility testing is available
• Clinically suspected serious catheter-related infection (e.g., chills or rigors with infusion through catheter or cellulitis around the catheter entry/exit site)
• Skin or soft tissue infection at any site
• Colonization with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, or penicillin-resistant *Streptococcus pneumoniae*
• Severe mucositis, if fluoroquinolone prophylaxis has been given and ceftazidime is employed as empirical therapy

Table 7 Recommendation for treatment of resistant bacteria

• MRSA: consider early addition of vancomycin, linezolid, or daptomycin
• VRE: consider early addition of linezolid or daptomycin
• ESBL: consider early use of carbapenem
• KPC: consider early use of polymyxin (colistin) or tigecycline

instability [4]. Table 6 describes the indications for addition of antibiotics active against gram-positive organisms.

Special attention for antimicrobial-resistant bacteria should be considered for patients with high risk of such infection, unstable condition, and the result of previous positive blood cultures. They include MRSA, VRE, extended-spectrum beta-lactamase (ESBL)-producing gram-negative bacteria, and carbapenemase-producing organisms, including *Klebsiella pneumoniae* carbapenemase (KPC). Recommendation for those patients are described in Table 7 [4].

Based on the patient's clinical finding or test results, antibiotics may be further adjusted. For example, for pneumonia or gram-negative bacteremia, carbapenem could be chosen and aminoglycoside may be added. For patient with abdominal symptoms or suspected *C. difficile* infection, metronidazole could be added.

Most of the patients with history of penicillin allergy actually tolerate cephalosporins. However, if the patient reports history of an immediate-type hypersensitivity reaction, such as hives and bronchospasm, combinations without beta-lactams and carbapenems should be chosen (e.g., ciprofloxacin plus clindamycin or aztreonam plus vancomycin) [4].

Low-Risk Patients

First, the classification of the patient as low risk and the decision for outpatient management should be carefully considered, with thoughtful attention to the patient's clinical and psychosocial status, as described above. Studies have shown the safety and feasibility of outpatient management with oral antibiotics or IV treatment for low-risk patients [43, 45–48, 71, 72]. However, again, selection of patients appropriate for outpatient management should be carefully determined, since current selection criteria describe above may misclassify high-risk patients to low-risk patients [9]. However, because oral therapy has several advantages, such as lower cost, lack of need for indwelling IV access, decreased toxicity, and improved patient acceptance [73], if the clinician determines that the patient is clearly in the low-risk group and has ready access to appropriate medical care, outpatient management with oral therapy and vigilant observation could be justified.

Even though the patient is in low-risk group, initial dose of oral or IV empirical antibiotics should be administered in a hospital setting. Then they may be transitioned to outpatient management after either a brief period of observation or short hospital admission.

Ciprofloxacin plus amoxicillin-clavulanate combination is recommended for oral empirical treatment. Patients with penicillin allergy may be prescribed clindamycin instead of amoxicillin-clavulanate. Monotherapy with levofloxacin or ciprofloxacin is not recommended; additionally, patients who are already receiving fluoroquinolone prophylaxis should not receive an oral fluoroquinolone for empirical treatment. Furthermore, patients with allergy to fluoroquinolones should not be managed in the outpatient setting [4, 9].

The patient could be discharged from the ED once the clinician determines that the patient is clinically stable and gastrointestinal absorption of the oral antibiotics would be adequate. However, it is also recommended to observe the patient in the ED for a short period of time, as the current evidence came from the studies which mostly observed the patients as early as 6–24 h [4, 73].

Antifungal Therapy

Empirical antifungal therapy and further evaluation for fungal infection are recommended for those who have persistent or recurrent fever after 4–7 days of empirical antibiotics in the setting of persistent neutropenia [4]. This is to treat occult fungal infection when the high-risk patient experiences persistent neutropenic fever despite the use of empirical antibacterial therapy [74]. Considering that the fever is a nonspecific sign of any infection and empirical antifungal therapy may cost more and cause adverse effects, whether to start antifungal therapy initially in the ED is necessary remains questionable.

Antiviral Therapy

Like antifungal therapy, empirical antiviral therapy for herpes simplex virus (HSV) or varicella-zoster virus (VZV) is not suggested for routine neutropenic fever care. Treatment

for HSV or VZV is only indicated when the patient has clear clinical and laboratory evidence of active viral disease [4].

However, for respiratory viruses, if the patient presents with influenza-like illness, first, respiratory virus test should be performed. The tests include polymerase chain reaction (PCR), direct antigen assay, or culture for respiratory viruses [4, 75]. In addition, neutropenic patients with symptoms of influenza should be considered for empirical treatment for influenza in the setting of influenza exposure or outbreak [4, 76, 77].

Granulocyte Colony-Stimulating Factors (G-CSF)

Routine use of therapeutic granulocyte colony-stimulating factors (G-CSF) has been controversial, but more recent guidelines do not recommend therapeutic use of G-CSF for established neutropenic fever [4, 78, 79]. Even though it may reduce the duration of neutropenia, the duration of fever, and length of stay in the hospital, there is no clinical benefit from its use. Considering its cost and potential adverse effect of G-CSF, but no clinical benefit, its use for neutropenic fever is not recommended.

Conclusion

Neutropenic fever is a potential life-threatening oncologic emergency. The patient should be assessed promptly by a physician and thoroughly examined. Empirical antibiotics are essential elements of treatment and should be started as soon as possible. Recently, risk stratification for guidance of management has become a more common practice. Once the patient is determined as low risk, and other social and logistic conditions are met, the patient can be discharged from the ED for outpatient management with close follow-up. It is important for the ED physician to be aware about the importance of the prompt empirical antibiotics and risk assessment for the appropriate disposition from the ED.

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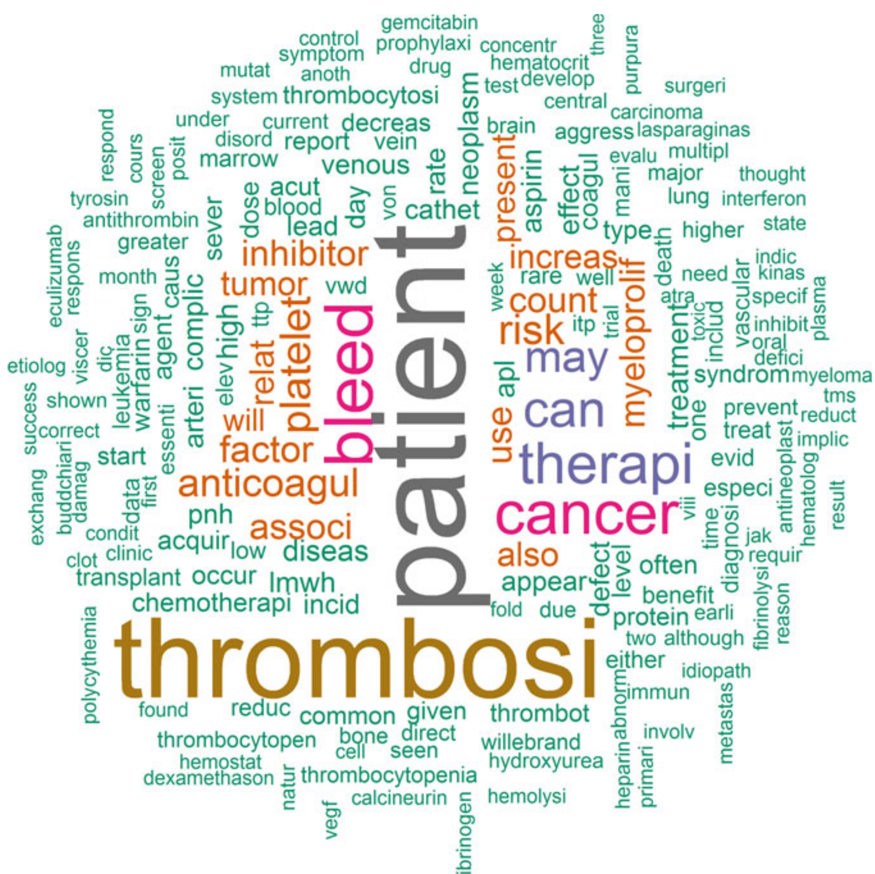
Bleeding and Thrombosis in Cancer Patients

Thomas DeLoughery



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Introduction

Cancer patients can suffer both bleeding and thrombotic complications which can impair both quality of life and survival. These complications can be due to the effects of the cancer itself or its therapy. This chapter will review these complications and offer guidance to diagnosis and treatment.

Bleeding

Bleeding Related to Coagulation Factors

Acquired von Willebrand Disease

Acquired von Willebrand disease (VWD) can complicate hematological malignancies, particularly lymphomas, myeloproliferative disorders, multiple myeloma, and monoclonal gammopathies, as well as solid tumors, including Wilm's tumor, adrenocortical carcinoma, lung cancer, and gastric carcinoma [1, 2].

Acquired VWD should be thought of when a patient with these types of tumors presents with excess bleeding—especially epistaxis or gastrointestinal bleeding [3]. Both type 1 (decreased total von Willebrand protein) or type 2 (loss of high-molecular-weight multimers) VWD can be seen.

Patients with acquired VWD have variable responses to therapy for acute bleeding [4]. Desmopressin is effective for patients with acquired VWD type 1 and 2, but the magnitude and duration of effect are often reduced. For bleeding or for surgical procedures, high doses of the von Willebrand concentrate or recombinant factor are indicated with careful monitoring of levels. For patients with very strong inhibitors that factor concentrates cannot overcome or with life-threatening bleeding, rVIIa may prove useful.

Acquired Factor VIII Inhibitors

Factor VIII deficiency is the most frequent acquired coagulation factor deficiency seen in cancer patients [5]. Patients will have prolonged aPTTs, a positive screening test for a factor inhibitor, and a low factor VIII level. For severe or life-threatening bleeding, recombinant VIIa is the treatment of choice [6]. The dose is 90 μg/kg repeated every 2–3 h until bleeding has stopped. The key step beside controlling bleeding is to eliminate the autoantibody with immunosuppression starting with prednisone 60 mg/day and adding oral cyclophosphamide 100 mg po plus rituximab either 375 mg/m^2 weekly × 4 or 1000 mg separated by 14 days. Eradication of the autoantibody does not require successful tumor treatment and should be attempted before major surgical procedures are planned.

Bleeding Related to Platelet Number and Function

Immune Thrombocytopenia

Immune thrombocytopenic purpura (ITP) has been reported in 2–4 % chronic lymphocytic leukemia and Hodgkin's disease [7]; ITP can occur during any part of the course of the tumor including when the patient has responded to antineoplastic therapy. The presentation of ITP in cancer patients is not different than in other with patients presented with petechia and other stigmata of bleeding. Why ITP occurs during the course of lymphoproliferative disease is not well understood, although a disturbed immune system could possibly predispose patients both to the lymphoproliferative disorder and to thrombocytopenia [8, 9]. Therapy for the ITP that complicates cancer is the same as that for classic immune thrombocytopenia. High-dose corticosteroids such as pulse dexamethasone 40 mg/day × 4 days (plus immunoglobulin, 1 g/kg iv if necessary) are given first, but if an adequate platelet count cannot be maintained, then the choice is between splenectomy, thrombopoietin agonists, or rituximab.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) should be suspected when a patient presents with thrombocytopenia, microangiopathic hemolytic anemia (schistocytes and signs of hemolysis), and any evidence of end-organ damage [10]. TTP has a unique presentation in cancer patients with evidence of metastatic cancer in the bone marrow and lungs [11]. These patients can have extensive intravascular tumor leading to thrombocytopenia and schistocytes. Plasma exchange is ineffective in these patients, but resolution of the TTP has been reported if the tumor is responsive to chemotherapy.

Therapy-Related Thrombotic Microangiopathy

Thrombotic microangiopathies (TM) can complicate a variety of therapies such as calcineurin inhibitors and gemcitabine [12]. The most common antineoplastic drug causing TM is gemcitabine with an incidence of 0.1–1 % [13, 14]. The appearance of the TM syndrome associated with gemcitabine can be delayed, and the condition often is fatal. Severe hypertension often precedes the clinical appearance of the TM. The use of plasma exchange is controversial but there are increasing reports of the successful use of the complement inhibitor, eculizumab [15].

TMs can complicate stem cell marrow transplants [16]. The incidence ranges from 15 % for allogeneic to 5 % for autologous bone marrow transplants. Several types of TMs are recognized in bone marrow transplantations. One is "multi-organ fulminant" which occurs early (20–60 days)

with the evolution of multi-organ system involvement and is often fatal. Another type of TM is similar to calcineurin inhibitors TMs. This occurs within days after the agent is started with the appearance of a falling platelet count, falling hematocrit, and rising serum LDH level [17]. With withdrawal of the agent, the TM resolves. A "conditioning" TM, which occurs 6 months or more after total body irradiation , is associated with primary renal involvement. Finally, patients with systemic CMV infections can present with a TM syndrome related to vascular infection with CMV. The etiology of bone marrow transplant-related TM appears to be different from that of "classic" TTP since alterations of ADAMTS13 have not been found in BMT-related TTP implicated therapy-related vascular damage. The therapy of bone marrow transplant TM is uncertain. Patients should have their calcineurin inhibitor doses decreased. Although plasma exchange is often tried, response is poor in with fulminant or conditioning-related TTP/HUS.

Specific Hematological Cancers Associated with Bleeding

Acute Promyelocytic Leukemia (APL)

Patients with APL have a higher risk of hemorrhagic death during induction therapy when compared with patients with other forms of leukemia [18]. The hemostatic defects in patients with APL are multiple with most having evidence of DIC at the time of diagnosis with bleeding still being the major cause of early death [19]. Life-threatening bleeding such as intracranial hemorrhage may occur at any time until the APL is put into remission. The etiology of the hemostatic defects in APL is complex and is thought to be the result of DIC, fibrinolysis, and the release of other procoagulant enzymes [18, 19]. Therapy of APL involves treating both the leukemia and the coagulopathy (Table 1). Currently the standard treatment for APL is trans-retinoic acid (ATRA) in combination with chemotherapy or arsenic [20]. This will induce remission in over 90 % of patients, and a sizable majority of these patients will be cured of their APL. ATRA therapy will also lead to the early correction of the coagulation defects, often within the first week of therapy. Given the marked beneficial effect of ATRA on the coagulopathy of APL and its low toxicity, it should be empirically started for any patient suspected of having APL while specific testing is being performed. Therapy for the coagulation defects consists of aggressive transfusion to maintain the fibrinogen level at over 150 mg/dl and the platelet count at over 50×10^9 L^{-1}.

Table 1 Acute promyelocytic leukemia

Consider diagnosis in any patient with leukemia presenting with coagulopathy
Start empiric all-trans-retinoic acid 45 mg/m^2/day in two divided doses while performing work-up
Coagulations goals
• Fibrinogen greater than 150 mg/dl
• Platelets greater than 50×10^9 L^{-1}

Myeloproliferative Neoplasms

Bleeding can be seen in many of the myeloproliferative neoplasms but rarely results in major morbidity [21]. In patients with essential thrombocytosis, the risk of bleeding appears to increase with platelet counts above one million—perhaps due to the large amount of platelets absorbing von Willebrand factor. Most bleeding in myeloproliferative neoplasms consists of platelet-type bleeding—mucocutaneous bleeding or bruising with only a few reports of major bleeding. The use of drugs that inhibit platelet function such as aspirin is associated with a higher incidence of bleeding. Patients with extreme thrombocytosis will respond to lowering the counts to below 1000×10^9 L^{-1} [1]. Patients with myeloproliferative neoplasms should be screened for VWD before surgery or starting antiplatelet therapy. Rare patients with myeloproliferative neoplasms will have an acquired factor V deficiency with symptomatic patients present with bleeding and variable elevation of the INR and/or aPTT [22].

Dysproteinemia

Multiple coagulation abnormalities have been described in patients with dysproteinemia which can lead to severe bleeding [23, 24]:

- Abnormal clot retraction
- Abnormal fibrin clot
- Anti-glycoprotein IIb/IIIa antibodies
- Factor VIII inhibitor
- Heparin-like anticoagulation
- Impaired fibrin polymerization
- Inhibition of thrombin time

Therapy for the hemostatic defects in the dysproteinemic syndromes includes removal of the offending protein, either by reducing synthesis by treating the myeloma with aggressive chemotherapy or by plasmapheresis if the patient is having acute symptoms.

Patients with amyloidosis can have a marked increase in easy bruising and other bleeding symptoms which may be the first clue to diagnosis [25]. The most common defect is an elevation in the thrombin time which is seen in 30–80 % of cases. Acquired deficiencies of factor X can also be seen. A rare but important cause of bleeding in patients is systemic fibrinolysis. The patients may have decreased levels of alpha

2-antiplasmin and an abnormal euglobulin clot lysis time. The use of fibrinolytic inhibitors such as EACA or tranexamic acid has both corrected laboratory tests of fibrinolysis and reduced bleeding symptoms. Like with myeloma, treatment of the amyloid will correct the bleeding diathesis.

Coagulation Defect Due to Therapy

Bleeding has been reported with the use of tyrosine kinase inhibitors used in CML therapy, but it's unclear if this is due to the drug effect or the underlying disease. Many of these agents have been reported to lead to in vitro platelet dysfunction, but for most patients this does not appear to be clinically significant [26]. Bleeding has also been reported with inhibitors of VEGF [27]. Bevacizumab in particular is associated with bleeding—especially after surgery or with treatment of squamous cell carcinoma of the lung. In these cases the bleeding may be more related to lack of wound healing and tumor necrosis. The BTK inhibitor ibrutinib is associated with a 5 % incidence of bleeding including subdural hematoma with the mechanism appearing to be via decreased platelet aggregation [28, 29].

Cancer and Thrombosis

Epidemiology

Thrombosis can be the presenting sign of cancer [30, 31]. As many as 10–20 % of older patients who present with an idiopathic deep venous thrombosis will be found to have cancer on initial evaluation. Furthermore, over the next 2 years up to 25 % of these patients will develop cancer. Certain presentations of thrombosis are more worrisome for underlying cancer as a cause of the thrombosis: warfarin-refractory thrombosis, idiopathic bilateral deep vein thrombosis, or both arterial and venous thrombosis. The cancers most frequently associated with thrombosis are adenocarcinoma of the lung and gastrointestinal cancers, especially pancreatic. Primary brain tumors are also associated with a higher risk of thrombosis as well as kidney, ovarian, and uterine cancers [30]. Thrombosis rates for breast and prostate cancer are not as elavated [32]. The coexistence of cancer and thrombosis has implications for both disease processes [33]. Cancer raises the risk of both anticoagulant induced bleeding and breakthrough thrombosis, while the presence of a thrombosis worsens the cancer prognosis.

Given the data that thrombosis can be an early sign of cancer, one question that commonly arises is should a patient who presents with an idiopathic thrombosis be aggressively worked up for cancer? Studies to date have not shown benefit of extensive evaluations of these patients for cancer and current recommendations are age-appropriate cancer screening and complete work-up of any worrisome signs—such as guaiac-positive stools.

Increasingly common in cancer patients is the finding of an "incidental" pulmonary embolism on a CT obtained for tumor staging or evaluation of response to chemotherapy. Despite the "incidental" nature of finding the thrombosis, the prognosis is just as ominous as any cancer-related thrombosis and these need to be aggressively treated with anticoagulation [34].

Rare patients can present with thrombosis and associated disseminated intravascular coagulation. These patients with tumor-related DIC have thrombosis in the setting of low platelets and decrease coagulation factors. These patients may also develop a non-bacterial thrombotic endocarditis and have multiple arterial embolic events.

The etiology of the cancer-related thrombosis is complex with many factors potentially playing a role [35, 36]. Tumors may directly activate factor VII by tumor-expressed tissue factor as well as factor X. Patients with cancer have elevations of inflammatory cytokines that can further augment the hypercoagulable state. Treatment of the cancer can also lead to thrombosis. As discussed below chemotherapy—especially cis-platinum, fluorouracil, asparaginase—increases the risk of thrombosis. Biological agents such as thalidomide and lenalidomide also increase thrombosis risk. Surgery for cancer patients increases the risk of thrombosis threefold over similar operations in non-cancer patients [37].

Treatment

Cancer-related thrombosis requires aggressive anticoagulation [38, 39]. Initial therapy of the thrombosis should be with low-molecular-weight heparin. Four randomized trials have shown that 3–6 months of therapy with LMWH is superior to warfarin with lesser rates of recurrent deep venous thrombosis. Currently it is unknown if continuing therapy with LMWH after 3–6 months would have the same positive benefit or if changing back to warfarin is prudent. Patients with high-risk thrombosis tumors such as lung or brain cancer may best be served by staying on LMWH. There is only limited data for the direct oral anticoagulants in cancer patients but they do appear safe and effective [40]. In patients unable to take LMWH, they are a reasonable option as their ease of use and lack of food and drug interactions makes them more flexible to use than warfarin, but more data is needed to see if they can supplant LMWH.

Patients who failed warfarin or direct oral anticoagulants need to be treated indefinitely with LMWH. The rare patient who fails LMWH may benefit either from raising the dose by 25 % or changing to fondaparinux [40].

Brain tumors or brain metastases are not a contraindication to warfarin. The only exceptions are brain metastases from thyroid, melanoma, renal, or choriocarcinoma as these tumor metastases have a high rate of bleeding [41]. It should be remembered that placement of an inferior vena cava filter without concurrent anticoagulation is associated with an unacceptable rate of complications, including death from massive thrombosis.

Specific Situations

Myeloproliferative Neoplasms

Thrombosis is the most common cause of death in the myeloproliferative neoplasms [42]. Correlation of thrombosis with blood counts depends on the underlying disease—patients with polycythemia rubra vera are at risk of thrombosis with hematocrits over 45 %, but those with essential thrombocytosis can have thrombosis with platelets in the $4–600 \times 10^9$ L^{-1} and as noted before may have greater risk of bleeding with counts greater than 1000×10^9 L^{-1}. Patients with myeloproliferative neoplasms have a higher risk of thrombosis even with relatively normal blood counts, suggesting an intrinsic defect in the blood cell or vascular endothelium leading to thrombosis.

Patients with myeloproliferative neoplasms have a predilection for several types of thrombosis. Patients with Budd-Chiari and other visceral vein thromboses have a high incidence of underlying myeloproliferative syndromes. Patients with essential thrombocytosis can also have platelet occlusion of the small digital vessels leading to erythromelalgia. These patients will have swollen, red, and very painful digits. The patients may only have slightly elevated platelet counts and are often misdiagnosed with arthritis. A diagnostic clue is that these patients will respond dramatically to a single aspirin per day.

Certain patients, especially those with Budd-Chiari syndrome, may have an "occult" myeloproliferative syndrome with may be no evidence of any hematological disorder but have genetic evidence of myeloproliferative disease with positive testing for the JAK2 mutation. Interestingly the CALR mutation—seen in 30–50 % of patients with essential thrombocytosis—has not been associated with visceral vein thrombosis in patients with normal blood counts [43].

Heparin followed by warfarin or direct oral anticoagulants is indicated for most patients with acute venous thromboembolism complicating the myeloproliferative disorders. In a few instances, liver transplantation has been successful in treating liver failure due to Budd-Chiari syndrome—but these patients require long-term anticoagulation.

Antiplatelet therapy is recommended for treatment of patients with arterial thrombosis. Low doses of aspirin (81 mg/day) are preferable in patients with myeloproliferative neoplasms because the risk of bleeding with aspirin is dose related. There is currently no data concerning the use of newer antiplatelet agents such as clopidogrel but may be reasonable for patients allergic to aspirin

In addition to antithrombotic therapy, treating elevated blood counts is also important for patients with a history of thrombosis. For patients with thrombocytosis, hydroxyurea (1 g daily to start) is the preferred therapy as trials have shown antithrombotic benefit. For younger patients who have concerns about hydroxyurea, weekly pegylated interferon starting at 45–90 μg is another consideration. For patients with polycythemia, reduction of the hematocrit to under 45 % with phlebotomy, hydroxyurea, or interferon is crucial [44]. There is increasing data for using the JAK2 inhibitor ruxolitinib for blood count control in patients intolerant of other therapy, and this is another treatment option [45].

A common issue is whether to reduce platelet counts or to give aspirin to patients with thrombocytosis who do not have a history of thrombosis. Platelet reduction with hydroxyurea or interferon should be considered in asymptomatic patient if they are older (>65 years) or they have atherosclerosis, risk factors for arterial .disease, or symptoms of vascular ischemia. Some studies indicate that an elevated white count or the presence of the JAK2 mutation may also be a risk factor for thrombosis [46]. All patients diagnosed with polycythemia should have their hematocrits reduced to less than 45 %.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

One of the leading causes of morbidity and mortality in patients with PNH is thrombosis with patients presenting with either venous or arterial disease [47–49]. PNH is also associated with a high incidence of visceral vein thrombosis. The cause of the hypercoagulable state is unknown, but complement-activated platelets have been implicated. In two large series, predating specific anticomplement therapy, the rate of thrombosis in PNH was 28–39 % with thrombosis leading to death in 58 % [48, 50]. The development of the complement inhibitor eculizumab has led to control of the hemolysis in most patients with PNH, and there is strong evidence it also reduces thrombosis rates [51]. Eculizumab should be used in any patient with PNH who has had thrombosis, severe hemolysis, or a significant PNH clone (>50 %). Although PNH is rare, patients with visceral vein thrombosis, thrombosis with unexplained high LDH levels, recurrent or warfarin-refractory thrombosis, or thrombosis in the setting of pancytopenia should be screened for PNH.

Venous Catheter Thrombosis

Central venous catheters are essential to many aspects of cancer therapy, but the clinically apparent thrombosis incidence for catheters is estimated to be 5–30 %. The signs of catheter thrombosis are nonspecific, and the incidence of thrombosis is thought to be underestimated (Table 2).

Table 2 Options for catheter thrombosis

Peripheral inserted central catheters
• Removal of catheter
• Reserve anticoagulation for very symptomatic patients
Tunneled central catheters
• Evaluated if line is needed
• If removed short-term anticoagulation if no bleeding risk factors
• If kept in place, 3 months of anticoagulation

Patients with catheter-related thrombosis often notice arm pain and swelling. Diagnosis of the thrombosis is made by Dopplers, but some patients may only have central vein thrombosis and may require venography or CT angiography to make the diagnosis. Many patients have the diagnosis found while undergoing scanning for other reasons.

Therapy is not well defined. Data is increasing for peripherally inserted central catheters that simply removing the catheter may be the safest approach as the risk of bleeding with anticoagulation is high—reserving anticoagulation for the severely symptomatic [52]. For thrombosis with tunneled lines, anticoagulation should be given—unless the risk of bleeding is substantial. One trial does show that one can keep the catheter in place with 3 months of anticoagulation [53]. Prevention of catheter thrombosis is difficult as prophylaxis has not been shown to be a benefit.

Antineoplastic Therapy

Adjuvant chemotherapy for breast cancer has been associated with an increased risk of both arterial and venous thromboembolism (in 5–7 % of patients) [54]. The thrombogenic stimulus is not clear, but this could reflect vascular damage by the chemotherapeutic agents or perhaps a reduction in natural anticoagulants such as protein C or protein S concentrations.

L-Asparaginase—an effective therapy for acute lymphocytic leukemia—is associated with thrombosis [55, 56]. The overall rate of thrombosis in children is 5 % but may be as high as 36 % if asymptomatic thromboses are included and can range from 5 to 20 % in adult. The rate of potentially devastating CNS thrombosis is approximately 1–2 % of patients with childhood all and up to 4 % of adults. Thrombosis usually occurs 2–3 weeks after the start of a course of therapy. Most patients recover, although serious neurologic defects or even death can occur.

The pathogenesis of the thrombotic complications of L-asparaginase may be related to decreased levels of natural anticoagulants antithrombin III, protein C, protein S, and plasminogen via general inhibition hepatic protein synthesis by L-asparaginase.

Patients with acute thrombosis should have levels of fibrinogen and antithrombin drawn before anticoagulation and if deficient supplemented to keep fibrinogen greater than 150 mg/dl and antithrombin greater than 60 %. Platelets need to be kept greater than 50×10^9 L^{-1} during acute anticoagulation.

There remains no consensus on prevention of thrombosis given varying results of clinical trials. Debate remains about effectiveness of either antithrombin or LMWH prophylaxis, but most centers use LMWH prophylaxis either at 40 mg/day or 1 mg/kg/day.

The anti-myeloma agents thalidomide and lenalidomide are both associated with substantial rates of thrombosis that can be as high as 36–75 % [24, 57, 58]. The incidence is higher with the use of dexamethasone and with chemotherapy, especially doxorubicin. These agents may have a direct toxic effect on the vascular endothelium promoting a prothrombotic state. Aspirin appears useful for thrombosis prevention in low-risk patients, while those who have had previous thrombosis, receiving dexamethasone or chemotherapy or have central lines, may benefit from warfarin or LMWH prophylaxis.

Targeted antineoplastic therapy also increases the risk of thrombosis [59]. Bevacizumab has been associated with an ~2-fold increase in arterial thrombosis [60] but not venous disease [61]. This may be a class effect of VEGF inhibition as the VEGF tyrosine kinase inhibitors such as sorafenib and sunitinib also increase arterial thrombosis 2.2-fold [62]. Several of the new tyrosine kinase inhibitors developed for treatment of chronic myelogenous leukemia also increase the risk of arterial thrombosis [63].

Use of Anticoagulants in Thrombocytopenic Patients

A common issue for which there is little guidance is management of anticoagulation in patients who are or are at risk of becoming thrombocytopenic [64]. For venous thrombosis full-dose heparin can be given to a platelet count of 50,000 μl^{-1} and prophylactic dosing down to 20×10^9 L^{-1} [65]. Aspirin given for primary prevention can be held until therapy is over, for secondary prevention would hold aspirin when platelets decrease to under 50×10^9 L^{-1}. For acute coronary events, patients should receive aspirin no matter what their platelet counts are [66].

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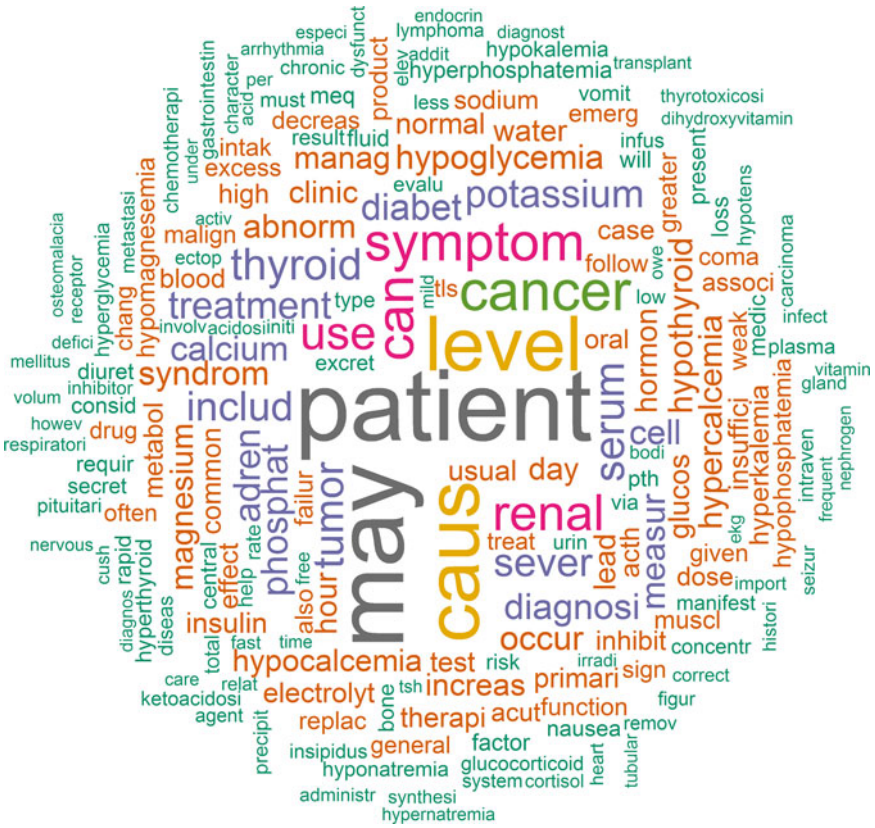
Endocrine and Metabolic Emergencies

Sai-Ching Jim Yeung



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Introduction

Routine clinical chemistry testing, including electrolyte and metabolic panels, is frequently ordered as part of an emergency center (EC) visit to identify abnormalities in electrolyte levels and acid-base imbalances and to monitor treatment of known abnormalities. In cancer survivors and patients with active malignancies presenting for emergency care, electrolyte and metabolic panel abnormalities are very common. Moreover, serum magnesium measurement is very often not part of the electrolyte and metabolic panels in many ECs, although it should be routinely performed for cancer patients because hypomagnesemia is highly prevalent in this population.

In addition to "reflex" treatments in the EC to normalize electrolyte and glucose levels, early diagnosis or initiation of the diagnostic workup to identify the underlying cause of an abnormality by the emergency physician will minimize morbidity and mortality. In general, the patient's medical, medication, and dietary histories will help determine the causes of abnormalities. Also, synthesis of physical examination findings with the histories will give clues for specific clinical syndromes (e.g., Cushing syndrome).

Metabolic Emergencies

Hypernatremia

Hypernatremia results from loss of balance between sodium and water owing to excess sodium intake, low water intake, high water loss, and changes in renal reabsorption of water and/or sodium.

Causes

- Inadequate water intake: obstruction of the gastrointestinal tract, treatment-induced nausea and vomiting, and treatment-induced mucositis. A debilitated bed-bound cancer patient may not have free access to water. Primary hypodipsia is loss of thirst due to abnormality in the supraoptic nucleus of the hypothalamus caused by a primary or metastatic malignancy or treatment (surgery or irradiation) of a central nervous system tumor.
- Increased water loss: diuretic use, high fever, burn, or diarrhea.
- Iatrogenic factors: inappropriate intravenous (IV) fluid administration, total parenteral nutrition, and hemodialysis.
- Diabetes insipidus:
  - Central: caused by changes affecting the anterior pituitary gland or related hypothalamic nuclei (e.g., neurosurgery, destruction by tumors, hemorrhage, head injury, infarction, and infection).
  - Nephrogenic: most familial nephrogenic diabetes insipidus cases are caused by mutations of the V2 receptor or aquaporin-2 water channel. However, these mutations are rare in cancer patients. Acquired nephrogenic diabetes insipidus can result from the use of some common drugs (e.g., demeclocycline, lithium, foscarnet, clozapine, amphotericin, glyburide, colchicine, acetohexamide, tolazamide, methoxyflurane) and chemotherapeutic agents (e.g., ifosfamide, vinblastine, streptozotocin).

Symptoms

The clinical manifestations of hypernatremia are primarily related to cellular dehydration, leading to central nervous system dysfunction, and are more pronounced with a higher level of sodium or faster rate of increase in sodium. Thirst is frequently the first symptom. Muscle weakness and central nervous system changes (restlessness, weakness, and lethargy) are usually not manifested until the sodium level is greater than 160 mEq/L, and the patient may become comatose. Diabetes insipidus is characterized by polyuria, urine hypoosmolality, and polydipsia. Symptoms of intravascular volume depletion may appear if water loss exceeds water intake.

Diagnosis

The cause of hypernatremia is usually evident according to history alone. Accurate measurement of fluid intake and output is helpful. A water deprivation test may differentiate between central and nephrogenic diabetes insipidus. Urine osmolality and sodium concentrations should be measured. A serum uric acid level greater than 5 mg/dL with polyuria and polydipsia is suggestive of central diabetes insipidus.

Management

- Total body water deficit can be estimated using the formula $(0.6 \times \text{body weight in kg}) \times ([\text{serum sodium level}/140] - 1)$. In patients with acute hypernatremia, free water can be replaced rapidly. In those with chronic hypernatremia, the serum sodium level should be reduced less than 2 mEq/L/h until the symptoms resolve. The remaining water deficit can be corrected in 48 h.
- Give water enterally or infuse IV solutions low in sodium (e.g., 0.2 % NaCl, dextrose 5 % in water).
- Central diabetes insipidus usually is treated with various dosages of desmopressin (DDAVP; 5–20 μg intranasally every 12 h, 1–2 μg subcutaneously once a day, or 0.1–0.2 mg orally twice a day).
- Nephrogenic diabetes insipidus may be managed with a low-salt diet and the use of thiazide diuretics to induce natriuresis and/or indomethacin. The use of drugs that contribute to nephrogenic diabetes insipidus should be discontinued, if possible.

Hyponatremia

Multiple organ systems (integumentary, gastrointestinal, cardiovascular, renal, and nervous) are integrated into regulatory networks for homeostatic control of intravascular volume and serum osmolality. Perturbations of these regulatory networks by cancer or cancer treatments frequently cause hyponatremia.

Causes

- Risk factors for hyponatremia in cancer patients include chemotherapy, nausea and vomiting, hydration with hypotonic fluid, pain, the use of opioid drugs, and stress.
- Syndrome of inappropriate antidiuretic hormone secretion, which is characterized by normal or increased intravascular volume, low serum osmolality, and inappropriately high urine osmolality in the absence of diuretic use, cirrhosis, heart failure, hypothyroidism, and adrenal insufficiency:
  - Cancers secreting antidiuretic hormone vasopressin (e.g., about 15 % of small cell lung carcinomas [SCLCs], 1 % of other lung cancers, 3 % of squamous cell head and neck cancers) [1].
  - Abnormal secretory stimuli for vasopressin (e.g., intrathoracic infection, positive pressure ventilation).
  - Cytotoxic chemotherapeutic agents affecting paraventricular and supraoptic neurons to release vasopressin (vinca alkaloids [vincristine and vinblastine] and high-dose cyclophosphamide).
- Renal salt wasting:
  - Tumor induced: mediated by atrial natriuretic peptide [2].
  - Drug induced: damage to the renal tubules and resulting defects in salt and water transport may be the major causes of hyponatremia associated with therapy with low-dose cyclophosphamide [3] and platinum compounds [4].

Symptoms

The signs and symptoms of hyponatremia include general weakness, fatigue, nausea, and vomiting, which are nonspecific. The severity of symptoms depends on the rate of decline and degree of hypo-osmolality. Severe symptoms usually appear as the serum sodium concentration falls below 120 mEq/L. The neurologic symptoms which include headache, behavioral changes, lethargy, confusion, seizure, stupor, and coma may manifest, and progressive cerebral edema may develop, causing brain damage, brain stem herniation, respiratory failure, and death. Identifying the causes of hyponatremia requires additional laboratory evaluations, including urinary sodium measurement, thyroid and adrenal function tests, and correlation symptoms with clinical history.

Diagnosis

Figure 1 outlines the evaluation and treatment of hyponatremia. Evaluation of intravascular volume status is very important in diagnosing the underlying cause of hyponatremia. Hypotonicity must be confirmed by measuring osmolality. Pseudohyponatremia caused by hyperlipidemia, hyperproteinemia, severe hyperglycemia, and administration of hypertonic mannitol must be excluded.

Management

- If the patient is not hypovolemic, free water intake may be restricted to 500–800 mL per day.
- Free water excretion can be increased by:
  - Drug-induced nephrogenic diabetes insipidus (e.g., demeclocycline at 600–1200 mg/day).
  - Loop diuretics (e.g., furosemide at 20–40 mg/day).
  - Blockade of V2 receptors to promote free water excretion (aquaresis, e.g., the use of conivaptan, lixivaptan, tolvaptan, and satavaptan) [5].
- Fludrocortisone (0.1–0.6 mg/day) is a mineralocorticoid that can be used to decrease renal sodium excretion.
- For patients with hypovolemia, oral intake of sodium may be increased using sodium chloride tablets along with intravascular volume expansion by infusing normal saline (0.9 % NaCl).
- For emergent cases of hyponatremia in which central nervous system symptoms are evident and significant, infusion of hypertonic saline (3 % NaCl) at a rate of 1 mL/kg per hour may be indicated with close monitoring in the intensive care unit.

Hyperkalemia

Hyperkalemia, an abnormally high potassium concentration in the blood, is usually associated with renal abnormalities in cancer patients in the absence of excessive intake of potassium.

Causes

- Diminished renal excretion of potassium occurs in patients with acute or chronic renal failure, renal hypoperfusion, or type 4 renal tubular acidosis.
- Drugs that can lead to decreased potassium excretion include potassium-sparing diuretics and angiotensin-converting enzyme inhibitors.
- Excessive oral potassium supplementation and inappropriate potassium content in IV fluid or total parenteral nutrition can lead to increased concentrations.

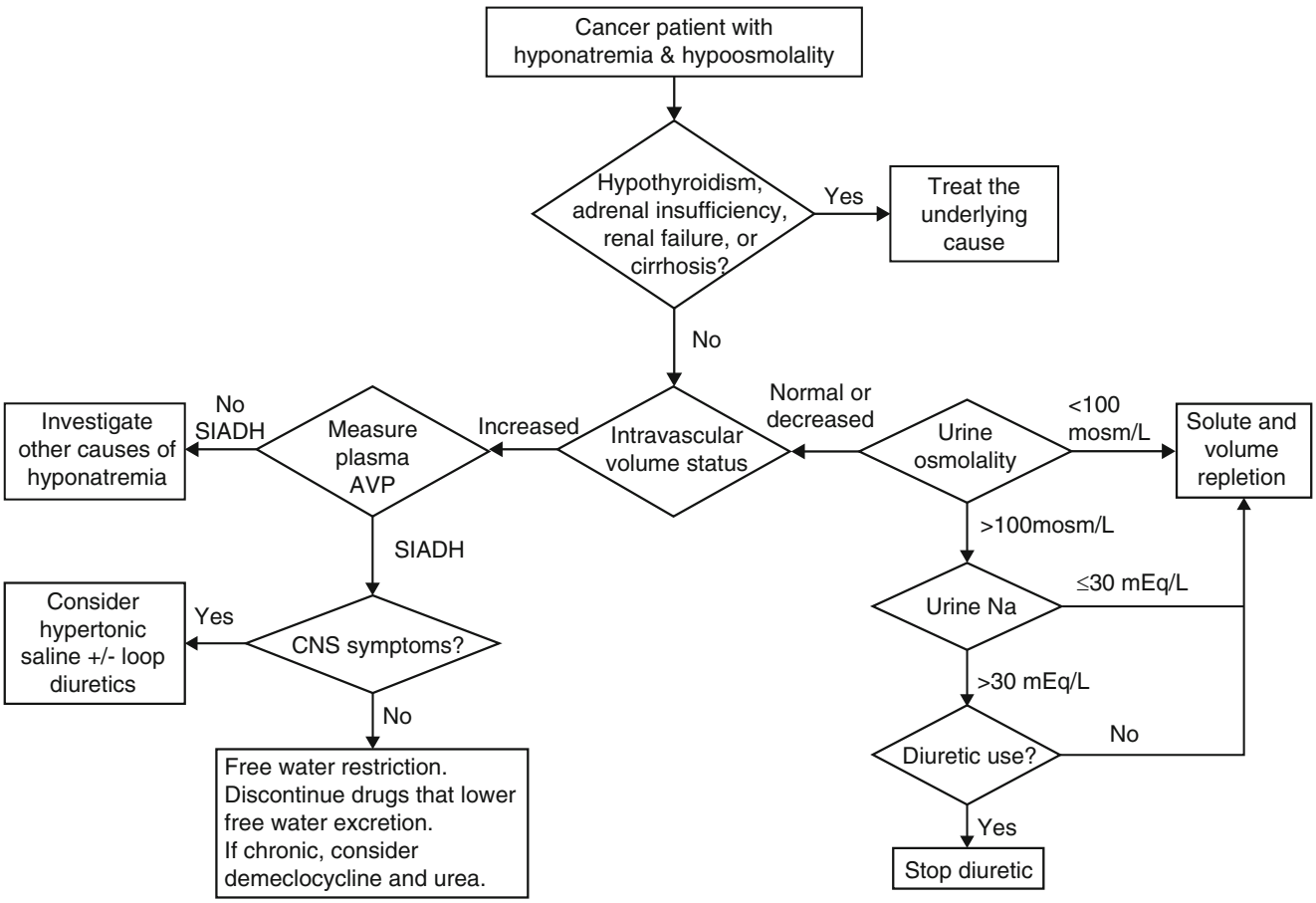

Fig. 1 Algorithm for the evaluation and management of hyponatremia. *SIADH* syndrome of inappropriate antidiuretic hormone, *CNS* central nervous system

- A significant release of intracellular potassium will cause hyperkalemia, as in cases of tumor lysis syndrome (TLS).
- Transcellular shift of potassium may be seen with insulin deficiency, β-blocker therapy, and acidemia, elevating serum potassium levels.
- Drug-induced hyperkalemia often occurs with pre-existing impaired renal excretion of potassium. The drugs commonly used by cancer patients that may cause hyperkalemia include cyclosporine A, tacrolimus, heparin, mitomycin-C, and pentamidine.

Symptoms

Severe clinical manifestations of hyperkalemia are usually absent until the serum potassium level is greater than 7.5 mEq/L. Some patients (e.g., those with chronic renal failure) can have high serum potassium levels without having any clinical signs or symptoms. Hyperkalemia also causes depolarization of excitable membranes. This membrane depolarization leads to excitability of nerves and muscles, causing cramps, muscle weakness, and paralysis. At a serum potassium level greater than 7.5 mEq/L, nonspecific symptoms, such as muscle weakness, cramping, and paralysis of different muscle groups, may occur.

Diagnosis

The most vital organ with excitable membranes is the heart. Electrocardiogram (EKG) changes and potentially fatal arrhythmias may occur in patients with hyperkalemia. An early EKG abnormality associated with hyperkalemia is peak T waves (Fig. 2) followed by progressive QRS widening to a "sinusoidal" wave (Fig. 3). Ventricular tachycardia, fibrillation, and asystole may occur.

Hypotension and hypoglycemia along with hyperkalemia suggest adrenal insufficiency. Serum electrolyte, blood urea nitrogen, serum creatinine, urine electrolyte, and arterial blood gas testing and urinalysis will often determine the cause of hyperkalemia.

Management

- If possible, discontinue medications that may contribute to hyperkalemia, such as potassium supplements, spironolactone, amiloride, β-adrenergic blockers, nonsteroidal

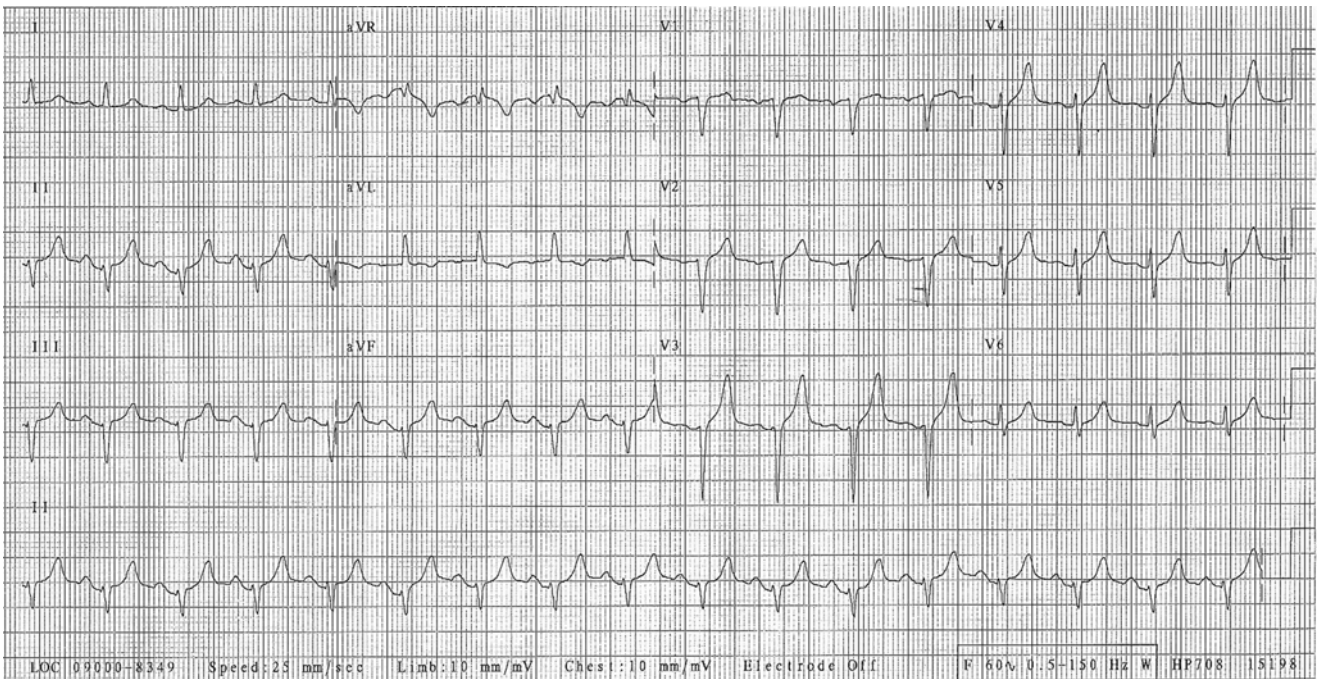

Fig. 2 Peaked T waves in an EKG of a hyperkalemic patient. The serum potassium level was 6.8 mEq/L

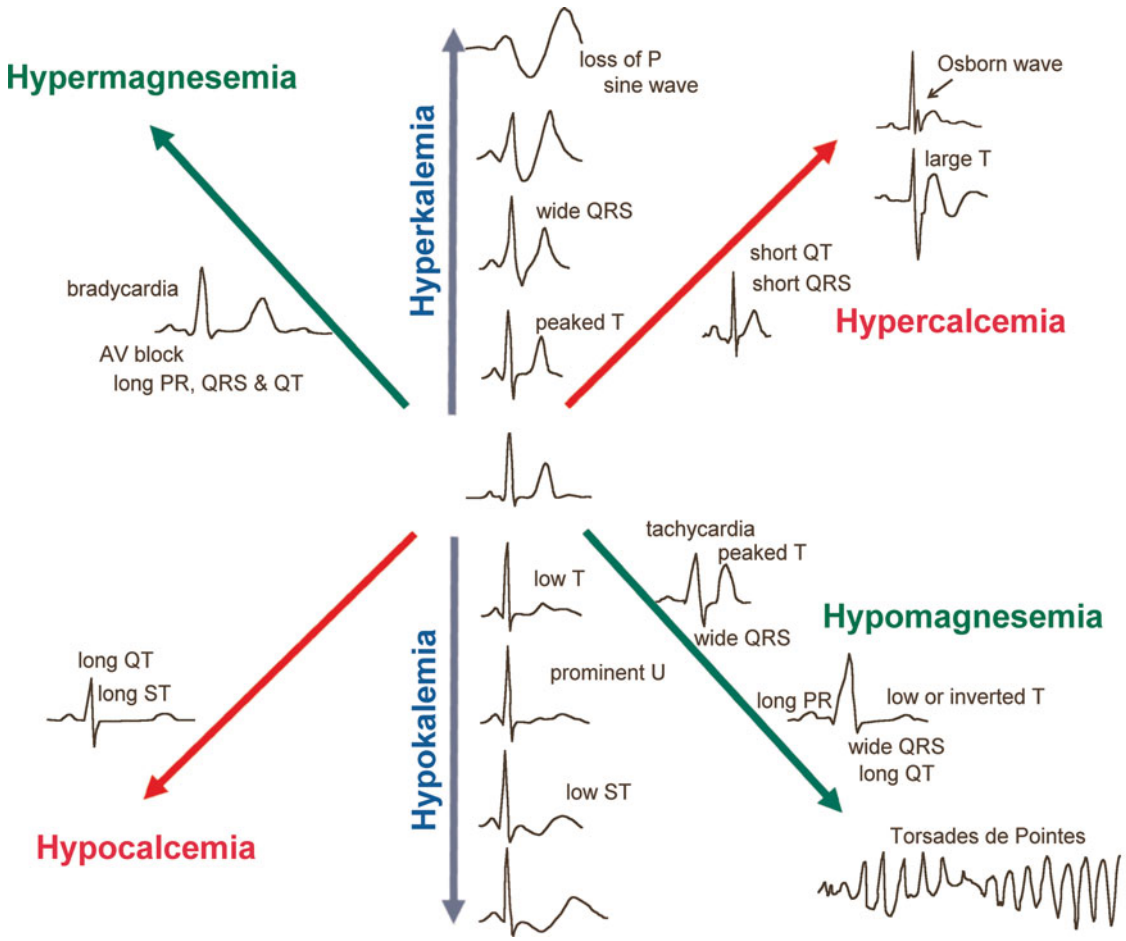

Fig. 3 EKG changes in the presence of electrolyte abnormalities. This figure was adapted from http://what-when-how.com/paramedic-care/diagnostic-ecgthe-12-lead-clinical-essentials-paramedic-care-part-7/ and http://www.mgwater.com/Seelig/Magnesium-Deficiency-in-the-Pathogenesis-of-Disease/ft/figure9-1.gif

anti-inflammatory drugs, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors.
- Hyperkalemia owing to treatment with the calcineurin inhibitors cyclosporine and tacrolimus may respond to treatment with fludrocortisone.
- For severe hyperkalemia (>6.5 mEq/L) and/or EKG changes, monitor EKG readings continuously and treat with the following:
  - IV calcium (1–2 g of calcium gluconate or 0.5–1.0 g of chloride).
  - IV sodium bicarbonate (1 mEq/kg).
  - IV glucose (usually 25 g) plus 6–8 U of regular insulin.
  - β-Adrenergic agonists (e.g., 2.5 mg of albuterol given via nebulized inhalation); loop diuretics may be used to promote natriuresis and kaliuresis.
- Ion exchange resins, such as sodium polystyrene sulfonate (Kayexalate), which can be administered orally (15–30 g/dose) or rectally as a retention enema (30–60 g/dose), may remove potassium from the body via the gastrointestinal tract.
- Emergent hemodialysis may be used in refractory cases.

Hypokalemia

Hypokalemia, an abnormally low potassium concentration in the blood, is a very common electrolyte abnormality in cancer patients.

Causes

- Potassium intake in cancer patients may decrease for various reasons, such as nausea, vomiting, anorexia, and gastrointestinal obstruction.
- Potassium may be lost from the gastrointestinal tract via vomiting or diarrhea and from the kidneys as a result of intrinsic tubular defects or type 1 renal tubular acidosis.
- The use of drugs such as loop diuretics, aminoglycosides, cyclophosphamide, ifosfamide, carboplatin, cisplatin, and amphotericin B may deplete potassium.
- Hypokalemia owing to excessive mineralocorticoid activity may result from deregulated aldosterone production by adrenal tumors or other renin-secreting cancers (renal [Wilms tumor, renal cell carcinoma, and hemangiopericytoma], lung [SCLC and adenocarcinoma], hepatic, pancreatic, and ovarian carcinomas) [6].
- The use of exogenous corticosteroids or fludrocortisone and Cushing syndrome, which includes ectopic secretion of adrenocorticotropic hormone (ACTH) by some cancers (e.g., SCLC, carcinoid tumors), may reduce potassium levels.
- Alkalosis, either respiratory or, on a larger scale, metabolic, may precipitate hypokalemia via a transcellular potassium shift. Drugs that cause potassium redistribution include insulin, β-adrenergic agonists, theophylline, and chloroquine.

Symptoms

Patients with mild hypokalemia (3.0–3.5 mEq/L) usually are asymptomatic. In those with severe hypokalemia (<3.0 mEq/L), symptoms may range from mild to severe (potentially fatal). Cardiac manifestations may range from flat T waves, T-wave depression, and prominent U waves to serious arrhythmias (ventricular tachycardia or fibrillation) (Fig. 3). Neurologic manifestations include muscle weakness, paresthesia, and paralysis.

Diagnosis

Medications used and dietary history will help determine the cause of hypokalemia. Physical examination will give clues regarding the presence of hypercortisolism. Measurement of serum electrolytes, including magnesium, blood urea nitrogen, and creatinine; urinalysis; and measurement of urine electrolytes will help diagnosis of renal potassium loss.

Management

If feasible, the oral route of potassium replacement is preferred over other routes. The IV route may be used in patients with severe hypokalemia or unable to tolerate enteral replacement. The rate of IV potassium administration should not exceed 20 mEq per hour, and it should be diluted in IV fluid and infused through a peripheral vein. The infusion rate may be as high as 40 mEq/h when administered through a central venous catheter. In general, the relationship between the degree of hypokalemia and total body deficit is linear. For each 1 mEq/L decrease in serum potassium level, the total body deficit is about 300 mEq. This deficit may be corrected over several days. Almost half of all cancer patients with hypokalemia also have hypomagnesemia. Potassium-sparing diuretics, such as amiloride and spironolactone, inhibit potassium excretion and may have a role in decreasing renal potassium wasting.

Hypermagnesemia

Hypermagnesemia is uncommon in general.

Causes

- Renal failure.
- Increased intake of magnesium in the presence of renal insufficiency.
- Excessive magnesium levels in IV fluid or parenteral nutrition.
- In the absence of renal insufficiency, hypermagnesemia owing to excessive intake of magnesium is very rare, as excess magnesium in the gastrointestinal tract leads to diarrhea.

Symptoms

The clinical manifestations of hypermagnesemia correlate well with the serum level of magnesium. Early signs include nausea, vomiting, weakness, and cutaneous flushing, which can occur when the serum magnesium level is greater than 3 mg/dL. With levels greater than 4 mg/dL, hyporeflexia and loss of deep tendon reflexes may occur. At levels greater than 5 mg/dL, hypotension and EKG changes (QRS widening, QT and PR prolongation, and conduction abnormalities) may occur (Fig. 3). Respiratory depression, coma, and complete heart block may occur at levels greater than 9 mg/dL. Asystole and cardiac arrest can occur at levels greater than 10 mg/dL.

Diagnosis

Excessive magnesium intake usually is evident in a patient's dietary and medication histories. Renal function should be assessed by measuring blood urea nitrogen and serum creatinine levels.

Management

- Medications and IV fluids containing magnesium should be discontinued.
- Patients with mild symptoms and normal renal function can be observed without intervention.
- Magnesium excretion can be accelerated by hydration with crystalloid fluid and loop diuretics.
- In severe cases with hypotension and/or cardiac arrhythmia, calcium should be administered intravenously to reverse respiratory depression, hypotension, and cardiac arrhythmia. Emergent dialysis should be considered to correct life-threatening hypermagnesemia in the presence of impaired renal function.

Hypomagnesemia

Magnesium is a major inorganic cation in the body, only 1–2 % of which is present in the extracellular space. Hypomagnesemia is defined as a plasma serum concentration of magnesium less than 1.5 mg/dL. However, magnesium levels that are persistently less than 1.8 mg/dL indicate depletion of total body magnesium. The prevalence of hypomagnesemia in hospitalized cancer patients is about 20 %.

Causes

- Low oral intake, impairment of renal reabsorption, prolonged IV feeding, chronic alcoholism, intestinal malabsorption, and diarrhea.
- The renal toxicity of chemotherapy (e.g., platinum-based drugs, cyclophosphamide, ifosfamide) and anti-infective medications (e.g., amphotericin, aminoglycosides) causes hypomagnesemia. Hypomagnesemia occurs in about 90 % of patients given cisplatin [7], and 10 % of hypomagnesemic patients have muscle weakness, tremors, and dizziness. Hypomagnesemia may persist long after cessation of cisplatin-based therapy.

Symptoms

Magnesium is needed as cofactors for a wide variety of enzymatic reactions, including those involving ATP and nucleic acid metabolism. Magnesium is also directly involved in the regulation of calcium and potassium metabolism. The clinical manifestations of hypomagnesemia may be nonspecific and include anorexia, nausea, vomiting, lethargy, dizziness, muscle weakness, tremor, muscle fasciculation, tetany, and tonic-clonic seizures.

Diagnosis

Hypomagnesemia is often associated with other electrolyte abnormalities, such as hypokalemia and hypocalcemia. Concurrent measurement of levels of other electrolytes, such as calcium, phosphate, and potassium, should be considered. Significant hypomagnesemia is associated with EKG changes (Fig. 3).

Management

Magnesium replacement is indicated for cancer patients when the serum magnesium level is repeatedly below normal. Oral replacement of magnesium is preferred over parenteral replacement when feasible. However, diarrhea may be a dose-limiting side effect of the former. When IV replacement is required, the usual practice is to replace half of the estimated magnesium dose over 1 day and the remaining half over the next 3–4 days.

Hypercalcemia

The incidence rate of hypercalcemia in cancer patients is about 1 % [8].

Causes

- Hypercalcemia of malignancy accounts for more than 90 % of hypercalcemia cases:
  - Parathyroid hormone (PTH)-related protein (PTHrP)-mediated hypercalcemia [9, 10] is a paraneoplastic syndrome associated with short survival durations. PTHrP causes hypercalcemia by binding to the PTH receptor and activating expression of the osteoblast-specific cell surface protein RANK ligand. Interaction between RANK ligand and the RANK receptor on osteoclast precursors causes increased osteoclast differentiation, bone resorption, and hypercalcemia. PTHrP production is commonly found in squamous

cell carcinoma; breast, neuroendocrine, renal, and prostate cancers; and melanoma cases.
  - Other tumor-secreted humoral factors, such as interleukin-1 and interleukin-6, prostaglandins, and tumor necrosis factor, may contribute to hypercalcemia.
  - In multiple myeloma cases, increased expression of RANK ligand causing localized osteoclast proliferation appears to be the most important cause of hypercalcemia [10].
  - Lymphoma cells commonly express 1α-hydroxylase, the enzyme that converts 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3 (calcitriol), leading to increased gastrointestinal absorption of calcium [11].
- Primary hyperparathyroidism should be considered in the differential diagnosis of hypercalcemia. No cancer treatments are identified as causing hypercalcemia; however, low-dose (2.0–7.5 Gy) external-beam irradiation of the head and neck increases the incidence of primary hyperparathyroidism by 2.5- to 3.0-fold, 29–47 years afterward [12]. Primary hyperparathyroidism may also develop in patients with multiple endocrine neoplasia, especially type 1.

Symptoms

Patients with mild hypercalcemia (calcium level <12 mg/dL) usually have no symptoms, whereas those with moderate or severe hypercalcemia are frequently symptomatic. Central nervous system symptoms are lethargy, ataxia, stupor, coma, mental status changes, and psychosis. Gastrointestinal tract symptoms are anorexia, nausea, constipation, ileus, dyspepsia, and pancreatitis. Renal signs are polyuria, nephrolithiasis, and nephrocalcinosis. Cardiovascular manifestations can be a short QT interval, ST segment depression, sinus arrest, and atrioventricular block (Fig. 3). Musculoskeletal symptoms are myalgia, arthralgia, and weakness. Severe hypercalcemia (>13 mg/dL) frequently causes depression of cerebral function or coma.

Diagnosis

Serum calcium levels should be interpreted in the context of protein binding (corrected calcium level = [0.8 x (normal albumin level – patient's albumin level)] + serum calcium level). Measurement of the ionized calcium level can confirm hypercalcemia. Laboratory studies of the following help diagnose the etiology of hypercalcemia: intact PTH, PTH-related protein, 25-hydroxyvitamin D_3, and 1,25-dihydroxyvitamin D_3. The combination of hypercalcemia and an elevated PTH level along with increased urinary calcium excretion provides reasonable evidence of primary hyperparathyroidism. Suppression of the PTH level below the normal range is found in cases of PTHrP- and calcitriol-mediated hypercalcemia, which can be diagnosed by measuring 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 levels.

PTHrP-mediated hypercalcemia is characterized by a suppressed PTH level and low or normal calcitriol level. This contrasts with the finding of elevated PTH and calcitriol levels in primary hyperparathyroidism cases. The characteristic clinical features of hypercalcemia in lymphoma patients include a suppressed serum PTH level, a normal or slightly increased phosphate level due to suppression of PTH, hypercalciuria, absence of bone metastasis, and an elevated serum calcitriol level [11].

Management

- The initial and first-line treatment of hypercalcemia is hydration via infusion of normal saline at rates ranging from 100 to 300 mL/h. Hydration alone can lower the serum calcium level by at least 10 % over 6–12 h. In patients with overall fluid overload, the use of a loop diuretic would be helpful.
- The use of calcium-containing medications and thiazide diuretics (which inhibit renal tubular excretion of calcium) should be discontinued.
- Bisphosphonates inhibit bone resorption by osteoclasts, and their peak impact on hypercalcemia is usually seen after a couple of days. Zoledronate (4–6 mg given intravenously over 30 min) [13] is more widely used than pamidronate (60–90 mg intravenously over 4–24 h) because of its greater potency and efficacy [14].
- Second-line agents include calcitonin (4 IU/kg salmon calcitonin given subcutaneously every 12 h). Calcitonin has a rapid onset of action, but its effectiveness may decrease within 2–3 days.
- Glucocorticoids (40–60 mg/day prednisone equivalent) may be used for hypercalcemia associated with myeloma and lymphoma.
- Denosumab (anti-RANK ligand antibody) is a new drug used for treatment of hypercalcemia of malignancy [15].
- Primary hyperparathyroidism can be cured via parathyroidectomy. Removal of an adenoma is usually curative, but in the context of multiple endocrine neoplasia type 1, the surgical procedure of choice is a three-and-a-half-gland parathyroidectomy [16].

Hypocalcemia

Hypocalcemia is a common complication of chemotherapy [17].

- Nephrotoxicity of platinum compounds: authors have reported hypocalcemia in 6–20 % of cisplatin-treated and 16–31 % of carboplatin-treated patients. Hypomagnesemia may decrease secretion of PTH and reduce its calcium-

mobilizing effects. Hypomagnesemia also inhibits formation of 1,25-dihydroxyvitamin D_3. Platinum compounds may inhibit mitochondrial function in the kidneys and thereby inhibit conversion of 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3.
- Plicamycin (mithramycin) and dactinomycin are two infrequently used antineoplastic agents that are known to cause hypocalcemia.
- Surgical procedures in the neck that remove or damage the parathyroid glands (e.g., total laryngectomy, total thyroidectomy) can cause primary hypoparathyroidism, leading to hypocalcemia.
- Vitamin D deficiency causes rickets and osteomalacia along with hypocalcemia.
- TLS can lead to hypocalcemia.

Symptoms

Hypocalcemia can be asymptomatic if it is mild. Life-threatening problems such as seizures, cardiac dysrhythmias, and laryngospasm can occur if hypocalcemia is severe. Acute hypocalcemia is characterized by neuromuscular irritability. Acute symptoms are muscle weakness, paresthesia, spasm, tetany, hyperreflexia, Chvostek sign, Trousseau sign, seizure, bronchospasm, laryngeal spasm, and respiratory failure. Cardiovascular presentations are bradycardia, hypotension, QT-interval prolongation (Fig. 3), congestive heart failure, and cardiac arrest. Chronic hypocalcemia with hypoparathyroidism causes extrapyramidal disorders, cataracts, and skin and hair changes.

Diagnosis

Measuring ionized calcium can exclude pseudohypocalcemia owing to low albumin and serum protein levels. In most cancer patients, the etiology of hypocalcemia is obvious. The major causes of hypocalcemia are hypoparathyroidism, hypomagnesemia, and chemotherapy toxicity. If the cause of hypocalcemia is not clear, laboratory measurement of intact PTH, magnesium, phosphate, 25-hydroxyvitamin D_3, 1,25-dihydroxyvitamin D_3, creatinine, and 24-h urinary calcium levels is helpful.

Management

- Severe hypocalcemia is treated parenterally with IV calcium chloride (0.5–1.0 g) or gluconate (1–2 g) given over 5–10 min.
- Hypomagnesemia is a common cause of hypocalcemia. Concurrent hypomagnesemia should be treated with IV magnesium sulfate followed by oral replacement of calcium.
- Chronic hypocalcemia is treated with oral calcium preparations (e.g., gluconate, carbonate) containing 1–2 g of elemental calcium per day.
- Patients with hypoparathyroidism often need life-long supplementation of calcium and vitamin D. Vitamin D supplements can be given in 1-hydroxylated form or as calcitriol.
- Recombinant $PTH_{1\text{-}34}$ (teriparatide) is now approved for treatment of osteoporosis. Its use in hypoparathyroidism remains to be studied.
- For hypocalcemia secondary to hyperphosphatemia, the latter often must be addressed first. See below for management of hyperphosphatemia.

Hyperphosphatemia

In the absence of renal failure, the fasting serum phosphate level is determined primarily according to the renal tubular reabsorption rate.

Causes

- A massive amount of phosphate can be released into the extracellular fluid via extensive cellular breakdown (e.g., TLS, rhabdomyolysis, hemolysis).
- Translocation of phosphate from cells in response to metabolic or respiratory alkalosis can lead to acute hyperphosphatemia.
- Chronic hyperphosphatemia is present in patients with hypoparathyroidism receiving long-term treatment with oral calcium and vitamin D.
- Excess phosphate intake (e.g., phosphate-containing laxatives), especially in the presence of renal insufficiency, can increase phosphate levels.

Symptoms

The clinical manifestations of acute hyperphosphatemia are similar to those of associated hypocalcemia. Paresthesia, muscle cramps, tetany, and QT-interval prolongation may be induced directly by severe hyperphosphatemia. Chronic hyperphosphatemia, especially associated with hypercalcemia, may lead to diffuse visceral deposition of calcium phosphate. Deposition of calcium phosphate in the kidneys may lead to renal failure.

Diagnosis

In patients with hyperglobulinemia, pseudohyperphosphatemia must be excluded by examination of a blood specimen that is free of protein (removed via precipitation with sulfosalicylic acid). The renal function of patients with hyperphosphatemia must be assessed. In addition, measurement of lactic dehydrogenase, uric acid, potassium, and calcium levels is necessary in the diagnosis and management of hyperphosphatemia due to extensive cellular lysis.

Management

- In patients with normal renal function, infusion of isotonic saline increases phosphate excretion.
- Administration of dextrose and insulin drives phosphate into cells, temporarily lowering the serum phosphate level.
- When hyperphosphatemia is life threatening, hemodialysis or peritoneal analysis should be considered.
- Phosphorus absorption should be blocked in the gastrointestinal tract using:
  - Aluminum hydroxide
  - Calcium-based phosphate binders (e.g., calcium acetate)
  - Nonabsorbable aluminum- and calcium-free phosphate binders (800–1600 mg of sevelamer taken with each meal)

Hypophosphatemia

Hypophosphatemia occurs in about 2–3 % of all hospitalized patients and about 30 % of cancer patients.

Causes

- Relative nutritional deficiency:
  - Hypophosphatemia in malnourished patients (especially alcoholics) results from a combination of magnesium deficiency, vitamin D deficiency, and malabsorption. Acute hypophosphatemia may occur in hospitalized patients with serious illnesses and preexisting phosphate depletion.
  - Refeeding with high-calorie content may lead to hypophosphatemia in severely malnourished patients.
  - Rapid cancer proliferation may cause hypophosphatemia (e.g., Burkitt lymphoma).
  - Rapid normal cell proliferation as with the use of granulocyte colony-stimulating factors, hematopoietic reconstitution after stem cell transplantation, or stem cell harvesting in preparation for transplantation can decrease phosphate levels.
- Renal wasting of phosphorus and calcium:
  - Tumor-induced osteomalacia is a rare paraneoplastic syndrome characterized by hypophosphatemia, excessive urinary phosphate loss, reduced 1,25-dihydroxyvitamin D_3 concentrations, and osteomalacia. Fibroblast growth factor-23 may be the humoral mediator of this paraneoplastic syndrome [18]. Tumors that lead to this clinical syndrome include mesenchymal tumors (osteoblastomas, giant cell osteosarcomas, hemangiopericytomas, hemangiomas, and nonossifying fibromas) [19] and, rarely, malignant tumors such as prostate and lung cancer.
  - Intrinsic renal tubular defects in phosphate reabsorption and acquired renal tubular defects (e.g., after treatment with ifosfamide [20], cisplatin [21], or estramustine [22]) may result in hypophosphatemia.
- Transcellular shift of phosphate (e.g., respiratory alkalosis, IV glucose administration, hyperalimentation, gram-negative sepsis, insulin therapy).
- Elevated PTH (primary hyperparathyroidism) or PTHrP (hypercalcemia of malignancy) levels.
- Accelerated bone formation (e.g., extensive blastic bone metastasis of prostate cancer, hungry bone syndrome after resection of parathyroid adenomas).
- Loss of liver function: the liver plays a major role in phosphate homeostasis. The serum phosphate level decreases after right or extended right hepatic lobectomy and in patients with hepatocellular carcinoma, complicating cirrhosis.
- Consumption of aluminum-containing medications/antacids.

Symptoms

Acute severe hypophosphatemia may lead to general neurologic findings such as lethargy, confusion, disorientation, and hallucinations and focal neurologic findings such as dysarthria, dysphagia, oculomotor palsy, anisocoria, nystagmus, ataxia, cerebellar tremor, ballismus, hyporeflexia, distal sensory deficits, paresthesia, and hyperesthesia. Severe neurologic symptoms, such as muscle paralysis, seizure, and coma, are observed only when the serum phosphate level is less than 0.8 mg/dL. In severe hypophosphatemia cases, reversible left ventricular dysfunction can occur.

Muscle weakness is the most common complaint. Bone pain is another prominent complaint of phosphate-depleted patients. Prolonged hypophosphatemia leads to rickets. Osteomalacia, a condition characterized by an unmineralized bone matrix, should be considered in osteopenic patients with bone pain and proximal myopathy. Waddling gait, bone tenderness, pseudofractures, and fractures can occur in patients with chronic hypophosphatemia. Osteomalacia and moderate to severe proximal myopathy are also characteristics of tumor-induced osteomalacia [23].

Diagnosis

Measurement of renal function and potassium, magnesium, ionized calcium, vitamin D metabolite, and PTH levels is helpful in the initial determination of the cause of hypophosphatemia. If urinary loss of phosphate is suspected, urine should be collected to measure the renal phosphate threshold/glomerular filtration rate to confirm phosphaturia.

Management

- Significant hypophosphatemia (phosphate level <2 mg/dL), especially in the context of underlying phosphate depletion, should be corrected promptly.

- Phosphate can be safely administered intravenously at an initial dose of 0.2–0.8 mmol/kg over 6 h (i.e., 10–50 mmol over 6 h). Higher doses (1.5–3.0 mmol/kg over 12 h) should be reserved for patients with phosphate levels less than 1.5 mg/dL and normal renal function.
- Mild hypophosphatemia can be treated with oral phosphate given in divided doses of 750–2000 mg per day.
- For tumor-induced osteomalacia, oral or IV supplementation of phosphate combined with vitamin D-based therapy is generally effective for eradicating or improving clinical symptoms. Complete surgical removal of the tumor is generally curative.

Hyperglycemia

Type 2 diabetes mellitus is a common disease, and a large number of cancer patients have it. Extensive epidemiologic data suggest an important role for type 2 diabetes mellitus in carcinogenesis [24–29] and cancer survival [30], and type 2 diabetes mellitus is associated with an elevated risk of pancreatic, liver, colon, gastric, breast, and endometrial cancers [24–29].

Causes

- Administration of glucocorticoids (e.g., for antineoplastic therapy in combination regimens, edema of brain metastasis, prevention of transplant rejection, graft-versus-host disease in bone marrow transplantation, nausea/vomiting) is probably the most common cause of drug-induced diabetes in cancer patients.
- Treatment with streptozotocin [31] or L-asparaginase [32] may result in insulin-deficient diabetes mellitus.
- Diabetes mellitus may also develop as a consequence of serious pancreatitis secondary to treatment with L-asparaginase.
- Interleukin-2 and interferons may cause toxicity to pancreatic β cells and lead to insulin-dependent diabetes [33].
- Some antineoplastic agents used in targeted therapy interfere with the insulin signaling pathway and can cause hyperglycemia. The use of mammalian target of rapamycin inhibitors (e.g., rapamycin [sirolimus], everolimus, temsirolimus) is associated with high incidence rates of hyperglycemia, ranging from 13 to 50 % in clinical trials [34]. The mechanism causing hyperglycemia is not clear but probably involves both decreased insulin secretion and insulin resistance. Some tyrosine kinase inhibitors (e.g., nilotinib, sunitinib) are associated with hyperglycemia. Others (e.g., imatinib, pazopanib) may be associated with hyperglycemia or hypoglycemia [34]. The molecular mechanism by which tyrosine kinase inhibitors affect glucose homeostasis is unclear.
- Tacrolimus, an immunosuppressive agent used to prevent graft-versus-host disease in bone marrow stem cell transplantation, also increases the incidence of diabetes, perhaps by damaging pancreatic β cells [35]. Patients who undergo allogeneic stem cell transplantation are likely to receive glucocorticoids, cyclosporine A, and tacrolimus and are at particular risk for diabetes mellitus [36].

Symptoms

Most patients with significant hyperglycemia have polydipsia, polyuria, and polyphagia. Dehydration of the lenses owing to hyperglycemia leads to blurry vision. Patients with hyperosmolar nonketotic coma experience mental status changes, hypotension, and severe dehydration. Nausea, vomiting, and abdominal pain are present in almost half of patients with diabetic ketoacidosis. Tachypnea with Kussmaul respiration, tachycardia, hypotension, orthostatic blood pressure changes, acetone breath, and severe signs of dehydration can be present in patients with diabetic ketoacidosis.

Diagnosis

A random plasma glucose level greater than 200 mg/dL or fasting plasma glucose level greater than 126 mg/dL on more than one occasion can indicate diabetes mellitus. Abnormal glucose levels may require further diagnostic evaluation with a glucose tolerance test, mixed-meal tolerance test, or glycosylated hemoglobin (hemoglobin A1C).

Diabetic ketoacidosis is diagnosed according to the triad of metabolic acidosis, hyperglycemia, and presence of ketone bodies in the urine or blood. Arterial blood gas testing will demonstrate acidemia and respiratory compensation for metabolic acidosis by hyperventilation. Also, the anion gap will be elevated, and serum ketone testing will be positive. A urine dipstick test for ketones can provide timely information for a quick bedside diagnosis. Absence of ketones from the urine practically excludes diabetic ketoacidosis. Leukocytosis may be associated with ketosis, but an infection must be considered in a precipitating factor for diabetic ketoacidosis. The serum creatinine level can be falsely elevated because of ketosis. Potassium, phosphate, and magnesium level abnormalities result from transcellular shifts caused by acidosis.

In patients with hyperosmolar hyperglycemic nonketotic coma, the plasma glucose level may be greater than 800 mg/dL, and the serum osmolality level may be more than 100 mOsm above normal. Mild ketosis may be present because of starvation, but ketoacidosis is absent. In severe cases, when volume depletion compromises tissue perfusion, lactic acidosis will develop.

In immunocompromised cancer patients in particular, sepsis must be ruled out as the precipitating event for diabetic ketoacidosis or hyperosmolar hyperglycemic coma.

Management

- In general, administration of insulin is required in patients who are insulin deficient.
- Diabetic ketoacidosis is decompensated catabolism triggered by a relative or absolute deficiency in insulin secretion.
- Treatment of diabetic ketoacidosis and hyperosmolar hyperglycemic coma:
  - Hydration with IV crystalloid fluid.
  - Regular insulin, which is usually given as an IV bolus of 0.1 U/kg followed by a maintenance IV infusion of 0.1 U/kg per hour. The amount of insulin required for treatment of hyperosmolar hyperglycemic coma may be less than that required for diabetic ketoacidosis.
  - Correction of electrolyte abnormalities while being aware of transcellular shift of electrolytes related to blood pH and the effect of insulin.
  - Identification of the precipitating factors (particularly important to rule out sepsis).

Hypoglycemia

Glucagon and epinephrine immediately stimulate hepatic glycogenolysis followed by gluconeogenesis and are the two major counterregulatory hormones in response to hypoglycemia. Other counterregulatory hormones are norepinephrine, cortisol, and growth hormone, but their effects on blood glucose are delayed.

Causes

- Cancer-related malnutrition, fat and muscle wasting, cirrhosis, and extensive liver metastases may impair glycogenolysis and gluconeogenesis.
- Adrenal insufficiency is associated with hypoglycemia (refer to the section on adrenal crisis below for a detailed discussion).
- In diabetic cancer patients receiving sulfonylurea or insulin, the most common cause of hypoglycemia may be delayed or decreased food intake. The kidneys contribute to overall gluconeogenesis during hypoglycemic stress in about one third of cases and are important for extrahepatic degradation of insulin. Moreover, a number of oral hypoglycemic drugs are excreted by the kidneys. Therefore, decline in renal function often leads to hypoglycemic episodes in diabetic patients.
- Tumor-induced hypoglycemia is an uncommon but challenging cause of morbidity for cancer patients. Three different clinical syndromes have been identified: (1) secretion of insulin by an islet cell malignancy, (2) insufficient gluconeogenesis due to near-complete replacement of hepatic parenchyma by a tumor, and (3) secretion of insulin-like growth factor II (IGF2), which activates the insulin receptor and causes hypoglycemia [37–39], by tumors (e.g., fibrosarcomas, hemangiopericytomas, hepatomas).
- Excessive glucose consumption by large tumors may cause hypoglycemia. Hypoglycemia may also occur in patients with lactic acidosis in the context of end-stage leukemia or lymphoma [40].

Symptoms

Hypoglycemia symptoms progress as the availability of glucose to the brain decreases. At a plasma glucose level of about 70 mg/dL, brain glucose uptake can be reduced, and counterregulatory hormone responses are triggered. At less than 60 mg/dL, autonomic symptoms such as hunger, anxiety, palpitations, sweating, and nausea become evident. When the glucose level is less than 50 mg/dL, the neuroglycopenic symptoms blurry vision, slurred speech, inability to concentrate, and confusion appear. When the glucose level is less than 40 mg/dL, the patient may become drowsy, confused, or combative. A prolonged decrease below 30 mg/dL can cause seizures, permanent neurologic damage, and death.

Diagnosis

Hypoglycemia is diagnosed using blood chemistry, but rapid bedside measurement of blood glucose should be expeditiously performed in the evaluation of all ED patients with altered mental status. The timing of symptoms relative to a fasting or postprandial state or to antidiabetic medication use can distinguish among various causes of hypoglycemia.

The most common presentation for paraneoplastic syndromes of hypoglycemia is fasting hypoglycemia, and patients are most likely to experience symptoms during normal periods of fasting, particularly during nocturnal hours. Simultaneous measurement of fasting plasma glucose, insulin, proinsulin, C-peptide, IGF1, and IGF2 during a period of hypoglycemia is the most important diagnostic tool for separating the first clinical type (insulin production) from the second (replacement of the liver by tumor) and third (IGF2) types. Proper diagnostic evaluation of cancer patients with fasting hypoglycemia usually will necessitate a 72-h fast in the hospital with endocrinology consultation.

Management

- For mild hypoglycemia (glucose level of 50–60 mg/dL), consumption of 15 g of simple carbohydrates, such as 4 oz of unsweetened fruit juice or a non-diet soft drink, is sufficient.

- For more severe hypoglycemia without loss of consciousness, 15–20 g of simple carbohydrates should be ingested quickly followed by 15–20 g of a complex carbohydrate, such as crackers or bread.
- For severe hypoglycemia with change in mental status, glucagon (1–2 mg subcutaneously or intravenously) or glucose (50 mL of dextrose 50 % in water intravenously) should be given promptly.
- The most effective therapeutic approach for non-islet cell tumor-induced hypoglycemia is to resect or debulk the tumor. If it is unresectable, reducing the tumor bulk via external-beam irradiation, intra-arterial chemoembolization, or percutaneous alcohol injection may be attempted.
- Counterregulatory hormones such as glucocorticoids (20–40 mg prednisone equivalent/day) and glucagon (1–2 mg intravenously or intramuscularly) may be administered to raise the blood glucose level. Glucagon infusion (0.5–2.0 mg/h) to stimulate hepatic gluconeogenesis is an effective therapy in patients with insulin-producing tumors or IGF2-mediated hypoglycemia [41].
- A continuous IV infusion of 5–20 % dextrose may be required to maintain normal blood glucose levels in some patients.
- Diazoxide (3–8 mg/kg/day in 2–3 divided doses) has been used successfully to inhibit insulin secretion, but it causes fluid retention, thereby limiting its usefulness at effective doses.
- Treatment of postprandial hypoglycemia is primarily dietary. The diet should have a low carbohydrate content. Administration of α-glucosidase inhibitors (acarbose or miglitol) may be helpful.

Tumor Lysis Syndrome

TLS consists of severe hyperphosphatemia, hyperkalemia, hyperuricemia, azotemia, hypocalcemia, and metabolic acidosis (out of proportion to renal insufficiency) owing to the massive release of cell contents and degradation products of dead tumor cells into the bloodstream [42].

Causes

Factors associated with increased risk of TLS include:

- Type of malignancy (e.g., acute lymphocytic leukemia, acute myeloid leukemia with a white blood count >75,000 μL^{-1}, Burkitt lymphoma). TLS can also occur in patients with nonhematologic malignancies, including small cell carcinomas, non-small cell lung cancer, breast cancer, and ovarian cancer.
- Responsiveness to therapy.
- Rapid malignant cell turnover.
- Large tumor burden [43]. Pretreatment serum lactate dehydrogenase levels, which tend to correlate with tumor bulk in patients with lymphoma or lymphocytic leukemia, may predict the risk of TLS.
- Pre-existing renal insufficiency.
- Acute renal failure shortly after antineoplastic treatment.

Symptoms

The symptoms of TLS are nonspecific. Common symptoms include nausea, vomiting, cloudy urine, weakness, fatigue, and arthralgia. Other signs and symptoms related to metabolic and electrolyte abnormalities include neuromuscular irritability, seizures, muscle weakness, and arrhythmia. Arrhythmia may cause sudden death in patients with TLS [44]. Precipitation of uric acid in the renal tubules may lead to nephropathy and acute renal failure [45]. The acute cause of death in TLS is arrhythmia secondary to severe electrolyte abnormalities (especially hyperkalemia) and renal failure. Early recognition of metabolic abnormalities and prompt treatment can prevent fatal outcomes.

Diagnosis

TLS can occur spontaneously, but it usually occurs within 72 h after chemotherapy in patients with leukemia or lymphoma. However, new therapeutic regimens may alter the timing of onset. Diagnosis of TLS requires a high level of suspicion because of few signs or symptoms in the early stages. Routine uric acid and electrolyte screening (including measurement of calcium and phosphorus levels) is indicated for patients with high tumor bulk or hematologic malignancies. Diagnosis of TLS may be based on the Cairo-Bishop definition [43, 46].

Management

- Once diagnosed, patients with severe TLS should undergo continuous monitoring of hemodynamic and electrocardiographic parameters in the intensive care unit.
- Management of hyperuricemia:
  - Allopurinol (≤900 mg/day).
  - Rasburicase (IV 150–200 μg/kg daily or one-time dosing with a rescue dose as needed) is a recombinant urate oxidase that converts uric acid to allantoin [47].
  - IV fluid hydration may be coupled with diuresis using loop diuretics (e.g., IV 20–200 mg furosemide every 4–6 h) and acetazolamide (IV 250–500 mg daily).
  - Urinary alkalinization by sodium bicarbonate or IV acetate infusion to increase the solubility of urate in urine should only be considered in cases of severe hyperuricemia when rasburicase is not available.

- Frequent electrolyte measurement (every 4–6 h) may be required (see the sections above on management of hyperkalemia, hypocalcemia, and hyperphosphatemia).
- Prompt dialysis should be instituted with continued monitoring until biochemical abnormalities resolve. Indications for dialysis in patients with TLS include:
  - Symptomatic hypocalcemia and a serum phosphorus level greater than 3.3 mmol/L (>10.2 mg/dL).
  - Severe azotemia and renal failure (creatinine level >10 mg/dL).
  - Persistent hyperkalemia (>6 mEq/L).
  - Severe hyperuricemia (>10 mg/dL).
  - Oliguria or anuria despite diuretic use.
  - Refractory acidemia.
  - Volume overload.

Endocrine Emergencies

Cushing Syndrome

Inappropriate secretion of ACTH, although uncommon, is an important cause of morbidity and mortality in certain types of malignancies. Paraneoplastic Cushing syndrome has at least two mechanisms: ectopic production of ACTH or corticotropin-releasing hormone (CRH), the hypothalamic peptide that normally stimulates ACTH synthesis and release.

Causes

- The most common cause of ectopic ACTH production is expression of proopiomelanocortin by a tumor, producing melanocyte-stimulating hormone and ACTH. The tumor most often associated with ACTH production is SCLC, although pulmonary carcinoid tumors, medullary thyroid carcinomas, islet cell malignancies, pheochromocytomas, and ganglioneuromas can also produce this hormone.
- Another cause of excessive ACTH production is tumor production of CRH [48]. Ectopic production of this peptide causes a clinical syndrome characterized by pituitary corticotrope hyperplasia, leading to adrenal cortical hyperplasia and Cushing syndrome. Identification of excessive CRH production requires that the clinician consider this possibility and measure CRH levels in the blood. Neoplasms that can produce CRH include medullary thyroid carcinomas, paragangliomas, prostate cancer, and islet cell neoplasms.

Symptoms

Patients with ectopic ACTH syndrome may present with clinical features of Cushing syndrome: easy bruising, centripetal obesity, muscle wasting, hypertension, diabetes, and metabolic alkalosis. Alternatively, patients with rapidly growing SCLC may present with a clinical syndrome characterized by wasting, muscle atrophy, profound hypokalemic metabolic alkalosis, and hypertension without the other clinical signs of Cushing syndrome.

Diagnosis

The hallmark of ectopic ACTH syndrome is an elevated plasma ACTH concentration. However, in the differential diagnosis of hypercorticism with an elevated plasma ACTH concentration, the clinician should consider the possibility of an ACTH-producing pituitary tumor [49]. Differentiation between pituitary production of ACTH and ectopic tumor production of ACTH or ectopic production of CRH should be performed by a consulting endocrinologist and therefore is not be discussed in detail herein. In brief, the diagnostic evaluation starts with confirmation of hypercortisolism and measurement of the plasma ACTH level followed by dynamic testing and may involve magnetic resonance imaging of pituitary or petrosal venous sinus sampling.

Management

- Medical management to inhibit cortisol production:
  - Metyrapone (1–4 g/day orally).
  - Aminoglutethimide (250 mg orally four times a day with upward titration).
  - Ketoconazole (200–400 mg twice a day orally) [50].
  - Etomidate rapidly inhibits cortisol synthesis at subhypnotic doses [51]. It may be titrated from 0.3 to 4.0 mg/kg per hour intravenously to normalize serum cortisol levels in some patients.
- Surgical removal or treatment with chemotherapeutic agents is the primary therapy for an ACTH- or CRH-producing tumor.
- Patients with rapidly progressive SCLC and ectopic ACTH syndrome have a unique challenge because of the need to initiate chemotherapy quickly. High susceptibility to opportunistic infections after initiation of chemotherapy will often lead to death or serious morbidity [52]. Laparoscopic adrenalectomy following normalization of electrolyte abnormalities and hypertension may be used to rapidly treat hypercortisolism to decrease the risk of infectious complication after chemotherapy.
- Replacement glucocorticoid therapy is required after adrenalectomy or during pharmacologic inhibition of cortisol production.
- Prophylactic therapy for opportunistic infections caused by *Pneumocystis carinii* or fungi should be considered if chemotherapy is initiated shortly after normalization of the serum cortisol level.

Adrenal Crisis

Cancer patients are at increased risk for adrenal insufficiency.

Causes

Central adrenal insufficiency:

- Radiotherapy is a common cause of insidious development of hypothalamic dysfunction; hormonal deficiency can manifest years after irradiation. In general, the rapidity of onset and severity of dysfunction depend on the total dose of radiation and rate of delivery. The somatotropic axis is the most susceptible, whereas the thyrotropic axis is the least susceptible to radiation [53–56].
- High-dose glucocorticoids may suppress the hypothalamic-pituitary corticotropic axis. In cancer patients in whom glucocorticoid-based therapy was recently discontinued, acute stress (usually caused by infection or sepsis) may precipitate an adrenal crisis.
- Acute central adrenal insufficiency may occur in cancer patients in the following settings:
  - Pituitary apoplexy
  - Autoimmune hypophysitis after starting cancer immunotherapy (especially with anti-CTLA4 or anti-PD1 antibodies)
- Metastasis to the hypothalamic region or pituitary gland is uncommon [57].
- Benign tumors such as pituitary tumors and craniopharyngiomas frequently affect this anatomic region and cause endocrine dysfunction.

Primary adrenal insufficiency:

- About 20–30 % of patients with bilateral adrenal metastasis have adrenal insufficiency [58], which occurs when more than 80 % of adrenal tissue is destroyed or replaced by metastatic cancer [59].
- Bilateral infectious adrenalitis: many cancer patients may be immunocompromised. In immunocompromised patients with hematologic malignancies or stem cell transplant recipients, infection of the adrenal glands by cytomegalovirus, mycobacteria, or fungi may lead to adrenal insufficiency.
- Bilateral adrenal hemorrhage (e.g., in coagulopathy and thrombocytopenia).
- Bilateral adrenalectomy (e.g., radical nephrectomy and contralateral adrenalectomy for renal cell carcinoma and bilateral adrenal metastasis).
- Autoimmune adrenalitis.
- The use of drugs that are known to inhibit glucocorticoid synthesis: etomidate [58], ketoconazole, aminoglutethimide, metyrapone, megestrol, and mitotane. At high doses, fluconazole and itraconazole may inhibit the cytochrome P450-dependent enzymes in glucocorticoid synthesis.

Symptoms

The symptoms of adrenal insufficiency include weakness, fatigue, nausea, vomiting, and weight loss. In patients with chronic primary adrenal failure, hyperpigmentation may occur. Acute adrenal crisis involves hypoglycemia and hypotension. The cachexia and weakness seen with adrenal insufficiency mimic cancer-related cachexia in patients with end-stage cancer. Electrolyte abnormalities due to adrenal insufficiency are difficult to distinguish from poor intake, malnutrition, side effects of chemotherapeutic agents, and paraneoplastic syndromes. Both pituitary apoplexy and hypophysitis may be accompanied by headache.

Diagnosis

The patient's medication history should be reviewed for recent glucocorticoid exposure and medications that may inhibit steroid synthesis. Screening tests include basal 8:00 a.m. plasma cortisol measurement, dynamic testing with 1 μg of cosyntropin (synthetic $ACTH_{1–24}$) or metyrapone (30 mg/kg given orally overnight), and insulin tolerance testing (insulin-induced hypoglycemia).

Without evidence of other metastatic disease, whether an adrenal mass is actually a metastatic tumor is critical to determining the appropriate antineoplastic therapy. In addition to hormonal evaluation, functional scintigraphy using ^{131}I-6-iodomethyl-19-*nor*-cholesterol, computed tomography, and magnetic resonance imaging may aid in the diagnosis of a unilateral adrenal mass greater than 2 cm [60, 61]. In immunocompromised patients, the possibility of infection of both adrenal glands with cytomegalovirus, mycobacteria, or fungi must be investigated. A high degree of suspicion for hypopituitarism is recommended for patients given ipilimumab or other drugs with similar mechanisms of action.

Management

If a cancer patient presents to an EC with hemodynamic instability, physicians may have insufficient time to wait for the results of serum cortisol measurement or other tests to evaluate adrenal insufficiency. Under such circumstances, empiric treatment with a stress dose of hydrocortisone should be considered based on risk assessment.

- In the event of circulatory instability, sepsis, emergency surgery, or other major complications, stress dosages of parenteral glucocorticoids should be given (e.g., 100 mg of IV hydrocortisone succinate every 8 h).
- Fludrocortisone (0.05–0.20 mg/day) for mineralocorticoid replacement.
- Treat hypotension with IV normal saline or other crystalloid fluid.

- Treat hypoglycemia immediately if symptomatic with dextrose 50 % in water (50–100 mL intravenously) followed by dextrose 5 % in water. If IV access is not quickly available, glucagon (2 mg) may be given subcutaneously or intramuscularly, but the effect may be delayed by about 10–20 min.
- If and when the patient is clinically stable, endocrinology consultation and ACTH stimulation testing should be arranged.

Hyperthyroidism

Thyrotoxicosis is a common disease, with a prevalence of 20–25 per 100,000 in the general population and a female/male ratio of 5:1.

Causes

- Graves disease, toxic multinodular goiters, and solitary toxic nodules are the three forms of primary hyperthyroidism that account for most cases of hyperthyroidism in the general population. The risk of Graves disease after radiotherapy for Hodgkin disease is estimated to be at least 7.2 times greater than that in the general population [62].
- Large quantities of iodide are present in many drugs (e.g., ~9 mg of iodine following a daily amiodarone dose of 300 mg), antiseptics (e.g., povidone-iodine), and contrast media used in radiology. Iodine-induced hyperthyroidism usually occurs in patients with underlying thyroid disease.
- Autoimmune thyroiditis may be precipitated by bioimmunotherapy for cancer with cytokines. In addition to being a source of excess iodide described above, treatment with amiodarone may induce thyroiditis.
- Radiation-induced painless thyroiditis with hyperthyroxinemia is an uncommon side effect of external-beam radiotherapy to the head and neck. Transient hyperthyroidism is usually followed by hypothyroidism.
- Thyroid metastasis occurs in 1.25–24.00 % of patients with metastatic carcinoma. However, thyrotoxicosis owing to follicular destruction by metastasis is rare.
- Structural homology in the human chorionic gonadotropin and thyroid-stimulating hormone (TSH) molecules as well as receptors provides the biochemical basis for the ability of human chorionic gonadotropin to stimulate the TSH receptor. Trophoblastic tumors, hydatidiform moles, and choriocarcinomas secrete human chorionic gonadotropin in large amounts, often causing hyperthyroidism. Hyperthyroidism is likely with a human chorionic gonadotropin level greater than 200 IU/mL.

Removal or effective treatment of the underlying tumor is the most effective therapy for clinical syndromes caused by excessive β-human chorionic gonadotropin production. Hyperthyroidism can be treated over the short term with thioamide if chemotherapy or other therapies for the underlying malignancy are likely to be effective. In patients with unresponsive tumors, thyroidectomy or the use of radioactive iodine may be required.

Symptoms

Thyrotoxicosis is characterized by a hyperadrenergic state. Sinus tachycardia, systolic flow murmur, and water-hammer pulse are common. Atrial dysrhythmias (atrial fibrillation, atrial flutter, and premature atrial contractions) and congestive heart failure are often observed. Eye signs include exophthalmos, lid lag, and upper lid retraction. Neuropsychiatric symptoms include agitation, anxiety, restlessness, fear, paranoia, and mood swings. Neuromuscular symptoms include fine tremor in the hands and proximal myopathy (common in the elderly). Gastrointestinal symptoms include hyperphagia, diarrhea, nausea, vomiting, and abdominal pain. Skin signs include flushed skin, hair loss, and pretibial myxedema. Apathetic hyperthyroidism is seen in the elderly, with prominent features of congestive heart failure, atrial fibrillation, and weight loss.

Diagnosis

Thyrotoxicosis is diagnosed by measuring thyroid hormone (thyroxine and triiodothyronine) and TSH levels. Measurement of free thyroid hormones instead of total serum thyroid hormones prevents changes introduced by variations in thyroxine-binding globulin levels. Pituitary and hypothalamic causes of thyrotoxicosis are very rare. Measurement of thyroid-stimulating immunoglobulin and anti-thyroperoxidase antibodies is helpful in evaluating autoimmune etiologies. A radionuclide scan is helpful in distinguishing hyperfunction of the thyroid gland from thyroiditis.

Thyroid storm should be considered in the differential diagnosis of hyperpyrexia in the emergency care setting, particularly in cancer patients with risk factors for Graves disease (e.g., bioimmunotherapy, history of irradiation of the neck or chest area) or tumors that may secrete human chorionic gonadotropin. Researchers have proposed a scoring system for thyroid storm and a set of diagnostic criteria for thyroid storm (e.g., fever, tachycardia, tachyarrhythmia, mental status changes) [63, 64].

Management

- Treatment of Graves disease includes antithyroid medications, radioactive iodine, and surgery.
- Treatment of thyroiditis primarily involves removing the causative factors and controlling the hyperadrenergic symptoms with β-blockers.
- If thyroid storm is highly likely on the basis of clinical criteria, diagnostic studies should be performed, and

therapy should be initiated immediately. In addition to support for systemic decompensation and correction of precipitating factors, acute management may involve the following:

- Propylthiouracil (100–600 mg/day) or methimazole (10–60 mg/day).
- β-Blockers, both cardioselective and noncardioselective, are important adjuncts in treating hyperthyroidism. β-Blockade provides rapid relief of hyperadrenergic symptoms and signs of thyrotoxicosis. High doses of propranolol (>160 mg/day) can inhibit peripheral conversion of T4 to T3.
- Saturated solution potassium iodide (3–5 drops) is administered orally every 8 h to block the release of thyroid hormones in patients with thyrotoxicosis. At pharmacologic concentrations (100 times the normal plasma level), iodides decrease thyroid gland activity via the Wolff-Chaikoff effect.
- Oral contrast agents also are potent inhibitors of T4-to-T3 conversion, making them ideal for treatment of severe or decompensated thyrotoxicosis. They are generally given after starting treatment with thioamide. Although physicians have used IV iodinated radiographic contrast medium to treat a case of thyroid storm, this approach is highly nephrotoxic, and its efficacy has yet to be firmly established.
- Other treatment options include corticosteroids (e.g., dexamethasone, which inhibits peripheral thyroxine conversion), colestipol, lithium, amiodarone, ipodate, iopanoic acid, and potassium perchlorate.
- Plasmapheresis and hemoperfusion are effective at removing excess thyroid hormone.

Myxedema Coma

The prevalence of hypothyroidism is 2–3 % in the general population, with a female/male ratio of 10:1. Therefore, preexisting or coexisting hypothyroidism is common in female cancer patients. Hypothyroidism may also be a complication of cancer or its treatment.

Causes

- Total or near-total thyroidectomy may be performed for a variety of oncologic reasons in the management of thyroid cancer, head and neck cancer, and thyroid metastasis. Thyroid replacement is required in this group of patients.
- Irradiation can cause primary, secondary, or tertiary hypothyroidism.
- Primary hypothyroidism is caused by thyroid cell destruction, inhibition of cell division, vascular damage, and, possibly, an immune-mediated phenomenon. Factors that increase the risk of primary hypothyroidism include delivery of a high radiation dose to the vicinity of the thyroid gland, long duration since radiotherapy, lack of shielding of the thyroid during radiotherapy, and combined irradiation and surgical treatments [65].
- Hypothyroidism after radiation therapy is related to the radiation dose, and the threshold for causing clinical hypothyroidism is about 10 Gy [62, 66].
- Chemotherapy
  - The incidence of primary hypothyroidism is increased in patients given multiple combination drug regimens [67, 68] with or without radiation [67].
  - L-Asparaginase, in addition to inhibiting synthesis of thyroid hormone-binding globulin as described above, may reversibly inhibit TSH synthesis and cause temporary hypothyroidism with decreased free T_4 levels [69].
  - Thyroid dysfunction is a recognized side effect of cytokine-based treatments. Treatment with interleukin-2 produces thyroid dysfunction in about 20–35 % of patients [70]. These patients have hypothyroidism, hyperthyroidism, or hyperthyroidism followed by hypothyroidism [71]. About 10 % of interferon-treated patients experience primary hypothyroidism [72]. Patients with antithyroid antibodies before therapy are at increased risk for cytokine-induced thyroid dysfunction.
  - Bexarotene, a retinoid X receptor-selective ligand used to treat cutaneous T-cell lymphoma, has caused secondary hypothyroidism in a dose-dependent manner [73]. In addition to suppressing transcription of TSH via a retinoid X receptor-mediated thyroid hormone-independent mechanism [74], bexarotene increases clearance of thyroid hormones via a metabolic pathway not involving deiodinase [75].
  - Sunitinib appears to have an antithyroid effect by inhibiting peroxidase activity [76] as well as inducing lymphocytic thyroiditis [77].
  - Sorafenib causes thyroid dysfunction (predominantly hypothyroidism) in about 20 % of patients, but less than 10 % of patients need thyroid hormone replacement [78].
- Using high-dose (100–1000 mCi) [^{131}I]-metaiodobenzyl guanidine to treat unresectable pheochromocytoma may result in primary hypothyroidism.

Symptoms

Hypothyroid symptoms are nonspecific and include fatigue, general weakness, cold intolerance, depression, weight gain, joint aches, constipation, dry skin, and menstrual irregularities. Signs of moderate to severe hypothyroidism include hypertension, bradycardia, coarse hair, periorbital edema, carpal tunnel syndrome, and delayed relaxation of the tendon

reflexes. Unusual signs of severe hypothyroidism include megacolon, cardiomegaly, and congestive heart failure.

Myxedema coma may occur in patients with hypothyroidism and become life threatening as the severity of hypothermia, bradycardia, and hypoventilation increases. Pericardial, pleural, and peritoneal effusions are often present. An ileus is present in about two thirds of cases. Central nervous system symptoms in these patients include seizures, stupor, and coma.

Diagnosis

The diagnosis of hypothyroidism is confirmed using thyroid function tests. In most cases, TSH and free T4 testing is adequate for initial evaluation. In patients with myxedema coma, serum thyroid hormone levels are usually very low, whereas the TSH level is quite high (except in cases of secondary hypothyroidism).

Anemia, hyponatremia, hypoglycemia, hypothermia, and hypotension can occur. Arterial blood gas measurement usually reveals retention of carbon dioxide and hypoxemia. An EKG often shows sinus bradycardia, various types and degrees of heart block, low voltage, and T-wave flattening.

Management

Recognition of hypothyroidism may be difficult in the emergency care setting. Thyroid function test results typically are not available expeditiously. The emergency physician's responsibility is to consider the diagnosis of hypothyroidism, provide acute care, and order the appropriate thyroid function tests to expedite diagnosis. Myxedema coma occurs most often in elderly hypothyroidism patients with a superimposed precipitating event, which must also be treated.

Rapid clinical diagnosis with early therapy may be lifesaving. In critically ill patients, if myxedema coma is highly suspected, 0.5 mg of levothyroxine should be given intravenously followed by 0.025–0.100 mg of levothyroxine a day. Other supportive measures, such as correction of hypothermia using slow rewarming and ventilatory and circulatory support, are critical.

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Pituitary Apoplexy

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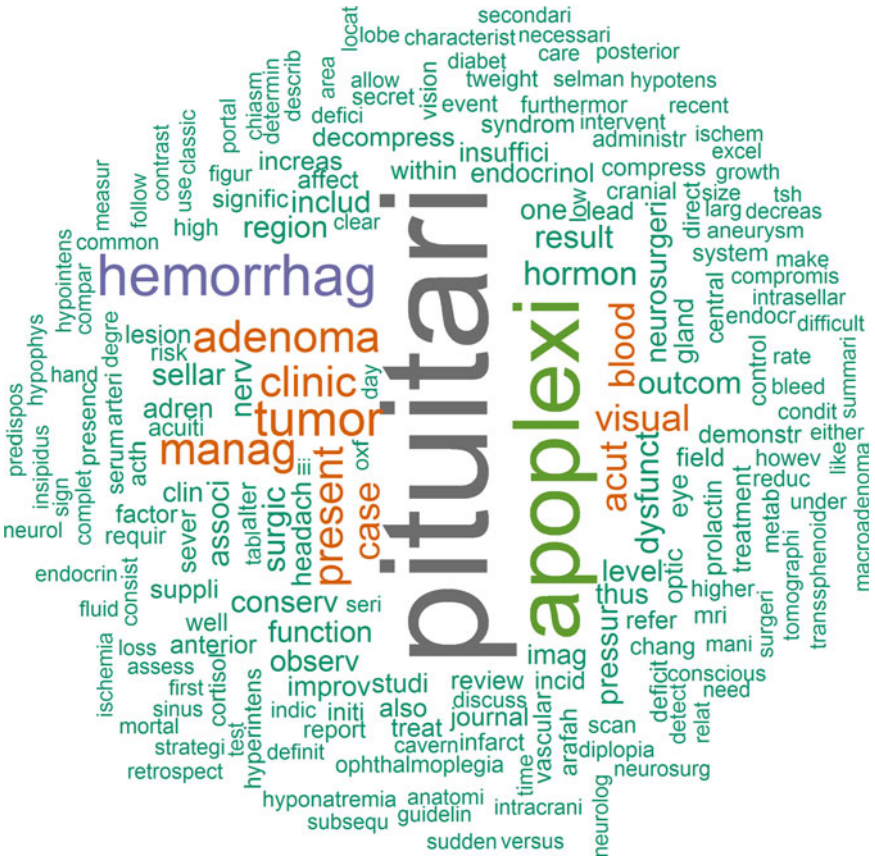

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Definition

Pituitary tumor apoplexy is a clinical syndrome, the hallmarks of which include headache, ophthalmoplegia, and altered level of consciousness. Hemorrhagic infarction of a pituitary tumor leading to rapid expansion of the contents of the sellar region and subsequent acute pituitary gland dysfunction is the underlying etiology for this syndrome. The first case of pituitary apoplexy was described by Pierce Bailey in 1898 [1]. However, the term "pituitary apoplexy" was first introduced by Brougham et al. in 1950 in a case report describing five cases of hemorrhagic infarction of pituitary adenomas [2]. The word apoplexy derives from Greek (*apoplēssein* = to strike down, disable) and means in modern parlance the sudden onset of a neurological deficit, as when a stroke, in a setting of bleeding, results in abrupt loss of function. While nowadays we refer to such bleeding as hemorrhagic stroke, the term apoplexy has remained in use to describe the hemorrhage in the pituitary region. Such hemorrhage in most cases occurs when a pituitary tumor is present, and as such, some authors argue that this condition would be more accurately described as pituitary tumor apoplexy [3].

Hemorrhage into a pituitary adenoma with resulting clinical symptoms is also called classical pituitary apoplexy. Spontaneous silent hemorrhage can occur in up to 25 % of pituitary adenomas, and when discovered incidentally during routine imaging or histopathologic examinations, it is referred to as subclinical pituitary apoplexy [4, 5]. Pituitary apoplexy has to be distinguished from hemorrhage into a Rathke cleft cyst, a very rare event whose clinical presentation is identical to pituitary tumor apoplexy syndrome [6, 7]. Furthermore, infarction of pituitary gland during a prolonged or severe period of hypotension is well described in pregnancy and post-partum and is referred to as Sheehan's syndrome [8]. The following discussion is dedicated to the diagnosis, management, and outcomes of classical pituitary apoplexy.

Anatomy and Physiology Review

To understand the clinical presentation of pituitary apoplexy, it is essential to review the contents of the sellar region and how the apoplectic event disturbs them (Fig. 1). Its clinical symptoms can be associated with the sudden onset of one (or more) of three events: the presence of intracranial blood, acute onset of pituitary gland dysfunction, and/or cranial nerve dysfunction.

The presence of acute intracranial blood is a major source of headache. While in most cases of pituitary apoplexy the blood is contained within the tumor, there can be subarachnoid extension of the hemorrhage. Thus, ancillary tests are necessary to rule out a vascular cause of subarachnoid blood such as an aneurysm or a vascular malformation.

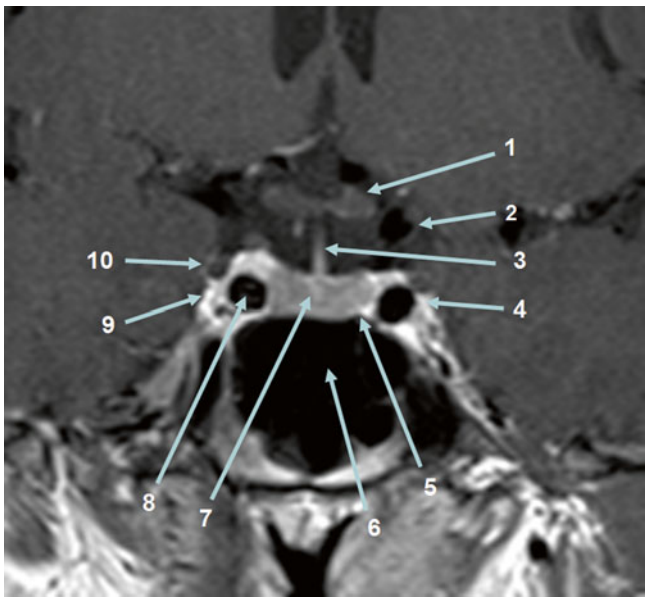

Fig. 1 Post-contrast MRI (coronal, T1-weighted image) showing the anatomical structures in the sella and parasellar region. (*1*) Optic nerve, (*2*) suprasellar internal carotid artery, (*3*) pituitary stalk, (*4*) lateral wall of cavernous sinus, (*5*) medial wall of cavernous sinus, (*6*) sphenoid sinus, (*7*) pituitary gland, (*8*) intracavernous carotid artery, (*9*) abducens nerve (VI nerve), and (*10*) oculomotor nerve (III nerve)

The pituitary gland is located within the sella turcica. It comprises two parts: an anterior lobe that produces six hormones, including growth hormone (GH), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and prolactin; and a posterior lobe, the site of delivery of oxytocin and vasopressin produced in the hypothalamus. Acute hemorrhage into the anterior pituitary can result in sudden cessation of secretion of one or more of these hormones. Of the above hormones, acute deficiency of ACTH is of upmost importance as it results in a blunted cortisol response to stress, which if severe enough can be associated with profound hypotension and hyponatremia. Although dysfunction of the posterior pituitary causes alteration of vasopressin secretion leading to central diabetes insipidus and associated hypernatremia, it is rarely observed clinically. Since almost all pituitary adenomas arise in the anterior lobe, they mainly affect its function. Prolactin, on the other hand, is secreted by the anterior lobe in response to pituitary stalk compression or by the adenoma itself. While acute alterations of serum prolactin level do not affect the clinical picture, initial and subsequent prolactin levels have prognostic significance and thus should be measured.

On either side of the pituitary gland are located the two cavernous sinuses. These venous structures enclose the internal carotid arteries as well as cranial nerves III, IV, and VI. The latter control eye movements, and dysfunction of any of these nerves results in abnormal eye movements on directed

gaze with the subjective report of diplopia. Finally, the optic nerves and chiasm are located in the suprasellar region, and with sufficiently large lesions, compromise of visual acuity and/or field may occur.

Clinical Presentation

Familiarity with the anatomical structures of the sellar region allows one to understand the symptoms that patients may experience with hemorrhage in that area. The spectrum of presentation of pituitary apoplexy correlates with the size of the hemorrhage and degree of injury to the surrounding structures. While small hemorrhages may be detected radiographically in otherwise asymptomatic patients, a condition referred to as subclinical apoplexy, large hemorrhages can present with an acute alteration of consciousness, cardiovascular collapse, and obtundation and can be life threatening. Between these two extremes lies a spectrum or constellation of clinical signs that can include headache, changes in vision including diplopia, and various degrees of pituitary hypofunction (Fig. 2). A given presentation may include one or many of the above signs and symptoms. The most common presenting clinical symptoms are summarized in Table 1.

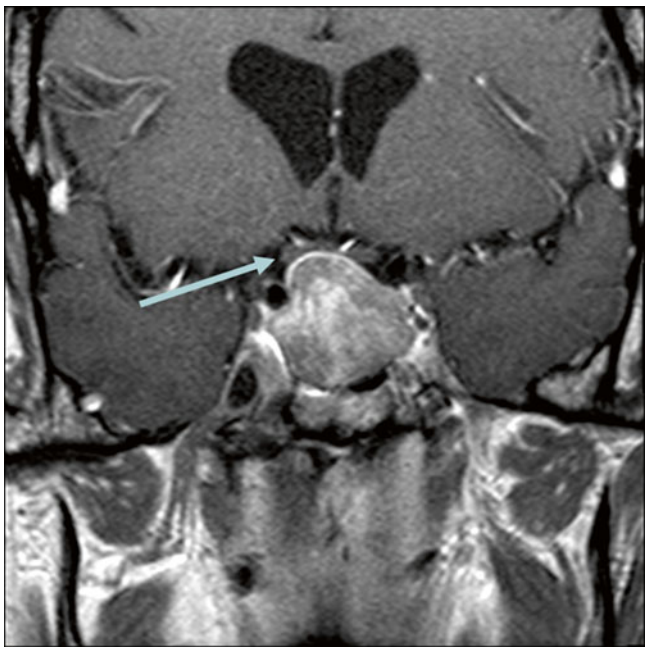

Fig. 2 Pituitary macroadenoma with intratumoral hemorrhage (=pituitary apoplexy). This tumor has expanded into the suprasellar space and compresses the optic nerve and chiasm (arrow), with resulting onset of severe headache and a temporal visual field deficit. The patient also has profound hypopituitarism. Surgical removal of this hormonally nonfunctional tumor is indicated

Headache

Headache is the most common symptom in pituitary apoplexy and is observed in 95 % of patients [9]. The etiology of headache is likely multifactorial. The rapid increase in pressure within the intrasellar compartment as a result of the hemorrhage causes stretching of the dura lining the sella and the resulting headache. Leakage of blood from the hemorrhagic tumor into the subarachnoid space can contribute as well. Vomiting is observed in 70 % of patients presenting with a headache and can stem from the increased intracranial pressure or from pituitary dysfunction [10].

Visual Disturbance

Visual symptoms in cases of pituitary apoplexy include either optic nerve dysfunction or diplopia. The optic apparatus, which includes the optic nerves, optic chiasm, and optic tracts, is located in the suprasellar compartment and can be subject to direct pressure from the expanding hematoma. This most commonly presents as bitemporal visual field restriction due to pressure against the undersurface of the chiasm. Direct pressure on one or both nerves or tracts could also result in changes in visual acuity, culminating in a central or junctional scotoma. The latter results in a superior temporal defect in one eye and decreased central vision in the other eye as a result of compression of anterior chiasm, the site of anteriorly looping fibers of Wilbrand's knee from the contralateral nasal retina.

Diplopia is another very sensitive presenting symptom of pituitary apoplexy. Cranial nerves that control eye movements, namely, III, IV, and VI, run within the cavernous sinus on either side of the sella and are highly susceptible to compression (Fig. 1). Cranial nerve III dysfunction is observed most frequently and can present as ptosis, a dilated pupil, and an eye that looks down and out with inability to adduct. Cranial nerve VI innervates the lateral rectus muscle of the eye and controls eye abduction; and thus, dysfunction results in the inability of the eye to look outwards.

Table 1 Common presenting clinical features of pituitary apoplexy

Clinical symptom
Headache
Nausea and vomiting
Decreased visual acuity
Visual field deficit
Diplopia
Cranial nerve palsy (III, IV, or VI)
Altered mental status
Seizure
Collapse/shock
Coma

Pituitary Dysfunction

Up to 80 % of patients with pituitary apoplexy present with pituitary dysfunction [9, 11–13]. While any of the pituitary hormones can be affected, acute decrease in ACTH secretion and the subsequent hypocortisolism is the most clinically significant. Acute adrenal insufficiency can precipitate hypotension (shock), but may also present with hyponatremia, hypoglycemia, nausea, vomiting, obtundation, and coma [14].

Serum prolactin levels at presentation may reflect the degree of pituitary compression and thus give an indirect albeit imperfect indication of intrasellar pressure. Low prolactin levels indicate a high degree of pituitary compression and less chance of recovery after a decompressive procedure [15].

While other pituitary hormones may be affected as a result of pituitary hemorrhage, the reported incidence of these abnormalities varies greatly. While ACTH dysfunction is most clinically important, it is crucial to identify dysfunction in other hormonal axes as well. Other hormones can also be affected with growth hormone deficit seen in 88 % of cases, ACTH dysfunction in 66 %, TSH abnormality in 42 %, and loss of FSH and LH in 85 % of cases of pituitary apoplexy [16, 17].

Incidence and Predisposing Factors

The true incidence of pituitary apoplexy is difficult to estimate, as many cases are asymptomatic. The reported incidence for symptomatic hemorrhage ranges from 2 % to 7 % of all pituitary adenomas [9, 11, 12]. In 80 % of patients with pituitary apoplexy, the initial diagnosis of pituitary apoplexy is made at the time the tumor is first discovered [18]. There is a slight male predominance for hemorrhage into the pituitary tumor, and most patients present in their fifth or sixth decade [13, 19, 20].

It has been estimated that pituitary adenomas are five times more likely to bleed compared to other types of tumors [21]. Several characteristics of pituitary adenoma have been identified that put patients at this increased risk of apoplexy. Gender, age, and tumor type have revealed no increased risk of apoplexy compared to matched controls [17]. An increased risk of hemorrhage is, however, observed in patients with a history of hypertension [9, 13], usage of anticoagulants or antithrombotic medications [22, 23], estrogen therapy [24], or dopamine agonists [12, 25] or dynamic testing of pituitary function [26, 27]. One factor more consistently associated with a higher incidence of apoplexy is tumor size, and macroadenomas are much more likely to present with intratumoral hemorrhage [11, 28–31]. Furthermore, some series have shown that in many cases there is an associated area of infarction within the tumor; thus it is not clear whether the initial event is infarction or hemorrhage [32, 33].

Several hypotheses have been put forward to explain what causes ischemia and hemorrhage in pituitary adenomas. One theory postulates that as a tumor enlarges, it compresses its own blood supply, eventually leading to ischemia and hemorrhage. On the other hand, tumor enlargement may be associated with outstripping its own blood supply, thus leading to ischemic necrosis. Higher incidence of hemorrhage into an ischemic or necrotic area within a pituitary adenoma may relate to the unique vascular supply of these tumors [34].

The unique blood supply to the pituitary gland has been implicated in predisposing these tumors to hemorrhage. The pituitary gland is supplied by the hypophyseal-portal system. Blood supply to the anterior pituitary comes from the superior hypophyseal arteries, branches of the internal carotid artery that travel along the pituitary stalk and form a rich vascular portal system. The posterior pituitary receives its blood supply from the inferior hypophyseal arteries, which are terminal branches of the meningohypophyseal trunk of the internal carotid artery. There are many anastomoses between the hypophyseal and the portal vascular networks [35]. Pituitary adenomas receive their blood supply from the portal system, as well as directly from the hypophyseal vessels. This exposes the pituitary adenoma to systemic blood pressures, and the presence of the rich and complex network of the portal system increases the risk of bleeding by fivefold compared to other tumors [10].

Inherent tumor characteristics have also been implicated in predisposing pituitary adenomas to ischemia and apoplexy [36]. Pituitary adenomas are highly active metabolic tumors that require a continuous supply of glucose and demonstrate a high glucose uptake in ^{18}F-fluorodeoxyglucose-PET studies [37]. Interruption of glucose supply results in rapid adenoma cell death and may lead to infarction [36]. Furthermore, pituitary adenomas have a low level of secretion of angiogenic factors such as vascular endothelial growth factor (VEGF) [38]; thus it is not surprising that they have a reduced vessel density on histological examination clinically observed as decreased contrast uptake on imaging studies [39]. Finally, perfusion studies have demonstrated very low blood flow in pituitary adenomas [40] likely as a consequence of the high intratumoral pressure that is typical for these tumors [41] thus predisposing pituitary adenomas to a higher risk of developing ischemia. In summary, the combination of the microvascular architecture of pituitary adenomas with the resultant low blood flow and the inherently high metabolic demand of adenoma cells makes these tumors very susceptible to ischemic injury during times of systemic blood pressure fluctuation and thus to development of intratumoral pituitary hemorrhage and clinical apoplexy.

Pituitary Apoplexy Workup

Differential Diagnosis

In a patient presenting with a severe headache, a number of other conditions should be considered and ruled out besides pituitary apoplexy. The differential diagnosis includes subarachnoid hemorrhage secondary to a ruptured aneurysm, meningitis, and hydrocephalus. When visual loss and ophthalmoplegia point to the sellar region, cavernous sinus thrombosis, brain abscess, or a growing cerebral aneurysm should be considered. Other clinical conditions to be considered as part of the differential diagnosis for pituitary apoplexy include temporal arteritis, ophthalmoplegic migraine, hypertensive encephalopathy, basilar artery occlusion, and brainstem stroke or hemorrhage [17, 34].

Diagnostic Imaging

Visualization of the hemorrhage within the sellar region is necessary to make the definitive diagnosis of pituitary apoplexy. Computed tomography (CT) of the brain is a good initial study for detecting acute blood in the sellar region (Fig. 3) [42]. A hyperdense lesion in the sellar region on a non-contrast CT scan is highly suggestive of hemorrhage within the first 3 days after the event. Although this modality of imaging is sensitive for hemorrhage, it is not necessarily specific. As intracranial aneurysms and calcifications associated with craniopharyngioma are also hyperdense on CT scans, it may be difficult to make a definitive diagnosis [34]. To characterize the lesion as well as the underlying pathology, magnetic resonance imaging (MRI) should be obtained [43].

The MRI T2-weighted gradient echo sequence is most sensitive for blood products and may detect even small hemorrhages. It is not, however, accurate at estimating the size or age of the hemorrhage. By surveying the corresponding T1- and T2-weighted sequences, it is possible to determine the age of the hemorrhage. The changes in signal intensity of the hemorrhage over time on T1- and T2-weighted MRI scans are summarized in Table 2. Furthermore, MRI allows better anatomical visualization of the pituitary gland and may help delineate the underlying tumor, as well as define the relationship of the tumor and the hemorrhage to the optic apparatus. It can also identify extension into either cavernous sinus and rule in or rule out an aneurysm [43, 44].

Laboratory Investigations

Fluid and electrolyte disturbance is frequently observed in patients with pituitary apoplexy. Hemorrhage into the pituitary adenoma may affect the function of the pituitary gland itself. In fact, reduced ACTH secretion and the resulting hypocortisolemia are observed in 80 % of cases [9, 13, 45]. Acute adrenal insufficiency may lead to hyponatremia and, in severe cases, to cardiovascular collapse. Therefore, determination of serum electrolyte levels and fluid balance status is critical to avoid missing adrenal crisis in patients with pituitary apoplexy. Symptoms of acute adrenal insufficiency include vomiting, abdominal pain, myalgia, joint pains, and severe hypotension, leading to hypovolemic shock [14].

Other pituitary hormones can also be affected. TSH deficiency is noted in 50 % of cases, and if preexisting, it may lead to increased morbidity and mortality of pituitary apoplexy in the context of concurrent ACTH deficiency. Disturbance of the gonadotropin axis is observed in 75 % of cases [9, 13, 45]. Prolactin levels should be measured, as lower levels of this hormone are predictive of the degree of pituitary compromise and of a higher likelihood of need for pituitary hormone replacement in the future [15].

Alteration of anterior pituitary function is often observed in cases of pituitary apoplexy. In contrast, function of the posterior pituitary gland is rarely affected. While transient hyponatremia in the acute period is frequently attributed to SIADH, permanent central DI is observed in only 3 % of cases [46, 47].

In summary, a patient with suspected pituitary apoplexy requires careful assessment of fluid and electrolyte balance. In addition, a complete blood cell count with differential should be obtained to assess for meningitis and for states of coagulopathy secondary to platelet dysfunction. Finally, a panel of hormone studies should be obtained to diagnose and monitor pituitary dysfunction. These should include random serum cortisol, free T4, TSH, IGF-1, and prolactin levels.

Emergency Department Management

Initial management of pituitary apoplexy in the emergency department should focus on supporting the patient's hemodynamic status and treating adrenal insufficiency. The major source of morbidity and mortality associated with pituitary apoplexy is acute adrenal insufficiency from which early series of patients reported mortality close to 50 % [2, 34]. However, in recent years there has been quite an improvement in outcomes associated with treatment of this condition largely attributed to improved ability to diagnose pituitary apoplexy with better imaging technology and to recognition and appropriate management of adrenal insufficiency.

The integral part of the initial treatment of pituitary apoplexy and the associated cortisol deficiency is administration of glucocorticoids. After drawing blood for a baseline measurement of serum cortisol, a "stress" dose of 100 mg of hydrocortisone is administered intravenously in patients with suspected adrenal insufficiency. This is followed by a

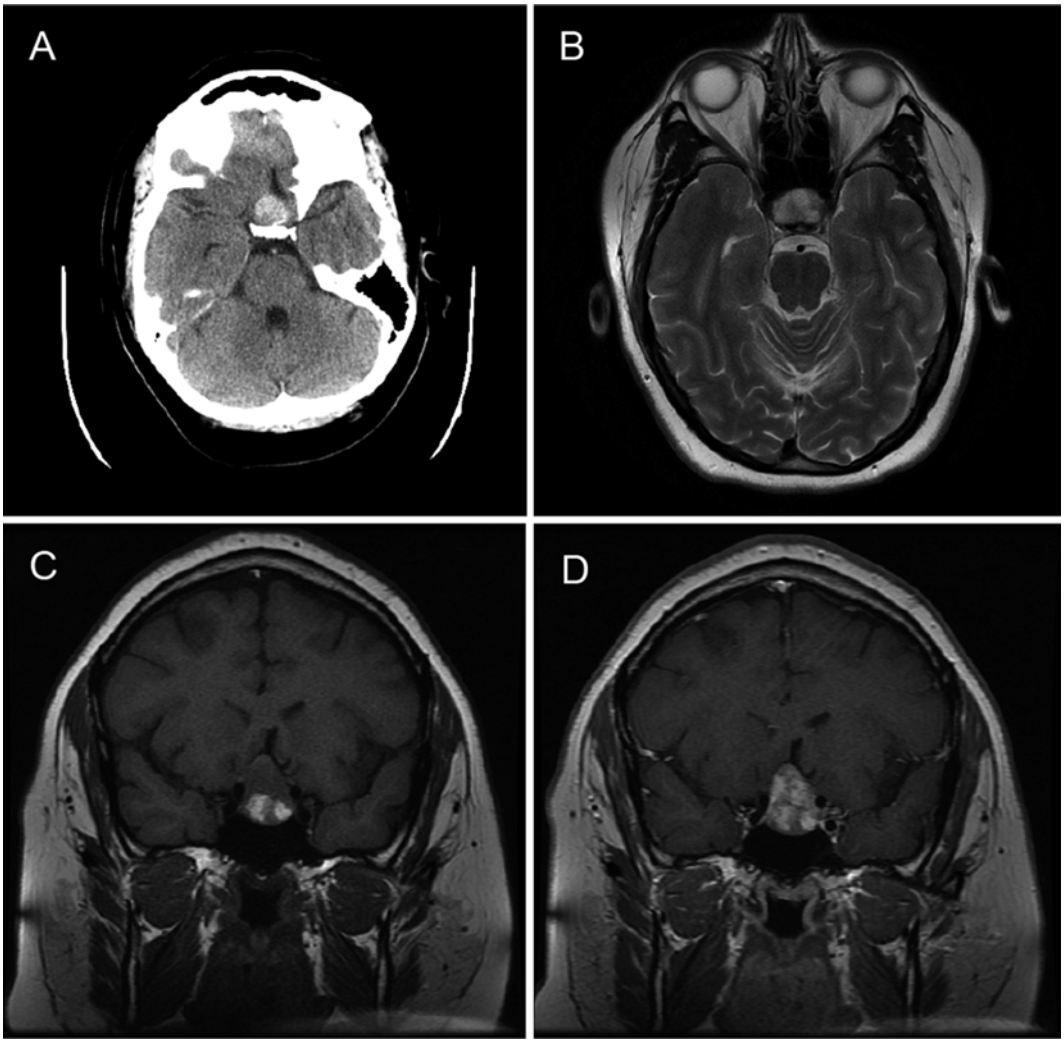

Fig. 3 Representative images for a patient with pituitary apoplexy. Non-contrast CT axial image (**a**) demonstrates a hyperdense lesion in the sellar region consistent with recent hemorrhage. The T2-weighted axial MRI image (**b**) demonstrates an expansile hyperintense lesion in the sellar region. The T1-weighted coronal slices through the sellar region (**c**, **d**) demonstrate a 2.5-cm lesion with an inferior hyperintense component consistent with subacute blood (**c**). The superior component of the tumor heterogeneously enhances with contrast administration (**d**), an appearance consistent with an underlying pituitary adenoma

Table 2 Typical appearance of blood on T1- and T2-weighted MRI images

Stage of hemorrhage	Time	T1	T2
Hyperacute	<24 h	Isointense	Hyperintense
Acute	1–3 days	Isointense	Hypointense
Early subacute	3–7 days	Hyperintense	Hypointense
Late subacute	7–14 days	Hyperintense	Hyperintense
Chronic	>14 days	Hypointense	Hypointense

short course of high-dose hydrocortisone (50 mg intravenously at 6-h intervals) with a subsequent slow taper based on the patient's clinical response. Patients are typically discharged on a maintenance dose of hydrocortisone (15–20 mg daily in divided doses) [14]. In addition to treating the adrenal insufficiency, in the acute setting glucocorticoids reduce the swelling associated with the underlying tumor and hemorrhage. Thus they minimize the pressure in the sellar region and may lead to symptom improvement.

Intravenous fluid administration to maintain euvolemia and support blood pressure should be instituted. To minimize the amount of edema associated with the hemorrhage, normal saline or Ringer's lactate should be used. If the patient presents with hyponatremia, attention should be paid to the rate of sodium correction to ensure that it increases by 12 mEq/L or less in 24 h [14]. Gradual correction helps to minimize the risk of central pontine myelinolysis, a devastating complication of sudden large shifts in serum sodium levels.

Neurosurgical Management

There are no clear guidelines for definitive management of pituitary apoplexy. In a subset of patients managed conservatively, it is difficult to predict who will ultimately require a surgical intervention. No randomized controlled studies are available to provide evidence of differences in outcomes in conservative versus surgically treated patients. Thus, the question remains unanswered whether operative or nonoperative management is best.

Traditionally, pituitary apoplexy has been treated surgically. In patients presenting with acute vision loss, worsening visual field deficit, or ophthalmoplegia, surgical intervention is indicated (Fig. 2) [9, 44, 48]. The "pituitary apoplexy score" (PAS) introduced in 2011 can be used for monitoring patients for signs of deterioration [44]. It incorporates assessment of level of consciousness, visual acuity, visual field deficits, and the presence of ocular nerve palsies. A PAS of four or greater, or an increasing score while the patient is under observation, may indicate the need for a surgical intervention [44, 49]. Furthermore, surgery should be offered to patients who have no improvement in their symptoms after 1 week of steroid administration [11, 50].

Recent retrospective case series demonstrate no difference in the visual and endocrine outcomes between patients treated conservatively and those who underwent surgery and thus make a case for conservative management of pituitary apoplexy [13, 45, 51]. These studies, however, suffer from a significant selection bias and do not have appropriately matched controls, since in most studies patients with larger tumors or more severe symptomatology undergo surgical decompression. One study looked at the imaging characteristics of pituitary adenoma, including ischemic and hemorrhagic tissue, in an attempt to predict the likelihood of success of conservative management [50]. The presence of a single larger hypodense area within the tumor on a CT scan and early radiographic evidence of tumor involution may be associated with a higher likelihood of clinical resolution of pituitary apoplexy [50]. Regardless of the management strategy chosen, the outcome after treating pituitary apoplexy is excellent, as demonstrated in a recent retrospective cases series of 87 patients [48]. While 20 % of patients were treated conservatively, there were no significant differences in outcome metrics between the two groups. Moreover, among those patients, one-third presented with a significant alteration of level of consciousness, but had an excellent recovery with conservative management [48].

One strong argument for conservative treatment can be made for hemorrhage into prolactinoma given that medical treatment is the standard of care for that tumor subtype at present. Dopamine agonists are effective at reducing prolactin levels and at reducing the size of the tumor [52]. However, if such a patient presents with worsening vision caused more by the hemorrhage than the tumor volume per se, it is reasonable to consider prompt transsphenoidal decompression of the optic apparatus.

The endoscopic or microsurgical transsphenoidal approach is used most often for decompression of hemorrhage into pituitary adenoma [34, 53]. This surgery confers low morbidity and mortality for the patient and provides adequate decompression of the neurological structures of the sellar region. Furthermore, because this approach for the most part allows access to the adenoma itself, it allows the surgeon to address the primary lesion in addition to the hemorrhage.

In summary, no clear guidelines exist to determine the optimal management strategy for pituitary apoplexy. A multidisciplinary team involving an endocrinologist, neurosurgeon, and ophthalmologist is necessary to determine the optimal direction of care. Patients with minor symptoms of pituitary apoplexy, or those who have clinical improvement after the apoplectic episode, can be treated conservatively with excellent recovery. On the other hand, patients with visual compromise, significant visual field deficits, and ophthalmoplegia require surgical decompression of the sellar lesion via a transsphenoidal approach.

Outcomes and Follow-Up

The goal of treatment of pituitary apoplexy is to improve compromised visual acuity, reduce visual field defect, and enhance pituitary function. Loss of vision resulting from pressure on the optic nerves has traditionally been thought to be difficult to restore. Nevertheless, if surgical decompression is undertaken within 1 week of the event, there is significant improvement in visual acuity [9, 54]. The success rate is much lower when the surgical intervention is delayed, implying that prolonged compression of optic nerves ultimately results in permanent nerve damage.

In patients who present with minor visual symptoms such as a small field cut, conservative management demonstrated a comparable rate of symptom improvement thus suggesting that conservative management with glucocorticoids is an alternative strategy [45]. The direct comparison of surgical versus medical management in pituitary apoplexy is complicated due to a lack of appropriately matched controls in the studies.

In contrast to the improvement in the visual symptoms, pituitary function does not recover as well after apoplexy. Nevertheless, 50 % of patients will have some improvement in pituitary function [15, 55], but 80 % of patients will require long-term supplementation of at least one hormone, usually cortisol or thyroxine [9, 45, 51]. Overall, testosterone

replacement is needed in 64 % of patients [11]. On the other hand, central diabetes insipidus is relatively uncommon, and DDAVP replacement is required only in about 20 % of patients. Interestingly, the rate of DDAVP requirement in the conservatively managed group of patients is low, while surgical decompression is associated with a higher rate of diabetes insipidus, observed in 23 % of patients treated surgically [48].

Summary

Pituitary apoplexy is a clinical syndrome associated with pituitary tumor hemorrhage that may result in visual acuity and field compromise, ophthalmoplegia, and pituitary dysfunction. Initial investigations should include a CT scan to detect the presence of acute blood and an MRI scan to delineate the size and extent of the adenoma and the hemorrhage. A complete endocrine work-up should be performed on admission, and acute cortisol deficiency should be corrected if present. Further management of a patient with pituitary apoplexy should include a multidisciplinary team consisting of a neurosurgeon, endocrinologist, and ophthalmologist, and a decision with respect to surgical versus conservative management should be made. Overall the outcomes of pituitary apoplexy are excellent.

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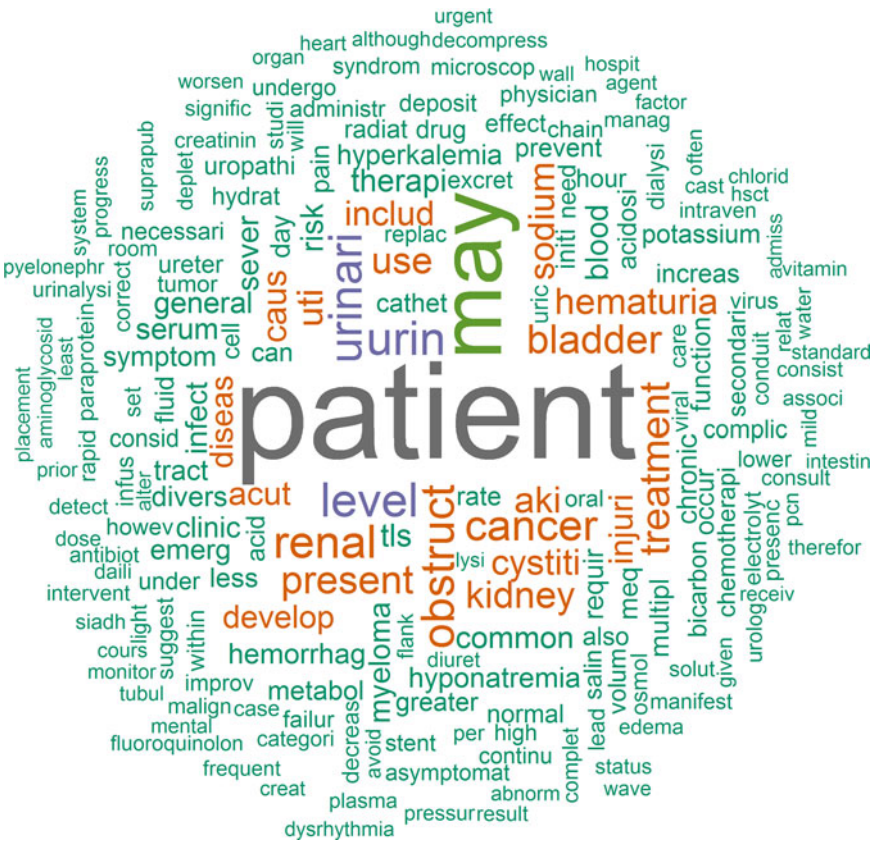
Nephro-urologic Emergencies in Patients with Cancer

Amit Lahoti



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Chapter Overview

Cancer patients commonly develop renal and urologic emergencies that require a multidisciplinary approach by the nephrologist, urologist, interventional radiologist, oncologist, and emergency department physician. Patients that develop acute kidney injury as a complication of cancer treatment have a higher mortality rate. Nephrology consultation is often needed to provide renal replacement therapy until kidney function recovers. Among patients with newly diagnosed multiple myeloma, more than one-half will present with acute kidney injury, and 10 % of them need dialysis. Renal function in these patients may rapidly improve with treatment of the myeloma. Emergency department physicians often treat cancer patients with severe metabolic derangements that require immediate interventions to prevent cardiac dysrhythmias or acute kidney injury. The presentation of hematuria is varied and can range from benign microscopic hematuria to severe hemorrhagic shock. Obstructive uropathy may occur anywhere along the urinary tract and generally requires urgent intervention by urology or radiology to decompress the renal collecting system.

Introduction

The kidneys are important in regulating electrolyte and acid-base levels, eliminating waste products and fluid and producing enzymes and hormones. Compared to other organs on a per-gram basis, the kidneys receive the highest amount of blood supply from the heart. Given their high vascularity, the kidneys are vulnerable to injury from toxins or drugs circulating through the blood. Obstruction of the lower urinary tract (e.g., ureters, bladder) may lead to obstructive nephropathy. Radiation may cause inflammation or fibrosis of the kidneys, ureters, or bladder months to years after therapy is complete. This chapter emphasizes some of the more common nephro-urologic problems that emergency department physicians encounter during treatment of cancer.

Acute Kidney Injury in Cancer Patients

Acute kidney injury (AKI) occurs in 4–7 % of all hospitalized patients and 13–42 % of critically ill patients with cancer. Up to 60 % of critically ill patients with cancer who develop AKI must undergo renal replacement therapy [1]. Development of AKI correlates with increased hospital length of stay, health care costs, and mortality rates [2]. AKI may also increase the toxic effects of chemotherapy, exclude patients from clinical trials, and limit further cancer treatment. The causes of AKI are generally classified into three main categories: prerenal azotemia, intrinsic renal disease, and postrenal obstruction (Table 1).

Table 1 Common causes of AKI in patients with cancer

Prerenal azotemia
Volume depletion
Nausea, vomiting, diarrhea
Decreased oral intake owing to mucositis (5-fluorouracil, methotrexate, taxanes)
Polyuria caused by hyperglycemia (steroids) or diabetes insipidus (pituitary tumor)
"Third spacing" (hypoalbuminemia, liver or peritoneal metastases, interleukin-2)
Insensible loss of fluid from skin lesions (mycosis fungoides)
Hemodynamic mediated
Sepsis
Renal arteriolar vasoconstriction (NSAIDs, calcineurin inhibitors, hypercalcemia)
Congestive heart failure
Hepatorenal syndrome/hepatic sinusoidal obstruction syndrome
Budd-Chiari syndrome
Intrahepatic inferior vena cava compression or thrombosis caused by hepatomegaly or a tumor
IV iodinated contrast agent
Abdominal compartment syndrome
Intrinsic renal disease
Acute tubular necrosis
Chemotherapy (cisplatin, ifosfamide)
Anti-infectives (amphotericin B, foscarnet, cidofovir, aminoglycosides, vancomycin)
Bisphosphonates
Sepsis
Prolonged prerenal azotemia
Allergic interstitial nephritis (penicillins, cephalosporins, fluoroquinolones, NSAIDs)
Crystal nephropathy (methotrexate, acyclovir, ciprofloxacin, sulfonamides, rifampin)
Osmotic nephrosis (IV immunoglobulin, mannitol, starch)
Thrombotic microangiopathy (post-HSCT, gemcitabine, prior radiation therapy)
Myeloma-related kidney disease
Postrenal obstruction
Bladder outlet obstruction (malignancy of the cervix, prostate, bladder, or uterus)
Retroperitoneal disease (metastasis, lymphadenopathy, fibrosis)
Hemorrhagic cystitis (cyclophosphamide, BK virus)
Ureteral strictures (prior radiation therapy, BK virus)

A standard definition of AKI has not been available until recently, which made research in this area difficult. Within the last decade, the RIFLE criteria for acute kidney injury were developed composed of the *r*isk, *i*njury, *f*ailure, *l*oss, and *e*nd-stage renal disease categories (Table 2) [3]. The risk, injury, and failure categories correspond to progressive levels of AKI based on change in serum creatinine and urine output. The loss and end-stage renal disease categories define patients needing dialysis for more than 4 weeks and 3 months, respectively.

Table 2 RIFLE criteria for AKI

RIFLE stage	Increase in creatinine level	Decrease in urine output
Risk	≥50 % from baseline or 0.3 mg/dL	<0.5 mL/kg/h × 6 h
Injury	≥100 % from baseline	<0.5 mL/kg/h × 12 h
Failure	≥200 % from baseline or need for dialysis	<0.3 mL/kg/h × 24 h or anuria × 12 h
Loss	Persistent AKI >4 weeks	
End-stage renal disease	Loss of renal function >3 months	

Numerous studies in varying populations have validated the RIFLE criteria as a prognostic marker for AKI. In a study of critically ill patients with cancer at our institution, more than 12 % of patients with a baseline creatinine level less than 1.5 mg/dL upon admission to the intensive care unit developed AKI. By multivariate analysis, the risk, injury, and failure categories of AKI were associated with a 1.3-, 3.0-, and 14.0-fold increase in risk of death, respectively, within 60 days after intensive care unit admission [4]. In another study, patients with acute leukemia who developed AKI had a progressive increase in mortality rate (3.8 %, 13.6 %, 19.6 %, and 61.7 % for the no-AKI, risk, injury, and failure categories, respectively) [5]. Relatively small increases in serum creatinine level correlate with increased mortality rates. Therefore, it is crucial for physicians to identify and treat early-stage AKI (i.e., the risk category in the RIFLE criteria) to prevent worsening renal injury and the need for renal replacement therapy.

A brief clinical exam and optimization of hemodynamics are necessary for patients presenting with AKI upon arrival to the emergency center. Volume depletion can manifest by orthostatic hypotension, tachycardia, poor skin turgor, dry mucous membranes, and low central venous pressure. Intravenous (IV) hydration with colloid or crystalloid solution should be administered until the patient is able to maintain a mean arterial pressure greater than 65 mmHg. Patients with prerenal azotemia may have a blood urea nitrogen-serum creatinine ratio greater than 20, a fractional excretion of sodium less than 1 %, a urine sodium level less than 20 mEq/L, and the presence of hyaline casts in urinalysis. A fractional excretion of sodium greater than 2 %, a urine sodium level greater than 40 mEq/L, and the presence of coarse granular casts in urinalysis are more suggestive of acute tubular necrosis. Patients with severe bladder outlet obstruction may have suprapubic pain and a palpable bladder. The use of a portable bladder scanner may quickly confirm obstruction by measuring an elevated postvoid residual urine volume (greater than 50–100 mL). Renal ultrasonography is sensitive in detecting hydronephrosis, although this characteristic finding of urinary tract obstruction may not manifest in patients with significant retroperitoneal disease.

There is much controversy as to the optimal solution for IV resuscitation of the patient with AKI, especially in the setting of sepsis. Colloid solutions such as IV albumin and starch have not proven to be more effective than crystalloid solutions and entail a significant cost disadvantage [6, 7]. Intravenous starch is directly injurious to the kidney by causing osmotic nephrosis of the renal tubules; thus, in general, its use should be avoided in patients with AKI. In addition, albumin and starch leak out of the intravascular compartment within hours after administration, thereby potentially worsening peripheral edema. We generally prefer using crystalloid solutions such as isotonic saline (0.9 % saline) for volume resuscitation. Interestingly, animal studies have demonstrated vasoconstriction of the renal arteries from chloride-containing solutions, which may lead to worsening renal function. However, low-chloride crystalloid fluids such as Plasma-Lyte or lactated Ringer's solution have not been shown to be consistently superior to normal saline in clinical outcomes. Early goal-directed therapy consisting of IV fluid resuscitation, transfusion to keep the hematocrit >30 %, inotropes, and vasopressor support should be considered in patients with sepsis. Continuous infusion of norepinephrine (2–12 μg/min) or vasopressin (0.01–0.04 U/min) is generally used if fluid resuscitation alone is not able to maintain a target mean arterial pressure of 65 mmHg. Placement of a Foley catheter should be attempted if the patient has signs of bladder outlet obstruction or urinary retention. Emergent placement of a percutaneous nephrostomy (PCN) tube may be necessary if the site of obstruction is above the level of the bladder outlet. The use of nephrotoxic medications and iodinated contrast agents should be avoided, if possible.

Renal replacement therapy may be required in patients who present with persistent hyperkalemia, extreme fluid overload, severe metabolic acidosis, uremia, or marked tumor lysis syndrome (TLS). Early nephrology consultation from the emergency center would expedite dialysis in these patients. Intermittent hemodialysis (IHD) is generally sufficient for volume and metabolic clearance in patients who are hemodynamically stable. However, patients with septic shock or severe TLS may require continuous renal replacement therapy (CRRT) in the intensive care unit. In patients with sepsis and AKI, CRRT has not shown a survival advantage over IHD, but may be preferable in preventing fluid overload.

Multiple Myeloma and AKI

Multiple myeloma is a clonal malignancy of plasma cells that results in the overproduction of immunoglobulins and their fragments which circulate in the blood (paraproteins). These paraproteins may cause injury by depositing in peripheral

organs such as the heart, kidney, and liver. AKI from paraprotein deposition in the kidneys is often the initial presentation of patients with multiple myeloma. Cast nephropathy may occur in the distal tubule when paraproteins filter through the glomeruli and bind to Tamm-Horsfall mucoprotein. Amyloid light chain amyloidosis (AL amyloidosis) may also occur when paraproteins undergo structural modification and deposit as microscopic fibrils in the glomeruli and vasculature. Lastly, light chains may deposit within the glomerular and tubular basement membranes, leading to light chain deposition disease.

The clinical presentation of AKI in patients with multiple myeloma varies from asymptomatic proteinuria to nephrotic syndrome and rapidly progressive renal failure. AKI is diagnosed in more than half of all patients with multiple myeloma at initial presentation, and 10 % of them need dialysis. Multiple myeloma should always be part of the differential diagnosis in elderly patients with unexplained acute or chronic kidney disease. Initial work-up for multiple myeloma consists of serum and urine protein electrophoresis as well as serum-free light chain assays to detect elevated levels of monoclonal proteins. Monoclonal proteins in the urine (Bence-Jones proteins) are not detected by routine qualitative dipstick urinalysis, which detects mainly albuminuria. However, paraprotein deposits from light chain deposition disease and amyloidosis may cause damage to the filtration barrier of the glomerulus, leading to significant albuminuria. In contrast, patients with classic myeloma cast nephropathy have minimal glomerular involvement and typically present with only mild albuminuria. Other clinical manifestations from light chain amyloid deposits include restrictive cardiomyopathy, hepatomegaly, carpal tunnel syndrome, and orthostatic hypotension. The definitive diagnosis is confirmed by examination of the renal biopsy revealing characteristic casts, light chains, or amyloid deposits.

Early aggressive treatment of patients who present with multiple myeloma and renal disease may help stabilize or improve kidney function. Initial hydration consists of infusion of normal saline, with a urine output goal of 2.5–3.0 L a day, which helps prevent the precipitation of casts within the distal tubule. Steroids are often used initially to decrease the production of paraproteins and alleviate end-organ damage. Aminoglycosides, IV contrast agents, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) may exacerbate renal injury and should be avoided. Hypercalcemia commonly occurs in patients with multiple myeloma and may aggravate acute kidney injury. If hypercalcemia does not resolve with the use of hydration, loop diuretics, and calcitonin, therapy with a bisphosphonate should be considered (e.g., 3–4 mg of zoledronic acid diluted in 100 mL of normal saline administered in an IV infusion for at least 15 min). Trials utilizing plasmapheresis to remove circulating paraproteins have not demonstrated significant improvement in clinical outcomes. The use of high-cutoff filters in hemodialysis is much more effective in removing paraproteins than plasmapheresis, and clinical trials studying its utility with concurrent chemotherapy are ongoing [8, 9].

Electrolyte Abnormalities

Tumor Lysis Syndrome (TLS)

TLS is a common life-threatening emergency in patients with cancer presenting to the EC. Tumor cells rapidly release potassium, phosphorus, and uric acid into the extracellular space and overwhelm the excretory capacity of the kidneys. Hyperkalemia may predispose patients to cardiac dysrhythmias and sudden death. Hyperphosphatemia and secondary hypocalcemia may lead to AKI, muscular irritability, cardiac dysrhythmias, and metastatic calcification. Uric acid may precipitate as crystals in the renal tubules and cause obstruction. TLS generally occurs in patients receiving chemotherapy, although it can occur spontaneously in patients with leukemia and lymphoma with very high tumor burden [10].

Patients with rapidly proliferating hematologic malignancies are at the greatest risk for TLS. Risk factors for TLS include a white blood cell count greater than 50,000/μL, elevated lactate dehydrogenase level, bulky disease, marrow or organ infiltration, advanced age, and chronic kidney disease. Cases of TLS in patients with a solid tumors undergoing chemotherapy and/or radiation therapy have been reported; however, patients with non-Hodgkin's lymphoma or acute leukemia are at greatest risk.

The identification of TLS is generally straightforward in patients who present with marked derangements in electrolyte levels. However, patients with impaired renal function secondary to an effective prerenal state, such as volume depletion or hypotension, may also develop hyperkalemia, hyperphosphatemia, and hyperuricemia. Unlike patients with TLS, these patients will develop rapid normalization of electrolyte levels and renal function with hydration and optimization of blood pressure.

Intravenous hydration to maintain adequate urine output in the setting of TLS facilitates excretion of potassium, phosphorus, and uric acid. Infusion of isotonic saline should be instituted 24 h prior to chemotherapy at 100 mL/m^2 per hour and titrated accordingly to maintain a urine output of at least 2.5 L a day. Conservative fluid management strategies may be necessary in patients with underlying congestive heart failure. Alkalinization of the urine with IV sodium bicarbonate prevents the formation of uric acid crystals but also increases the risk of calcium phosphate crystal deposition. Therefore, the routine use of IV fluids with sodium bicarbonate in patients with TLS is no longer recommended [10].

Therapy aimed at the normalization of uric acid levels is another important part of treatment of TLS. Until recently, the standard treatment of hyperuricemia involved daily administration of allopurinol (100–300 mg orally or intravenously) to decrease the production of uric acid. Patients with massive cell lysis may still develop dangerously high serum levels of uric acid. A relatively newer therapy, rasburicase (0.2 mg/kg [IV] daily for up to 5 days), promptly converts uric acid into allantoin, which is readily excreted. Serum uric acid levels often decrease until they become undetectable after rasburicase-based treatment. Subsequent studies have demonstrated that fixed doses of 3–6 mg may be just as effective as weight-based dosing. It is unknown whether the greater effect of rasburicase versus allopurinol in lowering serum uric acid levels translates into improved renal and patient outcomes.

Nephrology consultation should be sought for patients presenting to the EC with TLS who have peaked T waves on electrocardiogram (EKG), dysrhythmias, or oliguria. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and NSAIDs should be avoided in patients with TLS because they may worsen hyperkalemia and AKI. Although some patients deemed high risk of developing severe TLS have been preemptively started on continuous renal replacement therapy prior to chemotherapy, this is not a standard practice. Pseudohyperkalemia may occur in the setting of extreme leukocytosis, which may cause spurious elevations in serum potassium levels due to ex vivo lysis of white blood cells. The diagnosis should be considered in patients without other signs of TLS and the absence of EKG changes suggestive of hyperkalemia. If a patient is suspected of having pseudohyperkalemia, potassium measurement should be made on a lithium heparin plasma sample placed on ice or immediately on the whole blood by a point of care analyzer.

Hyponatremia

Hyponatremia (serum sodium levels less than 135 mEq/L) has been reported in 14–23 % of patients with cancer on admission to the hospital. Increased hyponatremia severity is a negative prognostic factor for survival in patients with non-small cell lung cancer, renal cell carcinoma, gastric cancer, and non-Hodgkin's lymphoma. The two most frequent causes of hyponatremia in patients with cancer are hypovolemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH). Common etiologies of SIADH include malignancy (e.g., the lung, gastrointestinal, central nervous system), pneumonia, drugs (e.g., antidepressants, haloperidol, carbamazepine, cyclophosphamide, platinum compounds, vinca alkaloids), nausea, and pain. Other considerations when assessing patients with hyponatremia in the setting of cancer include renal salt wasting secondary to chemotherapy, "tea and toast syndrome" resulting from malnutrition, water intoxication, and adrenal insufficiency secondary to adrenal metastases or steroid withdrawal.

Symptoms in patients with hyponatremia may be absent, mild (confusion, dizziness, nausea, and lethargy), or severe (seizures, coma, and death). The occurrence of symptoms depends primarily on the rate of decline in the serum sodium level as opposed to the absolute level. Adaptation of the brain to hyponatremia gradually occurs by the excretion of osmolytes from cells to prevent cerebral edema. Cerebral edema with eventual herniation of the brain stem may develop if the rate of decline in the serum sodium level outpaces the excretion of osmolytes. Immediate treatment is required to raise the serum sodium level until the patient is asymptomatic. If the decline in serum sodium level is more gradual, the patient may be asymptomatic or have only mild symptoms. Rapid correction of hyponatremia is not indicated in this situation.

Initial work-up for hyponatremia should include a physical examination to assess the patient's volume status, chemistry profile, plasma osmolality, urine electrolyte levels, and urine osmolality. Patients with volume depletion generally have urine sodium levels less than 20 mEq/L and concentrated urine (urine osmolality greater than plasma osmolality). Patients with hypervolemia (those with heart failure, cirrhosis, third spacing caused by peritoneal or liver metastases, hypoalbuminemia, or inferior vena cava compression or obstruction) have signs of fluid overload upon physical examination (e.g., edema, ascites, effusions) but are in an effectively prerenal state. Therefore, they also will have urine sodium levels less than 20 mEq/L and concentrated urine. Patients with SIADH have urine sodium levels greater than 40 mEq/L and inappropriately dilute urine (urine osmolality less than plasma osmolality). Patients with "tea and toast syndrome" have serum sodium levels less than 20 mEq/L along with appropriately dilute urine (urine osmolality less than plasma osmolality). Urine sodium levels are variable in patients with water intoxication, but urine osmolality is appropriately dilute, typically less than 150 mOsm/kg.

Urgent treatment is not indicated for hyponatremic patients who are asymptomatic or have only mild symptoms. Rapid correction of hyponatremia in these patients will increase the risk of osmotic demyelination syndrome. Patients with volume depletion should receive isotonic fluids such as normal saline. Otherwise, total fluid intake should be restricted to less than 1 L daily. Loop diuretics should be considered in patients with hypervolemia. The treatment of patients with SIADH consists of fluid restriction, salt tablets (initially, 1 g three times daily), and possibly loop diuretics. The introduction of vasopressin receptor antagonists has revolutionized treatment of hyponatremia in patients with hypervolemia or SIADH. These drugs block the effect of antidiuretic hormone on the collecting ducts of the kidney, thereby preventing water reabsorption and stimulating water diuresis.

Currently, two drugs within this class are available, oral tolvaptan (7.5–15.0 mg daily) and IV conivaptan (20-mg loading dose with 20 mg administered over the ensuing 24 h). Serial sodium levels should be monitored every 6 h with a goal correction rate of less than 10 mEq/L in 24 h.

Patients with severe symptoms need more urgent intervention with hypertonic saline and close neurologic monitoring. Treatment consists of infusion of 3 % saline at a rate of 0.8 mL/kg per hour and initial monitoring of serum sodium levels at least every 2–4 h. The infusion is continued until the sodium level is greater than 120 mEq/L, symptoms have resolved, or the rate of sodium level correction has exceeded 8 mEq within 24 h. Rates of correction in excess of 10–12 mEq per 24 h may cause osmotic demyelination syndrome, which results in altered mental status, quadriparesis, quadriplegia, pseudobulbar palsy, coma, or death. Therefore, frequent neurologic assessments and titration of the 3 % saline infusion to prevent overcorrection of hyponatremia are necessary.

Hyperkalemia

Hyperkalemia is a particular concern in patients presenting to emergency centers, as it can be life threatening. Common causes of hyperkalemia in patients with cancer include AKI, TLS, the use of certain drugs (e.g., calcineurin inhibitors, NSAIDs, angiotensin-converting enzyme inhibitors, trimethoprim-sulfamethoxazole, potassium-sparing diuretics), and metabolic acidosis. In most patients, the etiology is multifactorial.

Most patients with hyperkalemia are clinically asymptomatic unless their potassium levels are very high. Cardiac dysrhythmia is the most concerning manifestation. Electrocardiographic changes progress from peaked T waves, the absence of P waves, and widened QRS complexes to eventual sine waves. Skeletal muscle weakness may also be present in the setting of severe hyperkalemia. Stabilization of the myocardial membrane with IV administration of calcium gluconate or calcium chloride (2 g over 5 min) to counter the effects of hyperkalemia is imperative. A repeat infusion of calcium may be necessary for electrocardiographic changes to resolve. The next treatment is shifting of potassium to the intracellular space with administration of regular insulin (10 U intravenous), glucose (50 mL of 50 % dextrose intravenous), and inhaled beta-agonists. Sodium bicarbonate administration is helpful in patients with concurrent metabolic acidosis by shifting potassium intracellular as the acidosis is corrected. Sodium polystyrene sulfonate (15–30 g oral) is commonly given to facilitate potassium elimination from the gut. However, its clinical effectiveness is unproven in clinical studies, and its use has been rarely associated with intestinal necrosis [11]. If severe hyperkalemia persists despite correction of its underlying cause, an urgent nephrology consultation should be sought as dialysis may be necessary. For patients with milder hyperkalemia in the absence of T waves, monitoring serial potassium levels after discontinuation of the causative drug may be sufficient. Loop diuretics may be administered to patients with adequate renal function to enhance potassium excretion in the urine.

Urinary Diversions

John Simon performed the first urinary diversion in 1852 by creating a ureterorectal anastomosis in a patient with bladder exstrophy [12]. Subsequently, ureterosigmoidostomy became the procedure of choice in the early 1900s, but it was complicated by reflux nephropathy, metabolic acidosis, hypokalemia, and a high incidence of cancer at the anastomosis site. Physicians developed conduits using bowel segments as urine reservoirs with continuous drainage into a urostomy bag from a stoma in the abdominal wall in the 1950s; conduits used with the ileum had lower incidences of metabolic abnormalities than did those used with the jejunum. More recently, researchers developed neobladders with urinary excretion via a stoma in the abdominal wall or internally via the urethra. Unlike patients with conduits, those with neobladders do not suffer from incontinence, but they may need intermittent self-catheterization.

The intestinal epithelium normally secretes sodium and bicarbonate into the intestinal lumen and reabsorbs ammonia, ammonium, hydrogen, and chloride back into the blood. Therefore, patients with urinary diversions created from intestinal conduits are at risk for hyperchloremic metabolic acidosis secondary to bicarbonate loss in the urine. Risk factors for acidosis include conduits with large surface areas, increased urine-conduit contact times, jejunal (versus ileal) conduits, and underlying chronic kidney disease. If large segments of the ileum or colon are resected to make a conduit, the patient may experience diarrhea caused by bile salt malabsorption and secretion of chloride and water into the intestinal lumen. This may further exacerbate electrolyte abnormalities. Patients who have undergone ileal or stomach resection for conduit or neobladder creation may develop macrocytic anemia secondary to vitamin B_{12} deficiency. In patients with chronic liver disease, reabsorption of may lead to altered mental status. Metabolic abnormalities are uncommon in patients with urinary diversions created from the stomach because the gastric mucosa is relatively impermeable. However, metabolic alkalosis may develop in these patients secondary to H^+ secretion from the gastric lining and consequent bicarbonate retention in the blood, especially in the setting of chronic kidney disease.

The laboratory work-up for patients with urinary diversions includes serum electrolytes, blood urea nitrogen, creatinine, complete blood count, and urinalysis. Patients with chronic

metabolic acidosis may present with nausea, vomiting, and decreased appetite. Volume depletion may occur secondary to decreased oral intake and diarrhea. Altered mental status may indicate significant ammonia absorption (especially in patients with preexisting liver disease) or vitamin B_{12} deficiency. Macrocytic anemia as well as paresthesia may also suggest vitamin B_{12} deficiency.

Acidosis and volume depletion are best treated with a continuous intravenous bicarbonate infusion (150 mEq of sodium bicarbonate per liter of sterile water or D5W). Correction of acidosis decreases serum potassium levels; therefore, potassium should be given to patients who have hypokalemia on presentation prior to bicarbonate administration. Mild acidosis can be managed on an outpatient basis with oral supplementation of sodium bicarbonate (650-mg tablets equaling 7.7 mEq of bicarbonate or 1 mL of sodium citrate/citric acid [Bicitra] equaling 1 mEq of bicarbonate). Measurement of the vitamin B_{12} level should be performed in patients with urinary diversions who present with unexplained macrocytic anemia. Metabolic alkalosis caused by gastric urinary diversions in patients with chronic kidney disease responds well to treatment with H_2 blockers and proton pump inhibitors.

Hematuria

The presentation of hematuria in patients with cancer can range from mild to life threatening. Microscopic hematuria is defined as more than three red blood cells per high-power field but not visible to the naked eye, whereas gross hematuria is defined as visible discoloration of the urine from blood. In the general population, 5 % of patients with microscopic hematuria and up to 40 % of patients with gross hematuria have an underlying malignancy of the genitourinary tract [13]. Common causes of hematuria in patients with cancer are listed in Table 3. Patients with cancer may have hematuria from underlying malignancy, radiation treatment, chemotherapy, indwelling urinary catheters or stents, and viral infections.

The initial work-up for patients with microscopic hematuria includes urinalysis and a complete blood count to exclude an underlying bacterial infection. Patients with excruciating unilateral colicky flank pain radiating to the groin should undergo a computed tomography (CT) scan of the abdomen and pelvis with "stone protocol" to exclude underlying urolithiasis. Stable patients with urolithiasis less than or equal to 6 mm in diameter may excrete the stone in their urine spontaneously and may be monitored as outpatients with oral hydration and narcotics. Patients with urolithiasis greater than 6 mm in diameter generally need admission for IV hydration, narcotics, and urologic consultation. The presence of proteinuria, de novo hypertension, or unexplained renal failure concurrent with microscopic hematuria may suggest underlying glomerulonephritis, and a renal biopsy may be necessary to exclude glomerular disease. Gross hematuria commonly suggests lower urinary tract disease such as cancer or cystitis, in which case a CT scan of the pelvis as well as cystoscopy may be warranted. Patients with severe hematuria who present with hemodynamic instability will generally need ICU admission for IV hydration, blood products, and urgent urologic consultation.

Table 3 Common causes of hematuria in patients with cancer

Primary neoplasm
Urothelial
Renal
Prostate
Hemorrhagic cystitis
Chemotherapy (cyclophosphamide, ifosfamide)
Viral (BK virus, adenovirus, cytomegalovirus)
Radiation therapy
Coagulopathy
Factor deficiency
Disseminated intravascular coagulation
Systemic anticoagulation
Glomerulonephritis
IgA nephropathy
Postinfectious
Membranoproliferative
Pauci-immune (antinuclear cytoplasmic antibody disease or anti-glomerular basement membrane disease)
Thin basement membrane disease
Interstitial nephritis
Nephrolithiasis
Hypercalciuria (myeloma, bone metastases, parathyroid malignancy)
Hyperuricosuria (high cell turnover)
Infection
Cystitis
Prostatitis
Urethritis
Pyelonephritis

Hemorrhagic Cystitis

Hemorrhagic cystitis refers to the presence of lower urinary tract symptoms (dysuria, suprapubic pain, frequency) with gross hematuria. Cystoscopy reveals mucosal edema, hyperemia, and friability of the bladder wall. Most cases of hemorrhagic cystitis in patients with cancer are secondary to chemotherapy, radiation injury to the urothelium, or viral infection. Acrolein, a metabolite of cyclophosphamide and ifosfamide, may cause hemorrhagic cystitis within 4 h after IV infusion of the parent drug. To minimize this risk, sodium 2-mercaptoethanesulfonate (mesna) is administered prior to chemotherapy and binds to acrolein to form a nontoxic ester

that is readily excreted in the urine. To be effective, mesna must be present in the bladder at the time acrolein comes into contact with the urothelium. Mesna has decreased the incidence of hematuria and hemorrhagic cystitis following cyclophosphamide-based chemotherapy to less than 5 %. Aggressive IV hydration to dilute urinary acrolein and minimize the contact of acrolein with the bladder urothelium is also necessary to prevent cystitis.

The incidence of radiation cystitis ranges from 5 % to 18 % of patients with prostate, cervical, and bladder cancer. Acute radiation cystitis may develop within 4–6 weeks after treatment and presents with typical lower urinary tract symptoms secondary to acute inflammation and tissue edema. Symptoms may last for up to 3 months as the bladder mucosa slowly divides in the healing phase. Treatment is largely limited to symptom management and includes anticholinergic drugs and phenazopyridine. Patients who do not heal completely may progress to a chronic ischemic phase leading to necrosis and fibrosis of the bladder wall over the next several years. Patients develop recurrent urinary tract infections (UTIs), hematuria, urinary frequency, and nocturia. Other potential complications include bladder perforation and fistula formation. Fibrotic shrinkage of the bladder may occur up to 10 years after radiation exposure. The degree of injury in patients with chronic radiation cystitis is related to the cumulative dose and intensity of radiation therapy. Continuous bladder irrigation, endoscopic sclerosis, and hyperbaric oxygen therapy may be considered for patients with recurrent cystitis.

The most common viruses associated with cystitis in patients with cancer include adenovirus, cytomegalovirus (CMV), and BK virus (a member of the *Polyomavirus* family) [14]. Viral urinary tract infections (UTIs) should be strongly considered in the differential diagnosis of hematuria in patients after HSCT. Symptoms of viral UTI include fever, gross or microscopic hematuria, lower abdominal pain, dysuria, and urinary frequency and urgency. BK virus is the most common viral pathogen of the urogenital tract in patients after HSCT and may cause hemorrhagic cystitis, ureteral strictures, and interstitial nephritis. Although BK virus is normally colonized in the urogenital tract in most adults, it only causes infection in immunosuppressed patients. BK virus can be detected by the presence of "decoy cells" (renal tubular cells with viral inclusions) in urine cytology and quantified by polymerase chain reaction analysis of blood and urine samples. Adenoviruria is invariably associated with cystitis, in contrast to BK viruria which may be clinically asymptomatic in 50 % of patients after HSCT. Patients with severe adenoviral infection may present with systemic disease manifesting as hemorrhagic colitis, pneumonitis, hepatitis, or hemorrhagic cystitis. CMV is a relatively rare cause of cystitis and can be detected using polymerase chain reaction analysis. The antiviral drug cidofovir is active against BK virus, adenovirus, and cytomegalovirus, but its clinical use is limited by its nephrotoxicity. Quinolones and leflunomide have also been used to treat BK infection, although the evidence for their utility is weak. Ganciclovir and foscarnet also can be used to treat active CMV infections. An evolving therapy for viral infections after HSCT is adoptive immunotherapy using donor-derived cytotoxic T cells specific for adenovirus, BK virus, and CMV.

Regardless of etiology, standard treatment of hemorrhagic cystitis involves preservation of urinary flow using IV hydration and blood transfusions to correct any coagulopathies. If blood clots develop in the bladder, patients may experience suprapubic and flank pain from urinary obstruction. The physician must reestablish urinary flow by inserting a large-diameter 3-way transurethral catheter into the bladder and initiate manual or continuous lavage to remove the clots. If lavage at bedside is not successful, endoscopic clot evacuation under general anesthesia can be considered. Using a cystoscope, the urologist can directly visualize and disrupt clots, inspect the bladder to identify any controllable sources of bleeding, and cauterize bleeding vessels in the bladder wall. Intravesicular instillation of hemostatic agents (e.g., aluminum, placental extract, prostaglandins, formalin) may be necessary in the setting of severe hemorrhage. In refractory cases, bilateral PCNs may be necessary to preserve renal function and avoid dialysis.

UTI

Patients with cancer are susceptible to UTI secondary to neutropenia and chronic immunosuppression. In addition, biofilm formation along the surface of transurethral catheters, PCNs, and ureteral stents interferes with normal host defenses and facilitates bacterial colonization. Catheter-associated UTIs account for 40 % of all hospital-acquired infections, and risk factors for these infections include a long catheterization duration, female sex, diabetes, advanced age, and serum creatinine level greater than 2 mg/dL [15]. The most common organisms identified in UTI cases are *Escherichia coli*, *Klebsiella* species, *Staphylococcus saprophyticus*, *Enterobacter* species, and *Proteus* species. Common pathogens in patients with hospital-acquired UTIs include *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Candida albicans*. Patients who have diabetes, frequent UTIs, indwelling catheters, or hospital-acquired UTIs are considered to be at risk for complicated UTI and must undergo aggressive management. Other risk factors for complicated UTI include pregnancy, chronic immunosuppression, and recent antibiotic use.

The incidence rate of UTI in patients with urinary diversions is 33 % [16]. *E. coli* and *Proteus*, *Pseudomonas*, and *Enterobacter* spp. are the most frequently isolated organisms

in these patients. Alkaline urine predisposes patients to bacterial proliferation. Patients with urinary diversions who present with pyelonephritis or sepsis should be evaluated for obstructions or stenosis of the diversions. Routine urine cultures are not indicated for asymptomatic patients, as the bowel used to create the diversion is normally colonized with bacteria. Treatment with antibiotics should be considered for patients with urinary diversions who present with unexplained fever, cloudy urine, flank pain, or hematuria.

Symptoms of a lower UTI (cystitis) include dysuria, urinary frequency, acute hematuria, and suprapubic or pelvic pain. Patients with an upper UTI (pyelonephritis) may present with nausea or vomiting, flank pain, fever, rigor, and altered mental status. Urinalysis may be positive for bacteriuria (100–1000 cfu of bacteria/milliliter), pyuria (at least ten leukocytes/milliliter), leukocyte esterase, and nitrite. A transurethral catheter-associated UTI is indicated by the presence of clinical symptoms (e.g., fever, rigor, altered mental status, lethargy, flank pain, acute hematuria, decreased blood pressure, metabolic acidosis) and a urine culture with at least 10^3 cfu of bacteria per milliliter. For patients with indwelling urinary catheters, treatment of asymptomatic bacteriuria is not required unless the patient is pregnant or undergoing a urologic procedure with expected mucosal bleeding. In addition, pyuria alone is not diagnostic for catheter-associated UTIs [17]. Urine cultures are not routinely obtained for suspected uncomplicated cystitis but are suggested for treatment of persistent UTIs despite previous treatment or the presence of complicated cystitis, a catheter-related UTI, or pyelonephritis. Imaging studies for UTIs are generally not warranted unless a urinary obstruction or abscess is suspected.

Initial empiric antibiotic therapy for UTIs should be selected based on patient allergies, the presence of bacterial resistance, and cost. Treatment of uncomplicated acute cystitis includes oral administration of nitrofurantoin (100 mg twice a day for 5 days) or trimethoprim-sulfamethoxazole (160–800 mg twice a day for 3 days). If these agents are contraindicated, then a fluoroquinolone (3-day course) or beta-lactam (amoxicillin-clavulanate, cefdinir, or cefpodoxime proxetil; 3- to 7-day course) may be considered [18]. For complicated cystitis, a 7- to 10-day course of an oral fluoroquinolone is suitable. If parenteral therapy is warranted, agents such as fluoroquinolones, ceftriaxone, and aminoglycosides can be given once daily. Patients with catheter-associated UTIs should undergo replacement or removal of the catheter and receive a fluoroquinolone or cephalosporin for 7–14 days. If *Pseudomonas* infection is suspected, the patient should receive ciprofloxacin, ceftazidime, or cefepime. Vancomycin is appropriate for Gram-positive coccal infections until antibiotic susceptibility is determined. For pyelonephritis not requiring hospitalization, an oral fluoroquinolone (7-day course) or trimethoprim-sulfamethoxazole (14-day course) is appropriate. An initial one-time IV loading dose may be given prior to discharge from the emergency department (e.g., 1 g of ceftriaxone, 24-h dose of an aminoglycoside). For patients with pyelonephritis requiring hospitalization, appropriate IV antibiotics include fluoroquinolones, aminoglycosides with or without ampicillin, extended-spectrum cephalosporins, penicillins with or without an aminoglycoside, and carbapenems. For all UTIs, the antibiotic regimen should be tailored to the final antibiotic sensitivities as determined in urine culture. Patients with UTIs who are neutropenic (absolute neutrophil count <1500/μL) should be given treatment according to neutropenic guidelines.

Obstructive Uropathy

Obstructive uropathy is the impedance of normal urine flow anywhere from the renal tubule to the urethra. The resulting increase in intraluminal pressure generally occurs with hydroureter and hydronephrosis and may be unilateral or bilateral depending on the location of the obstruction. If left untreated, irreversible loss of kidney function will eventually occur. Common causes of obstructive uropathy in cancer patients are listed in Table 4. Primary tumors of the prostate, bladder, uterus, and cervix account for more than 70 % of malignancy-associated obstructions. The most likely cause

Table 4 Common causes of obstructive uropathy in patients with cancer

Upper urinary tract obstruction
Primary malignancy
Renal pelvis
Ureter
Ovary
Retroperitoneal disease
Metastatic cancer (cervix, bladder, breast, colon, ovary, prostate)
Lymphoma
Sarcoma
Fibrosis (idiopathic, radiation)
Ureteral strictures (radiation, polyomavirus)
Ureteral encasement (lymphadenopathy)
Urolithiasis
Lower urinary tract obstruction
Primary malignancy
Cervix
Uterus
Prostate
Bladder
Urinary retention
Medications (anticholinergics/antispasmodics, antihistamines, tricyclic antidepressants)
Spinal cord injury caused by vertebral metastases
Bladder calculus
Blood clots (hemorrhagic cystitis)
Fungus ball

of a urinary tract obstruction within 2 years after radiation therapy is a recurrent tumor; thereafter, the most common cause is radiation-induced fibrosis.

The clinical presentation of obstructive uropathy varies depending on whether the obstruction is (1) unilateral or bilateral, (2) acute or chronic, and (3) complete or partial. Acute obstructive uropathy may manifest as acute flank or suprapubic pain and worsening hypertension, whereas chronic obstructive uropathy symptoms may be more vague or completely absent. Patients with partial obstruction of the bladder or ureters may have polyuria, nocturia, and urinary frequency, whereas patients with bilateral complete obstruction may have anuria. Also, patients may have a palpable flank or suprapubic mass with tenderness upon clinical examination. Laboratory test results may be essentially normal in patients with unilateral disease if the unobstructed kidney is healthy and able to compensate kidney function. Abdominal ultrasonography is sensitive in detecting hydronephrosis, hydroureter, and filling defects in the bladder. However, ultrasonography may miss obstructions in patients with significant retroperitoneal disease or ureteral encasement, both conditions that may prevent dilation of the urinary tract. If ultrasonography is suggestive of an obstruction or clinical suspicion of an obstruction is high, a computed tomography scan using a stone protocol may help identify the site and delineate the cause of the obstruction. Also, isotope renography may be used to identify functional obstructions in indeterminate cases of obstructive uropathy. Using a portable bladder scanner, a physician can quickly determine whether a patient has a significant amount of postvoid residual urine (greater than 50–100 mL), which is suggestive of urinary retention or obstruction.

The first step in management of obstructive uropathy at the level of the bladder outlet is passing a small (14 French) urethral catheter into the bladder. In the male patient, a Foley catheter should be passed into the bladder to its hub, and urine return should be verified before inflating the balloon. This will prevent inadvertent inflation of the balloon in the prostatic urethra, which could cause mucosal laceration and bleeding. Patients with rectal, gynecologic, or genitourinary tumors are at particular risk for iatrogenic bleeding or lacerations when using urethral catheters. Care should be taken to avoid forcing a Foley catheter that is not passing easily into the bladder because of the risk of posterior urethral lacerations or even tears under the prostatic capsule, which may lead to extravasation of urine into the pelvis and perineum. This may rapidly progress to urosepsis and soft tissue infection.

Patients with obstructions above the level of the bladder may have to undergo decompression of the collecting system via placement of a ureteral stent or PCN. Subsequent management includes replacement of the stent or PCN every 3 months. Ureteral decompression in cancer patients is associated with increased morbidity and decreased quality of life [19]. Complications include infection, stent migration, pain at the insertion site, bladder spasms, recurrent obstruction, and leakage. Ureteral stents eventually fail in 16–58 % of patients with malignancies [20]. PCN placement has not proven to markedly improve survival rates in patients with advanced cancer and may adversely affect quality of life. However, ureteral decompression may be more valuable in patients with stone disease, ureteral strictures, and/or hemorrhagic cystitis. In the cancer setting, consideration of the patient's prognosis before decompression of the urinary system is important. Placement of a stent or PCN may be justified to improve renal function for further cancer therapy, alleviate pain, and prevent the need for dialysis or as part of treatment of urosepsis.

Key Practice Points

- The RIFLE criteria provide a standardized definition of AKI based on increases in serum creatinine level relative to baseline and have prognostic value in the care of patients with cancer.
- More than half of all patients with multiple myeloma will initially present with some degree of renal injury, and AKI may improve with immediate treatment of the underlying myeloma.
- Treatment of TLS includes aggressive IV hydration, rasburicase for hyperuricemia, and, possibly, dialysis for AKI.
- Vasopressin receptor antagonist drugs have revolutionized the treatment of hyponatremia associated with hypervolemia or SIADH, but administration of 3 % saline is still required for patients with hyponatremia and severe symptoms (seizures or coma).
- Hyperkalemia may not manifest clinically until potassium levels are severely elevated, and emergent treatment of it includes IV calcium to stabilize the myocardial membrane, IV insulin with glucose, inhaled beta-agonists, and dialysis in refractory cases.
- Urinary diversions created from bowel segments are often complicated by the development of chronic metabolic acidosis, hypokalemia, volume depletion, and vitamin B_{12} deficiency.
- Hemorrhagic cystitis commonly results from cyclophosphamide administration, radiation therapy, and viral infection after HSCT. Management of hemorrhagic cystitis includes IV fluids, bladder irrigation, antiviral drugs, and urologic consultation.
- UTIs are common in patients with cancer owing to underlying neutropenia, the use of chronic indwelling devices (transurethral catheters, ureteral stents, and PCNs), and creation of urinary diversions using bowel segments.
- Obstructive uropathy is a common complication of pelvic malignancies and generally requires intervention with a transurethral or suprapubic catheter, ureteral stent, or PCN.

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Oncologic Emergencies: Gastroenterology

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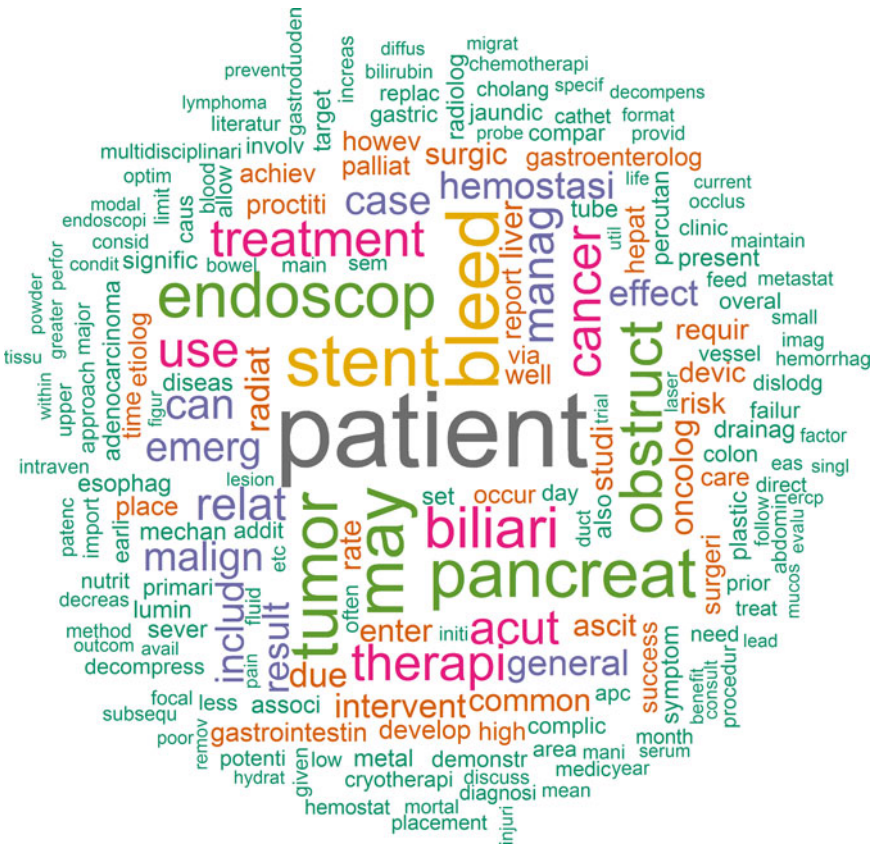

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Introduction

In the past, gastroenterology's involvement in oncologic care centered on endoscopic tissue acquisition for malignant diagnoses. With technologic advances in gastroenterology (GI), the field of interventional endoscopy has increasingly become married to cancer care from staging to surveillance to management of tumor or treatment-related emergencies. Oncologic emergencies in gastroenterology, much like that of other body systems, are related to the presence of cancer (the tumor itself or metastatic growth) or occur as a consequence of the treatments undertaken for cancer. In the GI tract, these include both structural derangements such as luminal or biliary obstruction as well as metabolic emergencies such as hepatic failure. In general, GI-related emergencies represent a minority of all oncologic emergencies, which are more often metabolic or hematologic and covered in other chapters of this book. Many GI-related oncologic events require timely evaluation; however, for the most part, they are not imminently life threatening. These events will be the focus of this chapter. Some types of GI oncologic emergencies are insidious and develop gradually over time until a clinical threshold is achieved (e.g., gastric outlet obstruction, jaundice), whereas others may manifest over hours (e.g., cholangitis related to biliary obstruction).

In some patients, the devastating emergency is the first presentation of cancer itself. Given the increase in outpatient oncologic care in modern-day practice, early signs and symptoms of an evolving gastrointestinal emergency or urgency may be overlooked by patients and families. As with any emergency, early recognition and diagnosis are paramount to effective management. Early consultation with a gastroenterologist to help in diagnosis and management may impact patient outcome, and thus, multidisciplinary care for complex oncology patients serves the patient best. This chapter will examine the most common cancer-related gastrointestinal emergencies, discuss their diagnosis, and review their treatment (Table 1). Specifically, we will address gastrointestinal hemorrhage, enteral and biliary obstruction, acute pancreatitis, hepatic decompensation, and urgent issues related to enteral feeding.

Table 1 The most common oncologic emergencies in gastroenterology

Gastrointestinal hemorrhage
Luminal obstruction
Acute pancreatitis
Biliary obstruction/cholangitis
Hepatic decompensation
Dysfunction of enteral feeding devices

Gastrointestinal Hemorrhage

Bleeding Related to Tumors

Neoplasia is considered an infrequent cause of upper gastrointestinal bleeding (UGIB), accounting for approximately 5 % of all UGIB cases [1, 2]. While oncology patients are at risk for common causes of gastrointestinal bleeding (peptic ulcer disease, gastroduodenal erosions, esophagitis, etc.), those patients that have solid tumors of the gastrointestinal tract, or metastatic lesions that involve the GI mucosa, pose a bleeding threat from the esophagus to the anus. This risk is further compounded by the presence of neutropenia and thrombocytopenia, as well as the use of anticoagulation in the setting of tumor-related thromboembolic disease. These factors, as well as the innate characteristics of the tumor, can make endoscopic treatment of bleeding a significant management challenge. Additionally, cancer-related bleeding overall is a poor prognostic sign. A large prospective study of over 3200 patients admitted with acute non-variceal upper GI bleeding demonstrated that those patients with neoplasia had 2.5 times (95 % CI, 1.32–4.46; $P<0.0001$) the risk of death when compared to those who bled from benign conditions [1]. Of those with cancer ($n=153$), the mortality rate was significantly higher in those with esophageal compared to cancer of the gastric cardia or gastric body (33 % versus 23.5 % and 7.2 %, respectively) [1].

Lesions in the esophagus (squamous cell carcinoma and adenocarcinoma), stomach [adenocarcinoma, gastrointestinal stromal tumors (GIST), lymphoma, carcinoid tumors, etc.], and proximal small bowel (adenocarcinoma, lymphoma, GIST, carcinoid tumors, etc.) are typically reached with a standard upper endoscope, while tumors in the jejunum and ileum often require the use of device-assisted enteroscopy, mainly in the form of single- and double-balloon enteroscopy or spiral enteroscopy. Colonic [adenocarcinoma, neuroendocrine (including carcinoid) tumors, etc.] and terminal ileal (adenocarcinoma, lymphoma) lesions are accessed via standard colonoscopy. Irrespective of the direction of endoscopic approach or the specific endoscope utilized, catheter-based devices (clips, injection needles, cautery devices) used to treat bleeding are advanced down the working channel of the endoscope and directed at the target lesion.

A variety of endoscopic techniques are available for the treatment of GI bleeding, and these modalities may also be applied to bleeding tumors although overall success rates of hemostasis are inferior compared to the endoscopic treatment of benign bleeding pathology. The main reason for the limited success of endoscopic therapy for tumor-related bleeding is that bleeding in such cases is not generally from a single exposed vessel (for which the majority of current endoscopic treatments are designed). Malignant bleeding

tends to be diffuse mucosal oozing from numerous small microvessels, and therefore focal targeting of therapy is less effective due to the generally larger surface area involved.

The literature on the efficacy of endoscopic therapy for bleeding directly due to the primary or metastatic malignancy is sparse and is mainly based on case reports and series [3, 4]. Thermal therapies, including heater probe, bipolar electrocautery, and argon plasma coagulation (APC), are perhaps the most widely used modalities for tumor bleeding. There have been a few case reports in the literature, but no trials comparing the efficacy of bipolar electrocautery and heater probe. A 1996 study by Savides and colleagues reported on the use of heater probe or bipolar electrocautery with or without epinephrine injection in six patients with focally oozing tumors. Initial hemostasis was achieved in all, but the 30-day rebleeding rate was 29 %, similar to those not treated endoscopically [2]. Several studies have evaluated the use of neodymium-yttrium aluminum garnet (Nd:YAG) laser for tumor palliation in the GI tract [5–9]. Immediate hemostasis rates of 90 % were achieved with the Nd:YAG laser for the emergent treatment of 18 patients with massive bleeding from gastric cancer; however, rebleeding occurred in 17 %, making laser therapy less suitable for definitive therapy [6].

Argon plasma coagulation (APC) is widely accepted as an effective modality for hemostasis as well as tissue fulguration and is readily available in most endoscopy suites and hospitals. It has generally replaced laser therapy due to its ease of use, low cost, and portability. The specific use of APC for palliation of upper GI tumor bleeding has not been well studied with very few small case series [10–12] related to its use in esophagogastric or rectosigmoid cancers. Much of the literature related to APC in the setting of malignancy focuses on its use as a curative therapy for early-stage cancers (i.e., treatment of high-grade dysplasia in the setting of Barrett's esophagus, which has now been largely replaced by radio-frequency ablation or cryotherapy) or for decreasing tumor bulk to maintain luminal patency for palliation of dysphagia in esophageal cancer which is discussed separately.

Spray cryotherapy is a newer endoscopic therapy that has been mainly used for the ablation of dysplasia associated with Barrett's esophagus (BE). Cryotherapy is a noncontact, targeted application of medical grade −196 °C liquid nitrogen by using a disposable 7 F spray catheter through the endoscope. Cryotherapy has been shown to completely eradicate high-grade dysplasia associated with BE in 97 % of treated subjects [13]. This technology has also been applied to bleeding tumors with a single case report demonstrating hemostasis achieved in locally unresectable hemorrhagic esophageal cancer [14]. A major advantage of cryotherapy over other catheter-based endoscopic therapies for the treatment of bleeding from cancer is the surface area of coverage with cryotherapy treatment (several square centimeters) compared to the focal treatment effect (several square millimeters) of other probe-based endoscopic therapies (such as heater probe, bipolar electrocoagulation, hemostatic clips, etc.). It is expected that more literature will be published on its use in malignancy given its ease of use and wide surface area coverage.

A novel modality for the treatment of gastrointestinal bleeding is the use of hemostatic powders. These inorganic powders are designed to control active bleeding by two mechanisms: (1) adhering to the bleeding site and forming a mechanical barrier when in contact with blood, tissue, and the extracellular matrix and (2) increasing local concentration of clotting factors while enhancing clot formation [15, 16]. Many of these products have been utilized in the military for temporizing battlefield-related injuries and show great hemostatic promise. There are currently three hemostatic powders available for endoscopic use, although none are currently approved for use in the USA. These include TC-325 (Hemospray™) (Cook Medical Inc., Winston-Salem, NC, USA), EndoClot™ PHS (EndoClot Plus Inc., Santa Clara, CA, USA), and Ankaferd Blood Stopper™ (ABS, approved in Turkey). Of all GI endoscopic therapies, hemostatic powders have thus far demonstrated the greatest potential for sustained hemostasis in malignancy. Chen et al. reported five cases of patients with GI bleeding due to gastroduodenal tumors in which bleeding was controlled in all cases, and rebleeding occurred in one patient with disseminated intravascular coagulation [17]. Similarly, Leblanc et al. treated five patients with GI neoplasms, achieving immediate hemostasis in all with rebleeding occurring in two patients which responded to subsequent treatment [18]. A few additional studies have described immediate and sustained hemostasis of such powders in tumor-related bleeding in the majority of its patients (case series of five to ten patients) [19, 20] with gastroduodenal and periampullary tumors. While these results are encouraging, the use of these agents in the USA is currently limited to research trials. They are being used in clinical practice in Europe and Canada; however, they have not received approval in the USA for routine clinical use. If approved for use in the USA, hemostatic sprays have the potential to offer an effective, easy-to-use method for treatment of GI bleeding.

Mechanical methods of endoscopic hemostasis are in the form of hemoclips and are currently in use, with overall relatively poor results due to their focal targeted area of therapy. Once again, most tumor-related bleeding is diffuse mucosal hemorrhage rather than from a single exposed blood vessel. Hemostatic clips have most commonly been used for prevention of bleeding following endoscopic mucosal resection, but can be applied to neoplastic lesions. Cheng et al. reported two cases of hemostasis achieved by hemoclip placement on

bleeding gastrointestinal stromal tumors [21]. Oftentimes, the bleeding tumor has several areas of active oozing, and mechanical disruption of the friable tumor with the use of a hemoclip may potentially worsen bleeding. Hemoclips are generally avoided in bleeding from tumors unless there is a focal targeted area of hemorrhage.

If endoscopic therapy fails to achieve hemostasis, angiographic evaluation by interventional radiology (IR) is generally the next step. While data on angiographic treatment of bleeding tumors is limited, angiography should be attempted as second-line therapy [22]. Access to the bleeding vessel may be achieved by selective catheterization in the distribution of the culprit vessel as evidenced by active contrast extravasation. Superselective embolization using microcoils or Gelfoam is highly successful in achieving hemostasis when the anatomy is favorable. However, given the nature of cancer-related bleeding, i.e., diffuse mucosal hemorrhage from multiple microvessels, embolization of the feeding blood vessel may place the patient at risk for ischemia from collateral damage.

In those instances when both endoscopic and interventional radiology interventions are not successful in achieving hemostasis or not possible, targeted radiation therapy (RT) should be considered. Overall, RT plays a crucial role in the treatment of gastrointestinal malignancies and in the management of hemostasis. The effects of RT on bleeding can be realized within a matter of days and a few fractions of treatment. In general, even though bleeding ceases, further treatment is undertaken to sustain a more durable response. RT causes damage to the intima of the blood vessels that supply the tumor, leading to capillary necrosis and thrombosis, and consequently hemostasis. This effect on tumor blood vessels as well as destruction of the tumor is the main mechanism by which RT is effective for hemostasis. Several retrospective studies on the role of RT on bleeding gastric cancers have demonstrated that palliative short-course RT is effective in hemostasis in 50–95 % of cases [23].

In general, palliative surgical resection is the last option for definitive care of GI bleeding related to cancers and is associated with a poor prognosis [24, 25]. A comparison of elective and emergency presentation of gastric cancer in 291 patients reported that overall 2-year survival was less in those that presented with emergency complications requiring operative intervention (25 % in emergency group versus 67 % who presented electively) [25]. Surgical resection is only appropriate for surgically fit patients, and prior literature has suggested a mortality rate of 10 % and morbidity rate of up to 30 % in cancer patients [26–28]. Surgery indeed is effective in hemostasis; however, improvement in survival is extremely low at 6 %, and the impact on the quality of life after palliative resection is not clear [27].

To date, there have been no trials comparing endoscopic therapy, surgery, or RT in the treatment of bleeding related to luminal tumor. Therefore, there is no clear answer as to which is the most effective treatment option. In general, the management approach is to enlist the least invasive method of hemostasis first (i.e., endoscopy, then interventional radiology, then radiation therapy, then surgery if necessary).

Bleeding as a Consequence of Treatment

Mallory-Weiss Tear

In patients receiving chemotherapy, nausea, vomiting, and retching are common. These symptoms place patients at risk for an upper GI bleeding related to a Mallory-Weiss tear, a mucosal injury at the gastroesophageal junction that exposes a bleeding vessel. This type of injury can produce significant bleeding especially in the setting of chemotherapy-induced thrombocytopenia. This condition can often be managed with endoscopic therapy alone with the use of electrocautery, epinephrine injection (for vasoconstriction and tamponade), or mechanical clips for hemostasis via upper endoscopy. If endoscopic therapy is unsuccessful in establishing hemostasis, IR angiography is the next step for arterial embolization via a femoral artery approach.

Radiation Proctitis

Radiation injury to the rectum and sigmoid may result from treatment of cancers of the prostate, cervix, rectum, anus, urinary bladder, and testes, occurring in up to 20 % of these treated cancer patients. It presents as persistent hematochezia which may be associated with tenesmus (Fig. 1). Acute

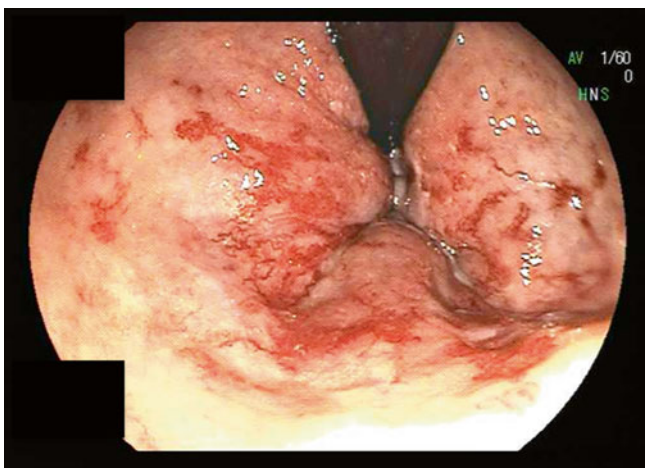

Fig. 1 Radiation proctitis. Endoscopic appearance of radiation proctitis, characterized by multiple telangiectasias in the rectum as seen on retroflexion in sigmoidoscopy (*Courtesy of Jeffrey Tokar, MD, Fox Chase Cancer Center, Philadelphia, PA*)

radiation proctitis occurs either during or within 6 weeks of RT, while chronic radiation proctitis often occurs several months to years following RT [29]. Risk factors include the total surface area of exposure, method of delivery, and cumulative radiation dose, with doses above 70 Gy resulting in long-term injury to the rectal mucosa [30]. Additional factors associated with the development of RT proctitis include prior GI or genitourinary surgery, endometriosis, diabetes, hypertension, collagen vascular disorders, and inflammatory bowel disease [31]. Most cases of radiation proctitis are self-limiting and respond to medical therapy. In general, rates of radiation proctitis may be decreasing as RT techniques are improving to allow more targeted delivery of higher doses of radiation. While supportive care is typically offered for mild cases, patients who develop persistent outlet-type bleeding may benefit from targeted therapy. There is a paucity of well-designed trials comparing medical and endoscopic therapy, making it impossible to identify the most effective approach to the management of chronic radiation proctitis.

Treatment for radiation proctitis is medical or endoscopic therapy. Sucralfate paste enemas are now commonly used to treat symptoms of radiation proctitis. Kochhar and colleagues reported its use in 26 patients, with durable remission of symptoms in a majority of patients with moderate to severe bleeding [32]. Several other reports have also demonstrated efficacy in improving symptoms of proctitis or proctosigmoiditis [32–34]. Given its overall low cost, minimal side effect profile, and ease of administration, sucralfate topical therapy is a reasonable first step.

Endoscopic therapy with argon plasma coagulation (APC) appears to be the most commonly utilized endoscopic modality for treatment of bleeding associated with radiation proctitis. It is easy to use, effective, widely available, safe, and less expensive than other therapies such as Nd:YAG laser. APC provides a predictable, noncontact, uniform, limited depth of coagulation (0.5–3 mm) to the target tissue, resulting in lower risks of perforation, stricture, and fistula formation [35, 36]. Studies have also demonstrated sustained remission of bleeding in patients with severe radiation proctitis (90 % in a mean follow-up of 18 months) [37]. Typically, more than one session of APC therapy is required, with durable hemostasis achieved after three sessions [38].

Other endoscopic treatments include radio-frequency ablation and cryotherapy [39]. Both these therapies have the advantage of allowing a broader field of treatment than the focal therapy of APC. Initial studies have demonstrated high rates of hemostasis (greater than 90 %) as well as minimal to no side effects (up to 19 months of follow-up) with both RFA and cryotherapy [40–42]. RFA has the benefit of inducing neo-squamous epithelialization which may prevent recurrence of symptoms, but this has yet to be studied formally [36].

Luminal Obstruction

Patients with GI malignancies are at risk for obstruction of the GI tract, which is the most common surgical emergency encountered in the cancer patient [43]. Obstruction is characterized by poor oral intake due to nausea, vomiting, abdominal pain, and paucity of stool or flatus passage. Abdominal X-rays or CT scans may reveal air-fluid levels and a transition point indicating the site of obstruction. Initial management is conservative, with bowel rest, intravenous fluids, antiemetics, electrolyte repletion, and nasogastric (NG) tube placement for decompression. In general, the majority of non-cancer-related bowel obstructions related to adhesions resolve in this conservative approach.

Malignant obstructions of the esophagus, stomach, duodenum, and colon can be alleviated by placing a self-expanding metal stent (SEMS) via endoscopy. Stents are placed with endoscopic and fluoroscopic guidance and are generally effective at maintaining patency in this setting (Fig. 2). SEMS has been shown to be a safe and effective means of

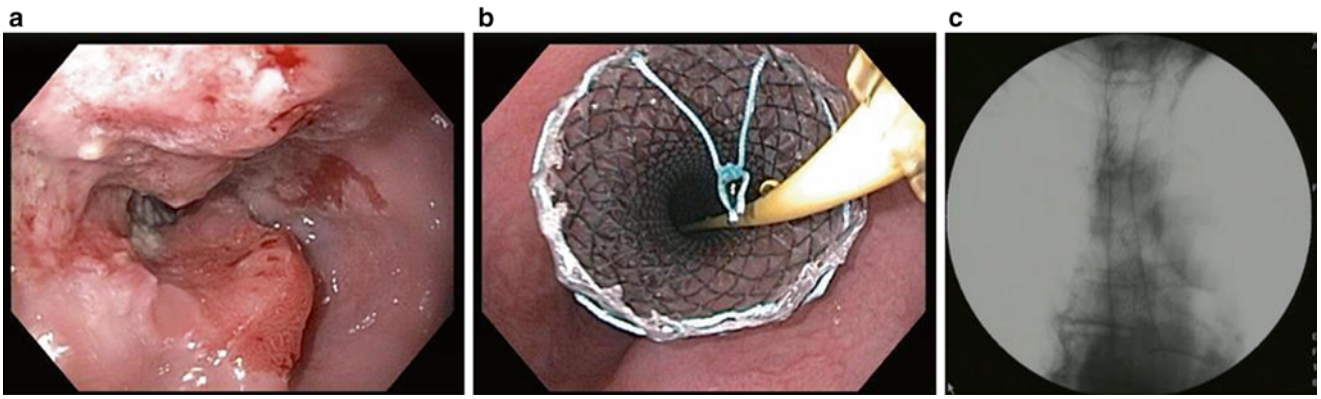

Fig. 2 Esophageal stent for obstructing esophageal mass. (**a**) Endoscopic view of an obstructing esophageal mass; (1) endoscopic view of an esophageal stent fully deployed, delivery catheter within the stent; and (**c**) fluoroscopic waist seen post-stent placement

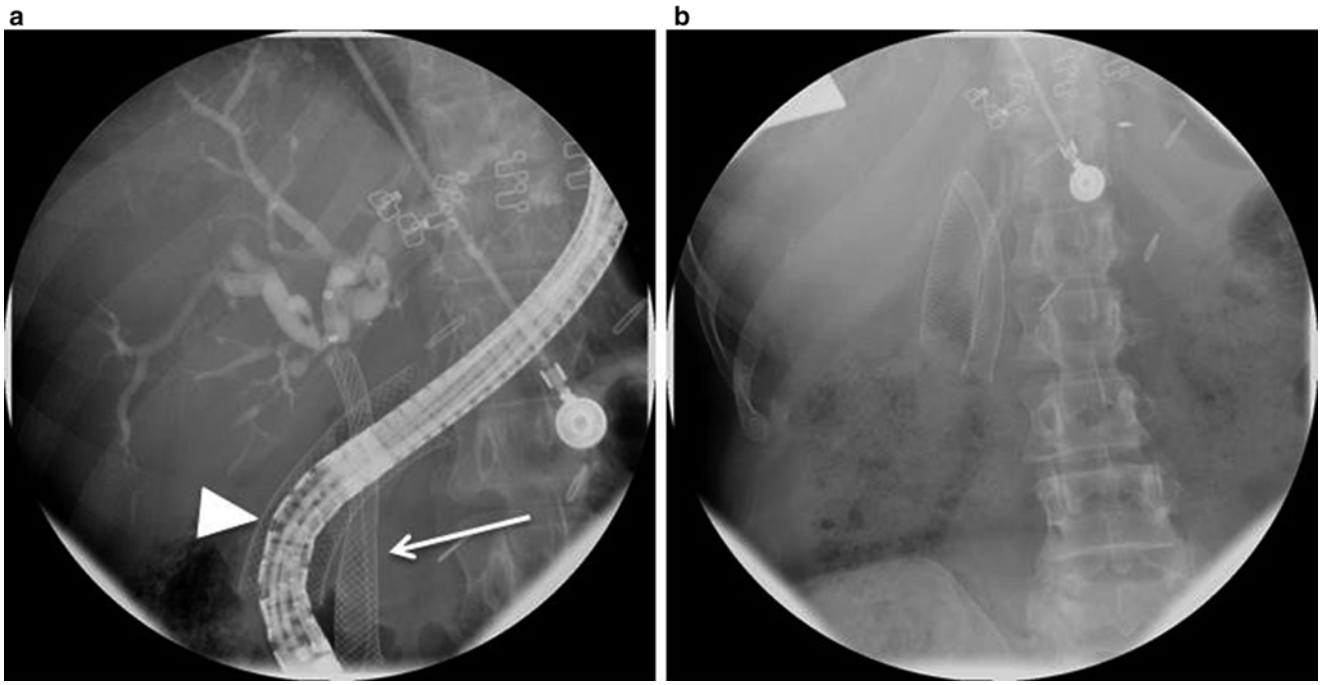

Fig. 3 Palliation of duodenal and biliary obstruction from pancreatic cancer (*Courtesy of Vinay Chandrasekhara, MD University of Pennsylvania, Philadelphia, PA*). (**a**) Fluoroscopic view of ERCP scope traversing the previously placed duodenal stent (*arrowhead*) in order to place the metal biliary stent (*arrow*). (**b**) Final fluoroscopic view of both stents

maintaining esophageal patency in the setting of malignancy. Provided that the stricture can be traversed endoscopically, the procedure has a very high technical success rate. Stent migration is the most common complication, occurring at rates ranging from 7 to 75 %, and patients should be made aware of this potential in the informed consent process [44, 45]. Post-procedure pain is also common, but often resolves after 48–72 h and can be managed with oral analgesics. Other considerations are the management of the induced acid reflux of the gastroesophageal junction that is bridged with the stent. As such, patients with esophageal stents are generally provided with a twice daily proton pump inhibitor as well as instructed to sleep at a 45° angle indefinitely. The decision to place a SEMS for esophageal cancer is institution dependent and best made in a multidisciplinary setting. In some cases, surgeons prefer not to have an esophageal stent in situ if the patient is a candidate for an esophagectomy and instead prefer to provide nutrition via a surgically placed jejunostomy tube (at which time, surgical ischemic conditioning of the future gastric conduit can be performed). Esophageal stents, in this instance, are reserved for palliative cases only. Alternatively, some practices routinely place SEMS for obstructing esophageal cancer to aid in nutritional improvement prior to neoadjuvant therapy and surgery.

Gastroduodenal stenting for malignant obstruction of gastric, duodenal, or pancreatobiliary cancers has technical success rates of 90–95 % according to multicenter retrospective studies [46] resulting in the ability to tolerate an enteral diet. Re-intervention rates are low (only 5 %), providing evidence that enteral stents achieve excellent palliation. Overall prognosis should be considered prior to palliative luminal stenting. If patient life expectancy is anticipated to exceed 6 months, a more durable approach such as a surgical bypass (gastrojejunostomy) should be employed. While generally well tolerated, the main complications of gastroduodenal stenting include stent migration, perforation, and stent obstruction by tumor or food. These obstructions can typically be resolved endoscopically by placing a stent within the originally placed stent [47–49]. Simultaneous biliary and gastroduodenal stenting is performed relatively commonly and has been shown to be a safe and effective means of palliation [50, 51] (Fig. 3). An additional consideration is that luminal stenting may not be effective for infiltrative-type gastric cancers in which motility is significantly compromised due to tumor (i.e., linitis plastica), rather than a true obstruction.

Finally, colonic stents have also been used in the setting of colonic obstruction for palliation and also for colonic decompression prior to surgical intervention (so-called bridge to surgery). Once again, similar to other luminal stenting, technical (>92 %) and clinical success rates (>89 %) are high, and adverse rates are generally low, although some studies raise concerns about perforation [52–54]. There are multiple studies evaluating the role of colonic stents with respect to bridge to surgery or allowing for a one step surgery (i.e., primary anastomosis versus an ostomy with subsequent

takedown and anastomosis). Overall, results from the available literature are highly variable largely due to multiple small studies, lack of homogeneity in patient populations, as well as definitions of success and treatments. Even meta-analyses of RCTs demonstrate significant heterogeneity [55]. Stents indeed allow for shorter hospitalization; however, 30-day mortality rates are no different than surgery.

For surgically unresectable disease, with a life expectancy <6 months, colonic stenting is the treatment of choice [56, 57]. In potentially curable disease, colonic stents should only be considered when surgical intervention is anticipated to shortly follow stent placement. A multidisciplinary discussion between the performing gastroenterologist, the colorectal surgeon, and oncologist is warranted to optimize patient outcomes, given the lack of clear data in this area [58].

Acute Pancreatitis

In patients with cancer, acute pancreatitis may occur as a result of pancreatic duct obstruction from tumor or as a result of chemotherapeutic agents. The diagnosis of acute pancreatitis is established by clinical symptoms, elevation of serum pancreatic enzymes greater than three times the upper limit of normal and imaging studies (CT or MRI with or without intravenous contrast). Mechanical obstruction of the main pancreatic duct or its branches is one of the etiologies of acute pancreatitis. While the most common reason for such an obstruction is gallstone disease, pancreatic neoplasms are recognized as an important cause of acute pancreatitis [59]. The risk of pancreatic adenocarcinoma after a single episode of acute pancreatitis is increased, with diagnosis that is often delayed for up to 2 years [60]. Age greater than 50 years, a history of smoking, weight loss of 10 lb or greater, serum bilirubin of 2 mg/dl, or alkaline phosphatase level greater than 165 U/ml as well as radiologic findings of distal pancreatic atrophy or mass had statistically significant association with the subsequent diagnosis of pancreatic adenocarcinoma on follow-up [61]. Pancreatic neuroendocrine tumors are an uncommon cause of acute pancreatitis, but also should be included in the differential diagnosis of acute pancreatitis, especially in patients older than 40 years in whom the etiology of acute pancreatitis is not clear [62].

Acute pancreatitis can sometimes be the first presentation of primary pancreatic or ampullary [63] neoplasms or metastatic disease to the pancreas [64], the latter of which has been described in patients with cancers of the lung, kidney, bile duct, and melanoma [65]. Malignancy-associated hypercalcemia may also be the cause of acute pancreatitis [66]. The risk of primary pancreatic cancer is significantly increased in patients with hereditary pancreatitis due to genetic mutations; the risk of pancreatic adenocarcinoma in these individuals is as high as 54 % by age of 75 years [67].

Acute pancreatitis may also develop in patients undergoing antineoplastic chemotherapy. While in general, less than 2 % of acute pancreatitis is drug induced, the development of acute pancreatitis has been infrequently associated with antineoplastic chemotherapy. While it is often impossible to definitively conclude that a particular drug is the etiology of pancreatitis without rechallenge, multiple cases of chemotherapy-induced pancreatitis have been reported, including with capecitabine, paclitaxel, bortezomib, vinorelbine, and ifosfamide. Rechallenge was not attempted in many of the reported cases [68]. Tamoxifen may act through induction of hypertriglyceridemia to induce pancreatitis [69]. It is important to recognize that patients receiving chemotherapy can develop acute pancreatitis independent of their tumor or therapy for malignancy due to common etiologies such as gallstone disease or alcohol.

The management of patients with acute pancreatitis involves administration of aggressive intravenous fluid hydration, analgesia, and bowel rest. Aggressive hydration is defined as 250–500 ml per hour (unless cardiovascular or renal indications dictate otherwise), with close observation of urine output and adjustment of hydration as needed, with the goals of decreasing blood urea nitrogen [70]. Early effective management of acute pancreatitis is critical to prevent multiorgan failure (renal failure, hypotension, respiratory compromise, and cardiovascular collapse) that can ensue as a result of the systemic inflammatory response syndrome [71, 72].

Inadequate early hydration may lead to any of these devastating consequences and is one of the most common clinical pitfalls in the management of acute pancreatitis. Furthermore, strict bowel rest (nil per os status, NPO) until patients are pain-free to limit pancreatic stimulation is a hallmark of initial management. The vast majority of patients have a mild course with inpatient admission for <5–7 days. In those cases in which the patient's clinical course dictates prolonged NPO status for more than 5–7 days, supplemental nutrition is indicated, preferably by enteral route with NG or nasojejunal (NJ) feeding. The optimal strategy is usually to allow the patient to consume nutrition per os; however, many patients are unable to meet the metabolic demands via only PO intake, and thus enteral nutritional supplementation should be instituted. In patients with acute pancreatitis, enteral nutrition significantly reduced mortality, multiple organ failure, systemic infections, and the need for operative interventions compared to those who received TPN. This was demonstrated in a meta-analysis of eight randomized controlled trials [73].

Patients who develop complications as a result of acute pancreatitis such as acute pancreatic fluid collections, pancreatic necrosis, or pseudocyst warrant a multidisciplinary discussion with gastroenterologists, including interventional endoscopists and pancreatic surgeons to optimize management of such complications.

Biliary Obstruction

Malignant obstruction of the biliary tree can arise from primary tumors of the bile duct (intrahepatic or extrahepatic cholangiocarcinomas) or from extrinsic compression and/or invasion of the bile duct by pancreatic, ampullary, or duodenal cancers and lymphadenopathy (peripancreatic or portal lymph nodes) or from metastatic spread to the biliary tree or liver. Biliary obstruction manifests as jaundice, acholic stool, dark urine, pruritus, abdominal pain, nausea, and weight loss. Cholangitis may occur as a result of biliary stasis and subsequent infection; however, in general, in the absence of prior biliary intervention or choledocholithiasis, ascending bacterial cholangitis is uncommon in patients with malignant biliary obstruction.

Biliary obstruction is diagnosed by abnormalities in serum bilirubin, alkaline phosphatase, and liver transaminases as well as imaging (ultrasound, CT, MRI) showing evidence of obstruction such as biliary dilation proximal to the site of obstruction. Once established, it is important to triage the urgency of biliary decompression. Patients with asymptomatic jaundice do not require biliary decompression unless their hyperbilirubinemia interferes with chemotherapy (i.e., some chemotherapeutic regimens require a normal bilirubin). Patients with intolerable jaundice or pruritus or poor nutritional status as a result of hyperbilirubinemia should have elective biliary decompression. Pruritus associated with hyperbilirubinemia can be debilitating and has been managed with antihistamines, corticosteroids, cholestyramine, and other medications with only limited success, and relief of obstruction is the mainstay of treatment. Those patients with signs and symptoms of acute cholangitis require urgent drainage and intravenous antibiotics.

Biliary decompression can be accomplished by endoscopic (endoscopic retrograde cholangiopancreatography, ERCP) (Fig. 4), percutaneous (interventional radiology), or surgical means. With the development and advances in endoscopic and percutaneous drainage procedures, surgical decompression is rarely utilized in modern clinical practice.

Endoscopic and percutaneous biliary drainage procedures have their individual risks and benefits. Common risks to both procedures include infection, stent occlusion, or migration. Endoscopic drainage via ERCP is considered relatively noninvasive, highly successful, and well tolerated. However, it carries risks associated with bleeding specifically from the biliary sphincterotomy site, intestinal perforation, and procedure-related pancreatitis (generally 3–7 %). Percutaneous transhepatic cholangiography (PTC) eliminates the potential for acute pancreatitis and intestinal perforation and requires less sedation than ERCP. It is highly successful especially in high-volume centers and, however, may be challenging in cases where there is no significant intrahepatic biliary dilation to serve as a target. This means biliary drainage may be necessary in the setting of gastroduodenal obstruction, although new endoscopic ultrasound-guided adjunct techniques allow for biliary drainage in this setting (i.e., choledochoduodenostomy). Percutaneous biliary drains can be replaced and exchanged with relative ease. Nevertheless, percutaneous biliary drainage does leave the patient with an external drain which may impact their quality of life, while endoscopic drainage obviates the need for external catheter drainage.

ERCP-placed stents can be plastic or metal (self-expandable metal stents, SEMSs). The advantage of plastic stents is their low cost and relative ease of removal, if needed, at the time of surgery. Plastic stents, however, have shorter life span due to their smaller diameter (maximum diameter of plastic stent is 12 French, 4 mm) and may not maintain patency long enough to allow for neoadjuvant chemoradiotherapy in cases of pancreatic adenocarcinoma. Up to 55 % of patients with ERCP-placed biliary plastic stents for malignant obstruction from pancreatic cancer require additional ERCP intervention for biliary obstruction or cholangitis related to stent occlusion [74]. Biliary SEMS do not adversely

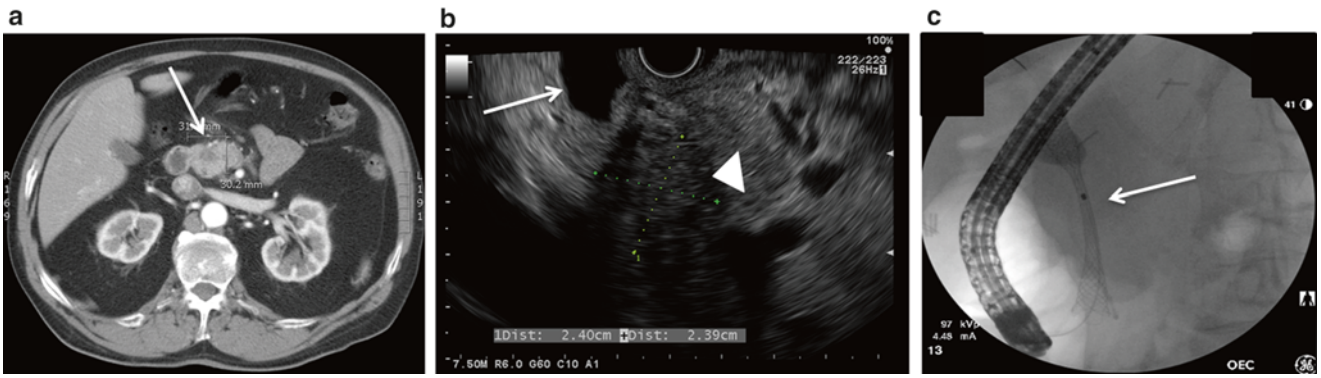

Fig. 4 Obstructing pancreatic adenocarcinoma. (**a**) A 2.5-cm ill-defined lesion in the pancreatic head on CT scan; (**b**) pancreatic head mass (*arrowhead*) resulting in biliary obstruction and dilated common bile duct (*arrow*) on endoscopic ultrasound; and (**c**) tight fluoroscopic waist within ERCP-placed self-expanding biliary metal stent for obstructing pancreatic head mass

affect surgical outcomes and are preferable for more durable stenting, however are relatively more expensive. When SEMS was compared to plastic stents in a retrospective fashion, metal stents did not increase postoperative complications, 30-day mortality, or anastomotic leak. While biliary metal stents have been shown to be superior to plastic stents for decompression caused by pancreatic adenocarcinoma by maintaining patency longer, stent occlusion may still develop. In a multicenter study of 241 patients treated with metal stents as part of preoperative protocol, 5.8 % of patients developed stent occlusion with a median time to occlusion of 6.6 months (range 1–20 months) [75]. Mechanisms of metal and plastic stent malfunction differ. Plastic stent may occlude due to formation of bacterial biofilm and sludge formation, or they may migrate proximally or distally and no longer span the obstructing biliary stricture. There may be tumor overgrowth covering the proximal end of the stent. Covered metal stents may have similar mechanisms for occlusion. Uncovered metal stents are less likely to migrate; however, there may be tumor or benign reactive tissue ingrowth, in addition to biofilm and sludge formation.

Patients with occluded biliary stents or percutaneous catheters may present with recurrence of their original symptoms that led to interventions, as well as jaundice, fever, chills, and abdominal pain, which can be absent in up to 20 % of the patients. Intermittent obstruction due to sludge and stones is possible. Imaging studies may show biliary dilation. Lack of pneumobilia (an expected finding in patients with patent biliary stents) may be a radiologic clue to biliary obstruction, but it is neither a specific nor sensitive finding.

The acute management of biliary obstruction with cholangitis in patients with malignancy is not different from patients with benign disease and involves management of sepsis with intravenous fluids, broad-spectrum antibiotics, and prompt establishment of biliary drainage via endoscopic or percutaneous methods. Endoscopic management options of occluded stents include removal of the occluded stent and placement of new covered or uncovered metal stent or plastic stent. Percutaneous catheter exchange in patients with prior PTC is the treatment of choice for acute cholangitis.

Management of these complicated patients necessitates a multidisciplinary team with input from medical, radiation, and surgical oncologists, the patient's primary care physician, interventional radiologists, and gastroenterologists to determine the optimal management strategy.

Hepatic Decompensation

Fulminant Hepatic Failure

Fulminant hepatic failure due to malignant infiltration of the liver is rare, but has been reported in case studies in the literature [76, 77]. These case reports have centered on diffuse infiltration by tumor cells (lymphoma and infiltrative carcinoma) rather than numerous hepatic metastases and could not be distinguished on cross-sectional imaging. Though it is a rare complication of metastatic liver disease, it carries a high mortality.

Patients usually present with jaundice, altered mental status, or bleeding. The etiology is due to replacement of hepatocytes with tumor resulting in the compromised liver synthetic function. As a result, there is decreased synthesis of albumin and oncotic proteins which promote the development of ascites, decreased conjugation of bilirubin resulting in jaundice, or obstruction of intrahepatic ducts from tumor resulting in jaundice, bleeding due to elevations in the prothrombin/international normalized ratio (INR) due to derangements in the synthesis of key clotting factors, and eventually decreased ability of the liver to process toxins resulting in encephalopathy. Cerebral edema may develop in patients with acute liver failure leading to increased intracranial pressure and risk of subsequent herniation. The early recognition of acute liver failure is critical given its overall dismal prognosis if left untreated. In cases in which the etiology is nonmalignant, lifesaving measures such as orthotopic liver transplantation should be considered. Clearly, when malignancy is the underlying etiology, recognition of hepatic decompensation is a sign of terminal prognosis.

Laboratory evaluation initially should include liver enzymes including AST, ALT, alkaline phosphatase, GGT, total and direct bilirubin, albumin, prothrombin time/INR, serum chemistries, ammonia level, and viral serological tests. Cross-sectional imaging may show diffuse hepatic involvement by tumor resulting in loss of hepatic reserve (Fig. 5). It is important to exclude a secondary etiology to liver dysfunction that may be at play and cause the sudden imbalance in liver synthetic function. Thus, hepatology

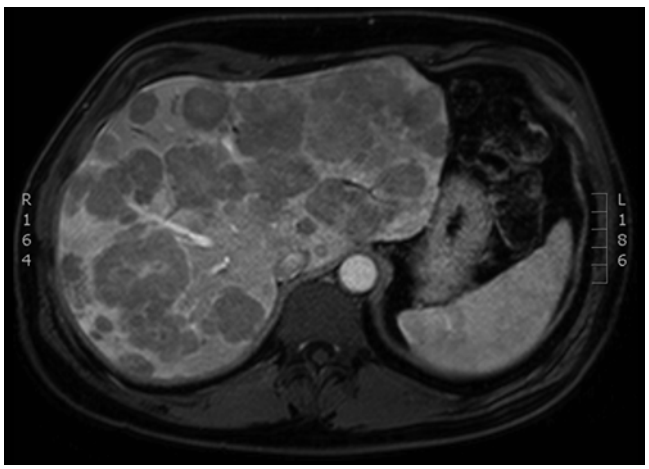

Fig. 5 Innumerable intrahepatic masses due to metastatic colorectal cancer resulting in jaundice and compromised synthetic liver function (*Courtesy of Alice Fung, MD, Oregon Health & Science University*)

consultation is appropriate. Additionally, it is important to exclude extrahepatic biliary obstruction as an underlying etiology for jaundice as therapy for biliary obstruction may lower the patient's bilirubin enough to allow for further oncologic treatment. In this vein, cross-sectional imaging (CAT scan of the abdomen or MRI/MRCP) and consultation with gastroenterology and interventional radiology may benefit the patient. In general, end-of-life malignant liver dysfunction rarely receives care from gastroenterology or hepatology. Nonetheless, it is important to exclude reversible contributing illness to a patient's declining hepatic function.

Ascites

Ascites, defined as free intra-abdominal fluid accumulation, may be a result of malignancy with and without liver involvement. Ascites may be detected due to the presence of abdominal distention and dullness to abdominal percussion. Abdominal ultrasound may be required to determine with certainty that fluid is present within the abdomen. Breast, lung, colon, and pancreatic primary malignancies are most commonly complicated by ascites [78]. In addition, significant intrahepatic tumor burden may result in liver dysfunction and subsequent ascites.

While there are many possible etiologies of ascites including cirrhosis, Budd-Chiari syndrome, pancreatitis, etc., we will focus on malignancy-related ascites. The serum-ascites albumin gradient (SAAG) has been used to categorize ascites as not related to portal hypertension and has a diagnostic accuracy of 97 % [79, 80]. In a patient with new ascites, a diagnostic paracentesis is performed in order to calculate this gradient and help identify the etiology. The pathophysiology of malignant ascites is not related to portal hypertension, and thus these patients have a SAAG <1.1 g/dl. There are several pathophysiologic mechanisms of malignant ascites including lymphatic obstruction by lymphoma or mass, low serum oncotic pressure due to various causes (including massive liver metastases with liver dysfunction), and exudation of proteinaceous fluid from tumor cells that line the peritoneum in patients with peritoneal carcinomatosis [78].

Unlike portal hypertension-related ascites in which the underlying pathophysiology involves a complex interplay of splanchnic and systemic vascular resistance coupled with sodium and water retention which in general responds to dietary sodium restriction, diuretics (such as furosemide or spironolactone), or intravascular volume expansion (intravenous albumin), the mainstay of the management of malignant ascites is large-volume paracentesis for symptomatic relief. This can be arranged as an outpatient via ultrasound guidance with interventional radiology or with gastroenterology. The timing and frequency of paracenteses are dictated by patient symptoms. In general, peritoneal catheters are avoided in these patients given the potential for loss of protein and hydration as well as potential to seed the catheter track. In patients with malignancy ascites related to ovarian cancer, tumor debulking and chemotherapy may be effective in ascites management (Sugarbaker technique).

Urgent Issues Related to Enteral Feeding Devices

Many patients with cancer battle with issues related to malnutrition. This is due to the prolonged negative balance of protein and energy below metabolic requirements that result from the tumor itself or intensity of treatments. As such, cancer patients may require supplemental enteral feeding via nasoenteral tubes, gastrostomy, or jejunostomy feeding devices. The type of enteral access is usually decided upon based on the length of anticipated need. Nasoenteric tubes are commonly used and have the benefit of relative ease of placement. Such tubes are utilized when the feeding is predicted to be approximately less than 30–45 days. Dislodgement of nasoenteric tubes is usually not of major concern as they are easily replaced and dislodgement can be prevented by the use of a nasal bridle device [81–83].

When long-term enteral access devices are needed, gastrostomy or jejunostomy tubes are the most common methods. Such devices may be placed by endoscopic (gastroenterology), percutaneous (interventional radiology), or surgical means. Once placed, it is recommended that these devices should not be removed for at least 6 weeks to allow the enterocutaneous fistula to mature prior to intentional removal. The patient should be made aware that once removed, the track can take up to 2 weeks to close and to expect some leakage during this time frame.

Enteral access replacement may be urgently needed in cases of unintentional dislodgement in order to prevent closure of the enterocutaneous fistula. If dislodgement occurs within 14 days of insertion, this track may not be mature, and "blind" reinsertion of a tube via the fistula should not be attempted [84] to avoid erroneous placement of the enteral device into the peritoneal cavity. The patient should be advised to call the provider who initially inserted the enteral device to arrange for reinsertion or present to the emergency department. In cases where the track is mature (>6 weeks from placement) and the device is dislodged, a temporary tube such as a Foley balloon catheter can be inserted in the track to maintain patency until the appropriate replacement device can be inserted and secured. This can be done at the bedside in any emergency department [85, 86]. By directly addressing the dislodged tube in a timely manner, the clinician may be able to avoid the need for an endoscopic, interventional radiology, or surgical replacement procedure.

Summary

GI-related oncologic emergencies represent a small proportion of all oncologic emergencies and herein discussed include GI bleeding, luminal and biliary obstruction, acute pancreatitis, hepatic decompensation, and dislodgement of enteral devices. These disorders require early recognition so that management can be directed efficiently. Additionally, it is important for the clinician, patient, and families to be aware of these possibilities to aid in early identification of such emergencies. A multidisciplinary approach to such patients and conditions, including consultation with oncology, radiation oncology, surgery, primary care, and gastroenterology to assist in management (which may include a therapeutic GI procedure), is likely to lead to optimal patient outcomes.

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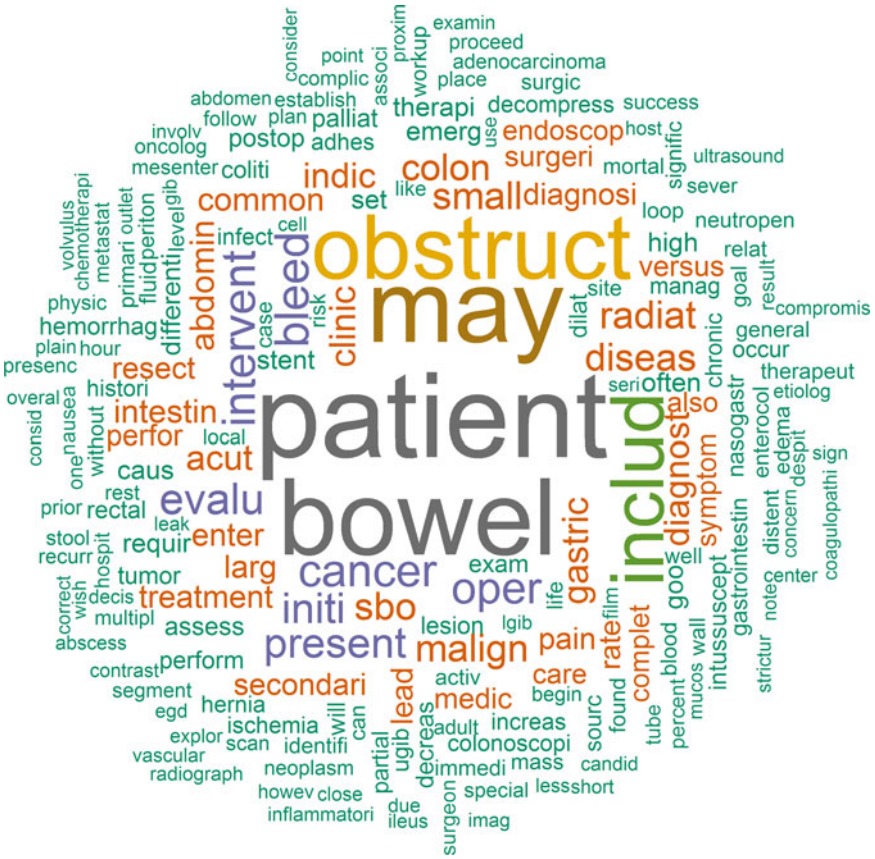
The Acute Abdomen

Analisa Armstrong and Alessandro Fichera



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Bowel Obstruction

Small Bowel Obstruction (SBO)

Small bowel obstruction (SBO) occurs when the flow of contents through the intestines is interrupted. Simple SBO may lead to intestinal dilation, hypersecretion, bacterial overgrowth, and vascular compromise. Closed loop obstruction may immediately compromise mesenteric blood supply leading to ischemia, necrosis, and potentially perforation.

The most frequent causes of small bowel obstruction are postoperative adhesions, malignancies, and hernias, respectively. Approximately two-thirds of SBO are secondary to postoperative adhesions. Malignancy is the second most common cause of bowel obstruction. Hernias, historically the most common cause of SBO, are now the third most common cause.

SBO may be classified as acute versus chronic, partial versus complete, simple versus closed loop, and gangrenous versus non-gangrenous. Cancer patients may have multiple causes for SBO including malignant mass (either extrinsic or intrinsic), postoperative adhesions, and post-radiation stricture. Patients with previous diagnosis of intra-abdominal malignancy have been noted to have high rates of cancer recurrence related to their SBO diagnosis [1].

An obstructing mass can be extrinsic and compressing bowel (e.g., carcinomatosis with implants) or intrinsic (e.g., small bowel adenocarcinoma, lymphoma). Obstruction in a patient with cancer may also be secondary to benign causes including fibrosis or stricture, postoperative adhesions or ileus, medical-related dysmotility, or treatment-related edema. Generally, small bowel malignant obstruction is more likely to be multifocal and extrinsic; large bowel obstructions are more likely to be single site and intrinsic in nature. The most common cancers leading to SBO are metastatic ovarian and colorectal adenocarcinoma with peritoneal implants, direct invasion, or carcinomatosis.

It is common for patients with known advanced primary or metastatic intra-abdominal malignancies to experience intestinal obstruction. Ovarian and colorectal malignant neoplasms are the most common metastatic tumors in the setting of SBO; however, SBO can also occur in patients with extra-abdominal primary tumors, such as melanoma, breast, and lung. Conditions associated with an increased risk of small bowel adenocarcinoma include adenomatous polyps, familial adenomatous polyposis, Peutz-Jeghers syndrome, and Crohn's disease. Conditions with an increased risk of lymphoma include celiac sprue, immunosuppression, HIV infection, *Helicobacter pylori* infection, and Epstein-Barr virus infection.

Clinical Presentation and Initial Assessment

Patients often initially present with nausea, emesis, and abdominal pain. Depending on the location of the obstruction as well as whether obstruction is partial or complete, patients may or may not initially present with abdominal bloating and distention. A patient with a proximal obstruction or tumor-encasing bowel may not present with distention.

Clinical evaluation of SBO should begin with identifying the where, when, and how of the patient symptoms—where the obstruction is (proximal or mid-small bowel versus large bowel), when symptoms started and their duration, and how complete (or partial) obstruction appears to be. A clinical estimate of the level of obstruction may be made from the periodicity of pain (short intervals tending to correlate with small bowel, long intervals with large bowel obstruction) and distention. The duration of symptoms should include any gradual or sudden changes in bowel habits, flatus, or bowel movements. Complete vs. partial obstruction may be inferred from current bowel activity.

Pain from SBO tends to be periumbilical and colicky initially. The colicky nature of pain is secondary to compensatory increased intestinal motility that initially occurs to counter the obstruction. However, such intestinal activity eventually subsides, and there are fewer contractions. As hypoactivity ensues and intraluminal pressure increases, microvascular perfusion may be compromised. Obstipation may ensue with complete bowel obstruction.

A differential diagnosis should include consideration of adhesive disease and hernias (including abdominal wall and internal hernias) as well as constipation, volvulus, stricture, and ileus due to chronic narcotic use, a not uncommon scenario in cancer patients. Additionally, neurogenic and metabolic etiologies should be entertained. History of surgeries, irradiation, and any anticholinergic medications is important.

A complete physical exam includes evaluation for hernias which may be the cause of small bowel obstruction and a rectal exam to evaluate for the presence of stool in the rectal vault, obstructing rectal lesions, fecal impaction, or occult bleeding. If the patient has an ileostomy or colostomy, the stoma should also be digitally examined to ensure no obstruction at the level of the fascia. Abdominal distention may lead to dyspnea. Jaundice should raise concern for involvement of the hepatobiliary tree, including lymphadenopathy at the porta hepatis or liver metastases.

The most important task in the initial assessment is to determine whether the patient requires immediate operative intervention. Indications for immediate operative intervention include incarcerated abdominal hernia, frank peritonitis, sepsis, or other findings concerning for ischemic bowel. Fever, tachycardia, increased fluid requirement, leukocytosis, and certainly signs of sepsis should raise concern for abscess or perforation in the setting of obstruction.

Diagnostic Workup

The diagnosis of SBO is often based on clinical findings; however computed tomography (CT) scan with IV contrast is an important tool in diagnosis and preoperative planning

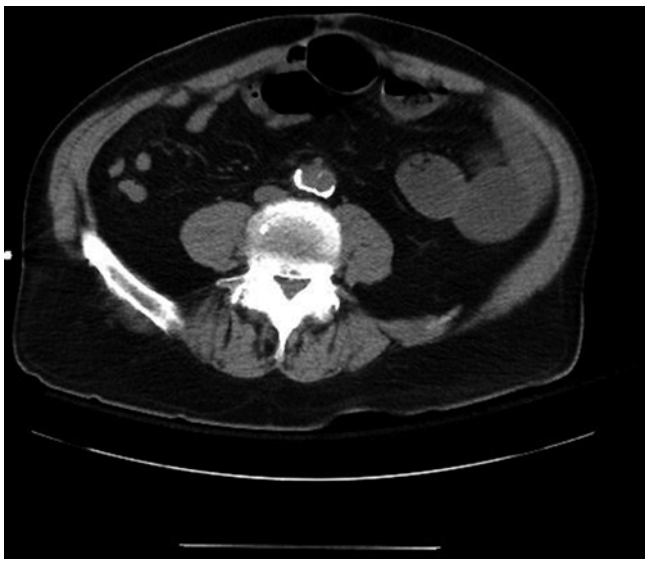

Fig. 1 CT—transition point in setting of complete mechanical SBO

in stable patients without indication for emergency exploration. CT may delineate a lesion, level of obstruction, the severity of obstruction including any transition point (Fig. 1) or closed loop obstruction, and other radiographic evidence of ischemia.

Radiographic signs of ischemia in bowel obstruction include a section of dilated small bowel adjacent to decompressed bowel, decreased enhancement, mucosal thumbprinting, bowel wall thickening, closed loop, mesenteric edema, pneumatosis intestinalis, and fecalization of small bowel. Air-fluid levels and bowel loops in the same place on supine and upright films indicate fixed adhesions. An abrupt cutoff with air-fluid levels suggests complete obstruction. Gas throughout the entire length of colon suggests ileus versus partial obstruction.

A single upright chest X-ray may exclude subdiaphragmatic free air, and it is a simple and quick test to determine the need for an emergency exploration especially in patients whose exam is unreliable (unresponsive, immunosuppressed, or elderly patients). It is the authors' preference to initially evaluate patients with SBO with plain abdominal films unless there is a clear indication for emergency exploration. Other diagnostic tools include plain films, small bowel series with water soluble contrast (Gastrografin) to assess partial obstruction, and abdominal ultrasound. Ultrasound may establish the SBO diagnosis with simultaneous distended and collapsed bowel segments, free peritoneal fluid, inspissated intestinal contents, paradoxical pendulating peristalsis, highly reflective fluid within the bowel lumen, bowel wall edema between serosa and mucosa, or a fixed aperistaltic loop.

Treatment and Operative Intervention

All patients should have initial management with volume resuscitation, bowel decompression and rest, and correction of metabolic abnormalities (Fig. 2). Unless there is indication for immediate intervention, initial pharmacologic management should be centered on antiemetics, analgesia, and anti-secretory medications. Prospective trials have evaluated the use of somatostatin with decreased distention and nausea, allowing for effective nasogastric tube decompression and symptom management in nonoperative candidates [2, 3].

Indications to proceed immediately to the operating room include clinical or radiographic evidence of bowel compromise and peritonitis. In patients with no prior history of operation, cancer should be suspected and a low threshold for prompt surgical exploration is indicated. Strangulation is associated with high mortality rates and conventional signs of vascular compromise may not always be present [4].

Intraoperatively, bowel viability may be determined by observation of peristalsis and color, Doppler ultrasound, and occasionally IV fluorescein and Wood lamp. Tumor debulking or even an oncologic resection may be feasible and indicated. Operative decision will include whether or not to restore bowel continuity, fashion a stoma, or leave the operating room and come back for a second look laparotomy in the unstable patient. If the lesion is felt to be a primary and resectable neoplasm in a stable patient, the tumor should be resected with a wide margin proximal and distal to the lesion of normal bowel including the lymph node basin for the involved segment.

Small bowel obstruction in the setting of suspected or known malignancy should include consideration and discussion of goals of care and overall disease burden. All efforts should be made to work collaboratively for a treatment plan incorporating patient and family values with a clear discussion regarding the limitations of surgery. A comprehensive treatment plan should include consultation with medical oncologists, palliative care specialists, gastroenterologists, radiologists, and dieticians.

A palliative, nonoperative approach to the intestinal obstruction should be entertained for patients with poor performance status, multiple sites of obstruction, carcinomatosis, or ascites. Recurrent obstruction may be as high as 50 % in these patients. Patients who are not operative candidates and do not respond to medical management may still benefit from endoscopic stenting or gastrostomy tube placement.

The goals of medical management should be aimed at limiting pain and improving quality of life. In cases of overwhelming cancer burden or transition to comfort care, artificial nutrition and hydration may be discontinued. The focus of care should be shifted to symptom relief and potentially hospice care.

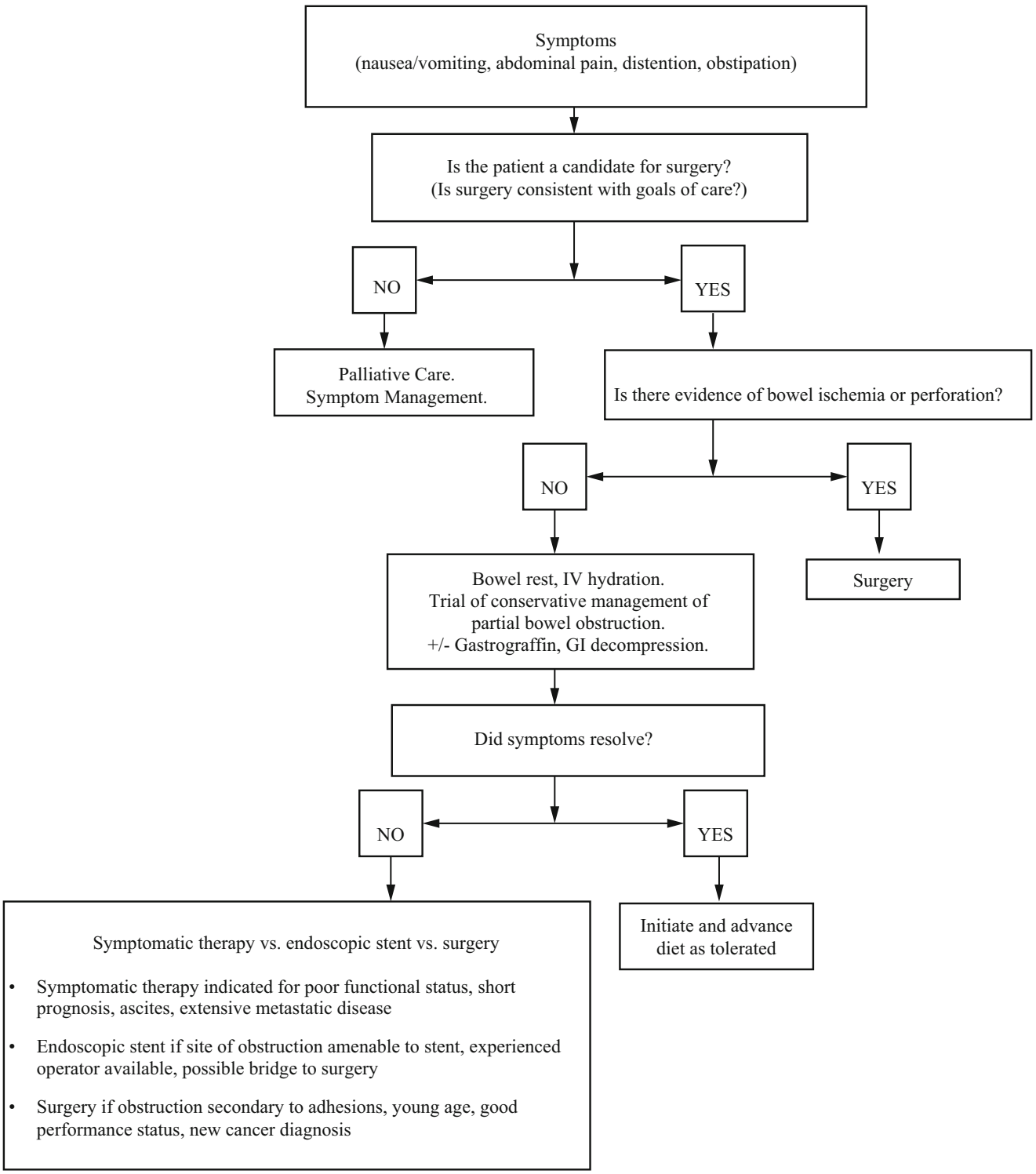

Fig. 2 SBO intervention algorithm

Large Bowel Obstruction (LBO)

Large bowel obstruction, while less common overall than SBO, is more likely to be secondary to malignancy. The majority of patients who present with large bowel obstruction are found to have colonic adenocarcinoma. Stenosis or abscess from diverticulitis is the second most common etiology for large bowel obstruction. Other etiologies for large bowel obstruction include colonic volvulus, generally cecal or sigmoid. Among sites for colonic obstruction,

the sigmoid colon is the most common followed by descending colon, splenic flexure, transverse colon, rectum, and ascending colon.

Clinical Presentation and Initial Assessment

Patients with LBO may present similarly to patients with SBO. Physical examination should again pay special attention to evidence of dehydration and hypovolemia as well as hernias with a rectal exam performed to evaluate for presence of stool in the vault, an obstructing rectal mass or bleeding.

Diagnostic Evaluation

Large bowel obstruction should be worked up similarly to SBO. While clinical diagnosis may be made with a thorough history and physical examination, most patients will undergo CT scan to evaluate extent and level of obstruction (Fig. 3). Other diagnostic tools may include plain abdominal x-rays, sigmoidoscopy (also therapeutic in the case of sigmoid volvulus), and a water soluble enema when the diagnostic differential includes colonic pseudo-obstruction.

Treatment and Operative Intervention

All patients should be placed on bowel rest with fluid resuscitation. If the ileocecal valve is incompetent and there is also small bowel distention, nasogastric decompression may be indicated. Partial colonic obstruction should be attempted to be treated conservatively with the hope that a patient can undergo a single-staged planned oncologic resection in an elective situation.

Additional options exist to bridge until operative intervention. Self-expanding metallic stents when feasible (Fig. 4) followed by elective laparoscopic colonic resection (Fig. 5) after stabilization and proper staging workup seem to result in lower blood loss, pain scores, incidence of anastomotic leak, and wound infection than those treated with emergency open surgery [5]. In one study, nearly three quarters of patients in the stented left sided large bowel obstruction group underwent successful one-stage operation versus closer to one quarter with emergency surgery. Initial technical success rates have been quoted as high as 90 % with prompt colonic decompression and overall 30-day mortality

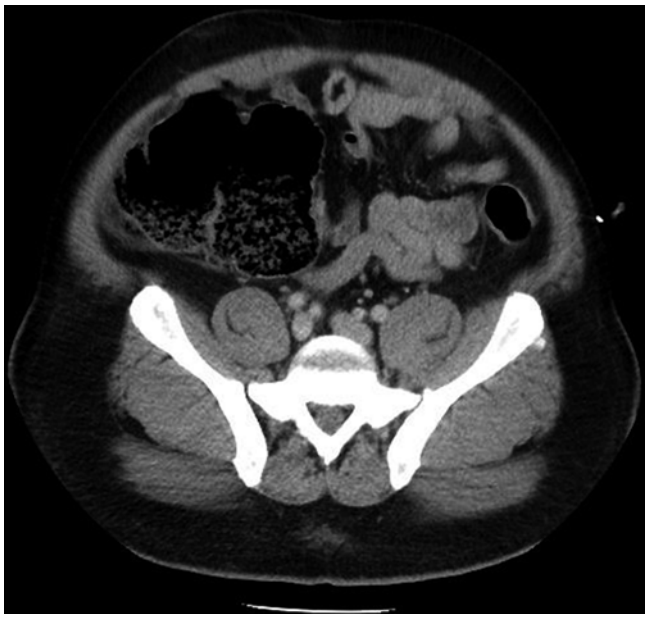

Fig. 3 CT—right colon/cecal dilatation in setting of partial LBO

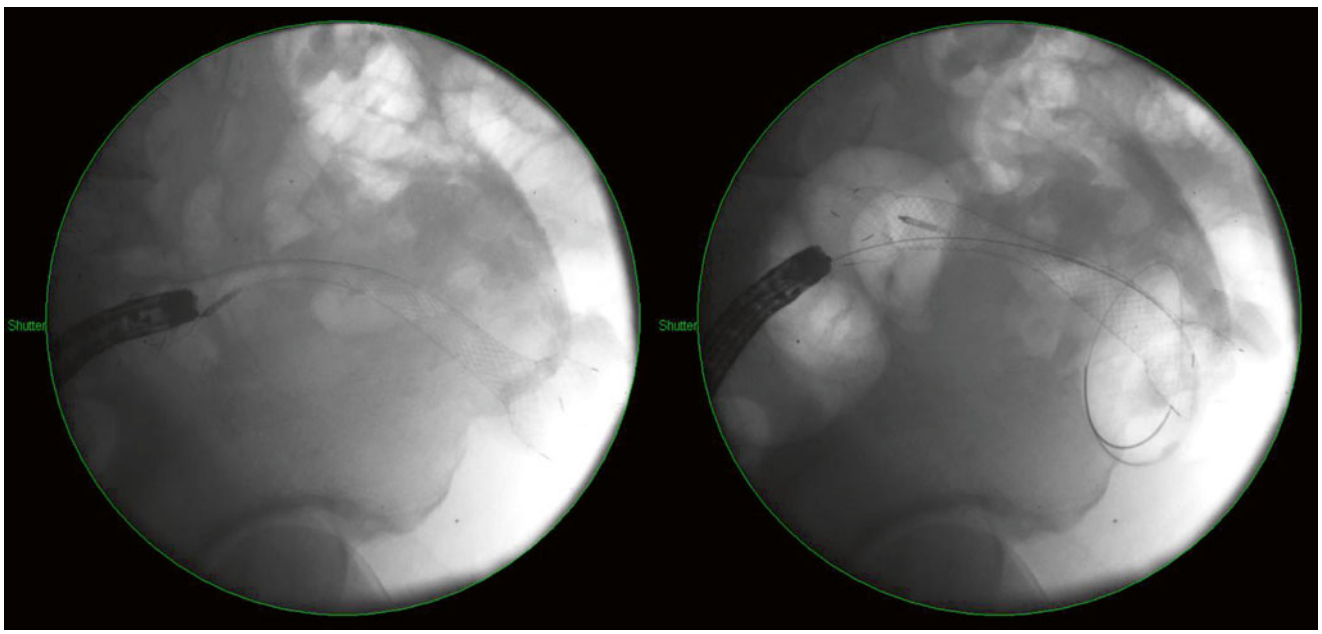

Fig. 4 CT—stent deployed in malignant bowel obstruction

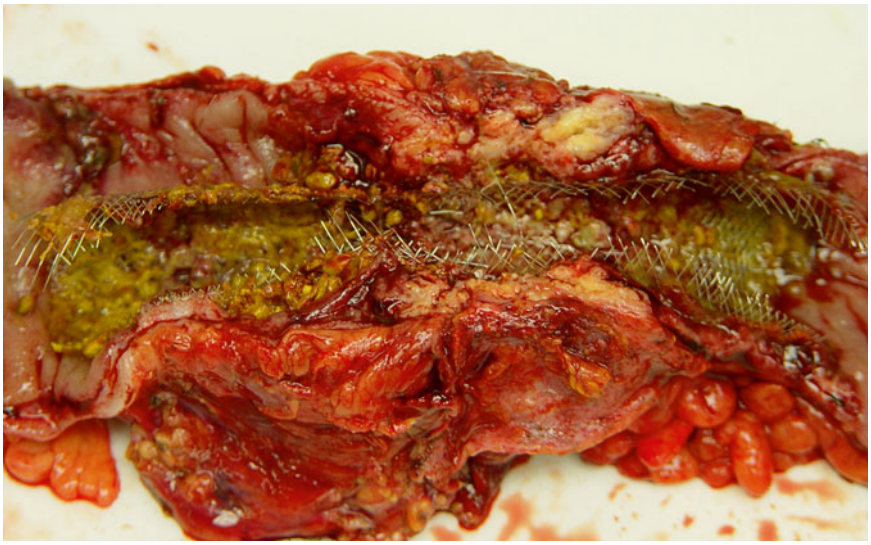

Fig. 5 Large bowel specimen with stent in place

of less than 2 % [6]. Nonetheless, given widely varied reported rates of technical failures and potential for bowel perforation, the presence of a skilled specialist and appropriate patient selection are of utmost importance.

In the palliative setting, colonic stenting results in faster resumption of oral intake and shorter hospital stay. Complication rates are relatively low but include stent migration, perforation, and re-obstruction [6, 7].

Emergent colonic surgery is associated with a significantly higher morbidity and mortality than elective surgery. The bowel is often friable and distended with significant stool burden, and the patients are often malnourished. Postoperative complications, re-obstruction rates, and readmission rates are high for palliative malignant bowel obstruction surgery [8, 9]. Should the decision be made to proceed with operative intervention without colonic stent, patients should be chosen for favorable prognostic features (no ascites, palpable masses), without frank perforation or chronic atony.

Gastric Outlet Obstruction (GOO)

Gastric outlet obstruction (GOO) commonly occurs in advanced gastric, duodenal, or pancreatic cancer. Less commonly, GOO is seen in cases of gallstone impaction, gastric polyp prolapse, PEG tube migration, or gastric volvulus.

Clinical Presentation and Initial Assessment

Patients will initially present with epigastric pain, nonbilious emesis, and weight loss with or without a history of malignant disease. Early symptoms may include early satiety and bloating. Patients with malignant disease may have a fairly short duration of symptoms, and symptoms may be intermittent until obstruction is complete.

Physical exam may reveal succussion splash. In metastatic gastric cancer, a left supraclavicular lymph node or periumbilical node may also be palpated as well as an abdominal mass in thin patients.

Diagnostic Evaluation

Initial examination may begin with an abdominal X-ray film. Patients with gastric outlet obstruction will have a gastric bubble if no nasogastric tube has been placed, with little or no air in the small bowel or the colon on radiographic imaging. CT imaging offers the advantage of identifying the obstruction and underlying lesion(s).

Barium swallow is a dynamic study and may distinguish GOO from delayed gastric emptying, anastomotic leak, or gastrogastric fistula in the postoperative setting. Evaluation will generally proceed to EGD which may be both evaluative and therapeutic with balloon dilation or self-expanding metallic stenting to improve gastric emptying. Differential diagnosis should include gastric dysmotility as well as dysphagia secondary to chemoradiation and anastomotic leak or gastric fistula in the postoperative setting.

Treatment and Operative Intervention

Therapy for GOO should begin with nasogastric decompression and fluid resuscitation. Goals of care will dictate intervention. For patients not able to tolerate surgery or with life expectancy less than 2 months, endoscopic stenting provides rapid and efficient palliation with minimal morbidity and a short hospital stay [10]. A minority of patients may be managed with prolonged nasogastric drainage and prokinetic agents alone.

Endoscopic stenting has been found across multiple series to have fast symptom relief with a shorter hospitalization compared to palliative surgery while palliative

resection resulted in better long-term outcomes in appropriate candidates.

For patients with good performance status and life expectancy of months to years or who fail endoscopic intervention, palliative gastrojejunal bypass may alleviate obstruction. In patients with GOO secondary to lymphoma, chemotherapy is the first-line indicated therapy. In patients with GOO secondary to newly diagnosed gastric cancer, endoscopic stenting may be utilized as a temporizing measure prior to complete oncologic workup and evaluation.

Gastrointestinal Bleeding (GIB)

Acute gastrointestinal bleed (Fig. 6) may present in the patient with established cancer diagnosis in a variety of clinical settings. Colorectal cancers are often also diagnosed after the onset of symptoms, including rectal bleeding.

Bleeding is categorized as upper gastrointestinal bleeding (UGIB) proximal to the ligament of Treitz versus lower gastrointestinal bleeding (LGIB). UGIB is associated with significant morbidity [11]. Diagnostic differential for UGIB

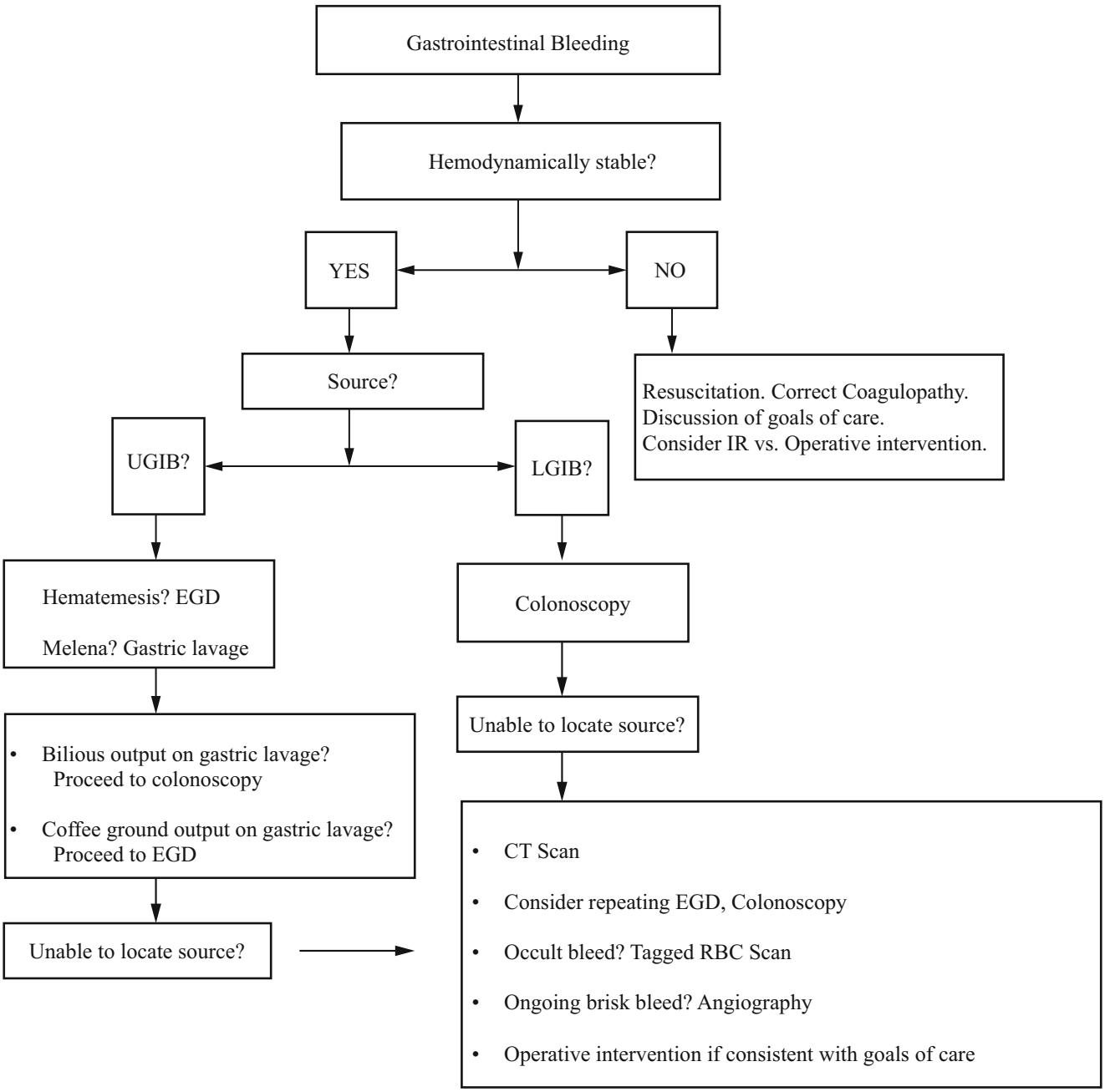

Fig. 6 Assessment and management of gastrointestinal bleeding algorithm

sources includes neoplasms such as GISTs, esophageal and gastric varices, Mallory-Weiss tears, acute hemorrhagic gastritis, and gastric/duodenal ulcers. Diagnostic differential for LGIB includes diverticular disease, neoplasm, radiation proctitis, inflammatory bowel disease (IBD), ischemia, infectious colitis, anorectal disease, coagulopathy, and arteriovenous malformations.

Clinical Presentation and Initial Assessment

Gastrointestinal bleeding (GIB) may present with melena, hematochezia, or hematemesis. Patients may endorse symptoms of hypovolemia including dizziness, dyspnea, or chest pain.

A history of prior episodes of bleeding is significant as 60 % of patients may rebleed from the same source [12]. Special attention should be paid to use of medications that may alter coagulation (Coumadin, aspirin, clopidogrel, NSAIDs) or alter hemodynamic response (beta blockers). Iron may turn stool black. Malignancy should be suspected in a patient with a history of smoking, alcohol abuse, or *H. pylori* infection.

Physical exam should begin with vital signs and an evaluation of hypovolemia. A complete abdominal exam including rectal exam with proctoscopy should be performed. Evidence of jaundice, caput medusae, or ascites may point to hepatic disease.

Diagnostic Evaluation

Initial triage should ensure adequate IV access is in place, either large-bore peripheral IV lines or a central line as indicated. Resuscitation is essential and coagulopathies should be corrected. Urinary output and mental status, markers of end-organ perfusion, should be monitored.

A nasogastric (NG) tube should be placed for gastric lavage. A positive aspirate of gross blood or coffee-ground appearance, indicated UGIB, should be followed by esophagogastroduodenoscopy (EGD). A bilious aspirate should be followed by colonoscopy. A clear aspirate requires the surgeon to follow clinical suspicion to EGD versus colonoscopy and often both. PPI therapy should be initiated at the suspicion for UGIB.

Treatment and Operative Intervention

Coagulopathies should be corrected in hemorrhaging patients. Severe thrombocytopenia may lead to spontaneous GI hemorrhage. The American Society of Clinical Oncology recommends a prophylactic platelet threshold for transfusion 10,000/μL for adult patients with leukemia, and multiple studies have found decreased frequency and severity in gastrointestinal hemorrhage in patients with platelet counts above 20,000/μL versus 10,000/μL or 5,000/μL [13].

EGD and colonoscopy may be both therapeutic and diagnostic. Erythromycin can be given prior to endoscopy to facilitate gastric emptying, decreasing the need for multiple endoscopic evaluations. Therapeutic endoscopic maneuvers include injection of vasoconstrictors or sclerotherapy, thermal coagulation, and mechanical occlusion of bleeding sites (including clips, bear claw, and over-the-scope clips application). In cancer patients with cirrhotic liver disease, rubber banding, sclerotherapy, or temporizing balloon tamponade may control hemorrhage.

Early endoscopy (<8–12 h from presentation) is ideal in a stable patient and will offer the best chance of localizing and identifying the source of GI bleed and intervening. Therapeutic intervention has been demonstrated to be most successful when performed within 12 h, with declining results as time passed. If bleeding recurs despite medical and endoscopic therapy, endoscopic intervention should again be attempted.

Other options for localizing a GI bleed include angiography, CT imaging, and tagged red blood cell (RBC) scan. CT may provide helpful identifying features for localizing a GIB, including hyperdensity of the peribowel fat, contrast enhancement of the bowel wall, vascular extravasation of the contrast medium, thickening of the bowel wall, polyps, tumors, and vascular dilatation. CT scanners have been noted to detect arterial bleeding at rates as low as 0.5 mL/min [14].

Tagged RBC scans are best for slow occult bleeds and may confirm the presence of an active bleeding site as slow as 0.1–0.5 mL/min. Mesenteric arteriography (for bleeding of at least 0.5 mL/min) may be useful for poor operative candidates where other measures have failed. Should embolization also fail during mesenteric angiography, and operative intervention ultimately required, the area may be still be identified for operative intervention with methylene blue infusion. A meta-analysis evaluating embolization therapy for non-variceal UGIB found a mean 84 % technical success rate and a 67 % clinical success rate. Angiographic embolization has a lower complication rate than surgery in the emergent setting for UGIB but higher rate of bleeding recurrence (34 % vs. 13 %) [15]. Arteriography may be therapeutic but requires active bleeding of more than 1 mL/min and should be reserved for patients with massive, ongoing bleeding in whom endoscopy is not feasible or colonoscopy fails to reveal the source of the hemorrhage.

Colitis may also be a special consideration in the patient undergoing radiation or chemotherapy. Radiation enteritis may lead to LGIB with a minority of patients even requiring hospitalization. Most patients with colonic ischemia respond to bowel rest, IV fluids, and antibiotics.

Indications for emergent operative intervention include hemodynamic instability despite maximal support measures, substantial bleeding (six units or more), or bleeding that is not controlled endoscopically. Rarely, operative intervention is required. Surgical options for LGIB include segmental colectomy when the source of bleeding can be localized. If no source is found, but bleeding is clinically significant and ongoing, a subtotal colectomy should be performed with an end ileostomy and rectal pouch leaving the patient in discontinuity. Such a situation is associated with high morbidity and mortality.

Neutropenic Enterocolitis

Neutropenic enterocolitis is a mucosal injury generally caused by cytotoxic drugs, allowing polymicrobial invasion and propagation by an impaired host defense system in the setting of profound neutropenia. Neutropenic enterocolitis can be fatal, resulting in bowel necrosis, perforation, and sepsis in an immunocompromised patient. The cecum is the most commonly affected bowel site likely secondary to its diminished vascularization and distensibility, and disease often extends to the right colon.

Clinical Presentation and Initial Assessment

The classic presentation of neutropenic enterocolitis is a patient with absolute neutrophil count <500 cells/μL, new abdominal pain, and fever. Most common timing is 2–3 weeks after receiving cytotoxic chemotherapy, when neutropenia is most profound. Patients may have nausea, vomiting, diarrhea, and hematochezia. Patients with prior episodes of neutropenic enterocolitis are at risk for future episodes.

Diagnostic differential should include graft-versus-host disease (GVHD) after allogeneic hematopoietic cell transplantation (HCT), infectious colitis including *Cytomegalovirus* (CMV) colitis and *Norovirus* in immunocompromised hosts, ischemic colitis (more commonly left sided), appendicitis, and colonic pseudo-obstruction.

Diagnostic Workup

Evaluation should begin with full infectious workup including blood and stool cultures and *C. difficile* toxin assays. CT findings may include bowel wall thickening, mesenteric stranding, bowel dilatation, mucosal enhancement, and pneumatosis (Fig. 7) [17]. Plain films may detect free air. Colonoscopy is relatively contraindicated and may cause cecal perforation.

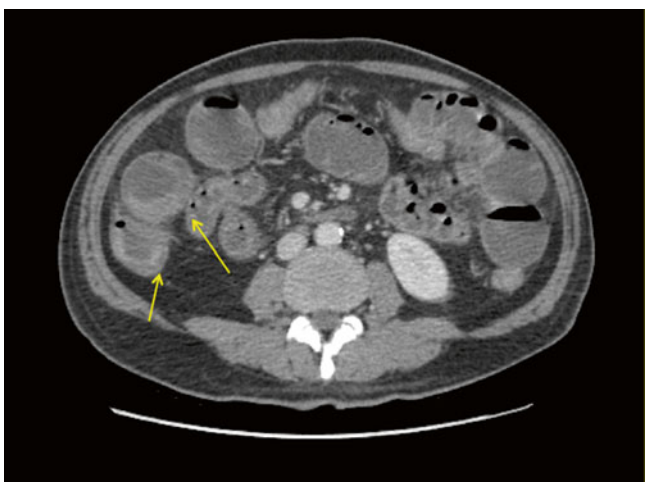

Fig. 7 CT—small bowel dilation with diffuse wall thickening and mucosal enhancement in setting of neutropenic enterocolitis

Treatment and Operative Intervention

Surgical intervention is indicated for patients with free perforation, peritonitis, and severe hemorrhage despite correction of coagulopathies that cannot be controlled with other means. In most patients, treatment should center on bowel rest, nasogastric decompression when significant small bowel dilatation is present, intravenous fluids, nutrition support, broad-spectrum antibiotics, and blood product support as needed. A broad-spectrum antibiotic regimen should include agents that are active against *Pseudomonas aeruginosa*, *Escherichia coli*, other enteric gram-negative bacilli, and anaerobes. Coverage for *C. difficile* should be included until ruled out. Antifungal coverage should be considered. Antidiarrheal agents should be avoided.

Malignant Intussusception

Intussusception is the telescoping of one part of the intestines into itself. In children, this process is benign and generally occurs at the ileocecal junction likely secondary to lymphatic hypertrophy and other benign etiology.

Intestinal intussusception in adult patients is rare (Fig. 8). In the adult population, intussusception is usually secondary to a malignant lesion acting as lead point (Fig. 9). Bowel telescoping will then lead to venous and lymphatic congestion, edema, and potentially ischemia and perforation.

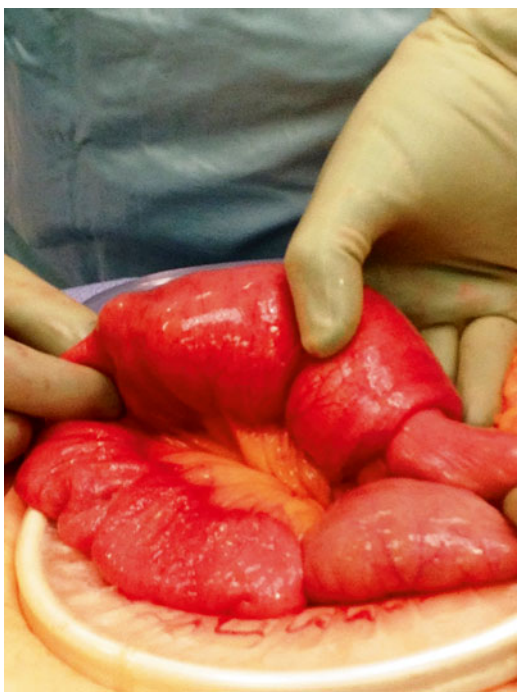

Fig. 8 Intraoperative intussusception with bowel telescoping

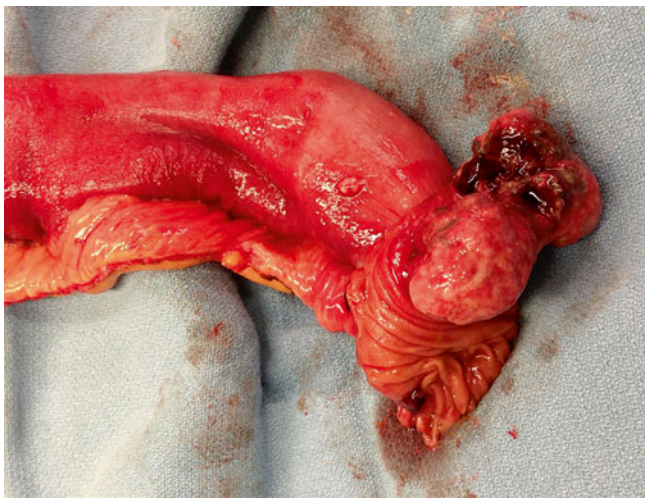

Fig. 9 Intraoperative intussusception with malignant lead point

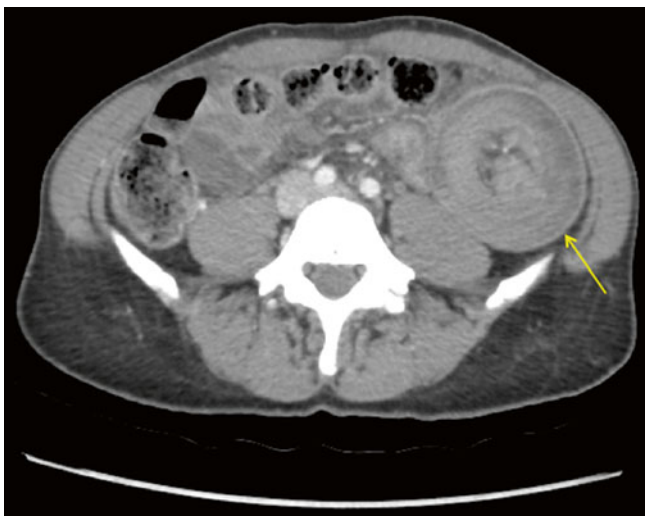

Fig. 10 CT—intussusception in adult with target sign

Clinical Presentation and Initial Assessment

Patients with intussusception may present with a waxing-waning pain of acute onset and short duration. Nonspecific findings may include nausea, vomiting, and obstipation.

Diagnostic Evaluation

Evaluation is centered on CT imaging for both diagnostic and operative planning purposes (Fig. 10). In thin patients, and when radiation exposure is a concern, ultrasound is often diagnostic.

Treatment and Operative Intervention

Intussusception in the adult necessitates surgical intervention, with resection of the involved segment and identification of lead point after thorough evaluation of bowel and peritoneal cavity. In one retrospective study, half of adult patients with intussusception were noted to have a malignant neoplasm [19]. In another retrospective review, 36 % of small bowel lesions and 80 % of large bowel lesions were malignant. All small bowel cancers were metastatic disease, and all large bowel malignancies were primary adenocarcinomas [18]. Appropriate oncologic workup should proceed once the patient is beyond the acute window.

Radiation Enteritis

Radiation enteritis is small bowel injury due to radiotherapy leading to inflammation, edema, and decreased bowel function. Radiation enteritis and radiation proctitis may be classified as acute vs. chronic and localized vs. diffuse. Despite attempts to protect the bowel from the radiation field when possible, gastrointestinal epithelium is especially susceptible to injury given its high proliferative rate. Cell damage in the mucosa leads to microvascular damage, inflammation, edema, and decreased absorptive capacity. Initial damage may be seen in hours and continue for weeks. Damage to the intestinal mucosa may lead to fibrosis, perforation, fistulae, or abscess.

Symptoms of acute radiation enteritis may occur transiently in up to 75 % of patients undergoing radiation therapy for abdominal and pelvic cancers. Chronic radiation enteritis may occur in closer to 5–20 % of patients [20, 21]. Patients at higher risk of developing acute radiation enteritis include those with already diminished splanchnic perfusion secondary to diabetes mellitus or atherosclerotic disease as well as patients with restricted mobility of the small intestine due to postoperative adhesions.

Clinical Presentation and Initial Assessment

Presentation may include nausea, vomiting, abdominal pain, bloating, cramping, diarrhea, or ileus. Given the diminished absorption compounding an often preexisting cancer-related anorexia, patients often are dealing with malnutrition and weight loss. Patients may bleed from ulceration, have signs of systemic infection from abscess, or present with obstructive symptoms. Patients with acute enteritis present within 3–6 weeks from last treatment, but patients with complications of chronic enteritis have been found to present up to 20 years from treatment.

Toxicity and the risk of radiation enteritis are increased with combined administration of chemotherapy and a host of factors that decrease bowel mobility. Factors associated with decreased bowel mobility include history of abdominal surgery, female sex, advanced age, thin build, and pelvic inflammatory disease. Additionally, dose fractions >2 Gy have been noted to increase the risk of toxicity.

Differential diagnosis includes tumor recurrence, inflammatory bowel disease (ulcerative colitis, Crohn's disease),

ischemic colitis, infectious colitis, STD proctitis (e.g., lymphogranuloma venereum, gonorrhea), and inflammatory bowel syndrome.

Diagnostic Evaluation

Diagnostic evaluation centers on colonoscopy versus sigmoidoscopy, which may be sufficient to establish diagnosis. CT scan may be important to rule of the presence of recurrent cancer or other causes for clinical picture. CT enteroclysis may also be useful in identifying mucosal abnormality consistent with radiation enteritis [22].

Treatment and Operative Intervention

Most cases of acute radiation enteritis are self-limited and should be treated with supportive therapy. Initial management includes elemental diet, IV hydration, bowel rest, and ± octreotide. Sphincter dilation may be required for anal strictures or stenosis.

Indications for operative intervention include complete obstruction, perforation, and hemorrhage persistent despite medical intervention. A fibrotic rectum may lead to severe tenesmus, requiring fecal diversion. Resection of radiated bowel may be performed with or without immediate restoration of intestinal continuity; however, anastomoses between irradiated segments of intestine have been associated with high leak rates [23]. In extreme cases fecal or urinary diversion may be performed for palliation without resection of injured tissue.

Conclusions

The acute abdomen in the patient dealing with either a new or established cancer diagnosis creates a special challenge for the surgeon to individualize decisions, keeping in mind goals of care and the patient's wishes. The surgeon must consider both a broad differential and cancer-specific considerations in considering differential diagnosis. Evaluation and intervention should proceed with the involvement of a multidisciplinary care team with the patient and his or her goals of lifestyle and therapy at the forefront. Caring for a cancer patient in the setting of an acute change in condition ultimately means knowing not only what is possible surgically and what is indicated medically but evaluating what is right for the patient overall.

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Colorectal Cancer Prevention and Emergency Management

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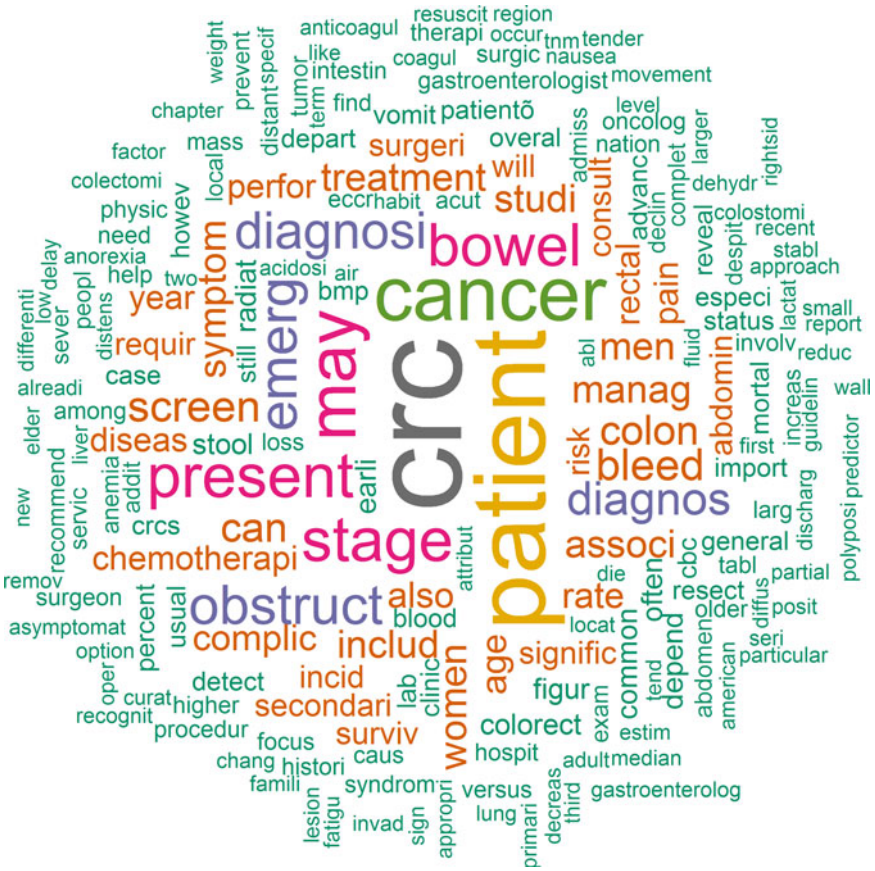

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Background

The lifetime risk of obtaining colorectal cancer is 1 in 20 [6] with a higher predominance in men compared to women. In 2014, it is estimated that CRC will be diagnosed in 71,830 men and 65,000 women. Of those, 26,270 men and 24,040 women will die from CRC [7]. Overall, CRC incidence and mortality rates are about 30–40 % higher in men than in women [8, 9]. The reasons for this are not completely understood, but gender differences in risk patterns may explain why a larger proportion of tumors in women are located in the proximal colon, 45 % versus 36 % in men [10]. In terms of age, 90 % of new CRC cases are diagnosed in people over the age of 50 [10]. The median age of colon cancer diagnosis is 69 in men and 73 in women—both of which are older than the median age of rectal cancer diagnosis of 63 in men and 65 in women [11].

Diagnosis of CRC

The diagnosis of CRC is not straightforward. First, the cancer can be discovered at any stage during progression, from asymptomatic cancer identified by screening through consultation with a general practitioner or gastroenterologist to presentation as a surgical emergency (usually with bowel obstruction or perforation) [12, 13]. If diagnosis is delayed and surgery is emergent or palliative in nature, it is associated with a substantially elevated risk of mortality [14], especially among the elderly [15]. However, if detected early, the 5-year survival rate is 90 % while still localized (i.e., confined to the bowel wall), 68 % for regional disease (i.e., lymph node involvement), and 10 % if distant metastases are present [16–19].

Risk for CRC is increased by genetic mutations (i.e., familial adenomatous polyposis, Lynch syndrome, juvenile polyposis, and Peutz-Jeghers syndrome), personal history (i.e., irritable bowel syndrome, Crohn's disease, and ulcerative colitis), and lifestyle factors (i.e., smoking, alcohol consumption, and diets high in fat and low in fiber). Early stage CRC does not usually present with symptoms. Therefore, screening is necessary to detect cancer at earlier stages. Patients with advanced disease may present with changes in bowel habits, blood in the stool, weakness, fatigue, shortness of breath, signs of intestinal obstruction (i.e., bloating, fullness, cramps, and pain), unexplained weight loss, pain with defecation, and thin stools. In addition to CRC, the differential diagnosis for these symptoms includes hemorrhoids, infection, and inflammatory bowel disease.

The ACS [20, 21] and National Comprehensive Cancer Network (NCCN) [22] provide recommendations for guideline CRC treatment by TNM stage. Specifically, resection is recommended for stages 0, I, II, and III CRC and chemotherapy is guideline care for stages III and IV of CRC. Surgery is the most common treatment for CRC with the usual operation being either a segmental resection, partial colectomy, or diverting colostomy in the case of obstruction. Especially for CRCs that have not spread, surgical removal may be curative [23]. The choice of operation depends mainly on the site of the disease (left-sided versus right-sided), the patient's physical condition, nutritional status, and age. The treatment for right-sided lesions is a right hemicolectomy. However, treatment of left-sided lesions is still undecided. There are many therapeutic options such as primary or staged resections, Hartman's procedure, subtotal colectomy, or colostomy. Other therapies involve nonoperative techniques such as laser therapy, colonic stenting, emergency endoscopy, and comfort measures.

Table 1 correlates the stages of CRC with the TNM categories and their associated management.

Table 1 Correlation between TNM categories and stage for CRC

Stage	TNM category	Interpretation	Colon cancer management	Rectal cancer management
0	Tis, N0, M0	Early stage cancer where the cancer is limited to the mucosa of the colon or rectum (Tis). No lymph node involvement (N0) or distant spread (M0)	Surgery	Surgery
I	T1–T2, N0, M0	The cancer has grown through the mucosa into the submucosa (T1) or muscularis propria (T2). No lymph node involvement (N0) or distant spread (M0)	Surgery	Surgery ± radiation
II	T3–T4, N0, M0	T3–T4 stage with no spread to lymph nodes (N0) or distant sites (M0)	Surgery ± chemotherapy	Surgery + chemotherapy + radiation
III	Any T, N1–N2, M0	Any *T* stage with spread to 1–3 (N1) or four or more (N2) regional lymph nodes. No distant spread (M0)	Surgery + chemotherapy ± radiation	Surgery + chemotherapy + radiation
IV	Any T, any N, M1	The cancer can be any *T* stage and any *N* stage and has spread to distant sites such as the liver, lung, peritoneum, or ovary (M1)	Surgery + chemotherapy ± other treatments (RFA, cryosurgery)	Surgery + chemotherapy + radiation

Adapted from the American Cancer Society (2005) [41]

Table 2 Summary of recommendations

Population	Recommendation	Grade
Adults, beginning at age 50 years and continuing until age 75 years	The USPSTF recommends screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 years and continuing until age 75 years. The risks and benefits of these screening methods vary	The USPSTF recommends the service. There is high certainty that the net benefit is substantial
Adults age 76–85 years	The USPSTF recommends against routine screening for colorectal cancer in adults 76 to 85 years of age. There may be considerations that support colorectal cancer screening in an individual patient	The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small
Adults older than age 85 years	The USPSTF recommends against screening for colorectal cancer in adults older than age 85 years	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits
Computed tomographic colonography and fecal DNA testing as screening modalities	The USPSTF concludes that the evidence is insufficient to assess the benefits and harms of computed tomographic colonography and fecal DNA testing as screening modalities for colorectal cancer	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined

Source: http://www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/colorectal-cancer-screening, accessed April 7, 2015

Trends in CRC incidence and mortality reveal overall declining rates, which have been attributed to reduced exposure to risk factors, early detection through screening and prevention through polypectomy, and improved treatment [24]. However, studies show a majority of U.S. adults are not receiving age- and risk-appropriate screening or have never been screened [18, 25–28]. Among CRC patients, only 39 % are actually diagnosed at an early stage, mostly due to these low screening rates [29, 30]. Significant delays in screening translate into worse outcomes in terms of stage of cancer at diagnosis, ability for curative treatment, likelihood of recurrence, and survival, especially among the elderly [31].

Current recommendations for colorectal cancer screening from the US Preventive Services Task Force are presented in Table 2.

The overall relative survival rate for CRC is 65 % at 5 years following diagnosis and 58 % at 10 years [11]. Forty percent of CRCs are diagnosed at a local stage, for which the 5-year survival rate is 90 %. Thirty-six percent of CRCs are diagnosed at regional stage, for which the 5-year survival rate is 70 %. Twenty percent of CRCs are diagnosed at a distant stage, for which the 5-year survival rate is 12 %.

CRC Diagnosis in the ED

The number of patients presenting to the ED who are subsequently diagnosed with cancer in the ED has increased [32, 33]. In 2006, for instance, EDs across the United States diagnosed 204,000 cases of cancer with 187,000 being malignant neoplasms requiring hospital admission [34]. A population-based study of 11,023 patients in Connecticut reported patients admitted from the ED with a CRC diagnosis were usually older (75+) and African American. An ED admission status was a significant predictor of distant stage in all patients [35]. A study of 151 patients in the United Kingdom examined the pathways to diagnosis of CRC. Despite considerable investment by the UK National Health Service in cancer diagnostic services for primary and specialty practices, 26 % of patients had an emergency diagnosis [36].

Diggs, Xu, Diaz, Cooper, and Koroukian [37] focused on predictors and the associated burden of emergency CRC resection (E-CCR), which has been defined as the "clearest evidence on an individual level for a failure of screening" [38]. This cross-sectional study of over 120,000 discharges nationally focused on patients who underwent the procedure emergently, finding older patients dually eligible for Medicare and Medicaid were at higher risk for E-CCR. There was also a threefold increase in hospital mortality, longer lengths of stay, and more than $250 million in additional hospital charges associated with E-CCR. This study was limited in its focus on one type of cancer and a particular procedure associated with CRC.

Early CRC may present to the ED with vague to no symptoms, which further emphasizes the importance of screening. Symptoms that may suggest CRC and the need for additional screening if not already diagnosed with CRC are presented in Table 3.

A positive family history of colon cancer should also raise suspicion for CRC on the differential.

Table 3 Emergent symptoms suggestive of CRC

• Bleeding from the rectum
• Blood in the stool or in the toilet after having a bowel movement
• Dark or black stools
• A change in the caliber or shape of the stool (i.e., narrow stools)
• Cramping or discomfort in the lower abdomen
• An urge to have a bowel movement when the bowel is empty
• Constipation or diarrhea that lasts for more than a few days
• Decreased appetite
• Unintentional weight loss
• Weakness and fatigue secondary to anemia

Findings on physical exam include grossly positive or guaiac stools. It is important to get basic labs (i.e., CBC and BMP) since blood loss from the cancer leads to anemia, specifically iron deficiency anemia. In the ED, a CT of the abdomen with contrast can help locate and characterize a mass. Timely evaluation of symptoms consistent with CRC is essential, even for adults younger than age 50. If stable, the patient can be discharged with referral to a gastroenterologist for colonoscopy and/or surgeon if a mass is found.

Oncologic Emergencies Associated with CRC

More common is the management of the complications of patients already diagnosed with CRC, which include bowel obstructions, perforations, rectal bleeding, and complications secondary to chemotherapy and radiation. The sections below describe the relationship between CRC and the respective complications and associated history and clinical findings with the appropriate emergency department management [39].

Bowel Obstruction

As a tumor grows, it may bleed or cause obstruction of the colon. Intestinal obstruction can occur when tumor growth has invaded the lumen of the large intestine. Up to 20 % of colon cancer in some series will present as bowel obstruction. This is more likely to occur in the left colon because it is narrower, with the splenic flexure particularly vulnerable [40].

Patients may present with diffuse, colicky abdominal pain, nausea, vomiting, and abdominal distension. They also may have decreased to no bowel movements and flatus. On physical exam, there will likely be diffuse abdominal tenderness and distension with high-pitched or absent bowel sounds. The patient may also be clinically dehydrated and in advance stages, be hypotensive, tachycardic, and febrile. Labs such as a lactate, CBC, and BMP may be helpful and reveal a metabolic acidosis. Imaging includes an acute series that reveals multiple air-fluid levels, more than 3 cm of dilatation of the small bowel, and/or more than 3 mm thickening of the small bowel (Fig. 1a, b).

An abdominal CT can also be very helpful in distinguishing between partial versus complete bowel obstructions as well as to assist in identifying the anatomic location of obstruction (Fig. 2). Intussusception primary or metastatic deposits to the bowel can contribute to obstruction (Figs. 3 and 4).

ED management includes symptomatic treatment with IV fluid boluses, antiemetics, and analgesia. An NG tube may be placed for a significant obstruction, especially if vomiting, and keeping the patient NPO for bowel rest. These patients require admission with gastroenterology and surgery consulting.

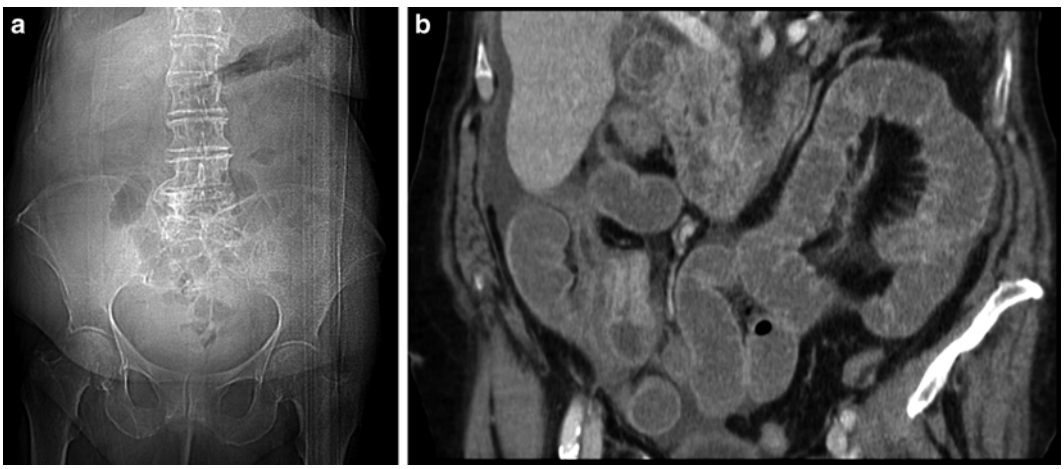

Fig. 1 (**a**) Small bowel obstruction on a KUB x-ray due to metastatic lobular breast cancer. (**b**) Coronal CT image revealing a segmental stricture in the right lower quadrant with thickened enhancement of the small bowel wall

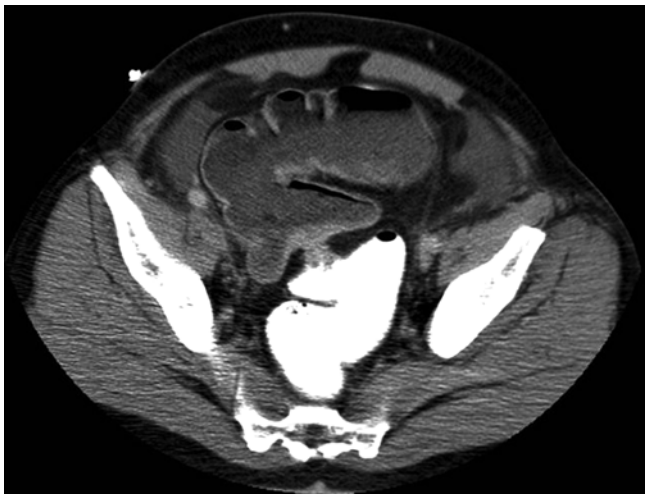

Fig. 2 Apple-core obstructing colon cancer following a barium enema demonstrated on an abdominal CT (axial). Note that the contrast material does not pass through the lesion retrograde and the upstream bowel appears to be distended

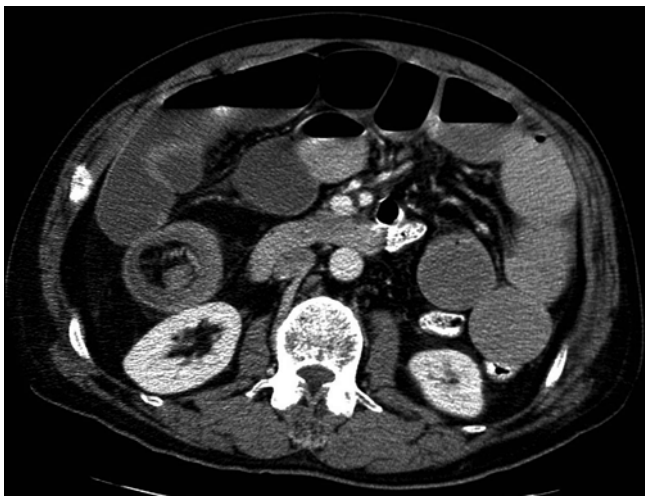

Fig. 3 Small bowel obstruction from intussusception secondary to melanoma metastasis, located in the right abdomen in front of the right kidney as demonstrated on an abdominal CT (axial)

Perforation

Patients with CRC may also present with bowel perforations as the CRC invades through the colon wall in more advanced stages. Patients may present with an acute onset of severe abdominal pain possibly associated with near or complete syncope. They are often unable to localize the pain but report worsening pain with any movement (parietal pain). Anorexia is common, but vomiting is often uncommon. On exam, the patient may have acute peritonitis with a rigid abdomen and rebound tenderness. Critical studies include an upright chest x-ray to ensure no air under the diaphragm. Free air can be seen in 70–94 % of cases. A CT abdomen/pelvis would be the definitive study if the CXR is inconclusive.

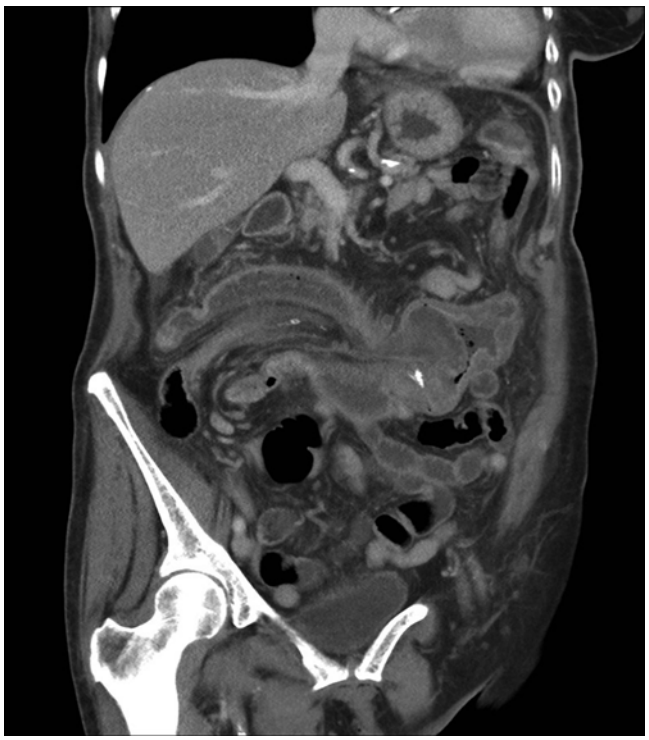

Fig. 4 Intussusception from a primary cecal tumor as demonstrated by an abdominal CT (coronal)

ED management includes IV fluid resuscitation and antibiotics (i.e., 3.375 g of IV Zosyn) Immediate surgical consults are required with patients with perforation.

Rectal Bleeding

Patients with CRC can present with blood in their stools in the setting of recent changes in their bowel habits (i.e., constipation). In general, cancers of the ascending colon tend to be larger and more frequently bleed. Cancers of the descending colon tend to be smaller and more obstructive. Predominant constitutional symptoms include anorexia, fatigue, weight loss, and presyncope. Patients can present from asymptomatic rectal bleeding to ill-appearing with pale conjunctivae, hepatomegaly (secondary to liver metastasis), abdominal or rectal mass, and/or guaiac-positive stools.

Labs include a lactate, CBC, BMP, and coagulation studies. A CBC often reveals microcytic anemia. A BMP can be indicative of an anion gap (lactic) acidosis that is secondary to hypoperfusion. Coagulation studies should be ordered if the patient is anticoagulated or has liver disease.

The ED management depends on the severity of the rectal bleeding. With significant bleeding, two large bore IV lines should be established and the patient should be volume-resuscitated with normal saline and cross-matched for two to four units of blood. If the patient is anticoagulated, FFP may be required to reduce the INR from 1.5 to 2.5. Vitamin K

may be needed if bleeding continues despite FFP. Surgery should be consulted if significant bleeding or obstructive symptoms. If stable with an occult lower GI bleed, outpatient oncology work-up may be appropriate.

Complications Secondary to Chemotherapy and Radiation

Patients in stages 1 and above of CRC may require chemotherapy and radiation which can present to the ED as severe nausea and vomiting. Chemotherapy often causes symptoms 2–3 days after treatment. The emergency medicine approach is dependent on the patient's clinical status. If they appear significantly dehydrated, labs should be drawn to rule out any electrolyte abnormalities. The patient may require IV hydration and antiemetics. The final ED disposition is dependent on the patient's clinical status (i.e., orthostatic, able to tolerate PO, etc.), and the patient's gastroenterologist, hematologist, and/or surgeon should be consulted.

Conclusion

Despite the decreasing incidence of CRC, emergencies secondary to this deadly cancer still exist. It is important for the ED physician to be able to recognize the signs and symptoms that may hint at a new CRC diagnosis as well as how to manage complications in patients with pre-existing CRC. The approach is multidisciplinary with consultation of gastroenterology, hematology/oncology, and surgery depending on the patient's presentation, however, most importantly is the emergent recognition and stabilization of these often complex patients.

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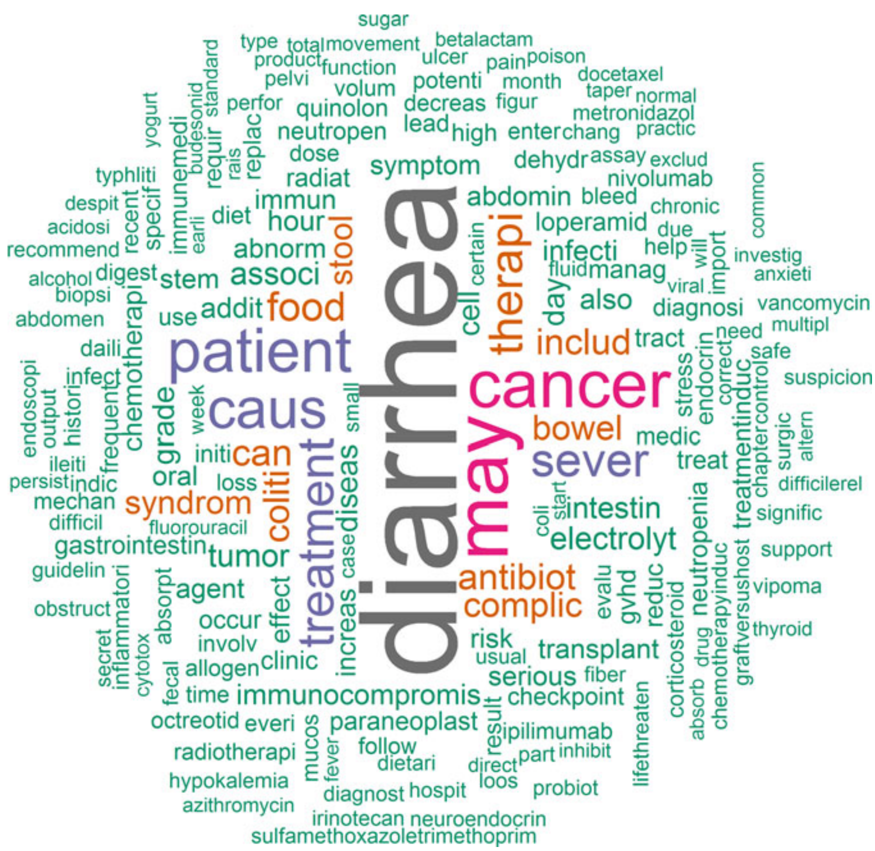
Diarrhea in Cancer Patients

Sai-Ching Jim Yeung



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Introduction

Diarrhea is a frequently occurring comorbidity or adverse event associated with therapy in cancer patients, causing electrolyte abnormalities, malnutrition, dehydration, and hospitalization. Diarrhea in cancer patients can be severe, and uncontrolled diarrhea may lead to life-threatening electrolyte abnormalities and severe dehydration. The need to avoid recurrence of serious diarrheal complications may lead to dose reduction of antineoplastic therapies with a corresponding loss of efficacy.

Causes

Although cancer and cancer treatments (chemotherapy, radiation therapy, targeted therapy, immune therapy) frequently cause diarrhea, emergency care providers must not forget causes of diarrhea that are unrelated to the cancer, e.g., lactose intolerance, food poisoning, viral gastroenteritis, side effects of non-cancer drugs, inflammatory bowel disease, and irritable bowel syndrome (Table 1). In this chapter, we shall focus on causes relevant to cancer and cancer treatments.

Paraneoplastic Syndromes

Certain cancers can cause diarrhea by secreting hormones, including:

- Carcinoid tumors
- Zollinger-Ellison syndrome (gastrinoma)
- VIPomas [neuroendocrine tumors that secrete vasoactive intestinal peptide (VIP) autonomously]
- Medullary thyroid carcinoma [sporadic, familial, or as part of Sipple syndrome (multiple endocrine neoplasia type 2 (MEN 2))]
- Neuroendocrine tumors as part of the Wermer syndrome [multiple endocrine neoplasia type 1 (MEN 1)]

Treatment-Induced Diarrhea

Chemotherapy

In addition to cancer cells, cytotoxic chemotherapy kills other fast-growing cells, including those in the intestinal lining. Certain chemotherapeutic agents can disturb the normal absorptive and secretory functions of the small bowel, resulting in treatment-related diarrhea [1]. Chemotherapeutic agents prominently associated with severe diarrhea include fluorouracil, capecitabine, irinotecan, paclitaxel, docetaxel, and vinorelbine. Diarrhea caused by irinotecan may be delayed (>24 h) and severe. Concomitant abdominal or pelvic radiotherapy and recent gastrointestinal surgery are associated with increased severity of treatment-induced diarrhea.

Radiotherapy

External beam radiotherapy (XRT) that focuses on the thoracolumbar spine, para-aortic lymph nodes, abdomen and pelvis for cervical cancer, colorectal cancer, prostate cancer, or metastatic cancer may cause diarrhea. Factors that predict the severity of XRT-induced diarrhea include total radiation dose, fractionation, volume of bowel exposed to radiation, and concurrent chemotherapy. Acute diarrhea may occur at about 10 Gy and may last up to 3 months after treatment while chronic radiation enteritis may begin months or even years after treatment.

Surgery

Surgical treatment of cancer may involve removal of sections of the gastrointestinal tract or organs with endocrine and digestive functions. Resultant anatomical changes may limit the ability of the gastrointestinal tract to absorb certain nutrients, e.g., fat, resulting in diarrhea. Bowel resection will lessen the surface area for reabsorption of water from food. Pancreatic cancer or its surgical treatment may compromise exocrine pancreatic function, leading to lack of digestion and malabsorption. Surgical changes in biliary anatomy will also

Table 1 Causes of diarrhea in cancer patients

Surgery related	Celiac plexus block, cholecystectomy, esophagogastrectomy, gastrectomy, pancreaticoduodenectomy (Whipple procedure), intestinal resection (malabsorption due to short bowel syndrome), vagotomy
Chemotherapy	Bortezomib, capecitabine, carboplatin, cisplatin, cytosine arabinoside, cyclophosphamide, daunorubicin, docetaxel, doxorubicin, 5-fluorouracil, erlotinib, gefitinib, imatinib, irinotecan, lapatinib, leucovorin, methotrexate, oxaliplatin, paclitaxel, sorafenib, topotecan
Radiation	XRT to the abdomen, pelvis, para-aortic lymph nodes, lumbar spine
Bone marrow transplantation	Conditioning chemotherapy, total-body irradiation, graft-versus-host disease after allogeneic transplants
Paraneoplastic	Carcinoid syndrome, medullary carcinoma of the thyroid, neuroendocrine pancreatic cancer (e.g., gastrinoma, VIPoma), pheochromocytoma
Infection	*Bacillus cereus*, *Campylobacter*, *Clostridium difficile*, *Clostridium perfringens*, *Cryptosporidium*, *Cytomegalovirus* (in immunocompromised hosts), *Giardia lamblia*, *Rotavirus*, *Salmonella*, *Shigella*
Fecal impaction	Liquid stool going around impacted stool
Comorbid diseases	Diabetes mellitus, hyperthyroidism, gastroenteritis, inflammatory bowel disease, HIV/AIDS
Psychological factors	Stress

Adapted from Table 2 at http://www.cancer.gov/cancertopics/pdq/supportivecare/gastrointestinalcomplications/HealthProfessional/Page5#_160

compromise emulsification of fat by bile salts and impair digestion and absorption of fatty food. Diarrhea is also part of the dumping syndrome which occurs when undigested food moves too rapidly into the small intestine. Dumping syndrome is associated with gastrectomy, gastroenterostomy, gastrojejunostomy, vagotomy, pancreaticoduodenectomy, and esophagectomy.

Bone Marrow Stem Cell Transplant

In stem cell transplantation, conditioning chemotherapy and total-body radiation may cause diarrhea. After engraftment, allogeneic stem cells, graft-versus-host disease (GVHD) affecting the intestinal tract is a significant cause of diarrhea, usually occurring between 10 and 100 days after transplant. GVHD of the intestine may resolve or become chronic.

Immune Checkpoint Therapy

Ipilimumab treatment is associated with diarrhea in up to 44 % of patients [2, 3]. Grade 3 or 4 diarrhea occurs in 18 % of patients at the dose of 10 mg/kg. Diarrhea also occurs in 21 % of patients receiving nivolumab. Diarrhea can also be due to immune-mediated colitis, which mainly involves the descending colon. Unlike inflammatory bowel diseases, colitis caused by immune checkpoint therapy can lead to obstruction and bowel perforation.

Infectious Enteritis

Viruses, parasites, and bacteria all can cause infectious diarrhea in cancer patients. Immunocompromised, neutropenia, and disruption of anatomical barriers place the cancer patients at increased risk for these infections. Recent exposure to antibiotics increases the risk of *C. difficile*-related diarrhea. Neutropenia alone increases the risk of infection of the intestine, leading to diarrhea and various degrees of abdominal pain.

Stress and Anxiety

The stress and anxiety associated with cancer and treatments also may cause diarrhea though mechanisms involving the autonomic and enteric nervous systems [4]. Conversely, diarrhea from any of the mechanisms noted above may cause psychic stress, making it difficult, and perhaps dangerous, to attribute diarrhea to psychic stress in the high-risk cancer population.

Symptoms

Important elements of the history of present illness include the frequency of bowel movements during the past 24 h (number of stools per day, incontinence, increase in ostomy output compared with baseline), the character of the fecal material (well formed, formed, semi formed, loose, very loose, and watery), and the time course of diarrhea [5]. Medication and dietary intake, as well as a history of recent travel, may provide additional clues regarding etiology. Weight loss and reduced urine output may indicate the severity of diarrhea.

Specific questions regarding the following should be sought: dizziness, fever, abdominal pain, nausea, vomiting, and blood in the stool. These questions are helpful in classifying the diarrhea as complicated or uncomplicated and guiding therapy [6].

The National Cancer Institute Common Toxicity Criteria (version 4.03) is a frequently used standard tool for assessing diarrhea severity (Table 2) [7], but it does not include assessment of duration of diarrhea and stool volume. These severity parameters and other coexisting symptoms that are predictive of serious complications were addressed in the clinical practice guidelines [6, 8].

Grade 3 or 4 diarrhea is classified as complicated. The diarrhea may be complicated and potentially serious if a

Table 2 NCI grading of diarrhea

Common toxicity criteria (version 4.03) for diarrhea	Grade					
	0	1	2	3	4	5
Colostomy absent	None	Increase of <4 stools/day compared with baseline	Increase of 4–6 stools/day or waking up to have bowel movements	Increase of ≥7 stools/day or incontinence or need for parenteral support for dehydration	Hemodynamic collapse or severe consequences requiring intensive care	Death
Colostomy present	None	Mild increase in loose watery output compared with baseline	Moderate increase in loose watery output compared with baseline but not interfering with normal activity	Severe increase in loose watery output compared with baseline or copious output that interferes with normal activity	Hemodynamic collapse or severe consequences requiring intensive care	Death

Adapted from http://nciterms.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=CTCAE&code=E10575&ns=ctcae

cancer patient with grade 1 or 2 diarrhea has the following: >6 loose bowel movements a day for >2 days, bloody stool or rectal bleeding, no urine output for >12 h, unable to drink for >1 day, weight loss due to diarrhea, diarrhea after several days of constipation, abdominal distension, or fever. In addition, moderate to severe cramping and nausea/vomiting, neutropenia, and the presence of systemic inflammatory response syndrome indicate potentially serious complications. Close monitoring and full investigation are warranted [6].

Diagnosis

Most chronic diarrheal paraneoplastic syndromes would have already been diagnosed in most cancer patients prior to the ED visit, and the diagnostic evaluation for specific paraneoplastic syndromes is out of the scope of this chapter. For cancer patients presenting to EDs with diarrhea, the goal of rapid evaluation is to identify life-threatening conditions and complications that require hospitalization.

Diarrhea causes dehydration, electrolyte abnormalities, and disturbed acid-base balance. Hypokalemia and non-anion gap acidosis are the main diagnostic features of severe diarrhea. Hypokalemia will necessitate aggressive potassium replacement. Prerenal azotemia or renal failure may result from severe dehydration. Other electrolytes, including calcium and magnesium, should be checked and replaced. Hypokalemia, hypomagnesemia, and hypocalcemia can cause EKG changes and cardiac arrhythmias (see Fig. 4 of the chapter on endocrine and metabolic abnormalities). In patients receiving chemotherapy, patients who progress to severe diarrhea despite taking loperamide, and patients with neutropenia or who are immunocompromised, additional evaluation includes an evaluation of the stool (fecal leukocytes, *C. difficile*, *Salmonella*, *E. coli*, *Campylobacter*) [6]. An abdominal X-ray series is helpful to exclude intra-abdominal free air and pneumatosis intestinalis (Fig. 1).

A history of allogeneic stem cell transplantation should put GVHD high in the list of differential diagnosis for diarrhea. Infectious colitis (e.g., cytomegalovirus colitis) would also be in the differential diagnosis for immunocompromised patients. Very often, an expeditious diagnostic colonoscopy with mucosal biopsy is indicated.

A history of or ongoing treatment with immune checkpoint inhibition therapy (e.g., ipilimumab and nivolumab) should raise the suspicion for immune-mediated colitis, the confirmation of which would also require endoscopy with or without biopsy. The suspicion for serious gastrointestinal complication (e.g., perforation and obstruction) should be high, and the threshold for CT imaging of the abdomen and pelvis should be low.

In the course of cancer treatment, many cancer patients experience infectious complications and have been exposed to antibiotics. *C. difficile*-related diarrhea should always be excluded in cancer patients with diarrhea who have recently been treated with antibiotics. Stool samples may be collected for *C. difficile* toxin assays or polymerase chain reaction assay.

A triad of neutropenia, abdominal tenderness, and diarrhea should raise the suspicion for neutropenic enteritis. Perhaps due to the neutropenia, abdominal pain or tenderness may not be very prominent despite the presence of significant infection. A CT scan of the abdomen and pelvis with intravenous and oral contrast can suggest neutropenic ileitis, typhlitis, and colitis (Fig. 2). MRI may be used if CT is contraindicated (e.g., if the patient is allergic to iodine contrast dyes).

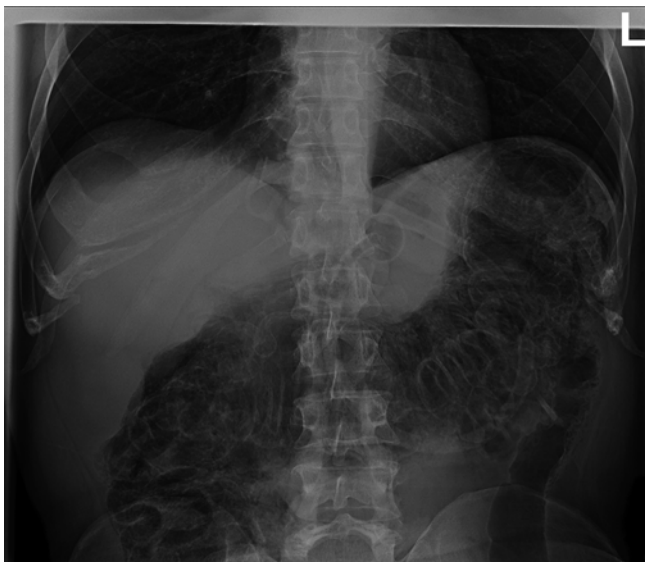

Fig. 1 Pneumatosis intestinalis

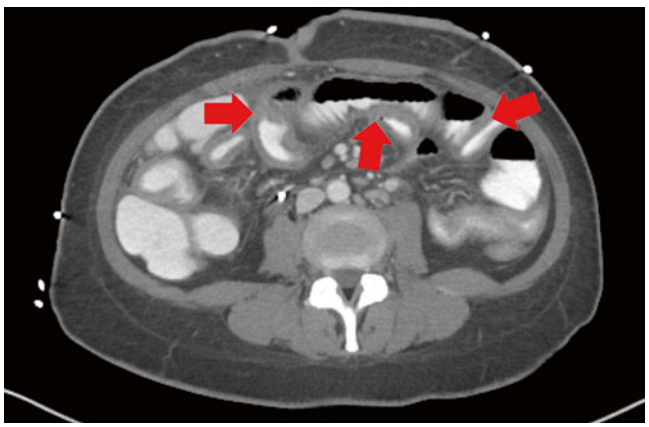

Fig. 2 CT scan imaging of a cancer patient with neutropenic ileitis. A neutropenic leukemic patient presents with profuse diarrhea and minimal abdominal pain but no fever. The CT scan demonstrated significant thickening of the wall of ileum (*arrows*) consistent with ileitis

Management

Although many causes of diarrhea in cancer patients require specific therapies, therapies aimed at decreasing or replenishing fluid and electrolyte losses are required [9].

Diet

Regardless of the cause of diarrhea, diet modifications may help to decrease the symptom burden of diarrhea. Foods that may worsen diarrhea should be avoided:

- Fatty, greasy, or fried foods
- Foods high in insoluble fiber content
- Gas-forming foods
- Foods with high sugar contents
- Hot liquids
- Dairy products or foods made with significant amount of dairy products
- Foods sweetened with sugar alcohols (e.g., sorbitol, xylitol, or mannitol)
- Foods that can irritate your digestive tract (e.g., caffeine such as coffee, strong tea, sodas, tomato juice, citrus juices, and alcohol)
- Tobacco

A low-fat, high-potassium diet with foods containing soluble fiber is recommended as 6–8 small meals and snacks each day. Drink plenty of room temperature clear liquids. The BRAT (bananas, rice, apples, toast) diet may reduce the frequency of stools.

The use of probiotics appears helpful in improving tolerance of and support for chemotherapy and radiation-related diarrhea. Sources of probiotics include foods such as yogurt, buttermilk, sauerkraut, and cottage cheese. Most clinical research involves *Lactobacillus* and *Bifidobacterium* to modify gut microflora [10]. However, probiotics are not recommended in immunocompromised neutropenic patients. Food is a potential cause of invasive infectious disease in immunocompromised patients, and *Lactobacillus acidophilus* bacteremia in a stem cell transplant patient with mucositis eating yogurt has been reported [11].

Medication Adjustment

Medications such as bulk laxative, stool softener, and promotility agents (e.g., metoclopramide) should be discontinued.

Correction of Dehydration and Electrolyte Imbalances

Initial treatment for severe diarrhea is aimed at correcting any volume, electrolyte, and acid-base abnormalities with IV normal saline, potassium chloride, and, if acidosis is severe, sodium bicarbonate. These abnormalities are frequently severe enough to necessitate hospital admission.

Pharmacologic Therapy

Treatment goals include slowing intestinal motility, decreasing intestinal secretions, and promoting intestinal absorption. Other pharmacologic therapies for the relief of diarrhea may be specific to the underlying mechanism.

- Opioids bind to μ-receptors in the gastrointestinal tract to decrease bowel motility and increase transit time:
  - Loperamide: 4 mg followed by 2 mg after each unformed stool up to 12 mg/day [6, 8]
  - Diphenoxylate
  - Codeine
  - Tincture of opium
- Anticholinergics:
  - Atropine
  - Belladonna
  - Scopolamine
- Adsorbents such as kaolin, clays, and activated charcoals have been commonly used and generally considered safe:
  - Kaolin
  - Pectin
- Absorbents give bulk to the fecal material, but one potential drug interaction is that they may bind and inhibit absorption of other oral antidiarrheal medications:
  - Wheat dextrin
  - Psyllium fiber
- Somatostatin analogues:
  - Octreotide: treatment usually start with 100–150 μg every 8 h
  - Lanreotide
  - Pasireotide
- Mucosal prostaglandin inhibitors has antisecretory effects:
  - Aspirin (may be useful for radiation-induced diarrhea)
  - Bismuth subsalicylate
- Corticosteroids reduce edema associated with obstruction and radiation colitis, reduce hormonal influences of some

endocrine tumors (e.g., VIPoma), and treat immune-mediated colitis:
  - Budesonide
  - Dexamethasone
  - Methylprednisolone
- Antimicrobials: Quinolone antibiotics are effective for salmonellosis. Depending on the degree of immunocompromised, antibiotic treatment may need to continue for several months. Some beta-lactam antibiotics (e.g., cefotaxime, ceftriaxone) and sulfamethoxazole-trimethoprim are alternatives. Campylobacteriosis may be treated with azithromycin or quinolone antibiotics, with addition of vancomycin for severe cases. Shigellosis is treated with quinolone antibiotics. Alternatives include sulfamethoxazole-trimethoprim and azithromycin. *C. difficile* may be treated with metronidazole or oral vancomycin. Enterotoxigenic *E. coli* are frequently resistant to ampicillin and sulfamethoxazole-trimethoprim. Quinolone antibiotics are generally effective. Enterotoxigenic *Bacteroides fragilis* is an emerging pathogen causing diarrhea, and metronidazole has excellent activity against this pathogen.
  - Bismuth subsalicylate: has direct antimicrobial effects on *Escherichia coli*
  - Sulfamethoxazole and trimethoprim
  - Beta-lactam antibiotics: e.g., cefotaxime, ceftriaxone
  - Quinolone antibiotics: e.g., levofloxacin, moxifloxacin, ciprofloxacin
  - Metronidazole
  - Oral vancomycin

Management of Specific Clinical Scenarios

Treatment-Induced Diarrhea

Based on controlled clinical trials and the clinical practice guidelines [6, 8], loperamide (4-mg initial dose followed by 2 mg every 4 h) is the standard first-line therapy for chemotherapy-induced diarrhea. After loperamide for the first day of chemotherapy-induced diarrhea that is mild, treatment may be escalated by adding octreotide, 100–150 μg every 8 h [5]. Severe treatment-induced diarrhea with complicated symptoms should be managed with IV fluids, octreotide acetate 100–150 μg SC three times daily or 25–50 μg/h IV with up to a fivefold escalation as needed, and administration of antibiotics until diarrhea has stopped for >24 h [6]. The updated guidelines stress the importance of recognizing early warning signs of complicated diarrhea and early intervention such as initiating antibiotic therapy [6].

Immune-Mediated Colitis [2]

Grade 1: Symptomatic treatment with loperamide, oral hydration, and electrolyte replacement. The American Dietary Association ulcerative colitis diet is recommended. Persistence or worsening diarrhea should prompt further investigation for bacterial, parasitic, or viral infection or the onset of inflammatory bowel disease by examination for stool leukocytes, stool cultures, and *C. difficile* assay and endoscopy with mucosal biopsy.

Grade 2: Oral diphenoxylate hydrochloride and atropine sulfate four times daily may replace loperamide, and budesonide 9 mg daily may be started. In persistent grade 2 or grades 1–2 diarrhea with bleeding, endoscopy should be performed to diagnose colitis. Diffuse ulceration and bleeding in the setting of grade 2 diarrhea may require corticosteroid therapy and indicates an increased risk of bowel perforation.

Grade 3 or 4: Treatment with IV corticosteroid (methylprednisolone 125 mg) and IV replacement of fluid and electrolytes should be initiated. Oral glucocorticoid therapy (prednisone 1–2 mg/kg/daily or equivalent) may be tapered over >4 weeks to ensure complete resolution or tapered over 6–8 weeks in patients with diffuse ulceration and bleeding. If corticosteroid therapy does not improve diarrhea within 72 h, infliximab at 5 mg/kg every 2 weeks is a second line treatment.

GVHD

Octreotide is also effective in diarrhea associated with GVHD [12, 13]. In addition to antidiarrheal agents and immunosuppressive medications, the diarrhea associated with

GVHD may be managed with a specialized five-phase dietary regimen [14].

Paraneoplastic Diarrhea

Initial treatment is directed toward correcting volume and electrolyte abnormalities. Somatostatin analogues control diarrhea in up to 90 % of patients. Glucocorticoids reduce symptoms in 50 % of cases. Tumor resection is the treatment of choice for long-term control of symptoms. In advanced disease, tumor debulking may relieve symptoms, but it is not effective in all cases. Hepatic artery radioembolization or transcatheter chemoembolization with doxorubicin or cisplatin [15], XRT, and percutaneous or intraoperative radiofrequency tumor ablation may be attempted to reduce tumor burden.

Summary

Cancer patients are prone to have diarrhea which can cause serious life-threatening complications. Cancer treatment-induced diarrhea is usually treated with supportive measures. Infectious causes of diarrhea must be ruled out in immunocompromised patients. Immunocompromised neutropenic cancer patients are at risk for ileitis, typhlitis, and colitis. Immune-mediated diarrhea caused by immune checkpoint therapy agents (e.g., ipilimumab, nivolumab, pembrolizumab)

or graft-versus-host disease after allogeneic stem cell transplantation can be serious. Careful diagnosis of the cause of diarrhea is very important to safely manage these cancer patients.

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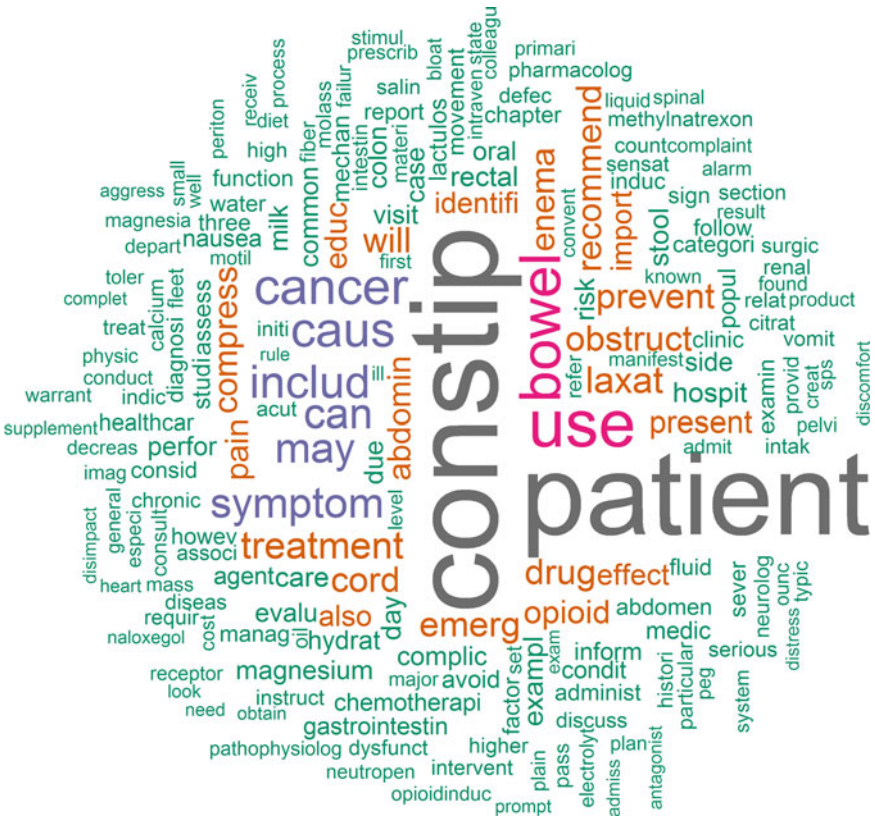
Constipation in Cancer Patients

Carmen Esther Gonzalez and Josiah K. Halm



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Introduction

The prevalence of constipation in the worldwide general population has been estimated to be in a range of 0.7% to 79% [1]. Constipation is a common gastrointestinal complaint in cancer patients and a common reason for emergency department (ED) visits for cancer patients, which is considered to be an avoidable [2, 3]. In 2013, out of 24,000 patient visits/year at a comprehensive cancer center emergency department in Houston, Texas, there were 12,099 visits in which one of the final diagnoses (as captured in administrative data using ICD-9 coding) was related to constipation. Constipation affects approximately 2–27 % of the population in western countries [4]. It also leads to higher healthcare costs related to hospitalizations, laxative sales, and primary care visits [5]. Ansari and colleagues [6] studied the cost utilization of hospital beds in patients with constipation in Victoria, Australia. During the fiscal year 2011, they found a use of a little over 9700 bed days at a cost of over $8 million for patients with a diagnosis of constipation. This is an avoidable condition for visits to the ED and hospitalization and a mostly benign symptom that should be recognized, prevented, and managed in the primary healthcare setting, to avoid complications and decrease the use of expensive resources.

There is no uniform definition for constipation, but according to the Rome III criteria, a patient must have experienced at least two of the following symptoms over the preceding 3 months: fewer than three bowel movements per week, straining, lumpy or hard stools, sensation of anorectal obstruction, sensation of incomplete defecation, and manual maneuvering required to defecate [7]. It is important to emphasize that the period of 3 months used in the Rome III criteria does not typically apply to the cancer patient population who may develop constipation in a more acute manner due to mechanisms that will be discussed in this chapter.

In cancer patients for whom the disease burdens and its treatment already affects their quality of life, the added symptom of constipation can be particularly distressing and debilitating. Constipation may be mild, intermittent, chronic, or easy or difficult to treat, and thus it is important for the provider in the ED to understand the etiology and pathophysiological process for effective management of the condition.

Clinical Manifestations

Patients with constipation may report symptoms of abdominal bloating, abdominal pain, pain on defecation, hard and/or small stools, straining, rectal pain, and the sensation that they cannot have a complete defecation, and some may report a sensation of blockage. Patients may report with other symptoms

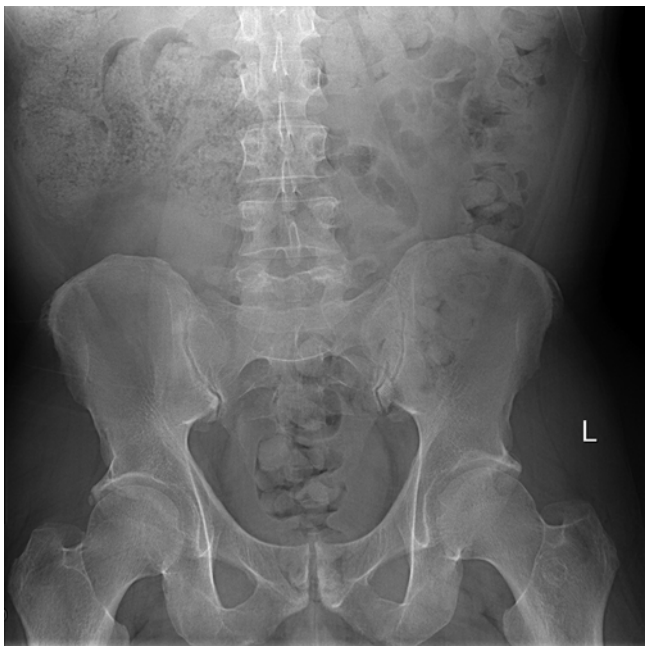

Fig. 1 Plain film of the abdomen of a patient with metastatic adenocarcinoma on opioids, who presented to the ED with abdominal pain and diarrhea. The patient has been taking antidiarrheal medications. Large amount of stool is evident throughout the colon

that they do not necessarily associate with constipation, such as spurious diarrhea (Fig. 1) and urinary retention. In the cancer population, symptoms of weakness in the lower extremities and urinary retention associated with constipation should not be ignored, as this could be related to cord compression.

The initial evaluation of the constipated cancer patient includes a careful history and physical examination. An important part of the history includes defining the nature and duration of the constipation and identifying secondary causes of constipation, including the temporal relationship between time of starting a drug and the onset of constipation. Some chemotherapy drugs including vinca alkaloids [8], thalidomide and analogs [9], vandetanib [10], and belinsotate [11] have a higher propensity to cause constipation. Also opioid use for pain control is very well known to be a significant cause of constipation [12]. Patients may also have comorbid systemic and neurologic disorders that impair colonic motility and contribute to constipation (Table 1). Patients may also be on other commonly known drugs that cause constipation (Table 2).

A complaint of recent and persistent change in bowel habits including alarm symptoms of rectal bleeding, abdominal pain, inability to pass flatus, and vomiting should prompt an evaluation to exclude bowel changes or organic disease, as they may be the initial finding of a malignant process.

Physical examination should be focused or thorough, depending on the distress level of patient. Mental status should be observed for other signs of somnolence or pruritus

Table 1 Systemic causes of constipation

Endocrine or metabolic	Diabetes, hyperthyroidism, dehydration
	Hypercalcemia, uremia, hypomagnesemia, hypophosphatemia
Neurologic dysfunction	Parkinson disease, spinal cord compression, sacral nerve compression, multiple sclerosis, stroke, autonomic neuropathies
Mechanical obstruction	From tumor masses, adhesions, radiation fibrosis, retroperitoneal diseases
Pelvic muscle impairment	Due to cancer invasion, hysterectomy, procedures
Psychological disorders	Depression, delirium, dementia
Connective tissue disorders	Scleroderma, amyloidosis, and mixed connective tissue disease
Other	Failure to thrive, dehydration, immobility, nutritional challenges, decreased fiber intake

Table 2 Common medications causing constipation

Antidepressant	Cyclic antidepressants, MAOIs
Anticholinergics	Benztropine, trihexyphenidyl
Calcium channel blockers	Verapamil
Antacids	Aluminum, calcium components
Nonsteroidal anti-inflammatory	Ibuprofen and diclofenac
Sympathomimetics	Pseudoephedrine
Opioids	Morphine
5HT3 antagonist antiemetics	Ondansetron

related to opioid use or the discomfort from abdominal bloating and distention. Other general recommendations will be to look for signs of medical comorbidities including hypothyroidism, hyperthyroidism, hypercalcemia of malignancy, and neurologic impairment of bladder and bowel from spinal cord involvement.

The abdominal examination will confirm distention, assessment of bowel sounds, and masses. A rectal examination will be important in assessing sphincter tone, anal fissures, and hemorrhoids, and stool impaction can be confirmed. Rectal examination should be avoided in the neutropenic patients, due to higher risk of complications [13].

Diagnosis

In the ED, a complete blood count; electrolyte, calcium, creatinine, and thyroid function tests; and urinalysis should be done to assess for dehydration, renal dysfunction, anemia, diabetes, and thyroid dysfunction. Imaging studies are used to rule out an acute process and include an initial flat plate radiograph of the abdomen and pelvis in assessing obstruction or colonic stool load. A CT scan of the abdomen and pelvis will be useful in determining if a structural cause is the culprit and if alarm symptoms are present including a family history of inflammatory bowel disease or colon cancer. The role of colonoscopy in the diagnosis of constipation alone without alarm symptoms is not recommended [14]. A Bowel Function Index (BFI) tool has been shown in cancer patients to predict opioid-induced constipation [15] and when administered in the ED, may be useful in the validation of constipation.

Mechanism and Pathophysiology of Constipation in the Cancer Patient

Constipation may originate from within the colon and rectum as a result of colon obstruction from tumors, outlet obstruction from—anatomical or functional—slow colonic motility, or spinal cord compression. Constipation originating from outside the colon will include the use of medication chemotherapy agents known to cause constipation, opioid use, dietary reasons including low-fiber diet, and systemic and neurologic diseases including psychological issues. Opioids bind to specific receptors in the gastrointestinal tract and nervous system to reduce bowel motility by both direct and anticholinergic mechanisms [15].

When Is Constipation an Emergency?

Constipation in the vast majority of presentations to the ED is uncomplicated; however, three major complications warrant vigilance and immediate treatment:

- *Bowel obstruction*. The obstruction could be of the small bowel or of the large bowel. The patients will likely present looking ill; with symptoms of nausea, vomiting, and cramping abdominal pain; and with inability to pass flatus. The abdomen may be distended. Conventional plain imaging can demonstrate dilated loops of bowel and fluid levels. A CT scan of the abdomen and pelvis may further help with the diagnosis and identify the cause, degree, and localization of the obstruction. If untreated, it could result in serious complications such as tissue death and infection of the peritoneal cavity or peritonitis. A patient with bowel obstruction will require hydration, nasogastric tube placement for suctioning, bowel decompression, antiemetics, analgesics, and surgical consultation (refer to the Treatment and Prevention section in this chapter).
- *Bowel perforation*. Stercoral perforation is rare but has been reported, the cause of which is ischemia and necrosis into the bowel wall due to fecal mass [16]. Caution is warranted here, as the use of enemas for the treatment for constipation could infrequently complicate into bowel perforation [17]. Acute perforation is a surgical emergency

(refer to the Treatment and Prevention section in this chapter). The patient typically presents with severe abdominal pain and can deteriorate quickly with signs of sepsis and shock. The abdomen will have signs of peritonitis on exam, although in patients chronically on steroids, the clinical and physical symptoms might not be so obvious. In conventional plain imaging, the diagnosis is made by the presence of free air. These patients require fluid resuscitation, intravenous antibiotics, and evaluation by surgery and hospital admission.

- *Constipation due to acute spinal cord compression*. In a cancer patient with cord compression, constipation might be the only symptom with which they present to the ED, and it is therefore important to create awareness in the ED physicians. The incidence of metastatic cord compression in patients with advanced cancer has been estimated to be approximately 15 % [18]. Symptoms include weakness in the lower extremities causing difficulty walking, bladder dysfunction, constipation, and back pain. Cord compression is an oncologic emergency. A patient with cancer who presents to the ED with constipation and other neurologic symptoms where suspicions for cord compression are identified should be emergently evaluated for the condition. In this case, constipation was probably the patient's presenting symptom, but the emergency is the cord compression. If cord compression is suspected, an emergent MRI of the spine should be obtained and 10 mg dexamethasone administered intravenously. Neurosurgery and/or radiation oncology should be consulted as indicated and the patient admitted to the hospital. For more information on cord compression, refer to the chapter on cord compression in this book.

Treatment and Prevention

Constipation in the majority of cases is preventable. When a patient comes to the ED and constipation is identified as a concerning medical issue, we should investigate further the precipitant factors and formulate a personalized plan for its prevention. It is necessary to perform detailed medication reconciliation and evaluate all drugs prescribed (e.g., opioids, ondansetron (Zofran) for nausea and vomiting, some antihypertensive such as calcium channel blockers, and others) or those obtained over the counter that can cause constipation (e.g., calcium supplements). A review of past medical history (PMH) and illnesses to identify those medical conditions that can cause constipation should be carried out. Inquiries should be made for mechanical conditions such as rectal neoplasm or radiation-induced fibrosis, which could be risk factors for obstruction. Especially in the cancer population, the use of a high-fiber diet or intake and fluid intake should be investigated, as the use of fiber without adequate hydration can provoke worsening constipation. Cancer patients treated at our comprehensive cancer ED are typically surprised when they are told they are constipated, especially if they have not been eating, believing that the lack of intake will not induce constipation. Plain films are recommended to rule out serious conditions such as bowel obstruction. A chemical profile in the ED is particularly useful to identify electrolyte imbalances such as hypokalemia, hypercalcemia, and uremia that are associated with constipation.

Once the causes of the constipation are identified, we can formulate a plan of action for emergent or urgent intervention in the ED and for outpatient management.

In the ED, the following steps are recommended:

First, identify those patients presenting with complicated constipation, indicating gastrointestinal obstruction, perforation, or those highly suspicious for cord compression, as they warrant immediate intervention and prompt surgical consultation. Some of these patients however could be terminally ill, in which case supportive or palliative care may be indicated. In those patients, it is important to consult with the primary oncologist first to discuss prognosis and care, especially if surgical or aggressive interventions are anticipated.

For patients that are not complicated, a combination of therapeutic interventions may be required. The following should be considered:

- Intravenous hydration. We recommend inquiring the patient's heart function status before attempting aggressive hydration. Some cancer patients could have concurrent cardiomyopathy due to cardiotoxicity induced by the treatment received. Careful and slow hydration is indicated in those patients with decreased ejection fraction or congestive heart failure.
- Correction of electrolyte abnormalities or endocrine dysfunction.
- Rectal approach. Rectal exams, manipulations, or disimpaction should be avoided in immunocompromised patients, particularly those that are neutropenic (absolute neutrophil count less than or equal to 1000/mm^3) due to risk of inducing bacteremia. In those patients with moderate to severe thrombocytopenia (platelet count equal or less than 50K/μL), there is a risk of inducing bleeding. Otherwise, if there is no contraindication, consider disimpaction and/or rectal enemas, such as milk and molasses [19].
- Pharmacologic agents administered orally. In most cases, this will be the first line of therapy, beginning with oral laxatives.
- Second-line pharmacologic agents administered orally. Consider methylnaltrexone for opioid-induced constipation where other conventional treatments have failed.
- When constipation is not resolved, or does not show signs of resolving, the patient should be admitted.

Pharmacology in the Treatment of Constipation by Categories

Osmotic laxatives. Polyethylene glycol (PEG) and lactulose are drugs in this category. These substances are poorly absorbable, causing the drawing and holding of water in the intestinal lumen. In general, they are well tolerated [20]. Lactulose can cause abdominal pain, gas, and bloating, and some patients may not tolerate these side effects. A study was conducted in an ambulatory setting in Europe of patients with cancer on opioids and the use of laxatives. PEG was the most commonly prescribed in comparison to sodium picosulfate (SPS) and lactulose. PEG and SPS had a higher tolerability in comparison to lactulose in this patient population [21].

Stimulants laxatives. Drugs in this category stimulate the production of gastrointestinal secretions. Bisacodyl (Dulcolax), senna (Senokot), SPS and cascara, and castor oil are examples. These drugs can cause nausea and abdominal discomfort. Chronic use of stimulant laxatives can cause hypokalemia, and some may cause severe diarrhea as in the case of the castor oil.

Saline laxatives. Milk of magnesia and magnesium citrates and Fleet Phospho-soda are examples of oral hyperosmotic drugs in this category. The magnesium, sulfate, citrate, and phosphate ions draw water into the intestines, causing liquid stool. Saline laxatives with magnesium ion are frequently used in the ED setting. Hypermagnesemia could be a serious side effect, and we recommend evaluating magnesium levels in those cancer patients already receiving magnesium supplements, and those with renal insufficiency, before administering the saline laxatives (milk of magnesia and magnesium citrate). Saline laxatives should not be used in patients with renal failure.

Mu-opioid receptor antagonist. Naloxegol (Movantik) and methylnaltrexone (Relistor) are peripherally acting mu receptor antagonists in the small and large intestines and are used for the treatment of opioid-induced constipation. In September 2014, the Federal Drug Administration in the United States approved the use of Naloxegol for adult patients with chronic noncancer opioid-induced constipation. This should be administered 25 mg orally once a day in the morning. Methylnaltrexone is given 12 mg or at 0.15 mg/kg subcutaneously once in a 24-h period. In a study conducted by Sawh and colleagues [22], they found benefits of this drug in critically ill patients who were treated with opioids and presented with gastrointestinal dysmotility causing constipation. Common side effects of these drugs are abdominal pain and nausea. Serious side effects could include opioid withdrawal, and with methylnaltrexone, a few cases of gastrointestinal perforation have been reported [23].

Lubricants. Docusate sodium (Colace) and mineral oil are examples of lubricants, which are administered orally. The action mechanism of these drugs consist of creating a waterproof film that coats the bowel and the stool mass, keeping moisture in the stool and making it soft and easy to pass.

Enemas. Enemas are commonly used in the ED. Examples include the Fleet enema milk and molasses enema. The Fleet enema uses a phosphorus salt and can cause hyperphosphatemia. It is important to avoid its use in patients with renal failure. Milk and molasses should not be used in patients with allergies to these products. Enemas should not be used in neutropenic or thrombocytopenic patients (refer to the section Treatment and Prevention).

Bulk-forming agents. These agents are used as gentle laxatives that act on the intestine causing the fecal material to retain water, making the feces softer. Examples of agents in this category are psyllium seed (Metamucil), methylcellulose (Citrucel), calcium polycarbophil (Fibercom), and wheat dextrin (Benefiber). These products should be considered for recommendation upon discharge from the ED; however, the importance of hydration and increased fluid intake when taking them should be specified.

Engaging Patients in the Treatment of Constipation: Instructions to Give on Discharge from the ED

Education is one of the most powerful tools patients and caregivers can have to prevent and treat the side effects of chemotherapy including nausea, vomiting, pain, constipation, and others. Mollaoğlu and Erdoğan [24] conducted a study that consisted of planned education by the healthcare providers, which included training sections and educational materials on symptoms and its management. This study found a correlation between education and the diminished incidence of chemotherapy side effects.

At MD Anderson Cancer Center, a bowel management program was created to address the educational needs of the multidisciplinary team caring for the patient, including the healthcare providers and the patient, with the goal of decreasing the number of patients admitted to the hospital strictly for the treatment of constipation. A patient at risk for constipation is assessed by utilizing a modified constipation risk assessment scale [25]. A CRAS score of $\geq$11 puts a patient at a moderate to high risk of constipation. Patients should receive written information or have access to online information on self-help for constipation. This educational material should describe the symptoms of bowel obstruction and instructions to go to the local ED if the patient identifies having those symptoms. The educational material includes instructions on when not to use enemas, for instance, if the platelet count is below 50,000 and/or if neutropenia is present. In the case of severe constipation, we recommend the use of Fleet mineral oil enema, which can be purchased at any pharmacy. We also provide information on how to prepare

and self-administer a powdered milk and molasses enema, which is highly effective. We also recommend the use of non-stimulant laxatives by mouth such as magnesium citrate (not to be used if there are kidney problems) or lactulose. If no bowel movement has passed, the same dose can be repeated the following day. The lactulose we recommend to use is 30 cc with 8 oz of water every 6 h if needed (the patient should be informed that this can produce increased gas). It may be practical for the patient with severe constipation to begin with the enemas and then the oral laxatives, in order to prevent nausea. The patient should be also instructed in setting goals for frequency of bowel movements, with recommendations of what to do if there has been no bowel movement on the expected day, for example, prune juice followed by 8 oz of a hot liquid or milk of magnesia (assuming normal kidney function), with 8 oz of water or liquids. Emphasis on prevention is most important, as are the recommendations to stay hydrated. If possible, a minimum of two quarts a day should be consumed, adding fiber 25–40 g/day to the diet with fluids. For people who are able to eat regularly (three meals a day) and are active, we recommend bowel training in order to have a bowel movement every day. However, during chemotherapy, many patients lose their appetite, and this technique may not work.

The emergency department physicians must ensure that patients who are prescribed narcotics or opioids in the ED are also educated in their side effects, including constipation. The patients should be guided to the use stool softeners or laxatives while on drugs that can cause constipation, particularly opioids.

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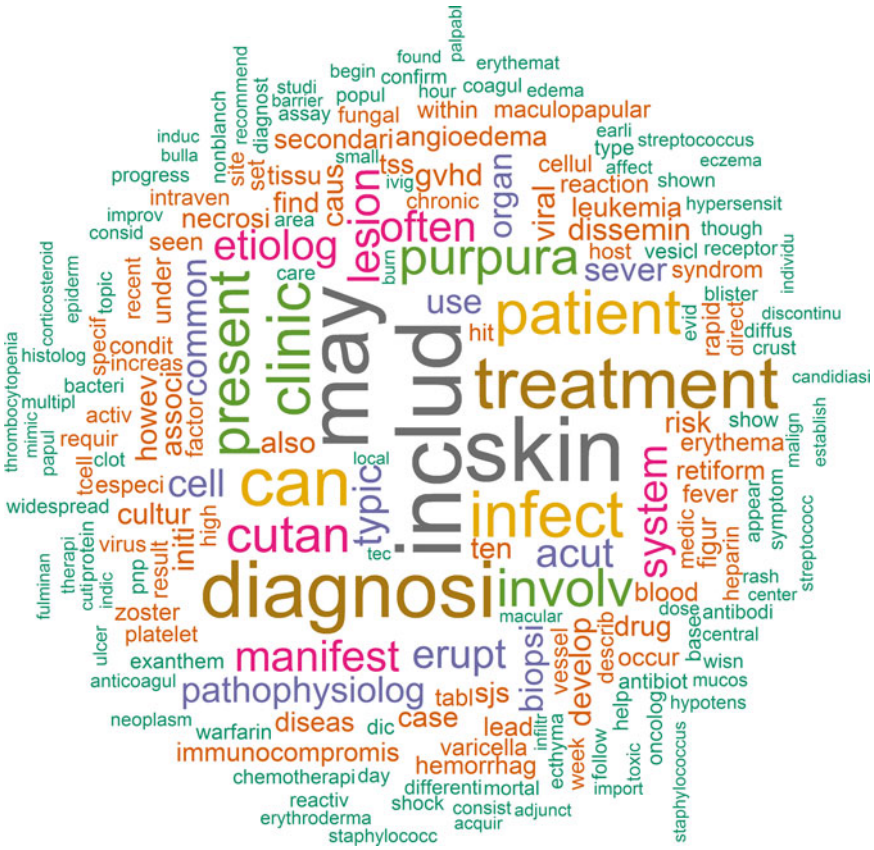
Dermatologic Emergencies in Oncologic Patients

Marisa Kardos Garshick, Laura Levin, and Joanna Harp



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Introduction

Oncologic patients can present with a wide range of common, serious, and at times life-threatening dermatologic conditions related to their underlying malignancy or to the treatment of their malignancy. Additionally, they may be at increased risk for infections, including cutaneous infections, secondary to immunosuppression. Recognition of the morphology of skin lesions (i.e., color, texture, shape, distribution, etc.) is an important step in the evaluation of these patients as it can greatly aid in making the diagnosis. It is particularly crucial for ED (emergency department) physicians caring for oncology patients to be aware of cutaneous manifestations that herald severe and life-threatening conditions to allow for quick recognition and initiation of the appropriate treatment. This chapter discusses the clinical presentation, pathophysiology, diagnosis, and management of these severe conditions organized by morphologic presentation (Table 1).

Maculopapular Eruptions

The differential diagnosis for maculopapular eruptions includes drug eruptions, viral exanthems, and, in the appropriate patient population, graft-versus-host disease.

*These authors contributed equally to this work.

Drug Eruptions

A maculopapular (exanthematous, morbilliform) eruption is the most common form of adverse drug reaction in hospitalized patients occurring in 57 % of patients with a cutaneous drug eruption [1]. The eruption consists of erythematous macules and papules scattered diffusely that may coalesce.

DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)/DIHS (Drug-Induced Hypersensitivity Syndrome)

Clinical Manifestations

When the symptom prodromes of including fever, lymphadenopathy, and facial edema are associated with a maculopapular drug rash, DRESS should be considered, and a work-up for systemic involvement should be performed. The cutaneous eruption involves a maculopapular rash that rarely presents with vesicles, pustules, or purpura (Fig. 1). The liver is the most common site of visceral involvement, but other systemic findings include arthritis, myocarditis, interstitial pneumonitis, interstitial nephritis, thyroiditis, and cerebritis. The clinical manifestations typically begin 2–6 weeks after initial exposure to medication.

Table 1 Cutaneous morphologies reviewed in this chapter

• Maculopapular eruptions
• Localized erythema
• Generalized erythema (erythroderma)
• Vesicles and pustules
• Blistering diseases
• Purpuric (non-blanching) eruptions

Pathophysiology/Etiology

DRESS is a delayed type IV hypersensitivity reaction that may involve impaired pharmacokinetics leading to the accumulation of drug metabolites. Genetic predisposition given the association with specific HLA alleles, viral reactivation, and the release of cytokines including interleukin 5 may play a role [2]. Common etiologies include the anticonvulsants, sulfonamides, allopurinol, dapsone, and antiretroviral medications.

Diagnosis

Diagnosis is made based on clinical findings of a maculopapular rash plus evidence of internal organ involvement, most commonly eosinophilia and transaminitis. However, any organ system may be involved, and eosinophilia is not required for diagnosis (thus the term drug-induced hypersensitivity syndrome (DIHS) is sometimes used). Biopsy findings are not specific in DRESS and show overlap features with ordinary drug eruptions.

Treatment

Early discontinuation of the suspected medication is necessary. Systemic corticosteroids (prednisone 1–2 mg/kg or equivalent) are the mainstay of treatment, and gradual taper with monitor for flares is recommended to prevent relapse.

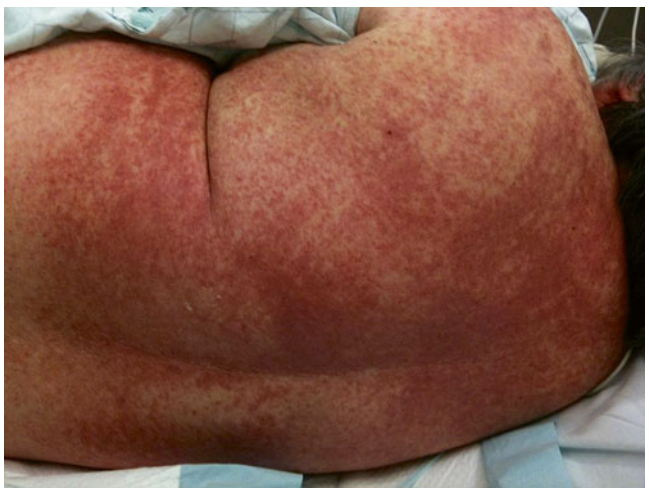

Fig. 1 Maculopapular eruption: diffuse erythematous macules and papules in a patient with DRESS secondary to allopurinol

The cutaneous and visceral manifestations may persist for weeks (rarely months), and patients should be monitored for late-onset thyroiditis.

Viral Exanthems

Viral exanthems often present with a maculopapular eruption that can mimic drug eruptions. They are commonly seen in the pediatric population and immunocompromised adults who are at higher risk of viral infection and reactivation.

Clinical Manifestations

Although viral exanthems typically present with a maculopapular eruption, they may also be scarlatiniform (diffuse small papules giving a sandpaper quality to the skin), petechial (non-blanching), or urticarial. Other clinical findings include fever, myalgias, arthralgias, nausea, vomiting, diarrhea, and malaise.

Pathophysiology/Etiology

Causes of viral exanthems include Epstein-Barr virus, cytomegalovirus, enterovirus, adenovirus, human herpesvirus types 6 and 7, parvovirus B19, measles (rubeola), rubella, and early human immunodeficiency virus. It is not known how viruses cause skin rashes, though it is likely related to immune system activation.

Diagnosis

It is not always possible to determine the exact viral cause; however, serologies, viral polymerase chain reaction assays, heterophile antibodies, and the presence of atypical lymphocytosis may be helpful. Skin biopsy may be useful in differentiating drug eruptions from viral exanthems; however, findings can be nonspecific.

Treatment

Viral exanthems are often self-limited with resolution after 1–2 weeks. Treatment includes symptom management and supportive care.

Graft-Versus-Host Disease (GVHD)

Acute GVHD commonly appears as a diffuse maculopapular eruption typically 3–6 weeks after stem cell transplant (SCT). GVHD is most common after allogeneic SCT; however, it may be seen following autologous and solid organ transplant.

Clinical Manifestations

The skin is the most commonly affected organ in acute GVHD, presenting with a maculopapular eruption. Individual lesions may be folliculocentric (centered upon a hair follicle) helping to distinguish from a drug or viral exanthem. A petechial component may be appreciated if the patient is thrombocytopenic. The liver and gastrointestinal systems are often also affected and, if severe, are associated with a high mortality. Chronic cutaneous GVHD has many clinical manifestations and can mimic lichen planus, lichen sclerosus, morphea, and scleroderma.

Pathophysiology/Etiology

In acute GVHD, SCT conditioning and damage to host tissues lead to the activation of host antigen-presenting cells. Donor T cells then proliferate in response to the activated antigen-presenting cells with subsequent activation of cytotoxic T lymphocytes and natural killer cells leading to tissue damage. Chronic GVHD is less well understood and is thought to involve donor T cells but also may involve B cells [3]. Risk factors associated with the development of GVHD include HLA incompatibility, unrelated donor, older age of recipient, peripheral blood stem cell source, and T-cell replete graft. In addition, the use of myeloablative-conditioning regimens is a specific risk factor for acute GVHD [4].

Diagnosis

The histology of acute GVHD shows varying degrees of keratinocyte necrosis, vacuolar changes at the dermal-epidermal junction, and a lymphohistiocytic infiltrate in the upper dermis, but a definitive diagnosis requires clinical correlation. The histology of chronic GVHD typically reflects the clinical pattern of the skin manifestations.

Treatment

Topical steroids are used to treat limited cutaneous acute GVHD; however, extensive cutaneous disease and other organ involvements often require systemic corticosteroids. Alternative and adjunct treatments for acute and chronic GVHD include phototherapy, other immunosuppressives including tacrolimus and mycophenolate mofetil, and extracorporeal photopheresis.

Localized Erythema

Cellulitis

Cellulitis is a superficial, diffuse inflammation of the cutaneous dermis and subcutaneous fat secondary to infectious process. Underlying immunosuppression and frequent disruptions of the skin barrier contribute to the development of this clinical entity.

Clinical Manifestations

Cellulitis presents with the acute onset of an erythematous, warm, tender plaque or plaques anywhere on the skin, usually over the lower extremities [5]. Cutaneous purpura may

Table 2 Differential diagnosis for cellulitis[a]

- Deep venous thrombosis
- Thrombophlebitis
- Lymphangitis
- Venous stasis dermatitis
- Allergic contact dermatitis
- Lipodermatosclerosis
- Erythema nodosum
- Deeper infection
  - Necrotizing fasciitis[a]
  - Osteomyelitis
  - Abscess
  - Pyomyositis

[a]Expanded upon in text

be present in the setting of thrombocytopenia or anticoagulation. Cutaneous edema can be severe leading to vesicle and blister formation. Cellulitis is almost always unilateral when located on an extremity. If findings are bilateral, an alternative diagnosis should be considered (Table 2). Patients are often afebrile, and increased white blood cell count is seen in less than half cases [5].

Pathophysiology

Cellulitis typically begins with organism entry through a disruption in the skin barrier especially in the setting of edema, trauma, ulceration, or a primary skin disorder such as eczema or tinea pedis. The etiology is usually bacterial (most commonly *Streptococcus* genus followed by *Staphylococcus aureus*); however, cutaneous fungal infections including histoplasmosis and cryptococcosis can mimic bacterial cellulitis, especially in the immunocompromised host.

Diagnosis

Diagnosis is typically clinical. Skin biopsy is usually not helpful as histopathologic findings may be nonspecific, and tissue culture is positive for an organism in only about 20–30 % of cases [5, 6]. However if cellulitis is worsening despite appropriate therapy, skin biopsy with tissue culture should be considered.

Treatment

Antibiotic therapy should be directed against streptococcal and staphylococcal organisms; however, broad-spectrum antibiotics including gram-negative coverage is often warranted in the immunocompromised host. Adjunctive treatments including elevation and compression in the case of an involved extremity and treatment of concomitant skin conditions that disrupt the skin barrier should be initiated.

On the differential diagnosis of cellulitis is an early necrotizing fasciitis, a rapidly progressive bacterial infection with necrosis of the deep subcutaneous tissue and fascia. Early infection presents with erythema and edema similar to cellulitis; however, this is quickly followed by the development of hemorrhagic bulla and non-blanching purpura that can progress to necrosis and gangrene within hours (Fig. 2). The most common etiology is *group A Streptococcus* though infections are often polymicrobial. Diagnosis is often made clinically, but imaging may demonstrate fascial thickening or air within the soft tissues. Treatment is emergent surgical debridement and broad-spectrum antimicrobials.

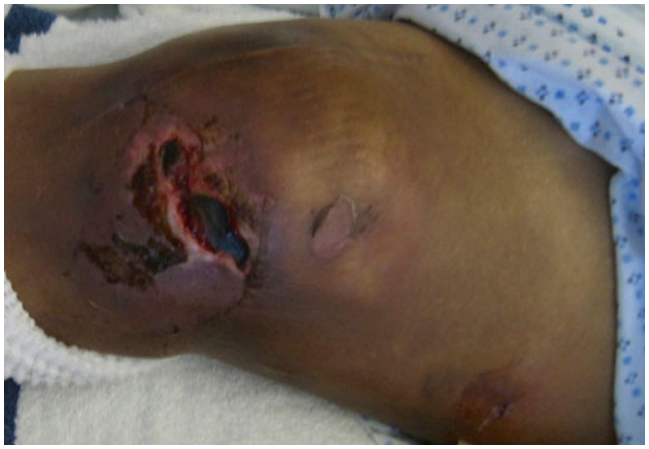

Fig. 2 Necrotizing fasciitis: rapidly expanding erythema, purpura, and necrosis secondary to a polymicrobial deep soft tissue infection on the right leg

Toxic Erythema of Chemotherapy

Toxic erythema of chemotherapy (TEC) describes a spectrum of cutaneous eruptions that are secondary to the cytotoxic effects of chemotherapy. Many terms have been used to describe these eruptions, including acral erythema, palmoplantar erythrodysesthesia, hand-foot syndrome, eccrine squamous syringometaplasia, Ara-C ears, and neutrophilic eccrine hidradenitis [7].

Clinical Manifestations

TEC describes the appearance of symmetric, erythematous and purpuric (non-blanching) patches, which can be associated with erosions, bullae, and desquamation (Fig. 3). Frequent sites of involvement include the elbows, knees, intertriginous areas, and acral sites including palms, soles, or ears. Other symptoms include burning, paresthesias, and pruritus. The lesions often develop 2–3 weeks after chemotherapy.

Pathophysiology/Etiology

TEC is thought to occur secondary to the cytotoxic effects of chemotherapy on the skin and sweat glands. TEC is often most pronounced in areas with a high density of sweat glands and may be attributed to the excretion of chemotherapy agents in the sweat [8]. TEC has been attributed to cytarabine,

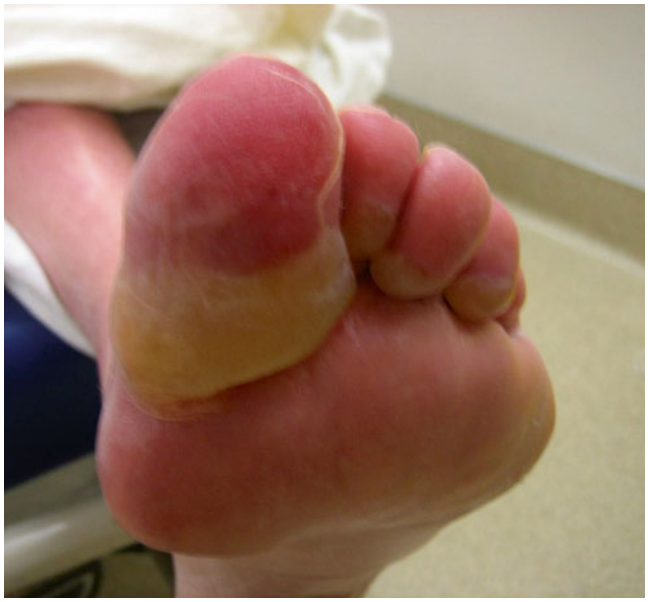

Fig. 3 Toxic erythema of chemotherapy: erythema and blisters secondary to sorafenib

doxorubicin, 5 fluorouracil, capecitabine, methotrexate, bleomycin, carboplatin, cisplatin, etoposide, gemcitabine, receptor tyrosine kinase inhibitors, cyclophosphamide, and melphalan, among others [7].

Diagnosis

The diagnosis can often be made clinically based on skin findings, distribution, and administration of causative agent. Biopsy may be helpful and shows cellular atypia, apoptosis of keratinocytes, vacuolar degeneration changes at the dermal-epidermal junction, and eccrine squamous syringometaplasia.

Treatment

Spontaneous resolution is the norm, but recurrences are possible with reexposure. Therapies target symptomatic relief and include cool compresses, analgesics, emollients, and topical corticosteroids. Topical 99 % dimethyl-sulfoxide, pyridoxine, pentoxifylline, and, in, severe cases, systemic steroids have also been used. Prevention includes dose reduction and lengthening dose intervals.

Leukemia Cutis

Leukemia cutis is a skin eruption that results from cutaneous infiltration of malignant cells in the setting of leukemia, most commonly acute myeloid leukemia.

Clinical Manifestations

Leukemia cutis classically presents with raised red-purple (plum-colored) papules or nodules, typically on the head, neck, trunk, and sites of prior trauma or scars but can arise in any location [9]. Lesions can be singular or multiple and may be the initial presenting manifestation of leukemia [10].

Pathophysiology/Etiology

It is not fully known why leukemic T or B cells migrate to the skin but is thought to be mediated by the expression of T and B cell receptors, in particular cutaneous lymphocyte antigen (CLA) and chemokine receptor 4 (CCR4). These receptors may interact with E-selectin and thymus activation-regulated chemokine (TARC/CCL17) on dermal postcapillary venules that home leukemic cells to the skin.

Diagnosis

Skin biopsy should be performed to confirm the diagnosis and rule out clinical mimics including cutaneous infection and Sweet syndrome (acute febrile neutrophilic dermatosis). Histology reveals dermal infiltration of neoplastic cells, leaving a grenz zone (space) between the dermis and epidermis [11].

Treatment

Management is aimed at treatment of the underlying leukemia. The development of leukemia cutis typically portends a poorer prognosis, with the exception of congenital leukemia with leukemia cutis [10].

Angioedema

Angioedema is the swelling of the deep dermis, subcutaneous, and submucosal tissues, most commonly on the eyelids, lips, and genitalia. It can involve the tongue and pharynx and, in such cases, become life threatening.

Clinical Manifestations

The affected area is edematous and tender with the surface appearing normal or slightly pink. Angioedema comes on abruptly and can last 2–3 days. Angioedema can occur alone or simultaneously with hives. Patients with angioedema or hives must be monitored for signs and symptoms of anaphylaxis with evidence of respiratory compromise, hypotension, and shock.

Pathophysiology/Etiology

The etiology of angioedema is determined by the clinical manifestations and is critical for appropriate treatment. Angioedema that occurs with hives is due to an immediate type I hypersensitivity reaction mediated by IgE and mast cell degranulation. It can be triggered by infection, foods, and drugs or may be idiopathic. Angioedema that occurs without hives may be related to an inherited mutation or acquired in the presence of an underlying malignancy or autoimmune disorder. This pathway is driven by deficient or

dysfunctional C1q esterase inhibitor, a critical enzyme in the complement and fibrinolytic cascade, leading to increased levels of bradykinin with resultant vasodilation and edema.

Diagnosis

Diagnosis of angioedema is often clinical; however, in the case of hereditary or acquired angioedema, low complement 4 (C4) level is seen both during and between attacks. C1q level is also low in acquired angioedema, helping to distinguish it from hereditary cases.

Treatment

Angioedema due to a type I hypersensitivity reaction may be treated with aggressive antihistamines and discontinuation of the offending agent if known. If there is concern for anaphylaxis, intramuscular or intravenous epinephrine should be used promptly. Recurring cases may require leukotriene receptor antagonists, immunosuppressants, and biologics [12].

Treatment for acute attacks in hereditary or acquired angioedema includes fresh frozen plasma, C1 inhibitor concentrate, kallikrein inhibitors, and bradykinin receptor antagonists [13]. Prophylactic and maintenance therapies include androgens (danazol, stanozol) and tranexamic acid, an antifibrinolytic [14].

Erythroderma

Erythroderma describes diffuse erythema of most if not the entire cutaneous surface often with exfoliative shedding of the skin. The differential diagnosis includes drug-induced, primary skin disorders, infectious etiologies, paraneoplastic, and others (Table 3).

Table 3 Differential diagnosis for erythroderma

- Drug induced
- Primary skin disorder
  - Psoriasis
  - Atopic dermatitis
  - Allergic contact dermatitis
  - Chronic actinic dermatitis
  - Seborrheic dermatitis
  - Pemphigus foliaceous
- Infection
  - Toxic shock syndrome[a]
  - Generalized dermatophytosis
  - "Norwegian" crusted scabies
  - Viral exanthem
- Neoplastic
  - Mycosis fungoides/Sezary syndrome[a]
  - Paraneoplastic phenomenon
- Graft versus host disease
- Others (rare): nutritional deficiencies, Kawasaki disease, cutaneous mastocytosis

[a]Expanded upon in text

Toxic Shock Syndrome

Toxic shock syndrome (TSS) is an acute, life-threatening infection due to a toxin-producing strand of *Staphylococcus* or *Streptococcus*. Patients with underlying chronic medical conditions including cancer are at higher risk for TSS.

Clinical Manifestations

In both staphylococcal and streptococcal TSS, patients become acutely ill with high fever, hypotension, and evidence of multiorgan system involvement. Influenza-like symptoms including chills, myalgias, headache, vomiting, and diarrhea are common. Cutaneous findings are relatively nonspecific including subtle, diffuse, blanchable erythema as well as edema and erythema of the palms and soles followed by prominent desquamation within 1–2 weeks. Mucosal findings include conjunctival erythema, anogenital erythema, and a strawberry tongue.

Pathophysiology/Etiology

In TSS, specific strands of *Staphylococcus* and *Streptococcus* produce toxins that act as superantigens leading to a widespread T-cell activation and cytokine release that cause fever, capillary leakage, and hypotension. TSS toxin 1 or enterotoxins A, B, C, D, E, and H cause staphylococcal TSS. Streptococcal TSS toxins include pyogenic exotoxins A, B, and C. Staphylococcal TSS is most often associated with focal infections including surgical wound infections, burns, osteomyelitis, sinusitis, septic arthritis, and tampon use in menstruating women [15]. Streptococcal TSS is more often seen in connection with bacteremia, cellulitis, or necrotizing fasciitis [16].

Diagnosis

Both staphylococcal and streptococcal TSS have specific diagnostic criteria required for diagnosis (Tables 4 and 5). Positive blood cultures are more frequently seen in streptococcal TSS than in staphylococcal TSS.

Treatment

Treatment includes rapid introduction of intravenous antibiotics against *Staphylococcus* and *Streptococcus*. Clindamycin has direct antitoxin properties and has been shown to improve patient outcomes in TSS [17]. The source of infection should be investigated and may be occult. Intravenous immunoglobulin (IVIG) and corticosteroids may be beneficial in severe and refractory cases [18, 19].

Mycosis Fungoides and Sezary Syndrome

Mycosis fungoides (MF) and Sezary syndrome (SS) are types of cutaneous T-cell lymphoma (CTCL) and both can present with erythroderma. MF is a T-cell lymphoma with initial

Table 4 Diagnostic criteria for staphylococcal toxic shock syndrome

Fever
Hypotension
Diffuse erythroderma
Desquamation (1–2 weeks after illness onset)
Three or more of the following:
• Renal dysfunction
• Gastrointestinal: vomiting or diarrhea
• Hepatic dysfunction
• Hematologic dysfunction
• Severe myalgias or elevated creatinine phosphokinase
• Altered mental status
• Mucous membranes erythema
Negative results of following tests, if obtained:
• Blood, throat, or cerebrospinal fluid cultures for another pathogen
• Serologic tests for Rocky Mountain spotted fever, leptospirosis, measles

Data from CDC: Case definitions for public health surveillance MMWR Morb Mortal Wkly Rep 1990; 39(RR-13):1. CDC: Case definitions for infectious conditions under public health surveillance. MMWR Morb Mortal Wkly Rep 1997; 46(RR-10):39

Table 5 Diagnostic criteria for streptococcal toxic shock syndrome

• Isolation of *group A Streptococcus*
• Hypotension
• Two or more of the following:
– Pulmonary dysfunction
– Liver dysfunction
– Renal dysfunction
– Coagulopathy
– Erythroderma of the skin
– Soft tissue necrosis (e.g., necrotizing fasciitis)

Data from: Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition. The Working Group on Severe Streptococcal Infections. JAMA. 1993 Jan 20;269(3):390–1

presentation in the skin but with potential involvement of the lymph nodes, blood, and internal organs. SS is a distinctive type of CTCL with leukemic involvement of malignant T cells.

Clinical

MF typically presents with patches and plaques and may progress to tumors or erythroderma (Fig. 4). SS generally presents with erythroderma often in the setting of lymphadenopathy and indurated facial features from the infiltration of malignant cells [20].

Etiology

The etiology of cutaneous T-cell lymphoma is not entirely known. Hypotheses include chronic stimulation of circulating skin-homing lymphocyte subsets that cause transformation to a monoclonal population. Mutations in genes controlling cell cycling and apoptosis have been identified and may be associated with disease progression.

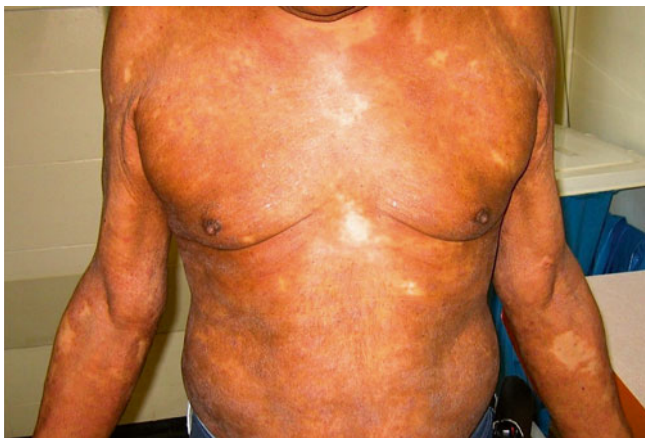

Fig. 4 Erythroderma: diffuse erythematous scaly plaques with small areas of sparing secondary to extensive mycosis fungoides

Diagnosis

Atypical lymphocytes within in the epidermis on skin biopsy are diagnostic of MF, though there may be overlap features with other chronic dermatoses. Diagnosis of SS requires the involvement of a clonal neoplastic T-cell population in the skin, lymph nodes, and blood. Evidence of peripheral blood abnormalities including greater than 20 % of circulating cells with cerebriform nuclei (Sezary cells), elevated CD4/CD8 ratio, or abnormal CD expression and T-cell receptor gene rearrangement testing from the skin or blood can aid in diagnosis. A recent study showed that the expression of programmed death 1 (PD-1) in skin biopsies strongly supports a diagnosis of SS [21].

Treatment

Patch stage MF may be treated with skin-targeted remedies such as topical steroids, topical nitrogen mustard, topical bexarotene, and phototherapy. Advanced MF presenting with erythroderma or systemic involvement and SS requires systemic therapies such as extracorporeal photopheresis, systemic retinoids, interferons, monoclonal antibodies, and chemotherapy regimens.

Vesicles and Pustules

The differential diagnosis for vesicular and/or pustular eruptions in oncologic patients is broad and includes infectious causes, inflammatory disorders, and drug reactions (Table 6).

Viral Infections

Varicella-Zoster Virus

Varicella-zoster virus (VZV) from the Herpesviridae family is the cause of varicella (chickenpox) and zoster (shingles). Both varicella and zoster are common infections seen in the oncologic patient.

Table 6 Differential diagnosis for common causes of vesicular/pustular eruptions in oncologic patients

• Drug
– Acute generalized exanthematous pustulosis (AGEP)
– Acneiform eruption secondary to epidermal growth factor receptor (EGFR) inhibitors
– Steroid induced acneiform eruption
• Inflammatory
– Pustular psoriasis
– Miliaria
– Allergic/irritant contact dermatitis
– Neutrophilic dermatoses
• Infectious
– Viral infections
Herpes simplex virus[a]
Varicella-zoster virus[a]
Coxsackie virus (hand, foot, and mouth disease)
– Bacterial
Bacterial folliculitis
Ecthyma[a]
Others: rickettsialpox, nocardiosis, listeriosis
– Fungal
Disseminated candidiasis[a]
Disseminated opportunistic fungal infection
– Atypical mycobacteria

[a]Expanded upon in text

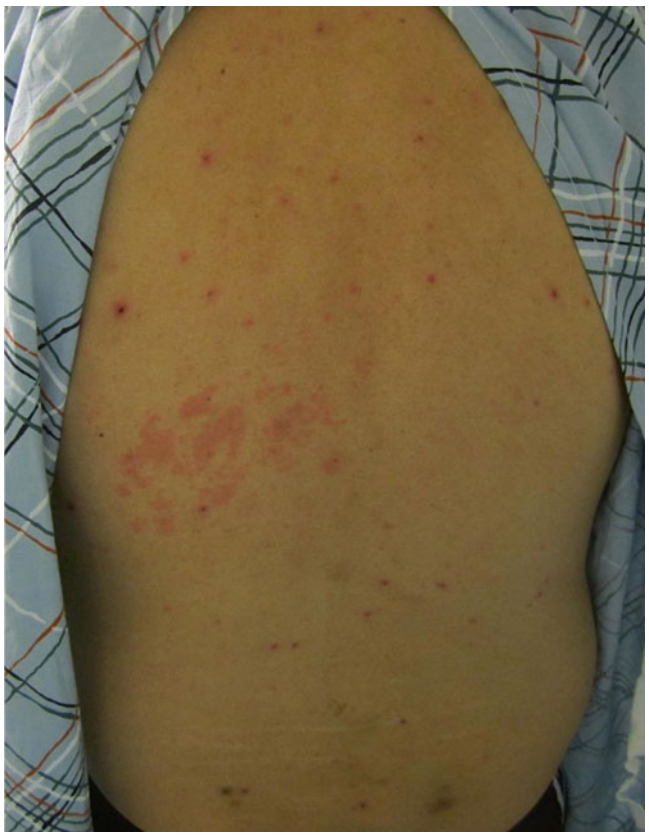

Fig. 5 Disseminated zoster: scattered vesicles on an erythematous base diffusely on the back with grouped vesicles in a dermatomal distribution on right mid-back

Clinical Presentation

Varicella begins with mild fever, malaise, and myalgias followed by an eruption of 1–3 mm clear vesicles with a red rim. Over the course of several days, the vesicles become pustular and often form a prominent central hemorrhagic crust. Varicella in adults and immunocompromised patients may be associated with higher risk of morbidity and mortality, often with more extensive crusting and risk of internal organ involvement.

Herpes zoster is the reactivation of latent VZV. Zoster initially presents with a prodrome of burning, tingling, and pruritus followed by the development of grouped vesicles on an erythematous base in a dermatomal distribution. When certain dermatomes are affected, extracutaneous complications can occur including ocular complications, facial paralysis, loss of taste, and deafness. In the immunocompromised and the elderly, pain and post-herpetic neuralgia may be more severe [22].

Disseminated zoster is defined as more than 20 vesicles outside the primary or contiguous dermatome (Fig. 5). Visceral involvement including pulmonary, hepatic, and central nervous system can occur in approximately 10 % of immunocompromised patients [23].

Pathophysiology/Etiology

Varicella is transmitted through airborne droplets or direct contact with vesicular fluid. After varicella infection, the virus travels to the dorsal root ganglion where it remains latent until reactivation. It is the reactivation of latent VZV that causes zoster (shingles), which may occur spontaneously or in the setting of stress, fever, local trauma, immunosuppression, or radiation.

Diagnosis

The diagnosis can be clinical; however, a Tzanck smear or direct fluorescence antibody assay can be used to confirm the diagnosis. Viral culture can be used; however, the results are not available for several days. Serologic assays and polymerase chain reaction may also be helpful.

Treatment

Antivirals can be used for varicella and zoster in immunocompetent patients to decrease the duration and severity if started within 24–72 h of rash onset. Intravenous acyclovir is recommended for varicella in immunocompromised individuals and disseminated zoster. Postexposure prophylaxis with varicella-zoster immunoglobulin is recommended for immunocompromised individuals and nonimmune pregnant women.

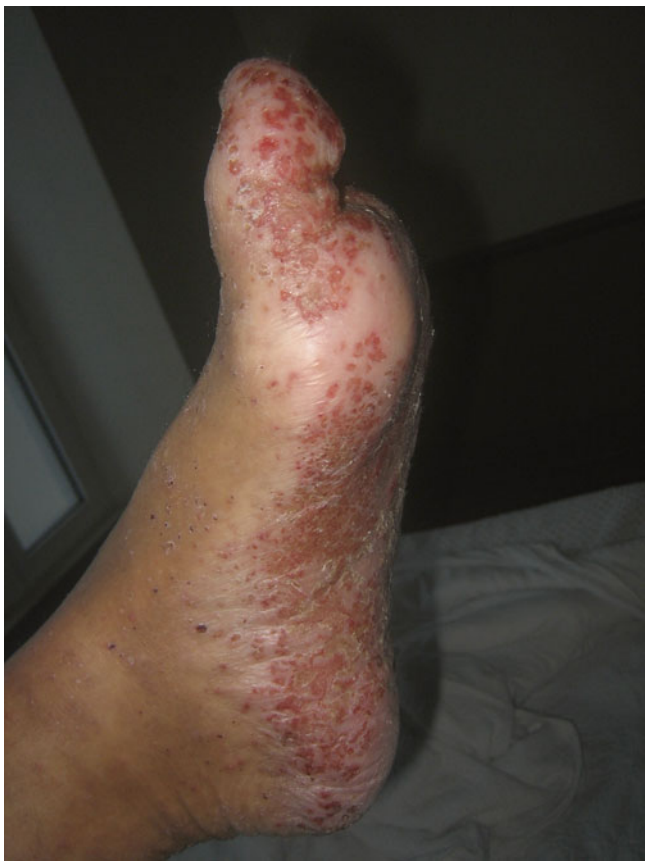

Fig. 6 Eczema herpeticum: diffuse 2–3 mm punched out erosions within an area of eczema on the foot

Eczema Herpeticum (Kaposi's Varicelliform Eruption)

Eczema herpeticum is the cutaneous dissemination of herpes simplex virus (HSV) in areas of a preexisting dermatitis, such as atopic dermatitis (eczema), mycosis fungoides, or other skin conditions with impaired skin barrier.

Clinical Presentation

Eczema herpeticum appears clinically as discrete 2–3 mm punched-out erosions with hemorrhagic crusts concentrated in areas of dermatitis (Fig. 6). Occasionally intact grouped vesicles or vesiculopustules may be seen, and the lesions may be superinfected with bacteria. Patients may have associated fever, malaise, and lymphadenopathy.

Pathophysiology/Etiology

Transmission of HSV1 is typically through direct contact with contaminated saliva, while HSV2 is transmitted through sexual contact. The virus then replicates at the site of infection and travels to the dorsal root ganglia, where it establishes latency until reactivation. Upon reactivation, the virus is able to spread via impaired skin leading to widespread involvement.

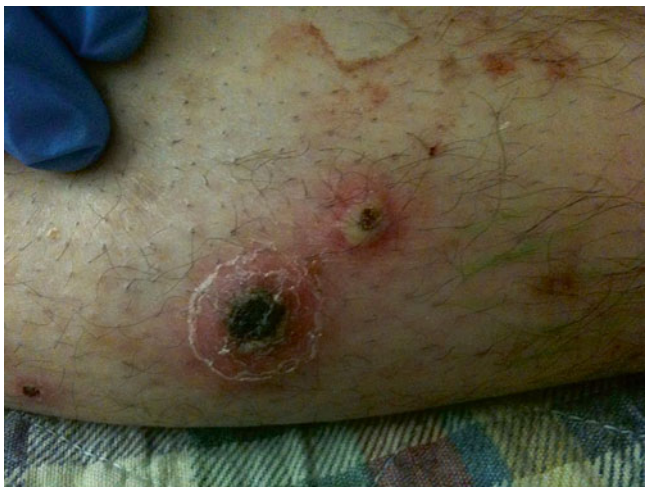

Fig. 7 Ecthyma: large pustules with central necrosis and crusting secondary to *S. aureus* bacteremia

Diagnosis

Diagnosis can be established through direct fluorescence antibody assays (DFAs), which is also able to distinguish between HSV and VZV. Other methods of diagnosis include viral culture, Tzanck smear, polymerase chain reaction, and serologic assays.

Treatment

Treatment includes the use of antiviral therapy for 10–14 days, especially if immunocompromised, until all lesions are crusted over. Severe cases may require hospitalization with empiric intravenous acyclovir while diagnostic studies are pending. If bacterial superinfection is present, antibiotics are necessary.

Bacterial Infections

Ecthyma

Ecthyma is an ulcerative bacterial skin infection that can be localized or widespread with systemic manifestations. Ecthyma gangrenosum is a specific term for ecthyma skin lesions secondary to bacteremia with *Pseudomonas aeruginosa*.

Clinical Presentation

Ecthyma initially begins as single or multiple vesiculopustules that enlarge over several days. Lesions then ulcerate and develop central necrotic adherent crusts (Fig. 7). When multiple lesions are present, patients may have fever, chills, malaise, and sometimes hypotension and shock. Bacteremia should be strongly suspected.

Pathophysiology/Etiology

Ecthyma is secondary to a localized skin infection or secondary to bacteremia with cutaneous seeding. Ecthyma may be due to gram-positive organisms including *Streptococcus* and *Staphylococcus* species and gram negatives such as *Pseudomonas*.

Diagnosis

The diagnosis can be made based on clinical appearance and gram stain and culture of the purulent base. Skin biopsy and tissue culture can confirm the diagnosis and organism. Blood cultures should be ordered especially when multiple lesions are present.

Treatment

Treatment includes systemic antibiotics and wound care with soaking and gentle debridement of adherent crusts and topical antibiotic ointment. Hospitalization and intravenous antibiotics are indicated when multiple lesions are present or in immunocompromised patients.

Fungal Infections

Disseminated Candidiasis

Disseminated candidiasis is an infection most often seen in the immunocompromised host and can affect any organ system including the skin.

Clinical Manifestations

Cutaneous manifestations of disseminated candidiasis include pustules and scattered erythematous macules, papules or nodules, often with a pale center. Other presentations include hemorrhagic bulla and purpura, especially in the setting of thrombocytopenia. Individuals are ill-appearing with tachycardia, hypotension, and fever.

Pathophysiology/Etiology

Candidal sepsis commonly occurs from *Candida* that has colonized the gastrointestinal tract or skin. *Candida albicans* is a common etiology of disseminated candidiasis, but *C. glabrata* and *C. tropicalis* can also be seen; *C. tropicalis* is more likely to produce cutaneous lesions and is common in patients with leukemia [24].

Diagnosis

Diagnosis can be established through skin biopsy and tissue culture or potassium hydroxide (KOH) preparation of purulent material. Budding yeast and pseudohyphae in the dermis are seen on biopsy. Evaluation also includes blood cultures, which may be negative, and evaluation for other organ involvement.

Treatment

In non-neutropenic patients, disseminated candidiasis can be treated with fluconazole. In neutropenic patients, amphotericin B, caspofungin, or voriconazole should be used. Any foci of infection such as lines and catheters should be removed.

Blistering Diseases

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe mucocutaneous reactions that are almost always triggered by medications. SJS/TEN may be more frequent in the oncologic population with one study showing a high incidence of TEN (6 %) in bone marrow transplant patients, though cases of TEN-like acute graft-versus-host disease (GVHD) were included [25].

Clinical Manifestations

SJS/TEN typically presents 1–3 weeks after initiation of the offending medication with blisters centered on non-blanching macules or atypical target lesions characterized by two distinct zones: a dark red center surrounded by a pale red outer ring (Fig. 8). Lesions tend to start proximally and on the face then spread distally. Individual lesions can rapidly coalesce

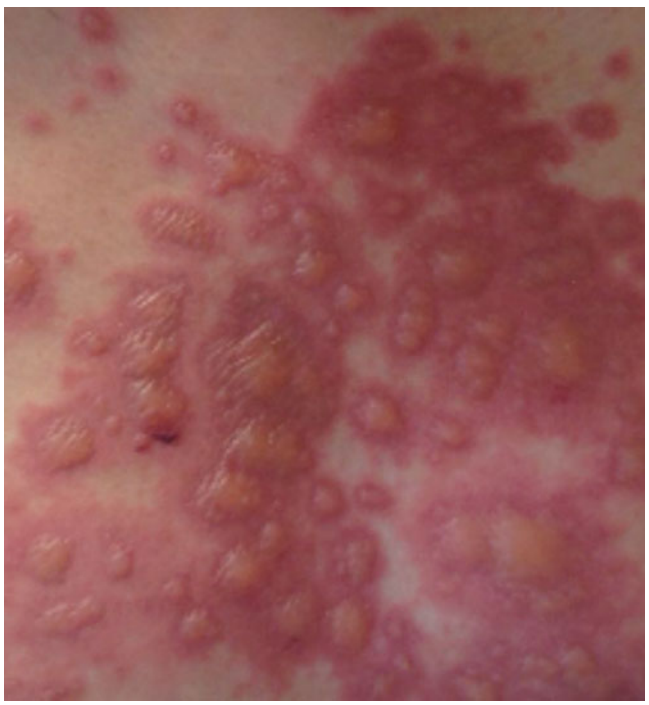

Fig. 8 SJS: coalescing blisters centered on non-blanching macules on the chest

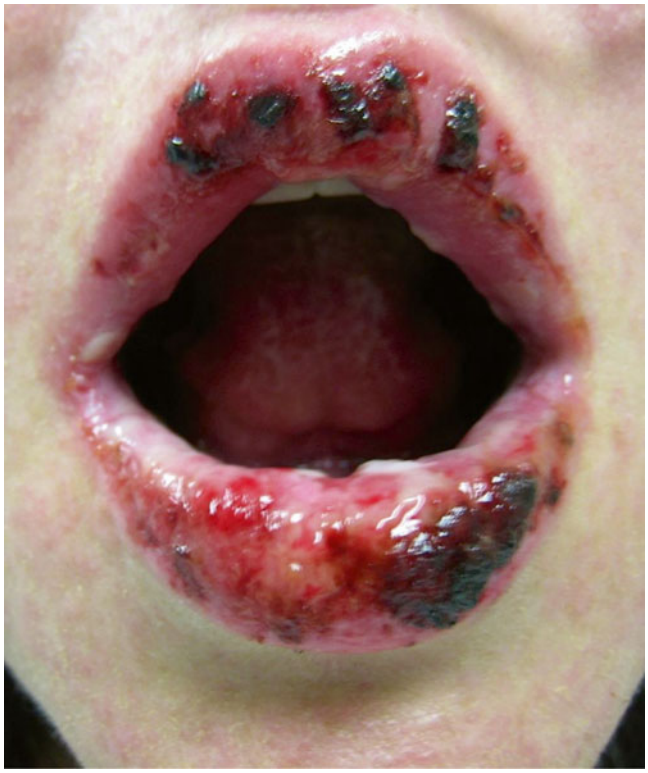

Fig. 9 Mucosal findings in SJS: erosions and hemorrhagic crusting

Table 7 SCORTEN severity of illness score in SJS/TEN

One point for each of seven criteria if present on admission
Age >40 years
Presence of a malignancy (cancer)
Heart rate >120
Initial percentage of epidermal detachment >10 %
Serum urea level >10 mmol/L
Serum glucose level >14 mmol/L
Serum bicarbonate level <20 mmol/L
SCORTEN predicted mortality rates
0–1: >3.2 %
2: >12.1 %
3: >35.3 %
4: >58.3 %
>5: >90 %

Table 8 Differential diagnosis for SJS/TEN

- Erythema multiforme[a]
- Staphylococcal scalded skin syndrome
- Pemphigus vulgaris/paraneoplastic pemphigus[a]
- TEN-like acute graft versus host disease[a]
- Linear IgA bullous dermatosis

[a]Expanded upon in text

followed by cutaneous necrosis and epidermal sloughing that can become widespread. SJS/TEN exist on a spectrum defined by percentage body surface area (BSA) of epidermal detachment: SJS defined as <10 % BSA, SJS/TEN as 10–30 %, and TEN as >30 %. Erythema multiforme (EM) was previously considered by many to exist on the spectrum of SJS and TEN but has more recently been classified as a separate entity with distinctive skin findings and etiology and a good prognosis [26].

Typically multiple mucosal sites (oral, ocular, and/or anogenital) are involved with erosions, ulcerations, and hemorrhagic crusting [27] (Fig. 9). In severe cases, gastrointestinal (GI) and pulmonary involvement occur. Patients are often febrile and can display signs of shock. Associated organ system involvement is frequently reported including hepatitis, acute renal failure, myocarditis, and bone marrow suppression. A recent survival analysis of SJS/TEN found the mortality rate to be 23 % at 6 weeks and 34 % at 1 year [28]. A validated scoring system has been developed to assess the severity of illness and predict mortality in SJS/TEN (Table 7).

Pathophysiology

The pathophysiology of SJS/TEN is unknown but likely multifactorial. SJS/TEN is classified as a delayed type IV hypersensitivity reaction involving cytotoxic T cells and soluble mediators including perforin, granzyme B, granulysin, and Fas-Fas ligand (FasL). Certain populations have specific human leukocyte antigen (HLA) types that are associated with a higher risk of development of SJS/TEN indicating a genetic component.

Diagnosis

Diagnosis can often be made clinically based on acute onset of blisters, targetoid (target-like) lesions, and epidermal detachment. Skin biopsy confirms the diagnosis and shows full thickness epidermal necrosis. Where available, frozen sectioning of skin biopsy samples allows rapid diagnostic confirmation within hours. Direct immunofluorescence should also be done to rule out other etiologies of blistering disease (Table 8).

Diagnosis may be more complicated in the setting of oncologic patients especially those that have undergone stem cell transplantation as severe acute GVHD can mimic SJS/TEN. Both diseases are at least partially mediated by cytotoxic T cells that target keratinocytes. Skin biopsies are usually indistinguishable though the presence of eosinophils may be suggestive of GVHD.

Treatment

The most important interventions that have consistently been shown to improve survival in SJS/TEN is prompt discontinuation of the offending medication and transfer to a burn unit, intensive care unit, or specialized care center. Supportive care consists of fluid and electrolyte balance,

wound care, monitoring, and early treatment of infection. An ophthalmology consult should be called whenever SJS/TEN is suspected. The use of prophylactic antibiotics is not recommended, as no survival advantage has been shown [29].

Literature regarding the benefit of adjunctive medications including intravenous immunoglobulin (IVIG) and systemic steroids is conflicting. Regarding IVIG, some studies have shown benefit in survival, while others have not [30]. A recent meta-analysis found no sufficient evidence to conclude that IVIG provides a clinical benefit in adults; however, high-dose IVIG (>2 g/kg) had a positive trend toward improved mortality [31]. Regarding corticosteroid, the literature is equally conflicting with some recent studies demonstrating possible benefit [32], while others show an increase risk of infection, duration of hospital stay, and mortality [33]. One recent study suggested that giving steroids early, in high doses, and for a short period of time may avoid the negative impact on wound healing and potential increased infection risk [32]. Interpretation of the literature is difficult as the dosing of adjunctive treatments, timing of initiation of treatment, and the use in specific patient populations have not been standardized. Further multicenter randomized controlled trials are needed.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus (PNP) is an autoimmune mucocutaneous blistering disease associated with an underlying neoplasm. PNP have been described in association with lymphoproliferative neoplasms including chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and Castleman's disease, though solid organ tumors including thymomas have also been reported [34].

Clinical Manifestations

PNP is characterized by painful mucosal ulcerations and a polymorphous skin eruption with an associated neoplasm. Mucosal involvement typically affects the oral mucosa, especially the lips; however, the conjunctiva, anogenital region, nasopharynx, and esophagus may also be involved. Skin manifestations typically appear later and are varied including nonspecific erythematous papules, target-like lesions, and blisters. Internal organ involvement has also been reported including pulmonary (classically bronchiolitis obliterans), thyroid, renal, and gastrointestinal tract.

Pathophysiology

Autoantibodies against plakins (periplakin, envoplakin) are diagnostic of PNP. Plakins are important proteins found in hemidesmosomes and desmosomes, which serve as vital structures in keratinocyte adhesion to other keratinocytes and to the underlying basement membrane. In some cases, these autoantibodies have been shown to be produced directly by the associated neoplasm [35]. Additional autoantibodies involved in PNP are desmoplakins 1 and 2 and plectin.

Diagnosis

Currently no single established set of diagnostic criteria exists for PNP. Most proposed definitions include mucosal involvement, detection of autoantibodies via direct and/or indirect immunofluorescence antibody testing against envoplakin and/or periplakin, and the presence of an underlying neoplasm.

Treatment

PNP often improves after the removal or treatment of the underlying neoplasm. Rituximab, which has increasing evidence for efficacy in pemphigus vulgaris, is recommended as first-line treatment for PNP [36]. Other treatments including prednisone, cyclosporine, cyclophosphamide, and IVIG have also shown efficacy [34, 37].

Purpuric (Non-blanching) Eruptions

Purpuric eruptions describe non-blanching skin lesions secondary to hemorrhage into the skin. Purpuric lesions may be flat (macular purpura), small and raised (palpable purpura), or larger and netlike (retiform purpura). It is important to recognize the features of macular purpura, palpable purpura, and retiform purpura as the differential diagnosis varies based on these morphologic differences.

Macular Purpura

Macular purpura describes flat areas of purpura of varying size. Lesions may be small (petechiae) or larger (ecchymoses). Macular purpura typically indicates hemorrhage into the skin secondary to low or dysfunctional platelets or vessel wall fragility in the absence of inflammation (Table 9).

Palpable Purpura

Palpable purpura describes small, raised, non-blanching lesions most commonly found on the lower extremities. Palpable purpura is the classic skin manifestation for cutaneous small vessel vasculitis (Table 10).

Retiform Purpura

Retiform purpura describes cutaneous lesions that have a netlike or stellate (starlike) pattern of purpura often with central necrosis or ulceration, reflecting damage to larger vessels with resultant cutaneous ischemia and hemorrhage (Fig. 10). Damage to the vessel may occur either through infiltration of the vessel wall or occlusion of the vessel lumen (Table 11).

Table 9 Differential diagnosis for macular purpura

Platelet related
• Low platelets
– Immune thrombocytopenic purpura (ITP)
– Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)
– Disseminated intravascular coagulation (DIC)
– Bone marrow failure
– Drug-induced thrombocytopenia
– Cirrhosis
• Abnormal platelets
– Congenital or hereditary platelet dysfunction
– Nonsteroidal anti-inflammatory drugs
– Renal disease
– Thrombocytosis
Non-platelet related
• Trauma/valsalva
• Infections (Rocky Mountain spotted fever, parvovirus B19)
• Capillary fragility (actinic damage, Ehlers-Danlos Syndrome)
• Anticoagulant medications
• Vitamin K deficiency
• Vitamin C deficiency

Table 10 Differential diagnosis for palpable purpura (cutaneous small vessel vasculitis)

• Inflammatory
– Connective tissue disease associated vasculitis
– Mixed type II and III cryoglobulinemia
– Henoch-Schonlein purpura
– ANCA+ vasculitis
• Infections (most commonly *Streptococcus*, HIV, hepatitis, tuberculosis)
• Medications
• Neoplastic (leukemic vasculitis, paraneoplastic phenomenon)
• Idiopathic

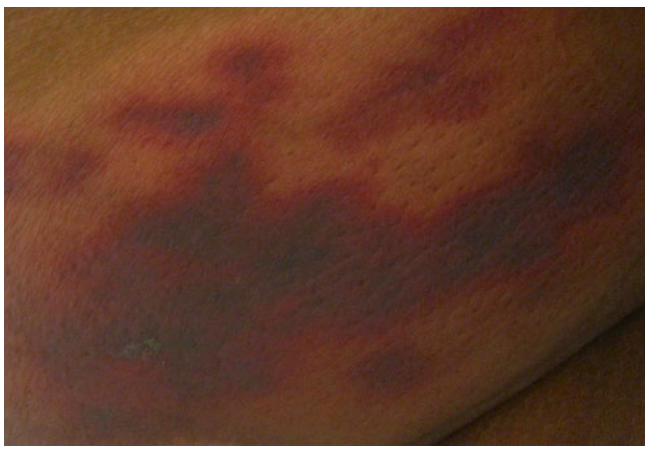

Fig. 10 Retiform purpura: netlike pattern of cutaneous purpura with central necrosis on the abdomen

Table 11 Differential diagnosis for retiform purpura

Vessel wall infiltration
• Vasculitis
– Septic vasculitis
– Mixed type II and III cryoglobulinemia
– Connective tissue disease associated vasculitis
– ANCA+ vasculitis
– Leukemic vasculitis
• Deposition (calciphylaxis, oxalosis)
Vessel lumen occlusion
• Thrombotic
– Abnormal coagulation
Hypercoagulable state (acquired or hereditary)
Warfarin induced skin necrosis[a]
Disseminated intravascular coagulation/purpura fulminans[a]
– Platelet plugging
Heparin-induced thrombocytopenia (HIT)[a]
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)
Myeloproliferative disorders
– Cold related (type I cryoglobulinemia, cryofibrinoginemia)
• Embolic: (septic, cholesterol, cardiac, air, fat emboli)

[a]Expanded upon in text

Acute Meningococcemia

Meningococcemia, a blood stream infection with *Neisseria meningitidis*, is a rapidly progressive disease with a fatality rate of 7–11 % [38]. Though its incidence is decreasing with increased vaccination in well-developed countries, its severity makes rapid recognition of paramount importance, especially in the immunocompromised host.

Clinical

Acute infection results in a constellation of symptoms including high fever, myalgias, neck pain or stiffness, and headache. Skin findings typically manifest with a diffuse petechial rash that rapidly progresses to retiform purpura with a central "gun-metal gray" color and necrosis. Hypotension and shock may develop, and patients should be monitored for disseminated intravascular coagulation.

Pathophysiology/Etiology

Acute meningococcemia is caused by transmission via droplet of *Neisseria meningitidis*, a gram-negative coccus. Disease typically develops 2 weeks after colonization of the pharyngeal mucosa. Cutaneous lesions of retiform purpura result from bacterial proliferation within the blood vessels creating vascular occlusion.

Diagnosis

Diagnosis of acute meningococcemia is clinical and should be suspected in any febrile patient with retiform purpura especially in the setting of headache and neck pain or stiffness.

Treatment should be initiated prior to results of diagnostic testing to prevent rapid spread of infection. Cerebrospinal fluid (CSF) culture is superior to blood culture and positive in 90 % of patients. PCR-based techniques on CSF approach a sensitivity of 100 % [38]. Skin biopsy with tissue culture can be helpful to confirm the diagnosis.

Treatment

Neisseria meningitidis is highly sensitive to high-dose intravenous penicillin G, ceftriaxone, and cefotaxime, and treatment should be initiated within 1 h of presentation. Rifampin should be given to close contacts, and the vaccine is available for high-risk groups [39]. Oncologic patients are not routinely vaccinated unless a risk factor, such as previous splenectomy, is present.

Opportunistic Fungal Infections

Infections from the opportunistic dermatomycoses including aspergillosis, fusariosis, cryptococcosis, and zygomycosis can range from localized cutaneous infection to disseminated infection with multiorgan system involvement. Leukemia and lymphoma patients are most at risk for deep fungal infections when neutropenic.

Clinical Manifestations

Disseminated fungal infections can present with a wide range of cutaneous lesions including retiform purpura, papulonecrotic lesions, pustules, and hemorrhagic bulla [40]. *Cryptococcus* may present with umbilicated papules that resemble molluscum contagiosum. Patients are typically febrile and appear acutely ill.

Pathophysiology/Etiology

Systemic mycoses may begin with primary skin infection or spread to the skin from a distant site of infection. Disruption of skin barrier or mucosa from burns, trauma, and indwelling catheters, along with impaired immunity, are predisposing factors.

Diagnosis

Diagnosis can be established with skin biopsy, tissue culture, and microscopic examination of lesional fluid. Serum assays for components of the fungal cell wall, including 1,3 beta-D glucan and galactomannan, can be used to screen for invasive fungal infection. Cryptococcal antigen is measurable in serum and correlates with fungal burden. Work-up should include chest X-ray and sputum culture to evaluate for pulmonary involvement.

Treatment

Expeditious treatment of deep fungal infection is key, and delay in treatment by as little as 2 h has shown to correlate with increasing mortality [41]. For many of the disseminated opportunistic mycoses, treatment is with intravenous amphotericin B. Voriconazole is first-line treatment for invasive aspergillosis. If *Cryptococcus* is disseminated to the CNS, addition of flucytosine is necessary. Prognosis is poor in disseminated disease but can be improved if neutropenia improves. Prophylactic treatment with fluconazole may help reduce the risk of infection.

Anticoagulant-Induced Skin Necrosis

Anticoagulant-induced skin necrosis is a term that includes heparin-induced thrombocytopenia (HIT) and warfarin-induced skin necrosis (WISN).

Clinical Manifestations

Both HIT and WISN present with retiform purpura secondary to occlusion of cutaneous vessels. Necrosis may develop centrally secondary to tissue ischemia. HIT is most commonly found at sites of medication injection and typically develops within 5–10 days of starting heparin or within 24 h in patients with recent exposure to heparin (Fig. 11). WISN typically develops 3–5 days after beginning coumadin, often on fatty sites, such as breasts, thighs, buttocks, and hips, and is preceded by pain.

Pathophysiology/Etiology

In HIT, circulating antibodies develop that simultaneously bind heparin and platelet factor 4 (PF4) causing platelet activation and subsequent aggregation leading to venous and arterial occlusion. For reasons that are not entirely clear, low-molecular weight heparins are less likely to cause platelet activation than unfractionated heparins [42].

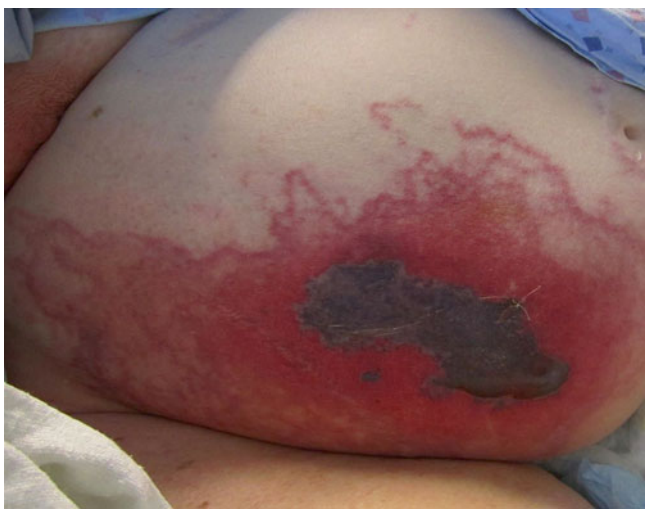

Fig. 11 Heparin-induced thrombocytopenia: retiform purpura with central necrosis at the site of heparin injection on the abdomen

Warfarin-induced skin necrosis results from the temporary imbalance in pro- and anticoagulant factors upon initiation of warfarin. Warfarin functions by inhibiting vitamin K-dependent coagulation factors. Protein C, an anticoagulant, is more rapidly inhibited by warfarin than procoagulant factors II, VII, IX, and X, leading to a temporary prothrombotic state. Risk factors include obesity, perimenopausal age, viral infection, and underlying hypercoagulable state.

Diagnosis

In both HIT and WISN, skin biopsies reveal a pauci-inflammatory thrombotic vasculopathy secondary to vessel occlusion. Subtle histologic variations in platelet thrombi (white clots) in HIT versus fibrin thrombi (red clots) in WISN can aid in differentiating the two histologically similar conditions [43]. In HIT, a rapid drop in platelets is typical resulting in absolute thrombocytopenia or a drop in platelets by at least 50 %. The diagnosis of HIT can be confirmed with HIT antibody testing including immunoassays and functional assays. WISN is typically a clinical diagnosis that requires a compatible histology and history of recent initiation or reintroduction of warfarin. Patients may also have a history of an underlying hypercoagulable state or a recent infection. Protein C and S analyses are not sensitive or specific markers [44].

Treatment

Treatment of HIT consists of immediate discontinuation of heparin and supplementation with an alternative anticoagulant, such as fondaparinux, danaparoid, lepirudin, or argatroban. Coumadin should be avoided initially but may be used once the patient has stabilized and platelet counts have recovered. Treatment of WISN involves immediate discontinuation of warfarin and administration of vitamin K and infusion of heparin at therapeutic doses. Fresh frozen plasma and protein C concentrate have been used to restore protein C levels and may be considered in the setting of life-threatening coagulation [44, 45]. It is recommended to bridge initiation of warfarin with heparin to avoid this phenomenon.

DIC/Purpura Fulminans

Infection, trauma, and malignancy among other insults can lead to imbalances in the coagulation system causing disseminated intravascular coagulation (DIC) with resultant simultaneous hemorrhage and thrombosis. If clotting is severe, purpura fulminans with acute, widespread retiform purpura and gangrene of the skin can develop.

Clinical

DIC presents with skin findings indicative of simultaneous bleeding and thrombosis including petechiae, ecchymoses, and mucosal bleeding as well as lesions of retiform purpura.

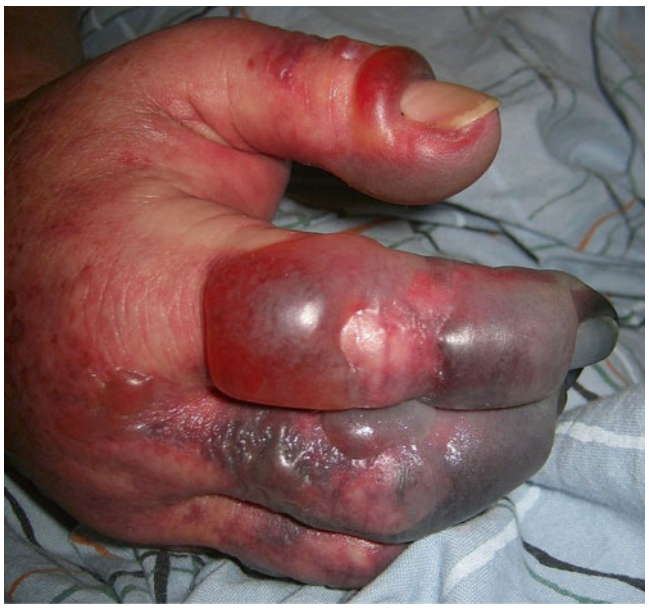

Fig. 12 Purpura fulminans: retiform purpura, blistering, and distal necrosis and gangrene of the hand

Purpura fulminans presents with rapidly progressive, widespread retiform purpura, hemorrhagic bulla, and symmetrical gangrene especially acrally (Fig. 12). Patients are acutely ill often with fever, shock, and evidence of multiorgan system involvement [46].

Pathophysiology/Etiology

Disseminated intravascular coagulation (DIC) and purpura fulminans are conditions in which systemic activation of coagulation leads to widespread clotting, particularly in small- and medium-sized vessels. Excessive clotting then leads to a consumptive coagulopathy where clotting factors cannot be generated as quickly as they are consumed and a bleeding diathesis ensues.

Diagnosis

Cardinal lab findings in DIC and purpura fulminans are consistent, independent of cause, and consist of thrombocytopenia, reduced plasma fibrinogen concentrations, increased fibrin and fibrin products, and prolonged clotting times. Skin biopsy may aid in diagnosis and shows a thrombotic vasculopathy [46].

Treatment

Treatment of DIC includes treatment of the underlying cause and aggressive management of hemodynamic stability. If serious bleeding is present, platelet transfusions and administration of fresh frozen plasma or cryoprecipitate may be indicated. The use of heparin is typically limited to patients with chronic, compensated DIC that have predominantly thrombotic manifestations. Protein C concentrate may be consid-

ered in cases of DIC secondary to hereditary or acquired protein C deficiency. Adjunctive hyperbaric oxygen and surgical debridement with skin grafting may prove beneficial in patients with extensive skin necrosis and gangrene [47].

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Gynecological Oncologic Emergencies

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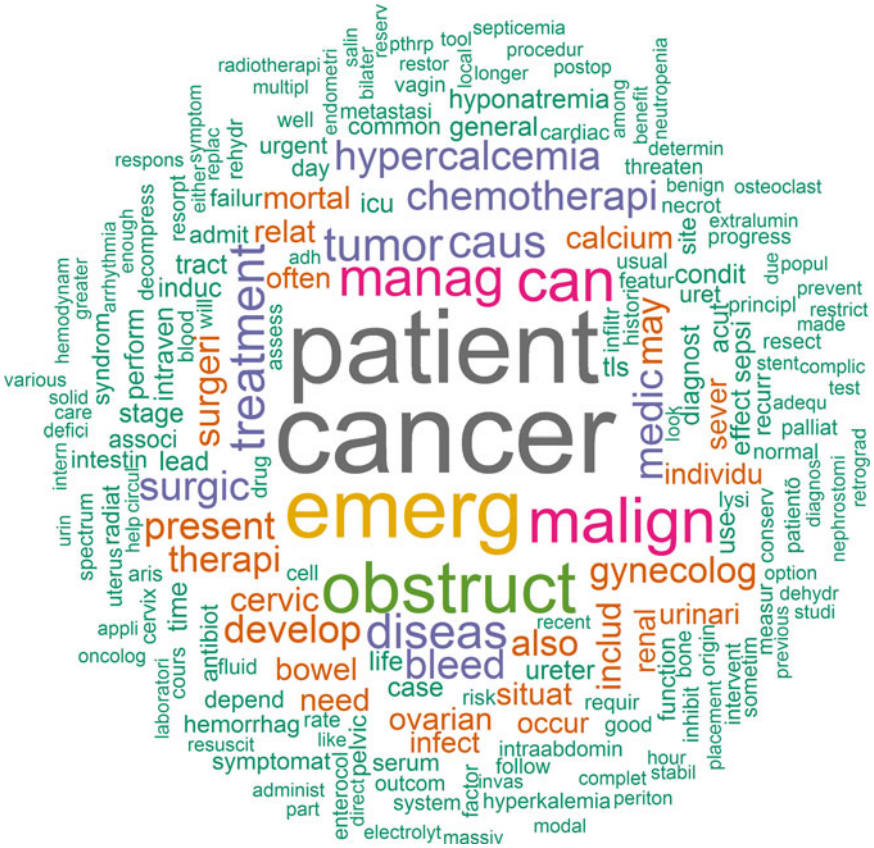

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Introduction

Patients who have been diagnosed with gynecological cancer could suffer emergencies from the beginning of the disease and throughout the course of the disease. While the reasons for emergencies are most often similar as in general population, there are several situations that could be attributed to cancer. Widely accepted is to divide emergency presentations on medical and surgical. Surgical emergencies related to cancer have a more favorable outcome than medical emergencies related to cancer. Mortality of cancer patients admitted to intensive care unit (ICU) for medical emergencies is 58 %, while mortality rate for surgical emergencies among cancer patients is 11 % [1, 2]. Medical emergencies could arise at any time in the course of malignancy even many years after cancer therapy is completed; therefore, medical staff should be aware of the patient's cancer history in details. Surgical emergencies include postoperative period when bleeding, injuries of urinary system, bowel injuries that are most often present, or emergencies following progression of gynecological cancer.

In addition to the malignancy itself, emergencies may also be induced by cancer therapies. Medical emergencies related to chemotherapy and radiotherapy could be severe and life threatening.

Cancer patients with medical and surgical emergencies have to be admitted to ICU and treated by multidisciplinary team including oncologist. In fact, late admission to ICU has been associated with greater mortality of critically ill cancer patients [3].

Patients with gynecological cancers present may experience various emergent situations with varied prognosis. Different modalities of treatment, stage of the disease, age of patient, and comorbidities determine the outcome of potential emergencies.

Medical Emergencies

Hypercalcemia

Up to 80 % of malignant hypercalcemia is caused by parathyroid hormone-related peptide (PTHrP) released by the tumor into the systemic circulation [4]. The effects of PTHrP represent a true paraneoplastic syndrome with systemic response, renal retention of calcium, bone resorption, changes in sensorium, arrhythmias, etc. (Table 1). Another mechanism involved in the pathogenesis of malignant hypercalcemia is increased bone resorption (osteolysis). Malignant hypercalcemia complicates 5–10 % of all cancers. Cervical, endometrial, and ovarian cancer can cause malignant hypercalcemia. Laboratory test measuring ionized calcium is a reliable diagnostic tool. Calcium above 3 mmol/L leads to dysfunctional GI tract, CNS, and kidneys. Clinical features of malignant hypercalcemia are renal failure and cardiac arrhythmias.

Table 1 Symptoms and signs of hypercalcemia [5]

Symptoms	Signs
Gastrointestinal	
Nausea	
Vomiting	
Anorexia	
Constipation	
Renal	
Polyuria	Dehydration
Thirst	Uremia
Hypercalciuria	
Nephrocalcinosis	
Neurological	
Lethargy	Muscular weakness
Drowsiness	Stupor
Weakness	Confusion
Disorientation	Dysarthria
Visual disturbance	Diminished reflexes
Pain	

Management

The basic principles of management include rehydration to restore glomerular function and the use of drugs to inhibit osteoclastic bone resorption (Table 2). Dehydration is an inevitable feature of symptomatic hypercalcemia, and aggressive rehydration is needed with 3–4 L of 0.9 % normal saline solution to increase urinary excretion of calcium. Bisphosphonates are used to inhibit osteoclast activity. Agent of choice for hypercalcemia is pamidronate, and it is highly effective leading to serum normalization of calcium in 3–7 days. If malignant hypercalcemia occurs as a result of humoral secretion by tumor itself, then surgical removal of tumor tissue can correct serum levels of calcium.

Urgent treatment is needed to normalize serum hypercalcemia, and even if mortality rate for malignant hypercalcemia is 50 %, there can be a palliative benefit to improve the symptoms [6].

Hyponatremia

Hyponatremia in women with gynecological cancer usually develops acutely within 48 h in emergent situations and requires determination of the underlying cause and urgent therapy. The most common causes of hyponatremia are chemotherapy (e.g., platinum-induced salt/wasting nephropathy) that is commonly used for ovarian cancer and ectopic tumor production of antidiuretic hormone (ADH).

Table 2 Management of hypercalcemia [7]

Medication	Usual dose	Points to remember
Normal saline	Rapid infusion 300–500 cc/h until euvolemic	Use caution in patients with heart failure
Furosemide	20–40 mg iv every 12–24 h	Only after adequate hydration
Pamidronate	60–90 mg iv	Adjust infusion time to creatinine clearance
Zoledronic acid	4 mg iv	Consider alternative treatment in patients with renal failure
Calcitonin	4–8 IU/kg sq or iv every 12 h	Tachyphylaxis occurs quickly
Steroids	Hydrocortisone, 100 mg iv every 6 h or prednisone, 60 mg orally daily	Role usually limited to lymphomas; anticipate hyperglycemia
Mithramycin and gallium		Of historical interest only
Denosumab	Under investigation	Currently approved only for the prevention of skeletal-related events from bone metastases

Table 3 Treatment of metabolic derangements in TLS [5]

Problem	Intervention	Dosages	Comments
Renal insufficiency and hypovolemia	Intravenous fluids	Normal saline, 3 L/m^2 daily	Use with caution if decreased systolic function
	Dialysis		For fluid-unresponsive oliguric renal failure or patients with CHF
Hyperuricemia	Allopurinol	100 mg/m^2 per dose orally every 8 h (maximum daily dose: 800 mg)	Drug-drug interactions with 6-MP and azathioprine; only effective for prophylaxis
	Rasburicase	0.15–0.2 mg/kg/d iv	Contraindicated in pregnancy and G6PD deficiency; costly
Hyperphosphatemia	Minimize phosphate intake	Minimal consumption of dairy and bread products	
	Phosphate binders (aluminum hydroxide or aluminum carbonate)	30 mL orally every 6 h	
	Dialysis		If no response to oral therapy
Hyperkalemia	Insulin (regular) 10 U iv		
	Dextrose	50 mL of 50 % dextrose iv push, then infuse 50–75 mL of 10 % dextrose over 1 h	
	Albuterol	20 mg nebulized	
	Dialysis		If no response to other therapies
	Calcium gluconate	1000 mg iv	If hyperkalemic EKG changes are noted
Hypocalcemia	Calcium gluconate	1000 mg iv (no faster than 200 mg/min)	Use with caution in severe hyperphosphatemia

6-MP 6-mercaptopurine, *CHF* congestive heart failure, *EKG* electrocardiogram, *G6PD* glucose-6-phosphate dehydrogenase, *iv* intravenously, *TLS* tumor lysis syndrome

Hyponatremia of less than 130 mmol/L is associated with weakness, confusion, headache, and seizures.

Management

Treatment of hyponatremia includes restricted fluid intake of around 500–700 mL per day and drugs which inhibit ADH action on the renal tubule. In life-threatening situations, slow infusion of hypertonic (3 %) saline can be administered.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) in gynecological oncology is described in patients with germ cell tumors [8] and solid tumors with liver metastases [9]. TLS can be induced by chemotherapy, radiotherapy, or ablation procedures. Tumor lysis syndrome occurs when cancer cells are released into the bloodstream spontaneously or induced by cancer treatments leading to sudden influx of electrolytes and nucleic acids into the circulation [8, 9]. The sudden development of hyperkalemia, hyperuricemia, and hyperphosphatemia can have life-threatening effects through multiorgan failure (Table 3). Hypocalcemia ensues as a consequence of hyperphosphatemia. Studies on animal model showed multiple emboli in microvessels due to debris of lysed tumor cells [10].

Management

Severe and particularly acute hyperkalemia during TLS may cause cardiac dysrhythmias and cardiac arrest. Emergency

Table 4 Criteria for sepsis [14]

General variables	Inflammatory variables[a, c]	Hemodynamic variables	Organ-dysfunction variables	Tissue-perfusion variables
Fever (core temperature >38.3 °C)	Leukocytosis (WBC count >12,000 mL^{-1})	Arterial hypotension (SBP <90 mmHg, MAP <70, or an SBP decrease >40 mmHg in adults or <2 sd below normal for age)	Arterial hypoxemia ($PaO_2/FiO_2 < 300$)	Hyperlactatemia (upper limits lab normal)
Hypothermia (core temperature <36 °C)	Leukopenia (WBC count <4000 mL^{-1})	SO_2 >70 % *b*	Acute oliguria (urine output <0.5 mL kg^{-1} h^{-1} or 45 mmol/L for at least 2 h)	Decreased capillary refill or mottling hypotension, Svo_2
Heart rate >90 min^{-1} or >2 sd above the normal value for age	Normal WBC count with >10 % immature forms	Cardiac index >3.5 L min^{-1} M^{-23}	Creatinine increase >0.5 mg/dL	
Tachypnea	Plasma C-reactive protein, INR, aPTT >2 sd above the normal value		Coagulation abnormalities (INR >1.5 or aPTT >60 s)	
Altered mental status	Plasma procalcitonin >2 sd above the normal value		Ileus (absent bowel sounds)	
Significant edema or positive fluid balance (>20 mL/kg over 24 h)			Thrombocytopenia (platelet count <100,000 mL^{-1})	
Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes			Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)	

WBC white blood cell; *SBP* systolic blood pressure; *MAP* mean arterial blood pressure; *Svo_2* mixed venous oxygen saturation; *INR* international normalized ratio; *aPTT* activated partial thromboplastin time. Infection, documented or suspected, and some of the following: *a* infection defined as a pathologic process induced by a microorganism; *b* Svo_2 sat >70 % is normal in children (normally, 75–80 %), and CI 3.5–5.5 is normal in children; therefore, *neither* should be used as signs of sepsis in newborns or children; *c* Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5 or <35 °C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function—altered mental status, hypoxemia, increased serum lactate level, or bounding pulses

management includes intravenous rehydration with glucose, insulin, and sodium bicarbonate to correct acidosis and drive potassium into the intracellular space and intravenous administration of 19 % calcium gluconate. Sometimes hemodialysis is necessary. Other cause of hyperkalemia in cancer patients is also septicemia, and the treatment is part of complex management of septicemia. Prevention of TLS is the key management in the patients who are likely to have good response on chemotherapy. Prevention of TLS includes intravenous hydration, premedication with allopurinol, and administration of sodium bicarbonate in order to maintain alkaline pH of urine.

Infections

Cancer patients have three- to fivefold greater risk of developing severe sepsis than the general population; thus, they are admitted to ICU because of infections more often [11]. More than 15 % of severe sepsis is among cancer patients [12] (Table 4). Cancer patients suffer from malnutrition and immune deficiency secondary to the malignant disease or its treatment [13]. A very important risk factor for developing life-threatening sepsis is neutropenia after chemotherapy. These patients should be closely monitored for evidence of infection.

Management

In the presence of fever, broad-spectrum antibiotics should be initiated, but before antibiotics, cultures of possible sites of infection should be performed looking for a specific site of infection (blood, urine, sputum, intravenous devices, recent surgical wounds, etc.). The longer the duration of neutropenia is, the more likely the infection would develop [15]. Recently, it became clear that the outcome of severe sepsis in cancer patients is individual and apart from a broad spectrum of antibiotics in the first few hours of sepsis; all other measures and interventions have to be individually tailored as if for cancer treatment as well (Fig. 1).

Gynecological malignancies in patients who have the highest risk for developing febrile neutropenia are ovarian cancer, cervical cancer if neoadjuvant chemotherapy is administered, and endometrial cancer also related mostly to chemotherapy (Table 5).

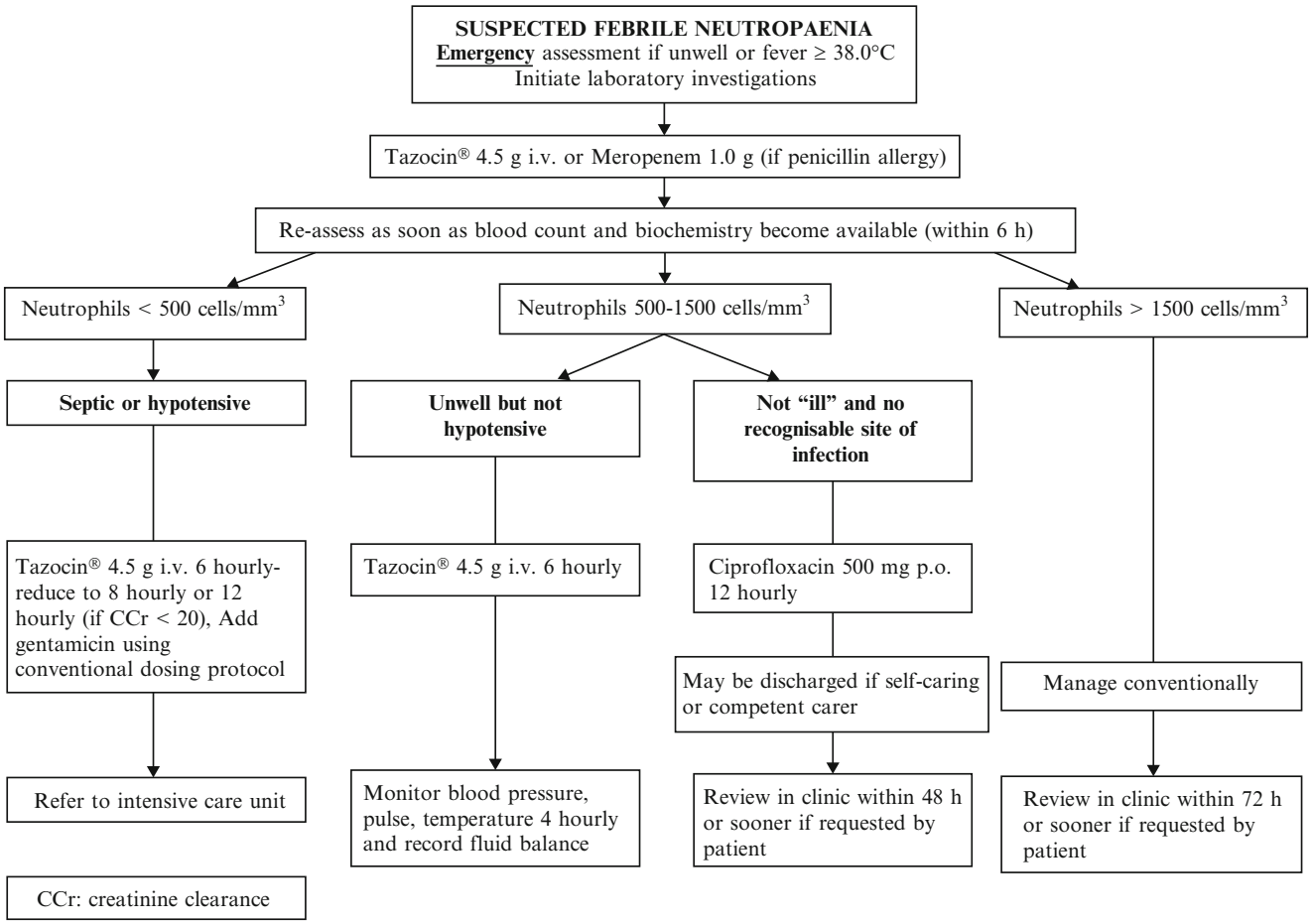

Fig. 1 Algorithm of initial management of febrile neutropenia [16]

Table 5 Risk assessment for febrile neutropenic patients [16]

High risk
• Significant medical comorbidity or clinically unstable
• Anticipated prolonged severe neutropenia (≤100 cells/mm^3 for ≥7 days)
• Hepatic insufficiency (five times ULN for aminotransferases)
• Renal insufficiency (a creatinine clearance of <30 mL/min)
• Uncontrolled/progressive cancer
• Pneumonia or other complex infections at clinical presentation
• Mucositis grades 3–4
Low risk
• No associated acute comorbid illness
• Anticipated short duration of severe neutropenia (≤100 cells/mm^3 for <7 days)
• Good performance status (ECOG 0–1)
• No hepatic or renal insufficiency

ECOG eastern cooperative oncology group, *ULN* upper limit of normal

Necrotizing Enterocolitis

Cancer patients can be admitted to ICU because of necrotizing enterocolitis, and then urgent therapy is needed. It usually arises from mucositis, and after developing as necrotizing enterocolitis, it is presented with a spectrum of diarrheal illnesses that can be fatal in granulocytopenic patient. This condition is more present in patients receiving intensive chemotherapy as for leukemia, but it can be observed during the treatment of solid gynecological malignancies.

Management

The therapy consists of antibiotics, intravenous fluids, nasogastric decompression, and sometimes surgery in case of bowel perforation.

Surgical Emergencies

Acute Blood Loss

Primary or recurrent neoplasms of the uterus, cervix, vagina, or vulva may present with small bleeds or with massive life-threatening hemorrhage. Hemorrhage due to metastasis can also be of various degrees. Massive hemorrhage can be the terminal event in late-stage disease. Vaginal bleeding commonly arises from bleeding metastasis. Bleeding from cervix

and uterus are emergencies which need different symptomatic and causative approaches.

Management

Immediate assessment of hemodynamic stability should be made, and also looking for coagulopathy is needed. Also an assessment of patient's general condition is needed so that adequate resuscitation is applied. Adequate volume replacement with crystalloids, followed by blood, should be given. In patients with cardiorespiratory impairment, titration against central venous pressure may be necessary. Replacement of platelets and clotting factors may be needed, and the management depends on individual situation. At first examination when heavy bleeding is diagnosed from the vagina, cervix, or uterus, the helpful measure is vaginal packing. After that, more lasting treatment should be planned. For vaginal, cervical, and uterine bleeding, definitive hemostasis could be performed with brachytherapy. Sometimes surgical ligation of the branches of the internal iliac artery may be required.

Intra-abdominal Bleeding

Intra-abdominal hemorrhage can occur directly from localized pelvic tumor because of its growth, infiltration of vessels, or previous chemotherapy and clotting factor deficiency, in the case of hepatic impairment.

Management

Assessment of hemodynamic stability, resuscitation and urgent surgery for localized bleeding tumor is based on individual situation, site of bleeding, and general performance of the patient. Radiation therapy could also be effective for most sites of intra-abdominal bleeding.

Intestinal Obstruction

Intestinal obstruction is most often associated with pelvic tumors. It is found in ovarian cancer (6–42 %) and cervical cancer (5 %) (Table 6). In ovarian and cervical cancers, there are often multiple levels of obstruction, and the obstruction occurs because of intraluminal infiltration or extraluminal compression. After surgery for ovarian or cervical cancer, patient can develop obstruction of bowels because of adhesions as well and also present as emergency case. Obstruction may be complete, subacute, or functional. Functional obstruction can occur because of chemotherapy and drug-related autonomic neuropathy or as ileus (e.g., perforation).

Presentation of obstruction includes vomiting, distention, dehydration, and variable bowel sounds, and usually, plain supine abdominal radiography is enough for diagnosis, but if there is any doubt, MRI could be a useful diagnostic tool.

Management

Therapy starts with conservative management restoration of fluid and electrolyte balance, alternatives for feeding, restriction of medication that have paralytic effect on the intestines, and nasogastric tube placement for decompression with stimulation of intestinal passage for distal obstructions [17]. This conservative regimen will keep the patient in optimal condition so that there will be enough time for diagnostic methods to identify the origin of the obstruction, stage of the malignant disease, and multidisciplinary evaluation. Minimally invasive methods include endoscopy, laboratory tests, and imaging studies. Conservative treatment provides time for diagnostic procedures as well as to see if the obstruction will resolve spontaneously but no longer than 3–7 days [18, 19]. After this period of time, decisions have to be made either for surgery or refraining from any intervention and further symptomatic and supportive care. When cause of obstruction is benign, laparotomy should be performed for adhesiolysis or bowel resection [20]. In the case of radiation enteritis, it is important to resect the entire diseased bowel segment to reduce recurrence, postoperative complications, and mortality [21]. In cases of malignant origin, surgical interventions such as bowel resection, bypass, or ileostomy may seem to provide in good palliation by reduction of symptoms and obstruction recurrence in progressive disease, but depend on the extent of the disease in the individual patient [22]. Surgery in patients with peritoneal carcinomatosis is related with a 30-day mortality of 21–40 % and high recurrence rate [23]. Noninvasive treatment and palliation of discomfort are reserved for patients with incurable disease with peritoneal metastasis [24]. Surgical options for obstruction of malignant origin depend primarily on the location of the tumor, extent of the disease, and clinical performance status of the patient [25]. As the patient's condition is often very poor in emergency setting, especially for patients with end-stage malignancy, emergency surgery is associated with morbidity of 61 % and overall mortality of 15–37 % [26].

Urinary Tract Obstruction

One of the most common causes for urinary tract obstruction is cervical cancer and other tumors in the pelvis obstructing lower parts of the ureter (Table 6). It can also develop following surgery, chemotherapy, or radiation. Acute ureteric obstruction causes painful spasm. Large pelvic masses such as ovarian cancer can cause bilateral ureteric obstruction

Table 6 Common locations, cause, and treatment options for obstructions [27]

Locations	Causes	Treatment options
Stomach	– Intraluminal tumor presence or invasion	– Conservative treatment (nasogastric decompression, restoration of fluid and electrolyte balance, alternatives for feeding)
		– Endoscopic stent placement
		– Surgical bypass or gastrectomy
Small intestine	– Postoperative adhesions	– Conservative treatment (nasogastric decompression, stimulation of stool passage, restoration of fluid and electrolyte balance, parenteral nutrition)
	– Postradiation strictures	
	– Strangulation or hernia	– Laparotomy for adhesiolysis, bypass, bowel resection, or ileostomy
	– Intraluminal tumor presence or invasion	
	– Extrinsic compression by tumor mass	
	– Peritoneal carcinomatosis	
Colon/rectum	– Intraluminal tumor presence or invasion	– Conservative treatment (nasogastric decompression, stimulation of stool passage, restoration of fluid and electrolyte balance, parenteral nutrition)
	– Extrinsic compression by tumor mass	– Endoscopic detorsion, stent placement, decompression, or ablation
	– Pseudo-obstruction (Ogilvie's syndrome)	– Laparotomy for bowel resection, bypass, or ileocolostomy
	– Volvulus	
	– Diverticulitis	
	– Intussusception	
	– Anastomotic strictures after surgical resection	
Urinary tract	– Extrinsic compression by retroperitoneal or pelvic mass	– Percutaneous nephrostomy catheter
	– Intraluminal tumor presence or invasion	– Endoscopic ureteric stent placement
	– Postsurgical fibrosis, structures, pelvic inflammatory disease	– Suprapubic or transurethral bladder catheter
	– Catheter-induced edema	– No indication for laparotomy
	– Postradiation strictures	
Airway	– Foreign body aspiration	– Tracheotomy/tracheostomy, intubation
	– Airway edema, hemorrhage, angioedema, or infection	– Bronchoscopy with tumor debulking, ablation, or stent placement
	– Tracheal stenosis	– Steroids
	– Intraluminal tumor presence or invasion	– Chemotherapy or external beam radiation therapy
	– Extrinsic compression by tumor of head, neck, and lung	– No indication for extensive surgical exploration
Spinal cord	– Compression, displacement, or encasement of dural sac by epidural metastases or locally advanced cancer	– Glucocorticoids
		– External beam radiation therapy
		– Hormonal therapy, chemotherapy
		– Surgical decompression by laminectomy

[28]. Obstruction is caused either by extraluminal compression on ureters or direct infiltration of tumor into ureters. Benign causes for acute obstruction of urinary tract in cancer patients can be fibrosis or pelvic inflammatory disease after surgery, catheter-induced edema, or strictures after radiation therapy [29]. If bilateral obstruction develops, then it leads to anuria and renal failure, with progressive rise in serum creatinine [30]. Obstruction of the urinary tract can lead to hydronephrosis and renal failure.

Ultrasound of the abdomen, cystoscopy, retrograde ureteric investigations, and CT scan are helpful diagnostic options.

Management

The basic principle of management is decompression of ureters because it secures renal function [31]. It could be accomplished by percutaneous nephrostomy or cystoscopy and retrograde placement of an internal ureteric stent [31, 32]. Percutaneous nephrostomy is a temporary measure used for patients with undiagnosed malignancy or in patients with cervical cancer who have available treatment modality and have good chance to respond to the treatment. Ureteric stent insertion is reserved for patients with advanced malignancy gaining symptomatic benefit for them.

Conclusion

Emergencies in patients with history of gynecological malignancy can occur at any time during the course of cancer disease and after that. Specific features of emergency presentations in those patients require knowledge of the patient's cancer history and medical knowledge of principles that should be applied in emergency situations. Therapy is individually tailored and depends on the underlying cause for emergency, stage of the malignant disease if still present, previous cancer treatments, and immunological and general condition of the patient.

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Ophthalmic Emergencies in Cancer Patients

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Introduction

While there are few ophthalmologic emergencies that are life threatening, there are a number of ocular conditions in cancer patients that require immediate diagnosis and management. This chapter reviews the differential diagnosis and management of common ocular or visual symptoms encountered in a cancer hospital-based emergency center. It is organized based on the symptoms that patients may present with to the emergency department, including acute visual loss, diplopia, red eye, proptosis, epiphora, ptosis, flashes, and floaters. A review of trauma-related ocular emergencies is outside the scope of this textbook, and the reader is referred to other texts for a detailed discussion of noncancer-related ocular emergencies [1, 2].

Acute Visual Loss

One of the most distressing ophthalmologic symptoms is the sudden loss of vision. The causes of sudden acute visual loss may be classified as those affecting the optic nerve, those affecting the retina, and those affecting the retinal vasculature.

The primary symptoms associated with optic nerve disease may include decreased visual acuity associated with a central visual field defect, decreased color vision and contrast sensitivity, and ocular pain on eye movement. A sensitive clinical sign for the presence of asymmetric optic nerve disease is a relative afferent pupillary defect (Marcus Gunn pupil) on the affected side using the swinging light test [3]. On ophthalmoscopy, the optic nerve head may appear swollen or pale. A red desaturation test may also be performed; when there is damage to the optic nerve, the affected eye sees the color red as a blanched orange-pink color.

Acute visual loss secondary to optic nerve disease in cancer patients can be due to a mass effect, either from a primary orbital tumor process (Fig. 1), secondary to an orbital metastatic process (Fig. 2), or from secondary extension of tumor from paranasal sinuses (Fig. 3), nasal cavity, or from the brain or skull base. Primary malignancies of the optic nerve include optic nerve glioma (Fig. 4), meningioma, craniopharyngioma, and medulloblastoma [4]. Infiltration of the optic nerve by leukemic or lymphomatous cells may also occur (Fig. 5) [5]. In addition, the optic nerve may be infiltrated by leptomeningeal disease from solid or liquid tumors. Invasive aspergillosis of the paranasal sinuses and/or orbit should also be considered in immunocompromised patients, as it is most prevalent among leukemic patients with granulocytopenia and is associated with a high mortality rate [6]. Optic nerve toxicity secondary to chemotherapeutic agents is another possible cause of optic neuropathy in cancer patients.

The most common noncancer-related cause of optic neuritis (optic nerve swelling) is multiple sclerosis; however, optic neuritis may also result from inflammatory conditions, such as Wegener's granulomatosis (granulomatosis with polyangiitis), systemic lupus erythematosus, and sarcoidosis, or it may be idiopathic. Infectious etiologies (including syphilis and Lyme disease) may also produce similar findings.

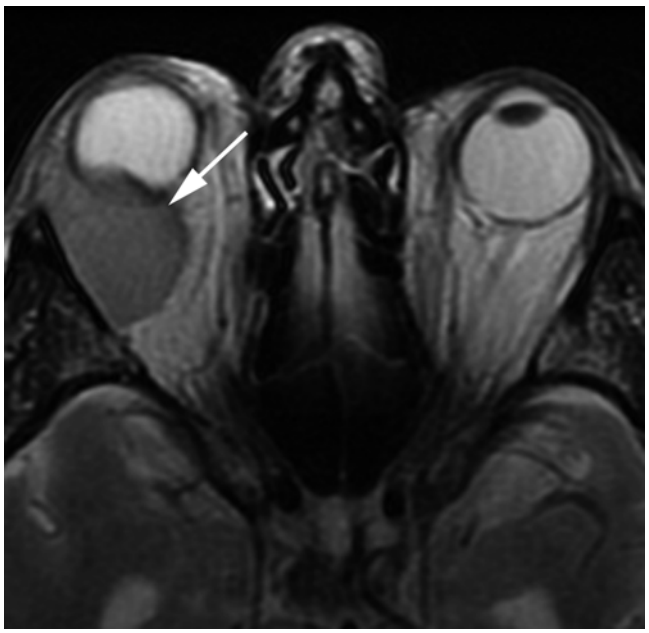


Fig. 1 Axial T2 image demonstrates an orbital lymphoma compressing the optic nerve and leading to visual loss (reprinted with kind permission from Springer Science + Business Media: *Ophthalmic Oncology*, Neuroradiology of Ocular and Orbital Tumors, 2011, 155, Debnam, J. Matthew)

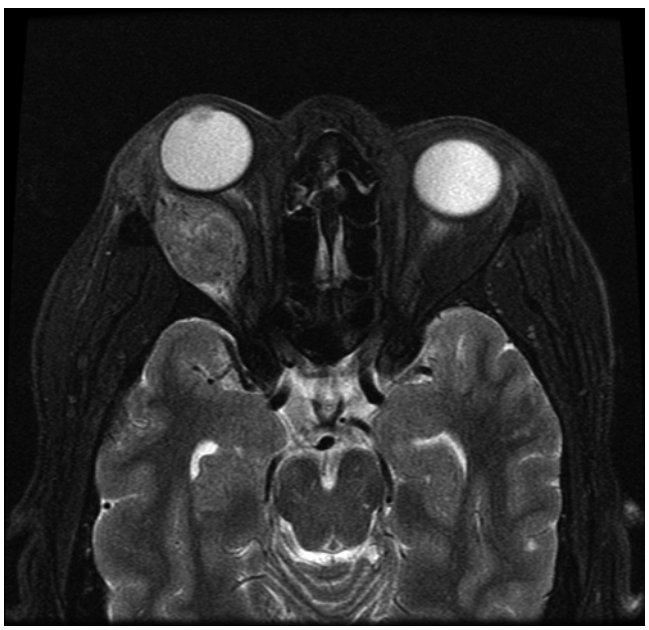


Fig. 2 Axial T2 image demonstrates metastasis from clear cell renal cell carcinoma to the right lateral rectus muscle. The patient presented with right eye pain, proptosis, diplopia, and blurry vision

In the elderly population or in patients with atherosclerosis, hypertension, and/or diabetes, the most common cause of acute visual loss of optic nerve origin is an ischemic optic neuropathy (Fig. 6). In the older population, giant cell arteritis is an important form of ischemic optic neuropathy that is sometimes associated with polymyalgia rheumatica [7]. Giant cell arteritis requires prompt diagnosis and treatment with high-dose systemic steroids to prevent progressive and sometimes bilateral visual loss. In diabetic patients or in the immunocompromised cancer patients, the possibility of orbital cellulitis or fungal infections such as mucormycosis or aspergillosis of the sinus with extension into the orbit should also be considered as a cause of optic nerve swelling and compression.

The preferred diagnostic test to evaluate optic nerve disease is magnetic resonance imaging (MRI) of the brain and orbit, with and without gadolinium, fat suppressed. MRI can usually demonstrate the extent of optic nerve disease, although may be normal in the early stages of leptomeningeal disease [8].

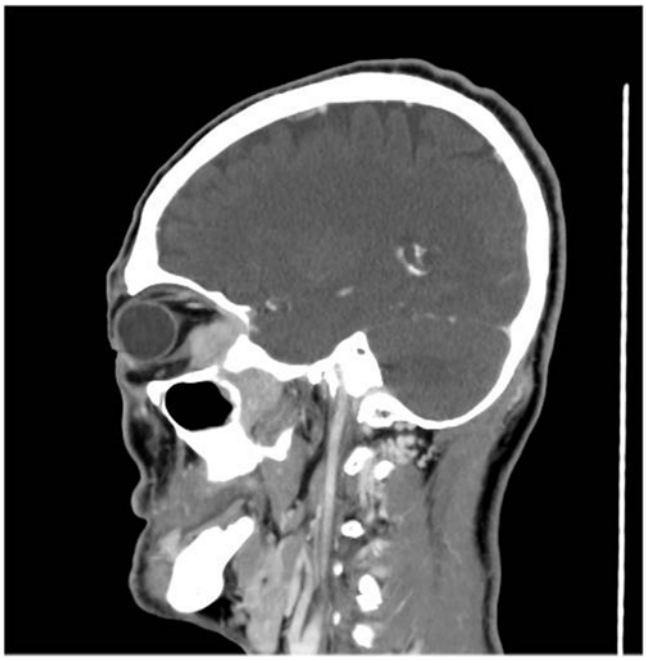


Fig. 3 Computed tomography sagittal plane demonstrates a nasopharyngeal carcinoma invading the orbit posteriorly through the inferior orbital fissure (reprinted with kind permission from Springer Science + Business Media: *Ophthalmic Oncology*, Secondary Orbital Tumors Extending from Ocular or Periorbital Structures, 2011, p. 83, Roman Shinder and Bita Esmaeli)

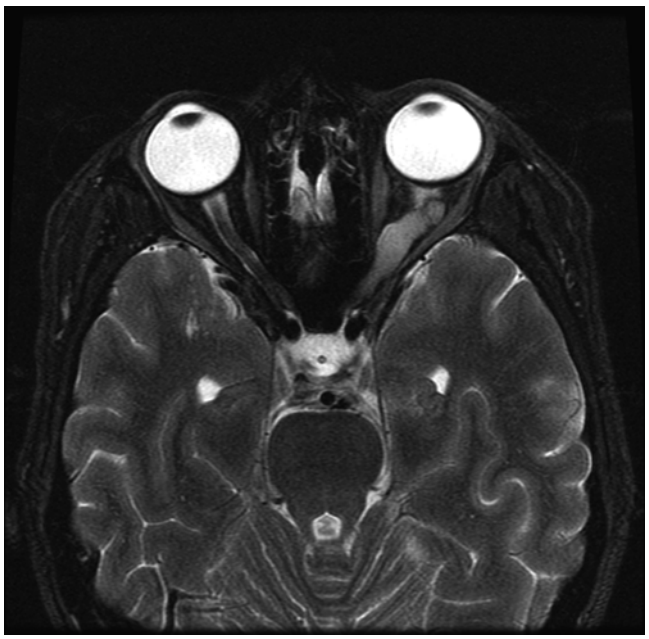
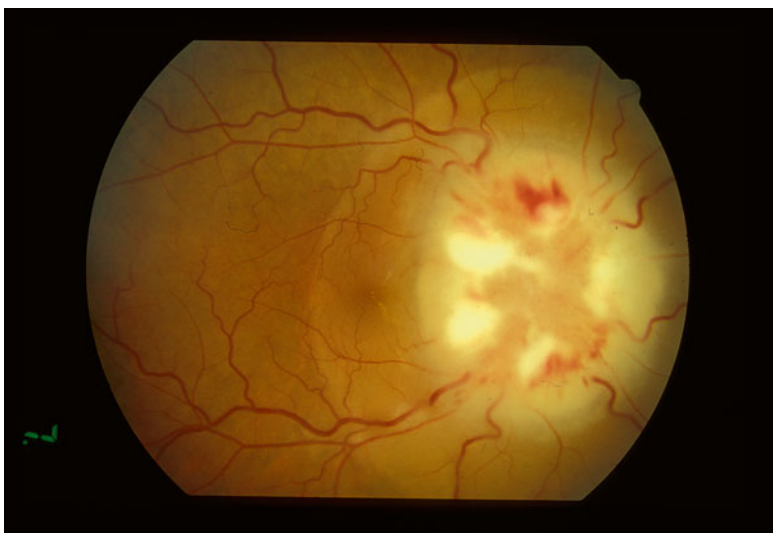


Fig. 4 Axial T2 image demonstrates left optic nerve glioma in a 61-year-old female who presented with visual loss in the left eye

Fig. 5 Fundus photograph demonstrates infiltration of the optic nerve by leukemic cells, causing progressive visual loss



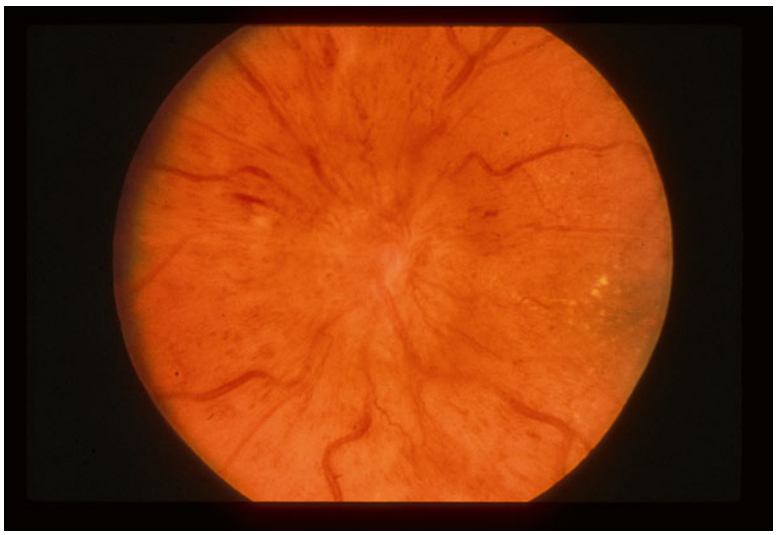


Fig. 6 Fundus photograph demonstrates ischemic optic neuropathy in a patient with diabetes mellitus who experienced acute painless loss of vision

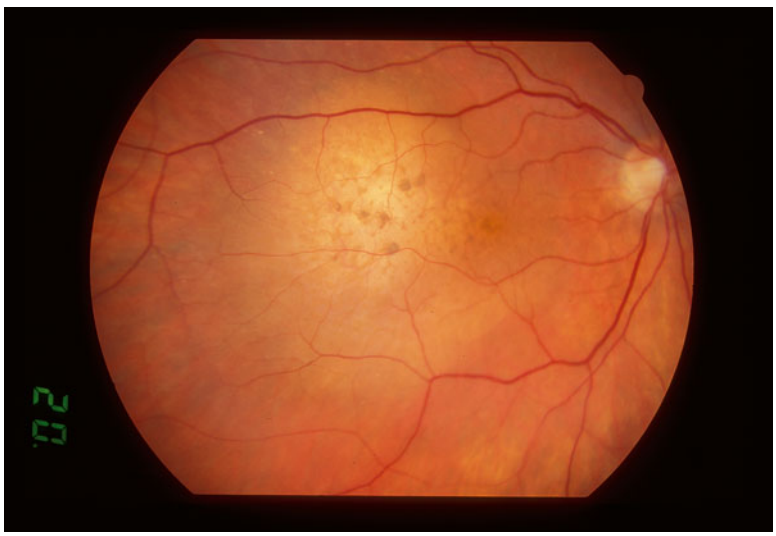


Fig. 7 Fundus photograph demonstrates a choroidal metastatic lesion causing elevation of the choroid and metamorphopsia

The management of optic nerve disease depends on the etiology. In cancer patients, the initial management may include systemic antibiotics or antifungals, chemotherapy, external beam radiation therapy, high-dose steroids, or surgery [9–11].

Retinal disease (particularly if it involves the macula, where visual acuity is most sensitive) may cause acute visual loss. Symptoms associated with retinal disease include decreased vision, metamorphopsia, flashes of light, new floaters, and a "curtain" over the visual field. A dilated fundus examination is necessary to correctly diagnose the retinal causes of acute visual loss.

Rhegmatogenous retinal detachment is the most common type of detachment, and it occurs when there is a tear or break in the retina, allowing fluid to accumulate in the subretinal space, separating the neurosensory retina from the underlying retinal pigment epithelium. In cancer patients, serous and exudative retinal detachments may result from leukemic or lymphomatous infiltration of the choroid and/or subretinal space, choroidal metastatic lesions (Fig. 7), or less commonly, from primary intraocular tumors such as uveal melanoma. Serous and exudative detachments occur despite the absence of a hole, tear, or break. Opportunistic infections such as those with *Cytomegalovirus* (CMV) (Fig. 8), herpes simplex virus (HSV), herpes zoster virus (HZV), and *Candida* may cause retinitis in immunocompromised patients. Retinitis due to HSV or HZV may cause rapid visual loss to "no light perception" within 24 h [12]. It is important to diagnose the infectious forms of retinitis in a timely fashion so that the appropriate systemic therapy can be initiated as soon as possible.

Another very common cause of visual loss among cancer patients is retinal hemorrhage secondary to thrombocytopenia (Fig. 9) [13]. Prompt referral to an ophthalmologist is

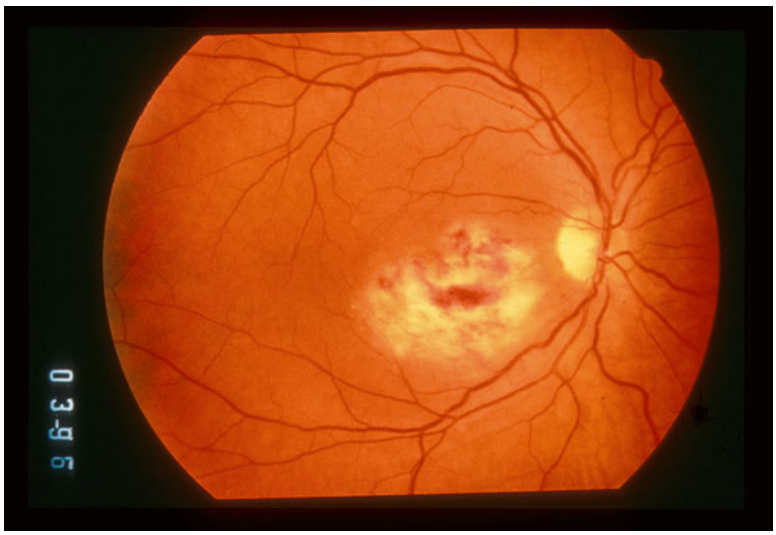


Fig. 8 Fundus photograph demonstrates CMV retinitis, characterized by necrosis and hemorrhage often in the posterior pole

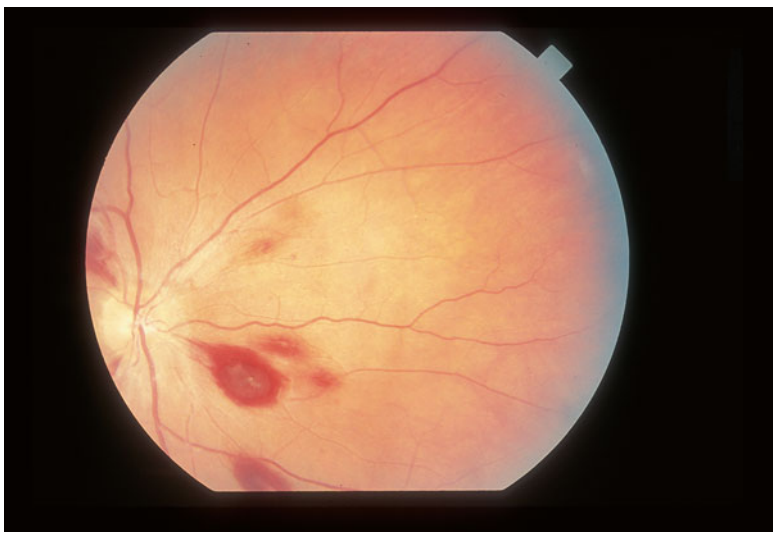


Fig. 9 Fundus photograph demonstrates spontaneous retinal hemorrhage in a patient with acute myeloid leukemia and thrombocytopenia

necessary for appropriate diagnosis and management. Treatment for rhegmatogenous detachments includes urgent laser photocoagulation or surgical management. For all other etiologies, timely treatment of underlying disease including chemotherapy and/or radiation for metastatic lesions and intravenous and/or intravitreal antiviral and antifungal therapy for opportunistic viral infections is necessary.

Obstruction of the retinal vasculature can also cause acute visual loss. Retinal vascular obstruction usually results from thrombi or emboli and is more likely to occur in patients with hypertension, atherosclerosis, or diabetes. However, cancer patients have the added risk of neoplasm-associated hypercoagulability [14]. Central retinal artery occlusion (CRAO) or central retinal vein occlusion (CRVO) may lead to devastating visual loss. Involvement of the smaller vessels may lead to partial visual acuity or visual field loss. Most occlusive vascular events are not reversible although they require prompt diagnosis and follow-up to address the underlying medical problems and to prevent future ocular complications from ischemic retinopathy. The visual prognosis depends on the extent of retinal ischemia. Particularly, the ischemic variety of CRVO can be complicated by secondary neovascular glaucoma and may require panretinal photocoagulation and intravitreal anti-VEGF inhibitors [15]. Prompt referral to an ophthalmologist is recommended when a retinal vascular event is suspected.

Diplopia

Diplopia (double vision) is a common symptom in cancer patients. The first thing to establish is whether diplopia is monocular or binocular and whether it is horizontal or vertical. In addition, true diplopia must be distinguished from blurred vision, in which the image is blurred but is not in fact double. If diplopia persists after one eye is covered, the patient has

monocular diplopia, which is almost certainly not a neurologic problem. The usual causes of monocular diplopia include refractive error or media opacity (i.e., cataract). In contrast, if diplopia is present only when both eyes are open, it is binocular in nature, and there is usually an underlying neurologic or extraocular motility problem. Binocular diplopia can be horizontal, vertical, or torsional [16]. Extraocular motility exam should be performed to assess whether only one or multiple cranial nerves are affected and for any signs of ptosis.

Specific neurologic causes of binocular diplopia include cranial nerve III, IV, or VI palsies, or a mechanical process that may limit the function of the extraocular muscles. If only one cranial nerve or extraocular muscle is affected, then a simple noncomitant diplopia may develop. In contrast, leptomeningeal disease or any space-occupying lesion in the orbital apex, superior orbital fissure, or the cavernous sinus may affect multiple cranial nerves at the same time, resulting in a more complex pattern of diplopia.

While cranial nerve palsies can be secondary to an ischemic event (particularly in patients with hypertension, diabetes, or atherosclerosis), in cancer patients, the most common etiology is tumor extension in the orbital apex or cavernous sinus. Extraocular muscles may also be compressed or entrapped by a mass, or they may be infiltrated by inflammatory or neoplastic processes. Opportunistic infections, particularly fungal infections secondary to mucormycosis or aspergillosis, may extend into the orbit from the paranasal sinuses. A high index of suspicion for fungal cellulitis or pansinusitis is necessary to make the correct diagnosis and initiate therapy for these potentially fatal infections in immunocompromised patients [17].

Another important but less common cause of third cranial nerve palsy, particularly if pupillary fibers are involved, is a cerebral aneurysm. This is not unique to cancer patients but should be considered on the differential diagnosis of a patient with an acute onset of third cranial nerve palsy.

In the emergency evaluation of a patient with an acute onset of diplopia, an imaging study (ideally, an MRI brain and orbit with and without gadolinium, fat suppressed) is often necessary to rule out or establish the diagnosis and extent of orbital or cavernous sinus involvement if any.

If a cerebral aneurysm is suspected, magnetic resonance angiogram (MRA) or computed tomography angiography (CTA) of the brain is indicated.

The treatment of diplopia depends on the underlying cause and (usually in cancer patients) entails treatment of the underlying tumor or infectious etiology. The patching of one eye or temporary Fresnel prisms may help the patient symptomatically until the exact cause and treatment for diplopia is determined.

Red Eye

There are many possible causes of a red eye in cancer patients. It is helpful to classify the causes of a red eye on the basis of intraocular structures that may be the cause of inflammation on the surface of the globe. Any disease process that can cause inflammation in the conjunctiva, cornea, iris, anterior chamber, ciliary body, or sclera can present as a red eye. Therefore, it is important to perform a comprehensive ophthalmologic examination to identify the correct cause.

Conjunctivitis is probably the most common cause of a red eye. Conjunctivitis can be due to infectious etiology such as bacteria (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Chlamydia*, *Neisseria gonococcus*) or viruses (adenovirus, herpes simplex virus [HSV]) [18]. However, occasionally, the cause is not infectious. The inflammatory causes of conjunctivitis include toxic conjunctivitis secondary to the excessive or inappropriate use of topical antibiotics (medicamentosa), allergic conjunctivitis, and acute or chronic ocular graft-versus-host disease.

Subconjunctival hemorrhage and hemorrhagic chemosis are benign conditions that may cause asymptomatic, sudden, painless red eye (Fig. 10). Conservative management with lubrication of the eye and observation for spontaneous resolution over several weeks is appropriate.

Superficial keratopathy secondary to ocular graft-versus-host disease (GVHD) or as a side effect of cancer chemotherapeutic agents such as arabinosylcytosine (ara-C) can cause ocular surface irritation, corneal epithelial defects, and possibly a red eye [19, 20]. Many other chemotherapeutic agents such as docetaxel and 5-fluorouracil are secreted in the tear film and may lead to conjunctivitis. Slit-lamp

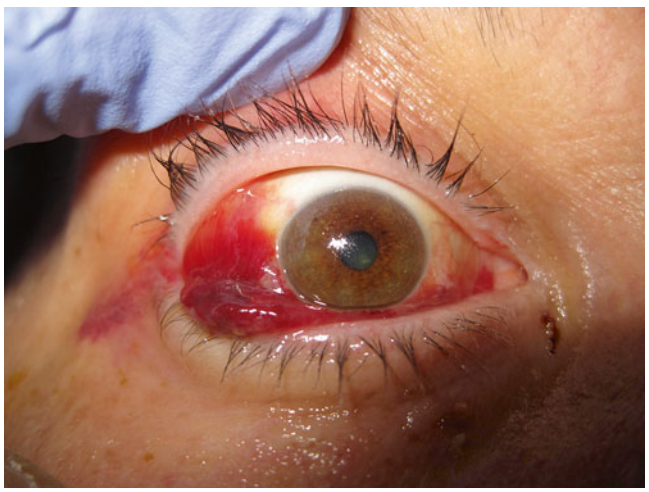


Fig. 10 Subconjunctival hemorrhage, causing painless red eye, in a 57-year-old patient who has a history of acute lymphoblastic leukemia and low platelet count (30,000/μL)

examination of the cornea using topical fluorescein dye and cobalt-blue light to assess for decreased tear film, punctate epithelial erosions, pseudomembranes, serosanguinous exudates, and corneal epithelial defects is performed to evaluate for most forms of superficial keratopathy. The management of conjunctival or corneal problems secondary to ocular GVHD entails the use of topical lubricants, cyclosporine drops, punctal plugs, and topical and/or systemic administration of immunosuppressive agents such as steroids and tacrolimus [21]. Superficial keratopathy secondary to ara-C use is treated with topical steroids, lubricating artificial tears and ophthalmic ointment, and in refractory cases by lowering the dose of ara-C.

Another common cause of superficial keratopathy in cancer patients is exposure keratopathy secondary to facial palsy. Facial paralysis secondary to the compressive effects of a parotid mass or due to ablative surgery for malignancies in the parotid area can result in inadequate eyelid closure and chronic corneal exposure [22]. The immediate treatment of exposure keratopathy entails the use of lubricating artificial tears and ophthalmic ointments. If facial paralysis is expected to last longer than a few weeks, periocular surgery, such as placement of a gold weight in the upper eyelid, repair of paralytic lower eyelid, and a lateral tarsorrhaphy, should be considered [23].

Infectious keratitis is another important cause of red eye and can be caused by bacterial (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Neisseria gonococcus*, *Moraxella*, *Pseudomonas aeruginosa*), viral (adenovirus, HSV, HZV),or fungal (*Candida*, *Aspergillus*) organisms [24]. Herpes zoster ophthalmicus occurs when varicella-zoster virus is reactivated in the ophthalmic (V1) division of the trigeminal nerve and is associated with immunosuppression, and it may be a harbinger of increased risk of cancer [25] or other immunocompromised states. It may present with periorbital vesicle formation in a unilateral, V1 dermatomal distribution with associated red eye and pseudodendritic fluorescein-staining pattern under cobalt light. Prompt diagnosis and treatment of HZV with systemic antiviral agents like acyclovir and topical agents is appropriate. The diagnosis and management of infectious keratitis requires the direct involvement of an ophthalmologist. Management often involves obtaining corneal cultures and instituting topical fortified antibacterial, antiviral, or antifungal agents.

Acute angle-closure glaucoma may also cause a painful red eye. It occurs in patients who have narrow angles that become blocked by the iris. Symptoms and signs of acute angle-closure glaucoma are pain, redness, blurred or "steamy" vision from corneal edema, halos around lights, and a mid-dilated pupil. The intraocular pressure can rise to 50–60 mmHg, and urgent medical treatment to lower the pressure is necessary to avoid permanent vision loss. There are many causes of acute angle-closure glaucoma, and prompt diagnosis is necessary for appropriate treatment. Anticholinergic or sympathomimetic medications dilate the iris and lead to crowding of the anterior chamber angle peripherally [26]. A mass in the ciliary body or choroid can also push the iris forward and cause angle closure [27]. Primary intraocular tumors such as uveal melanomas or medulloepitheliomas may be present in the angle and may obstruct the aqueous outflow. The medical management of angle-closure glaucoma in the emergency department includes the immediate use of topical antiglaucoma medications, and systemic carbonic anhydrase inhibitors are often necessary to bring the intraocular pressure down to a safe level. For primary acute angle-closure glaucoma, the patient should be referred to an ophthalmologist for consideration of a laser peripheral iridotomy after the intraocular pressure has been brought down to a safer level with medications [28].

Inflammation of the iris, ciliary body, or choroid is referred to as uveitis. In addition to red eye, uveitis can present with pain, photophobia, blurred vision, and miosis. Anterior chamber cells and flare noted during slit-lamp biomicroscopy are the hallmarks of iritis or uveitis. Uveitis is thought to be idiopathic in about 50 % of cases or can be associated with various autoimmune processes such as rheumatoid arthritis, lupus, ankylosing spondylitis, and Wegener's granulomatosis (granulomatous polyangiitis) [29]. In immunocompromised patients, infectious causes of uveitis must be considered. The most severe form of intraocular infection, endogenous endophthalmitis, can initially present as mild but progressively worsening uveitis [30]. Once the diagnosis of endogenous endophthalmitis is suspected, blood culture and vitreous biopsy are often necessary to identify the causative infectious organism. Prompt referral to an ophthalmologist is necessary for diagnosis and management. Treatment for uveitis due to noninfectious causes includes the judicious use of topical steroids and cycloplegic drops to decrease the inflammation in the anterior chamber and prevent ciliary body spasm. For suspected endogenous endophthalmitis, broad-spectrum intravenous antimicrobial therapy is administered until sensitivity results are available from the vitreous biopsy cultures. Intravitreal injection of antibiotics or antifungal drugs is the treatment for endogenous endophthalmitis, and in some cases, a surgical vitrectomy may be necessary both for diagnostic and for therapeutic purposes [31, 32].

Epiphora

True epiphora (excessive tearing) results from an obstruction of the tear drainage apparatus. Epiphora must be differentiated from pseudoepiphora, which may be caused by ocular

surface irritation due to conditions such as dry eye syndrome, ocular graft-versus-host disease, and exposure keratopathy. The most common cause of epiphora in the general population is primary nasolacrimal duct blockage which is due to obstruction of the nasolacrimal duct at its junction with the lacrimal sac [33]. Primary idiopathic nasolacrimal duct blockage occurs more frequently in women and is involutional in nature. In cancer patients, however, the most common etiology for epiphora is likely to be (a) mechanical blockage of the tear drainage pathway secondary to either primary lacrimal sac or nasolacrimal duct cancers or from extension of tumors from the paranasal sinus or nasal cavity [34], (b) canalicular and nasolacrimal duct stenosis secondary to chemotherapy [35, 36], or (c) canalicular or nasolacrimal duct obstruction secondary to radiation therapy [37, 38]. Common chemotherapeutic agents that are known to cause canalicular stenosis include S-1, 5-fluorouracil, mitomycin C, and docetaxel (Taxotere) [39–42]. Nasolacrimal duct obstruction may also occur secondary to local toxicity or active uptake of radioactive iodine used in the treatment of thyroid carcinoma [43–45]. Because timely diagnosis of early canalicular stenosis in patients receiving these agents can lead to early insertion of silicone tubing in the nasolacrimal duct and therefore prevention of further narrowing of the canaliculi, appropriate referral to an ophthalmologist early in the course of therapy with these agents is crucial.

Acute dacryocystitis is another important cause of epiphora. The infectious causes for acute or chronic dacryocystitis include *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* [46]. Clinical signs associated with dacryocystitis are epiphora, mucopurulent discharge upon pressure over the lacrimal sac, and erythema and edema over the lacrimal sac. Initial treatment for infectious dacryocystitis involves systemic antibiotics and warm compresses. A dacryocystorhinostomy may be necessary to prevent future episodes of dacryocystitis, particularly in immunocompromised patients [47].

Proptosis

Proptosis (outward protrusion of the eye) may be caused by an orbital mass or a diffuse inflammatory or infiltrative process involving the retrobulbar space. Other possible associated symptoms and signs may include diplopia, decreased vision, and multiple cranial neuropathies secondary to involvement of the orbital apex.

The most common primary cancer affecting the orbit in adults is lymphoma (Fig. 11) [48, 49]. Orbital lymphoma can be the extranodal manifestation of systemic lymphoma or may be the only site of lymphomatous involvement [50, 51]. Other benign or malignant tumors that can cause proptosis include optic nerve glioma, meningioma, orbital hemangioma, sarcoma, and metastatic lesions [52]. The most important cause of sudden and progressive proptosis in children is orbital rhabdomyosarcoma [53]. Another important cause of proptosis, particularly if associated with pain and inflammatory signs, is orbital pseudotumor. The diagnosis of orbital inflammatory syndrome (orbital pseudotumor) is a diagnosis of exclusion and should be made only after an orbital biopsy specimen proves to be negative for malignancy [54]. Timely diagnosis with diagnostic imaging (preferably MRI brain and orbit with and without gadolinium, fat suppressed) and orbital biopsy is important for institution of appropriate therapy. Management of proptosis consists of treatment of the underlying cause. It is important to avoid the administration of systemic steroids until the diagnosis is clearly established, ideally on the basis of an orbital biopsy in addition to MRI to rule out lymphoma, orbital metastasis, or rhabdomyosarcoma as the underlying cause of proptosis. The use of anti-inflammatory agents can mask the clinical signs and symptoms, delay diagnosis, and lead to a lower yield for an orbital biopsy. Prompt referral to an orbital and oculoplastic surgeon is appropriate when a patient presents with acute proptosis. An experienced orbital specialist may be able to recognize common radiographic features of common orbital lesions and sometime avoid a biopsy, but in most instances, if radiographic features are not classic for a benign vascular lesion such as hemangioma, the most appropriate next step after an imaging study is an orbital biopsy or complete excision of the mass depending on the radiographic features.

Orbital cellulitis may also present as proptosis, and it is associated with visual loss, decreased and painful extraocular movements, and general orbital congestion. Orbital cellulitis

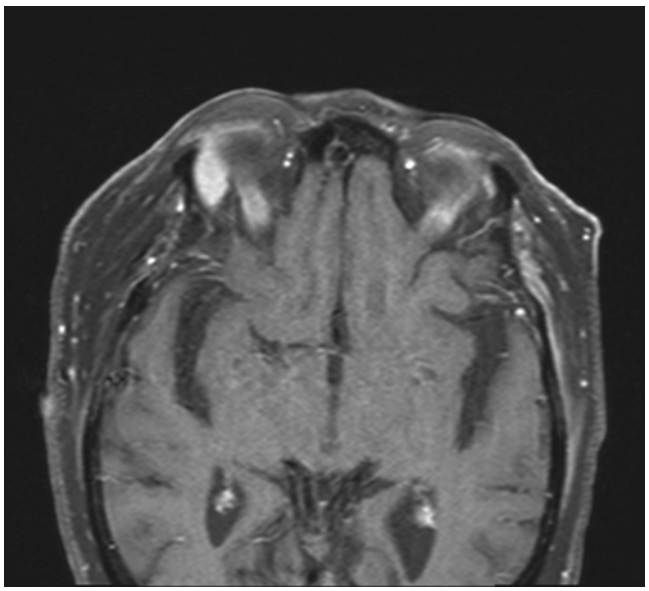


Fig. 11 Axial T1 image demonstrates a right lacrimal gland lymphoma in a 75-year-old female who presented with a slow-growing painless mass and mild proptosis

usually results from the direct extension of infection from the paranasal sinuses, especially the ethmoidal sinus [55]. However, direct inoculation from trauma, extension of an eyelid infection, and septicemia may also cause orbital cellulitis [56]. The causative infectious organisms are typically *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, or fungi such as *Aspergillus* [57]. Orbital cellulitis may be complicated by the formation of an orbital abscess or by direct extension of infection into the cavernous sinus and the brain, a complication with a high risk of mortality [58]. Immediate treatment with systemic antibiotics and antifungals is prudent when orbital cellulitis or an orbital abscess is suspected. An orbital abscess can be diagnosed by computed tomography (CT) or MRI and usually requires immediate surgical drainage, particularly if it is associated with progressive visual loss or proptosis [59].

Proptosis can also be caused by orbital hemorrhage. Possible causes include postoperative hemorrhage, trauma, and hematologic disorders [60]. The patient's vision and intraocular pressure (IOP) should be immediately assessed because retrobulbar hemorrhage may cause a compressive optic neuropathy that may lead to permanent visual loss. If the vision is decreased or the IOP is elevated above 30–35 mmHg, a lateral canthotomy and cantholysis should be considered in the emergency department to expand the orbital volume and relieve orbital pressure [61]. In the pancytopenic cancer patients who are often pancytopenic due to chemotherapy, more conservative measure such as the use of pressure-lowering glaucoma drops may be more appropriate and should be tried first as a canthotomy may lead to continuous oozing and bleeding from the orbit. Orbital emphysema can rarely yield findings similar to those of orbital hemorrhage, and a lateral canthotomy and cantholysis or needle decompression may also be indicated if symptoms and signs of compartment syndrome of the orbit occur [62, 63]. The usual cause of orbital emphysema is trauma or a history of tracheal or thoracic surgery [64].

Ptosis

Ptosis (droopiness of the upper eyelid) can be gradual or sudden in onset. As with other symptoms discussed in this chapter, determining the underlying cause is the most important aspect of the management of ptosis in the emergency department. The most common cause of ptosis in adults in the general population is involutional ptosis. In children, a congenital abnormality of the levator muscle is the most common cause of ptosis. In cancer patients, the most common cause of ptosis is neurologic. A palsy of the third cranial nerve due to primary or metastatic tumors of the base of the skull can cause ptosis, decreased extraocular muscle movement, and a dilated pupil. Perineural invasion secondary to cutaneous carcinomas of the facial skin can also cause multiple cranial neuropathies, including a third nerve palsy [65].

Another neurologic cause of ptosis is Horner's syndrome. Horner's syndrome refers to the triad of ipsilateral mild ptosis ($\leq$2 mm), miosis of the pupil, and anhidrosis [66]. A mass effect anywhere along the path of sympathetic fibers can cause Horner's syndrome. This three-neuron chain originates in the hypothalamus. The second-order neurons originate in Budge's center (C8–T2) and wind over the lung apex. The third-order neurons originate in the superior cervical ganglion, where they follow the carotid artery and then the fifth and sixth cranial nerves before they accompany the third cranial nerve to the eye. When ipsilateral miosis is associated with ptosis, Horner syndrome must be ruled out. Associated signs and symptoms may be helpful in determining the location of the lesion causing Horner syndrome. For example, ataxia, nystagmus, and weakness may indicate a first-order Horner syndrome from a brain tumor whereas coughing, hemoptysis, or shoulder pain may indicate a lung process (the so-called pancoast tumor) and thus a second-order Horner syndrome. Another common cause of Horner syndrome at the cancer center is iatrogenic causes such as surgery or radiation in the cervical and neck area. Heterochromia in children usually indicates congenital Horner syndrome and does not require extensive work-up or treatment. Pharmacologic testing with cocaine or apraclonidine may result in reversal of anisocoria in patients with Horner syndrome and can help in confirming the diagnosis; hydroxyamphetamine drops may also help localize the lesion [67].

Another cause of ptosis may be mechanical. For example, inflammatory changes in the upper eyelid due to orbital or paranasal sinus infection, surgical trauma, or external beam radiation therapy may cause temporary ptosis. An isolated tumor in the upper eyelid, such as a lacrimal gland carcinoma or lymphomas, or plexiform neurofibromas, or any other tumor that extends to the superior orbit, may also lead to mechanical ptosis of the upper eyelid.

Flashes and Floaters

Flashes of light, "showers of new floaters," and a "curtain" coming down over the visual field can be ominous symptoms of vitreoretinal traction, possible retinal tear, or retinal detachment (please refer to "acute vision loss" section mentioned earlier in the chapter). A thorough dilated funduscopic examination by an ophthalmologist is necessary to determine the exact nature of vitreoretinal pathology and to rule out retinal tears or retinal detachment in patients who complain of an acute onset of flashes and floaters, particularly if these symptoms are associated with a loss of vision.

Vitritis (inflammation of the vitreous gel) can be caused by intraocular neoplasms, most commonly leukemia and

lymphoma, and it can present with the onset of floaters and gradual loss of vision [68]. In patients whom intraocular leukemia or lymphoma is suspected, a MRI brain/orbit with and without contrast is necessary to evaluate for central nervous system (CNS) involvement as the CNS is frequently involved [69]. A vitrectomy and vitreal biopsy may be required to make a definitive diagnosis [70].

A common benign condition that can also cause the acute onset of flashes and floaters is acute posterior vitreous detachment, which is mostly secondary to senescence or trauma [71, 72]. Various forms of retinitis, endogenous endophthalmitis, and posterior uveitis may also present with the same initial symptoms. Management of endophthalmitis includes blood cultures, possible vitreous biopsy to determine the causative organism, and immediate intravenous antibiotics.

Conclusion

Ophthalmologic emergencies in cancer patients are multifaceted. In most instances, consultation with an ophthalmologist is necessary to insure the timely diagnosis and management of these conditions. A general understanding of the different components of an eye examination and the differential diagnosis for common ocular presentations may help the oncologist or emergency physician with triaging, work-up, and initial treatment of these conditions until the patient can be examined by an ophthalmologist.

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Psychiatry and Oncologic Emergencies

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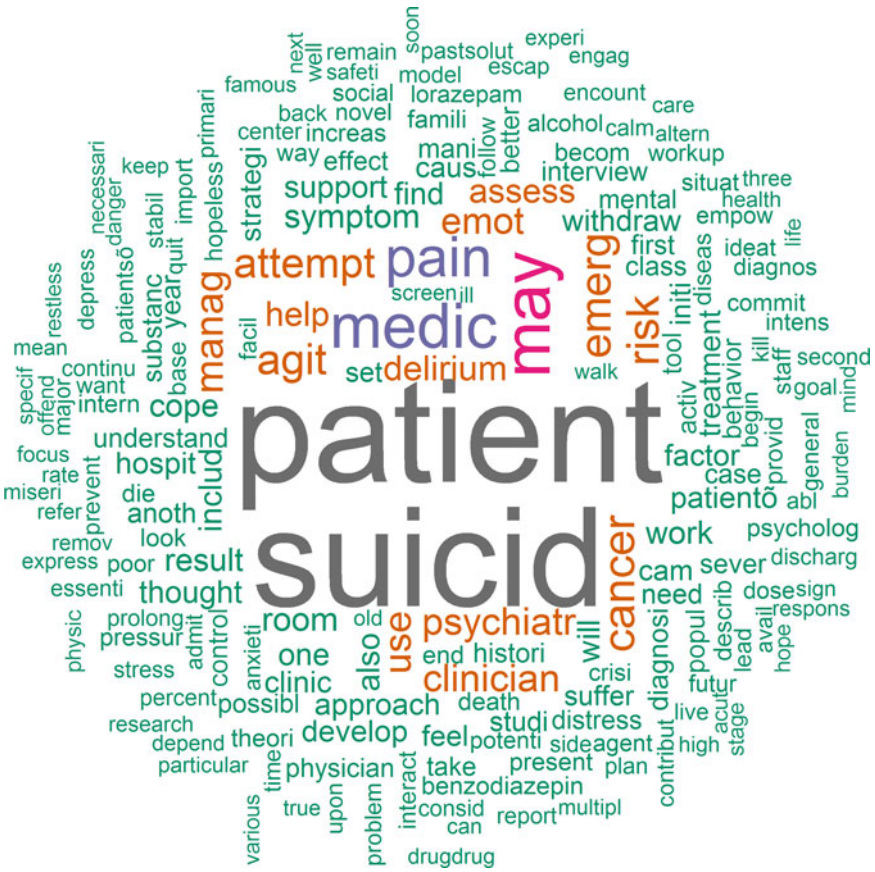

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Agitation

Whatever the cause, an agitated patient may quickly become a danger to both himself and medical staff. The behavior displayed by an agitated patient—becoming verbally and physically aggressive and combative, pulling out intravenous lines, drains, or catheters—may be very frightening not only for staff but for neighboring patients and their visiting family and friends.

Engaging the Agitated Patient

Upon initial encounter, staff should address the agitated patient in a nonthreatening tone, allowing the patient to express any fears or concerns. As soon as possible, the patient should be isolated from other patients, visitors, and nonessential staff (preferably in his room), while attempting to remove any potentially dangerous objects from within the patient's reach. Staff or visitors that have either established trust or a positive rapport with the patient should be employed during the initial encounter, while those that are the target of the patient's complaints, aggression, or paranoia should be removed from the environment as soon as possible. If agitation escalates and is such that sedative medication is warranted, the patient should be offered oral medication prior to intramuscular or intravenous administration. While the above scenario evolves, a member of the treatment team should gather any pertinent medical, psychiatric (including any history of violence), and substance use history. After the situation has resolved and patient is calm, staff involved should be allowed to process the experience and express their feelings and any concerns, with the goal of learning from the experience and providing support to the team [1]. Subsequent, close monitoring of the patient is necessary until they are no longer an immediate threat of danger to themselves or others.

Causes of Agitation, Workup, and Management

When encountering a patient in the emergency department suspected of having a psychiatric illness, it is imperative not to automatically assume that they are experiencing an exacerbation of mania or psychosis, being expressed as agitation. The examining physician should first rule out any underlying medical process or derangement, to ensure that there is no emergent and potentially reversible problem that would have otherwise been missed. A psychiatric diagnosis should be considered but not decided upon until all medical possibilities have been eliminated from the differential diagnosis.

Delirium

Delirium (also referred to as encephalopathy, altered mental status, acute confusion) has been described as far back as 2500 years ago, and its key features include acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness [2, 3]. The pathophysiology of delirium is quite poorly understood, despite various mechanisms and theories proposed thus far. Several studies have reported the prevalence of delirium in the emergency department setting to be around 10 %, with emergency department physicians correctly diagnosing between 17 and 35 % of those patients [4, 5]. It is thus imperative to conduct a thorough evaluation, paying close attention to history that may be available via family or friends, as well as neurological and cognitive exam findings. To help support one's suspicion of delirium, various clinical instruments have been developed and are used to assist with solidifying the diagnosis. Depending on the hospital setting, time available, and/or particular subspecialty of the physician, a specific clinical instrument may be favored over another. The confusion assessment method (CAM) is a clinical instrument that has gained much popularity and is widely used around the world, translated in multiple languages. The CAM has a sensitivity of 94–100 % and a specificity of 90–95 % in hospital settings, takes only 5 min to perform, and has become somewhat of a standard screening tool in clinical studies of delirium, used across multiple settings, including the emergency department and ICU [3, 6] (see Table 1).

Diagnostic Workup and Management of Delirium

Once the patient has confidently been diagnosed with delirium, the physician must now begin a thorough workup to determine the etiology. Along with taking the patient's vital signs, one may start with the following labs: CBC, UA, LFTs, TSH, B12, folate, ABG, Chem-7 (to look for any signs of infection, dehydration, metabolic/electrolyte derangements), and serum alcohol level/drug panel (to look for any possible source of intoxication/poisoning). One may also need to consider an EKG, Chest X-ray, EEG, brain imaging, and lumbar puncture. An EEG may show diffuse background slowing in the case of delirium or may also demonstrate benzodiazepine/medication effect. In cancer patients, brain imaging and/or lumbar puncture may be necessary to rule out cerebral vascular accident, metastatic/leptomeningeal disease. Additional diagnostic workup may be tailored to the preliminary results obtained from the above. The goal is to find an underlying cause(s) for the confusion/agitation; that way the physician may work to correct the problem in hope that the delirium will resolve.

Table 1 Confusion assessment method (CAM) diagnostic algorithm

Feature	Clinical characteristics
1. Acute onset and fluctuating course	Usually obtained by friend, family member, or nurse and is shown by positive response to the following questions: Is there evidence of an acute change in mental status from baseline? Did abnormal behavior fluctuate during the course of the day?
2. Inattention	Shown by a positive response to the following question: Did the patient have difficulty focusing attention, easily distractible, and have difficulty keeping track of what was being said?
3. Disorganized thinking	Shown by a positive response to the following question: Was patient's thinking disorganized or incoherent, rambling or irrelevant conversation, unclear or illogical flow of ideas, and unpredictable switching from subject to subject?
4. Altered level of consciousness	Shown by any answer other than "alert" to the following question: Overall, how would you rate patient's level of consciousness, alert, vigilant, lethargic, stupor, or coma?

Adapted from Inouye et al. [3]
[a]The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4

Management of Agitation

If during the medical workup, the patient becomes agitated, belligerent, and medication is warranted to help keep the patient calm, there are options available, but the physician must approach medication selection with caution. Many patients with cancer in active treatment are usually on multiple medications, including various antibiotics, antifungals, and chemotherapeutic agents that may potentially increase the risk of QT prolongation, which could then result in the development of a cardiac arrhythmia (torsades de pointe, ventricular fibrillation). In an attempt to minimize this risk, we first offer the patient an oral second-generation antipsychotic, such as olanzapine 5–10 mg, quetiapine 50–100 mg, or risperidone 1–3 mg. If either the patient refuses or the physician has no choice but to emergently help calm the patient, our next choice is haloperidol 5 mg IM or 2 mg IV, and if a subsequent dose is needed, may then consider the addition of lorazepam 1–2 mg IM or IV. Of note, haloperidol and lorazepam may both be repeated until the patient calms but must allow 30 min in between dosing to give medication sufficient time to take effect, as well as to monitor for adequate patient response. Again, the reason for passing on medications, such as ziprasidone or chlorpromazine, is an attempt to minimize the risk of QT prolongation, though these medications are indeed routinely used in the management of acute agitation at other institutions. If Haldol IM or IV is needed, especially if more than one dose is needed, we would also recommend daily monitoring of QT interval, such as with a 12 lead EKG. As QT interval begins to approach 500 ms or greater than 20 % of patient's baseline, then medication will need to be stopped and switched to an alternative. Ideally, lorazepam or any other benzodiazepine should not be considered a first choice, as this class of medication may actually worsen confusion and/or cause disinhibition; however, in the case of alcohol withdrawal (discussed later in this chapter), this class of medication is quite necessary.

Medication Side Effects

The following classes of medications are the most common culprits in causing primary side effects that may manifest as psychiatric symptoms, delirium, or agitation in a cancer patient population: antiemetics, chemotherapeutic agents (immunomodulators/immunosuppressants), and anticonvulsants. Antipsychotic class medications used in the treatment of gastroparesis and severe nausea, such as metoclopramide, promethazine, prochlorperazine, or haloperidol (alone or as part of the combination cocktail ABH), all have the potential to cause extrapyramidal symptoms, more specifically in the short-term, akathisia. It is not uncommon to see a patient present to the emergency department, reporting the acute development of severe anxiety, insomnia, restlessness, and inability to remain still, and may even be observed pacing back and forth in the exam room. If the patient has no prior history of such anxiety, and they are taking one of the above medications which may induce akathisia, it is necessary to hold the possible offending agent and switch to another antiemetic such as ondansetron or lorazepam. To help relieve the patient's feeling of severe restlessness in this particular situation, short-term treatment with propranolol, diphenhydramine, or benzodiazepine class medication should help manage the side effect. Medications that have more recently shown promise in combating akathisia are those with antagonistic effects at the 5HT-2A receptor, such as mianserin, cyproheptadine, mirtazapine, and trazodone [7]. Glucocorticoids, tacrolimus, mycophenolate, IFN-alpha, IL-2, and other immunosuppressants/immunomodulators may potentially affect mood, causing symptoms ranging from depression, mania, irritability, agitation, to psychosis. Ideally, treatment with the offending agent should be stopped, and if agitation/delirium were to develop, treatment may be initiated as described above (see "Management of Agitation" section). Anticonvulsants such as valproate (especially at supratherapeutic doses) and levetiracetam have been associated with mood changes, irritability, delirium, and agitation [8]. As noted above, discontinue the offending agent as soon

as possible and try to manage any resulting agitation as described above.

Drug-Drug Interactions

In addition to QT prolongation, another potentially serious drug-drug interaction that we look for is any that may result in serotonin syndrome. Signs and symptoms of serotonin syndrome may include tachycardia, hypertension, shivering, diaphoresis, hyperthermia, mydriasis, hypertonicity/hyperreflexia, tremor/myoclonus, rhabdomyolysis, and seizure. Any combination of tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), monoamine oxidase inhibitor (MAOI) antidepressants (not to forget mirtazapine and trazodone), opiate pain medications (meperidine, methadone, fentanyl, codeine), antibiotics (linezolid), and stimulant class medications (amphetamine, MDMA, cocaine) may result in serotonin syndrome [9]. Treatment is largely supportive, and the first step should include removing the offending agent. Patient should be kept well hydrated, cooling blankets used if available, and for severe myoclonus and agitation, lorazepam IV may be used. For more severe symptoms, the use of cyproheptadine and/or dantrolene may be needed, at which point admission to the ICU would be most appropriate [9].

Substance Withdrawal

Substances most dangerous to discontinue abruptly include alcohol, benzodiazepine, and barbiturate class medications, as when most severe, may result in death from malignant arrhythmia, respiratory arrest, or prolonged seizures and hypoxemia [10]. We are oftentimes asked to assist in the management of patients experiencing withdrawal symptoms from opiate pain medications and, more rarely, illicit stimulant drugs. The presentation of alcohol, benzodiazepine, and barbiturate class medications is essentially identical, beginning with tremulousness ("the shakes," which may feel and be expressed as anxiety), diaphoresis, nausea, emesis, diarrhea, and restlessness that may begin within 24–72 h after the last drink [10]. If untreated, symptoms may progress to hallucinations, autonomic instability, seizures/delirium tremens, and death. Management of withdrawal symptoms includes initiating a benzodiazepine infusion and subsequent taper (lorazepam used preferentially due to its multiple routes of administration), beginning with doses of 0.5–2 mg IV every 30 min to 4 h, depending on the patient's particular needs/drinking habits. Concurrently with the above, IV hydration and thiamine/folate replacement should be instituted to minimize the risk of developing alcohol encephalitis. Withdrawal symptoms from opiates include muscle soreness and aches, rhinorrhea and lacrimation, pupillary dilation, piloerection, nausea, emesis, diarrhea, and irritability. Though patients may experience severe discomfort, become quite restless and agitated, possibly from combination of withdrawal symptoms and uncontrolled pain, the withdrawal from narcotics is not quite the life-threatening ordeal, as is the case with alcohol, benzodiazepines, and barbiturates. Management of opiate withdrawal is largely supportive and may be accomplished with or without the use of narcotics. It may be appropriate to resume the patient's home pain medication regimen or even restart their medications at a reduced dose to address their withdrawal symptoms. If for whatever reason, the treating physician decides that narcotic class medications should not be used, then the patient may be supportively treated with hydration, antidiarrheals, non-opiate pain medications, and clonidine to help dampen noradrenergic hyperactivity (flushing/hot flashes, diaphoresis) [11]. The management of stimulant withdrawal is also supportive and much less intense than the measures taken above. Patients will likely feel tired and sleepy and may have increased appetite, though tiredness and fatigue will improve as they catch up with lost sleep.

Suicidal Thoughts or Attempts

Shortly after finishing the manuscript of her famous novel "Between the Acts," 59-year-old Virginia Woolf drowned herself in River Ouse in 1941. "I know how unpleasant it is to be locked out, and I thought how it is worse, perhaps, to be locked in," Woolf wrote in her novel "A room of its own." After struggling for years with undiagnosed bipolar disorder, she decided to end it all. She was a famous English writer; she had vision, wisdom, fame, and a very happy married life. She herself said "you cannot find peace by avoiding life." Then what went wrong? Why did she commit suicide? Was it fear, loss of control, unbearable emotional or physical pain, or escape from stress or unbearable guilt?

Patients who commit suicide come to crossroads where they are not able to find the best solution to their crisis and find suicide to be the easiest and perhaps only way to escape. Suicide is prevalent in all patient population but may be twice more frequent in cancer patients than in the general population. One population-based study in Norway carried out from 1990 to 1999 indicated that the risk of suicide was highest in the first months after cancer diagnosis and declined in later years [12].

Psychiatric emergencies include suicidal attempts or thoughts, substance dependence and intoxication, delirium, agitation, violent behavior, panic attacks, psychosis, and extreme physical and emotional pain [13]. In this article, I focus on emergent consults for suicidal thoughts or attempts. Emergency department consults for suicidal ideations may not result from true suicidal thoughts. Almost 50 % of the time, this may be from high anxiety after being diagnosed with cancer, pain, emotional suffering, abandonment, or distress after relapse.

Psychological Theories of Suicide

Sigmund Freud described suicide as a representation of aggression turned inward against an internalized object. An individual has an internal conflict that cannot be resolved owing to a great burden of misery that overcomes all other forces. *Herbert H Krauss* further expands upon Freud's viewpoint that suicide may be a result of failure to achieve goals or of a dysfunctional relationship, and killing oneself is really the killing of an unattainable object. *Edwin Shneidman* explains the theory of suicide termed "egotic suicide," which results from a conflict of internal aspects of self to which the only response is ending of the personality [14]. *Karl A Menninger* described suicide as a self-directed instinct with three hostility components, the wish to kill, the wish to be killed, and the wish to die [15].

Aaron Beck, famous for his work on cognitive behavioral therapy, talks about the role of hopelessness in suicidal patients. In particular, he talks about the triad of hopelessness and negative feelings toward self, toward future, and, in general, toward anything in the world. He says such patients feel that no matter what, nothing will change in their lives.

Another important consideration to keep in mind is that not everyone who attempts suicide will die by suicide. Completed suicide depends on two factors, the desire to die and the capability to do so. T.E. Joiner explained this in the interpersonal-psychological theory of suicidal behavior. Three studies tested the theory's hypotheses. The first study focused on the imbalance between the sense of belonging and the burden resulting in suicidal ideation. In the second study, researchers determined that individuals with high numbers of past suicide attempts acquire greater capability to have successful attempts than those with fewer attempts. The third study examined the interaction of acquired capability and perceived burden resulting in clinician-rated risk of suicidal behavior [16].

Statistics

Suicide is the twelfth leading cause of death in the USA. In 2013 the total number of deaths by suicide was 38,364 death rates per 100,000 US standard populations [17]. In studying the incidence of suicide in cancer patients in the Surveillance, Epidemiology, and End Results (SEER) program, Stephanie Misono found that suicide rate in cancer patients from 1973 to 2002 was 31.4 per 100,000 person-years among cancer patients but 16.7 per 100,000 person-years in general population [18]. Also the suicide rate in single white men increased with age at cancer diagnosis. Increased risk of suicide was also associated with advanced stage of the disease [18]. About half of suicide victims used fire arms to commit suicide. The second most common method of suicide was suffocation [19].

Risk Factors

In the general population, 90 % of the suicides occur in patients with clinically diagnosed mental illness [20]. The suicide rate is high in patients with a history of substance use, family history of suicide, previous suicide attempts, hopelessness, easy access to lethal weapons, or poor social support system [21]. Major depression has been the primary risk factor for suicide in both cancer patients and the general population [18]. In cancer patients, hopelessness and abandonment are the key factors contributing to suicide [22]. Patients with certain types of cancer are at greater risk for suicide than others; this includes head and neck cancers and patients with lung cancer. An advanced stage of cancer and progression of the disease increase the risk of suicide in patients [18]. In a study by Farberow et al. [22], 86 % of suicides in cancer patients occurred during terminal or preterminal stages of the disease. Pain and loss of bodily functions such as loss of bladder and bowel control and the inability to eat or speak reduces the threshold for committing suicide [22].

Clinical Challenges and Initial Work on Suicidology

Mental health providers remain on their toes when challenged with suicidal patients, especially in the emergency setting. To keep these patients safe and help them cope better during a crisis, understanding the intensity of the psychological pain and empowering these patients with tools to deal with it are essential. Owing to the economic, societal, and legal changes in the past 20 years, the burden on clinicians and psychiatric facilities and pressure from insurance companies, the comfort of hospitalization for any suicidal patient has disappeared. Keeping a patient hospitalized until stable is always a battle between insurance companies and psychiatric facilities. In many cases, suicidal patients are discharged 1 day after admission by the attending clinicians only to follow up in the outpatient setting [23]. These patients go back into their surroundings only to face the intolerable, inescapable emotional pain. They have no tools to deal with their suffering, remain distressed, and become chronically suicidal. This has led to increased stress for the clinicians when encountering suicidal patients in the emergency setting. Clearly, a novel approach to empowering these patients with coping strategies to end their suffering and emotional pain is needed [23]. The old theories that suicide is unpredictable may not be true, because in most cases, suicidal patients do give warning signs to their clinicians, family, or friends [24]. Also, the myth that talking about suicide increases the risk of it is simply not true [24].

Understanding the conflicts in the mind of a suicidal patient is essential to helping him or her. Over the past three decades, much work has been devoted to understand-

ing the pathophysiology of a suicidal mind and the triggers that lead to suicidal attempts in a depressed or chronically suicidal patient. Dr. Norman L. Farberow, a psychologist and one of the founders of modern suicidology, has spent many years attempting to understand the risk factors contributing to suicide and developing strategies to prevent it. Dr. Edwin S. Shneidman a psychology professor at the University of California developed the cubic model of suicide. In this model, he describes three major risk factors that will trigger a suicidal patient to cross over and make a suicide attempt. Also, Aaron Beck, although famous for his work on cognitive behavioral therapy, was recognized for his contribution in the field of suicidology. He designates hopelessness as a trigger and one of the major factors leading to suicide. Another factor contributing to suicide is self-hate, which has been the focus of Roy Baumeister's work [23].

Need for a Novel Approach to Suicidal Patients

Based on the work of all of these clinicians and researchers, Dr. David A. Jobes, a clinician-researcher and the second-generation suicidologist, developed a novel approach to assessing an actively suicidal patient. His work and strategy are based on the cubic model of suicide described by Dr. Shneidman (Fig. 1). This model consists of three factors, pain, press, and perturbation. Hopelessness and self-hate are other factors leading to suicidal ideations. Instead of immediately hospitalizing any suicidal patient, Dr. Jobes developed an interactive approach in which the patient and clinician travel the difficult path together, analyze the compelling factors leading to suicidal thoughts, and find the solution with alternate coping tools. Dr. Jobes believes in empowering the patients with strategies that will work in crisis and will help the patients to cope better when severely depressed. He named this novel approach as "Collaborative Assessment and Management of Suicidality" (CAMS) [23]. After the success of the initial research and extensive discussion, CAMS was slowly introduced to various mental health clinics.

The first and the most important consideration is the identification of the suicide risk as soon as possible. If situation permits and the patient is cooperative enough, this can be achieved using a symptom-based screening tool. Self-reporting screening tools are very helpful and alert the clinician to any suicidal thoughts or intent. In the emergency setting, we do not have the luxury to use the screening tools, and the entire responsibility falls on clinicians' interviewing skills to assess the suicidal intent and manage the patient accordingly. Working in the premier cancer center in the USA with more than 10 years of experience, I have interviewed many suicidal patients in the emergency setting. Most of these patients did not want to die; they were looking for an escape from their misery and intense psychological pain and suffering.

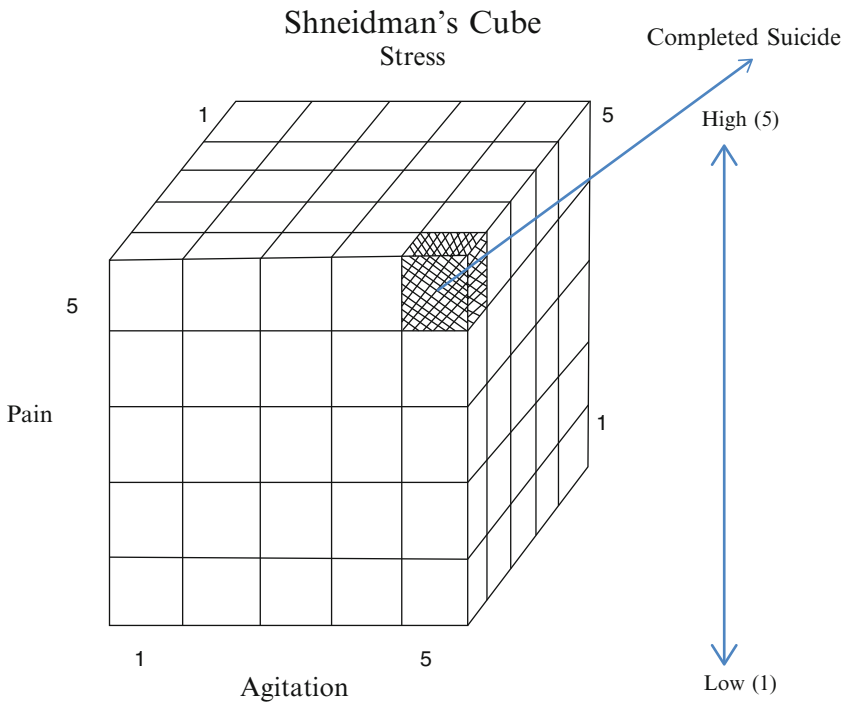

Fig. 1 Shneidman's cubic model of suicide. From: Shneidman, ES. A Psychological Approach to Suicide. In: VandenBos GR, Bryant BK eds. Cataclysms, Crises, and Catastrophes: Psychology in Action; 1987. p. 147–183. Washington, DC: American Psychological Association

Narrative of a Suicidal Patient in the Emergency Center

Late on Friday afternoon, I received a page from the emergency center to evaluate an actively suicidal patient. Upon arrival, I saw Mr. S, a 64-year-old gentleman with a history of prostate cancer, looking extremely distressed and saying he does not want to live anymore and wants to die. He did not engage and refused to answer any questions. His wife, who brought him, said he had been having excruciating pain in his legs over the past 2 weeks after being discharged from the hospital. He was hospitalized for surgery to fix a pathological fracture in one of his long bones. According to his wife, his pain was very well controlled during hospitalization. Since discharge, he has not been able to sleep or rest because of his pain. She added that this was his third visit in the past 2 weeks, and pain medications prescribed for him did not work. On further evaluation and reassurance, he said that he did not want to die if his pain were controlled. Pain service was called in, and he was admitted. His pain was controlled with intravenous pain medication, and he was able to sleep that night. The next morning Mr. S was calm and smiled when he saw me. I remember him saying, "Life is good." Now, he is emotionally stable although still fighting the consequences of his cancer diagnosis and living the "life after cancer."

Clearly many of our patients are not truly suicidal, and if their pain and suffering can be carefully managed, they will continue to live. Unbearable pain is one condition that makes patients think that the only option out of their miserable situations is death. Hence, better pain control is essential for mental and emotional well-being.

On occasion, we receive consults from the emergency center for truly suicidal patients. These are patients who either have a new diagnosis of cancer or have received news of progression of their disease in spite of treatment. Many of these patients have struggled with cancer for a long period of time and now feel exhausted. Some of these patients feel guilty about bringing emotional and financial stress to the family, while not contributing in any way. They believe the only way to escape from their miserable life and prolonged distressing battle is to end it all. A thorough psychiatric history, by a compassionate listener, and emotional support are essential for such patients. In these cases, patient safety takes priority. If the patient is admitted to the hospital, he or she is assigned a 1:1 sitter and given medication to control anxiety and stress. Patients are followed regularly during hospitalization until stable and discharged with follow-up plans. In other cases, these patients are transferred to psychiatric facilities for their safety until they are stabilized with therapy and medications.

Miss K is a 47-year-old white woman with a history of breast carcinoma after surgery and chemotherapy with relapse of the disease who was brought to the emergency department after a suicidal attempt. She was drowsy and semicomatose after she took an overdose of pain pills. She lives alone and had a heated phone argument with her ex-husband, in which she threatened to kill herself. She was not alert enough to engage in an interview with the clinician, so her information was obtained from her ex-husband. He reported that she was extremely distressed to find out about the relapse of her disease and that she would have to go for another course of chemotherapy and probably another surgery. She was also suffering from pain after a central line placement the day before her suicide attempt. Ms. K was admitted for medical stabilization and interviewed the next morning. She was distressed and emotionally unstable. Ms. K reported that she would not attempt suicide again if she could be saved from having to undergo chemotherapy and surgery. She reported having flashbacks of the treatment she went through 2 years prior. Her main concern was a poor social support system and no help while she is sick. Upon further inquiry, she endorsed symptoms of major depression and thoughts of being dead rather than going for further treatment. Ms. K had to be transferred to a structured unit in a psychiatric facility for stabilization and psychiatric care.

This was a major task as she did not have private insurance and had to go to a facility that honors Medicaid. Another barrier in her care was her diagnosis of active cancer. Most psychiatric facilities do not take patients who have intravenous lines placed, have active cancer diagnoses, or are medically unstable. After 24 h of continuous efforts and waiting, we were able to find her a bed in a psychiatric hospital. Ms. K was admitted there for 5 days, with follow-up in our clinic. She continued her cancer treatment but still goes through emotional ups and downs. She is not compliant with her medications or psychiatry clinic appointments. Patients like Ms. K are always a risk for another suicide attempt. Our goal is to empower these patients with better coping strategies, enhancing their social support systems, and control their physical and emotional pain.

General Guidelines for Assessment of Suicidal Patient

The Joint Commission requires emergency department suicide evaluation for certain patients with primary psychiatric diagnoses, including substance abuse. American Psychiatric Association also has published the guidelines for suicide risk assessment. This is to reduce inpatient suicide attempts and to promote patients' safety. Nurses are trained in conducting interviews with patients and assessing imminent risk. Based on the results of the initial interview, a more in-depth interview is carried out by the mental health provider. Patients are placed in two groups based on the clinical judgment of their

suicide risk. Those with minimum risk of suicide and good social/family support may be released from the emergency department, whereas those with a high-risk and poor social support are admitted for stabilization.

CAMS

The collaborative assessment and management of suicidal patients is not only a specific clinical approach but also a philosophy in working with suicidal patients. It enables clinicians to travel the difficult path along with suicidal patients to understand their misery and help them find solutions. Using CAMS clinicians are able to understand why and how suicide has become patients' only route of escape from their misery. CAMS is designed to optimize patients' motivation and their ability to find means of coping. Initially, patients rely on clinicians and then themselves when developing better ways to cope. The CAMS theory is based on the facts that most suicidal patients do not want to die, their basic instinct of survival remains alive, and they attempt suicide to end their emotional pain and suffering. Many of these patients tell others of their psychological and emotional pain and that they are thinking of ending it all. If help is provided in time, suicide is preventable. The aim of the CAMS approach is to ensure no attempted or completed suicides, minimum distress, development of alternate ways of coping, and finding a meaning to patients' existence.

Patients who attempt suicide suffer from intense emotional pain. The way to reduce this pain and suffering is to raise patients' threshold for pain and ability to cope. With the help of the clinician, the patient tries to ameliorate the root cause of his or her pain. "Press" focuses on pressure in patient's mind leading to suicidal thoughts or plans. Pressure may be external or internal. External pressure could be caused by a job related stress, poor family psychodynamics, poor finances, or loss of a loved one. Internal pressure could be caused by substance use or abuse, from mental illness with hallucinations, delusions, paranoia, or intense guilt. With the help of clinicians, patients develop better coping strategies to deal with external and internal pressures.

Perturbation is the most important factor in the cubic model of suicide. It refers to a state of being emotionally disturbed and upset. Many patients feel psychological pain and have external or internal pressure, but very few commit suicide. Those who attempt or commit suicide have intense psychological energy, which is the driving force pulling them over the edge. This driving force is strong enough to overcome the basic instinct of survival. The responsibility for recognizing this stage falls on the clinician, who then assesses the risk of discharging an imminently suicidal patient.

In the initial interview, a Suicide Status Form is used with CAMS. The initial assessment on this form focuses on six Likert scales, which consist of pain, press, agitation, hopelessness, self-hate, and behavioral risk.

Patients, on suicide status, are being tracked by ongoing risk assessment and management. In one study about half of the patients enrolled in the program experienced resolution of their suicidal ideations in 6–11 sessions [23].

After resolution of active suicidal thoughts, some patients may choose to continue undergoing psychotherapy for ongoing support and emotional stability. However, about 20–50 % of patients choose not to continue psychotherapy, as they feel empowered with tools to better cope with stressful situations [23].

CAMS: The New Approach to Assessment of Suicidal Patients

In this approach, the dynamic is one of collaboration. Sitting next to suicidal patients, clinicians make the patients understand that the solutions to their problems lie within them. They look for answers to the problems and work together to find better alternatives to coping than suicide. Clinicians focus on patient's emotional pain and understand the need for deeper assessment of patients' suffering. Patients fill out the SSF form in their initial visit.

A treatment plan is laid down then. The first step is to ensure patient's safety. Any weapon, drugs, or means that can be used to attempt suicide is removed. Coping strategies, including crisis card strategy, is the philosophy of collaborative empowerment of the patient. Using this strategy, the patient writes five things on a card that he or she will do in a crisis. This list may include walking the dog, going for a walk, listening to music, or taking a hot bath. This is protherapeutic and involves behavioral motivation. Other approaches can be considered during a crisis as well, such as a hope kit, which is a shoe box filled with meaningful mementoes from the patient's life. A hope kit may contain letters, pictures, ribbons, or anything that brings back good memories and provides hope for the future. Patients are also encouraged to remain active by going out for a walk, exercising regularly, or journaling.

Another important aspect of building a safe environment for suicidal patients is creating a linkage to the future. Clinicians remind patients to look for any connection with the future such as a son's upcoming graduation or holding a daughter's hand while walking down the aisle at her wedding. Such a future connection and thoughts of upcoming life-affirming moments may induce a desire to be present in the future. Faith also plays an important role in many cases, as patients will avoid taking any actions that go against their faith. All of these strategies may fail however, leaving patients feeling distressed and unable to handle their situations. Therefore, they should be given access to therapists or call an emergency center to get help. Hotline numbers should be available and posted on their refrigerator.

Suicide is preventable, but prevention requires early recognition of true suicidal thoughts or plans by clinicians, working

closely with suicidal patients to understand their emotional pain, finding solutions to their problems, and empowering them with coping strategies. For early recognition of suicidal patients, question, persuade and refer (QPR) gatekeeper training for suicide prevention may be the first step in training the staff to recognize these patients and refer them for proper care and handling [25]. Early recognition by nursing staff or social workers, professional interviewing with mental health providers, empathic psychotherapy sessions, and provision of resources have been successful in most cases in stabilizing these patients and preventing suicide.

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Chemotherapy-Induced Toxicities

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Central Nervous System (CNS) Toxicities

CNS toxicity encompasses many different syndromes such as headache, somnolence, confusion, seizures, aseptic meningitis, cerebellar dysfunction, encephalopathy, intracranial hemorrhage, stroke, myelopathy, hearing loss, blindness, dementia, and coma. Risk factors for developing CNS toxicity depend on the chemotherapy but may include high dosages, intrathecal or intraventricular administration, frequent administration, renal dysfunction, and hepatic dysfunction [1, 2]. This section will focus on the more common neurotoxicities and their associated chemotherapy; however, a more extensive list of neurotoxicities caused by chemotherapy can be found in Table 1.

Table 1 CNS toxicities and associated chemotherapy agents [1–3]

CNS toxicity	Agent	
Intracranial hemorrhage	Anti-angiogenic agents [a]	Asparaginase
Encephalopathy	Asparaginase Busulfan Carmustine Cisplatin Cytarabine Fluorouracil Ifosfamide	Lomustine Melphalan Methotrexate Paclitaxel Procarbazine Vincristine
Posterior reversible encephalopathy syndrome (PRES)	Anti-angiogenic agents[a] Cisplatin	Capecitabine Fluorouracil
Seizures	Busulfan Carmustine Cisplatin Cytarabine Fluorouracil	Ifosfamide Lomustine Methotrexate Paclitaxel Vincristine
Cerebellar syndrome	Cytarabine	Fluorouracil
Stroke	Anti-angiogenic agents[a] Cisplatin	Methotrexate
Aseptic meningitis	Cytarabine	Methotrexate
Myelopathy	Cytarabine	Methotrexate
Ototoxicity	Carboplatin	Cisplatin
Blindness	Carboplatin Cytarabine	Lomustine Vincristine
Dementia	Methotrexate	

[a]Anti-angiogenic agents include bevacizumab, sorafenib, and sunitinib

Chemotherapy Agents Implicated

Methotrexate

Neurotoxicity from methotrexate can present in many different forms. Intrathecal methotrexate can cause aseptic meningitis in greater than 10 % of patients [4]. Patients typically experience headache, nausea, vomiting, nuchal rigidity, and fever. This can occur 2–4 h after methotrexate administration and last up to 12–72 h. Although this toxicity is generally self-limiting, corticosteroids such as dexamethasone can be given to prevent or treat methotrexate-induced aseptic meningitis [4].

Methotrexate neurotoxicity can also present at different times. Acute reactions can occur as soon as hours after drug administration and can include aseptic meningitis as mentioned above, somnolence, seizures, stroke-like symptoms, or mental status changes [2]. Subacute neurotoxicity can present as confusion, ataxia, hemiparesis, and seizures and generally occurs 5–10 days after therapy [1]. Lastly, chronic or delayed neurotoxicity can present months to years later, and symptoms can include dementia, personality changes, leukoencephalopathy, gait disturbances, aphasia, coma, and death [1, 2, 4]. These toxicities may be related to concurrent radiation, concomitant chemotherapy, or larger cumulative doses [1, 2].

MRI imaging may reveal white matter damage, diffuse white matter hyperintensities, ventricular enlargement, cortical calcifications, or cerebral atrophy [1, 2]. Leucovorin rescue therapy may reduce neurotoxicity risks associated with methotrexate [4].

Cytarabine

The primary neurotoxicity caused by cytarabine is cerebellar dysfunction (dysarthria, ataxia, nystagmus), occurring in 10–20 % of patients at doses greater than 27–36 g/m^2 occasionally with encephalopathy and seizures [1, 2, 4]. This is more commonly seen with higher doses (>6 g/m^2), in elderly patients, or in patients with renal or hepatic dysfunction [2]. The onset is generally 3–8 days after drug administration and usually resolves upon drug discontinuation but can last up to months [2]. Brain imaging will depict cerebellar atrophy and reversible white matter changes on the MRI [1]. Other CNS toxicities that can be seen with cytarabine include blurred vision, burning eye pain, blindness, confusion, somnolence, and myelopathy [1].

Ifosfamide

Up to 10–30 % of patients receiving ifosfamide can experience some form of neurotoxicity, generally in the form of encephalopathy. Confusion is the most prevalent symptom, occurring in up to 80 % of patients. Hallucination and psychosis can occur in up to 30 % of patients, and other neurotoxicities such as lethargy, personality changes, extrapyramidal symptoms, hallucinations, seizures, and dysarthria are less common and can begin within 24 h of drug administration [1]. These toxicities are usually reversible within a few days of

drug discontinuation, but cases of coma and death have occurred [5].

Risk factors of ifosfamide neurotoxicity include high doses, low albumin (potentially related to hepatic dysfunction), renal dysfunction, tumor in the lower abdomen/pelvis, pretreatment with cisplatin, oral administration, shorter intravenous (IV) infusion time, and prior CNS disease [4–6]. It is postulated that ifosfamide neurotoxicity is due to a metabolite that crosses the blood–brain barrier [5, 6].

Brain imaging for ifosfamide neurotoxicity usually shows no abnormalities, and diagnosis is generally based on exclusion of other causes [5]. Although symptoms usually resolve spontaneously, methylene blue has been reported to shorten recovery time and prevent recurrence [5–7].

Busulfan

Busulfan readily crosses the blood–brain barrier and is commonly used in high doses in conditioning regimens for patients undergoing hematopoietic stem cell transplantation [8]. The most common neurotoxicity in patients receiving high-dose busulfan is seizures, oftentimes warranting seizure prophylaxis prior to administration of busulfan. The incidence of seizures in patients who do not receive seizure prophylaxis ranges from 5 to 15 % [4]. Seizure onset typically occurs within hours of busulfan administration but may occur up to 24 h after the dose is complete [4, 8]. Busulfan-induced seizures generally present as tonic-clonic seizures, but electroencephalography (EEG) abnormalities can be present without apparent seizures. Historically, phenytoin has been used as seizure prophylaxis in patients who receive busulfan, but caution is warranted with this agent due to its effect on busulfan metabolism. Other agents that have been recommended include levetiracetam in combination with benzodiazepines [8].

Cisplatin

The most common form of neurotoxicity seen with cisplatin is ototoxicity (presenting as tinnitus and hearing loss), occurring in up to 33 % of patients. The ototoxicity that occurs is oftentimes irreversible and is potentially related to higher doses and a longer duration of therapy [9]. Ototoxicity can also be seen in carboplatin, although it is less common. Other forms of CNS toxicity seen with cisplatin include encephalopathy, cortical blindness, stroke, seizures, and focal deficits [1].

Treatment

The treatment of chemotherapy-induced neurotoxicity generally involves prompt discontinuation of the offending agent. Depending on the chemotherapy, rechallenge with dose reductions and/or longer intervals between cycles may be considered [1]. In many cases, neurotoxicity is reversible upon discontinuation though it may take months for recovery; however, it can be irreversible and lead to permanent CNS damage.

Table 2 Agents that can cause peripheral neuropathy

Nucleoside reverse transcriptase inhibitors	Anti-infectives	Miscellaneous
Didanosine	Isoniazid	Altretamine
Lamivudine	Metronidazole	Amiodarone
Stavudine	Nitrofurantoin	Arsenic Trioxide
Zalcitabine		Miglustat

Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) can significantly affect patient's quality of life [10]. In addition, this chemotherapy toxicity can also result in excessive healthcare costs and resources utilized [11]. Certain factors may put patients at higher risk for nerve damage. These include type of chemotherapy agent used, duration of treatment, cumulative dose, age, diabetes, alcohol use, and use of concomitant neurotoxic agents (see Table 2) [12].

Pathophysiology

The exact cause of CIPN differs between classes of chemotherapy agents. In general, these agents cause damage to peripheral nerves by harming microtubules and interfering with microtubule-based axonal transport, causing mitochondrial disruption, or via their cytotoxic effects on DNA [13].

Clinical Features

Peripheral neuropathy is clinically defined as any form of damage, inflammation, or degeneration of peripheral nerves. Patients may experience sensory nerve damage in addition to motor and autonomic nervous system damage [14, 15].

- Most often symptoms are sensory, including paresthesia and pain.
- Symptoms may occur at any time during treatment, even after treatment is stopped.
- Symptoms are most often symmetrical.
- Symptoms start in fingers and toes and spread proximally.

Chemotherapy Agents Implicated

Taxanes (Paclitaxel/Docetaxel)

Paclitaxel has an incidence of peripheral neuropathy around 60 %, compared to docetaxel which has an incidence around 15 %. Cumulative doses greater than 1000 mg/m^2 for paclitaxel and 400 mg/m^2 for docetaxel increase the risk of CIPN. Additional risk factors include duration of infusion, simultaneous administration of platinum-based compounds, and any history of peripheral neuropathy [16].

Platinum-Based Compounds (Cisplatin, Carboplatin, Oxaliplatin)

Approximately 60 % of patients receiving cisplatin therapy in doses of 225–500 mg/m^2 will experience CIPN. The incidence with oxaliplatin is relatively high as well and can range from 60 to 75 %. The cumulative dose, cold temperatures, time of infusion, and preexisting peripheral neuropathy are all factors that can increase the risk of toxicity with oxaliplatin. Carboplatin is much less likely to cause neurotoxicity compared to the previous agents. In most cases the peripheral neuropathy improves or resolves within a year of completion of therapy; however, in some cases, the damage is not reversible [16].

Vincristine

At cumulative doses of 30–50 mg, vincristine can cause CIPN in up to 60 % of patients. These symptoms are reversible upon discontinuation of therapy [16].

Bortezomib

Bortezomib can cause grade 1–2 CIPN in up to 75 % of patients, while 12 % experience grade 3–4 toxicity. The main risk factor is cumulative dose. Administration route can also have an effect as seen by less toxicity with subcutaneous administration [16].

Thalidomide

The incidence of CIPN with thalidomide has been reported in up to 44 % of patients. Two similar agents, lenalidomide and pomalidomide, do not appear to have as significant neurotoxicity as thalidomide [16].

Ixabepilone

The incidence of CIPN for ixabepilone ranges from 40 to 88 % and usually occurs at doses above 40 mg/m^2 [16].

Treatment

Several agents have been tested for efficacy in treating CIPN. Those agents that have shown no benefit include amitriptyline, nortriptyline, and lamotrigine. Limited evidence is available for use of α-lipoic acid and venlafaxine, and larger studies are needed to evaluate their efficacy [12]. The most commonly used treatments for CIPN include topical amitriptyline/ketamine, gabapentin, pregabalin, and duloxetine. Characteristics of each medication can be seen in Table 3.

Table 3 Characteristics of agents used in the treatment of CIPN

Agent	Dose	MOA	Adverse effects	Comments
Topical amitriptyline/ketamine	Apply 2–3 times daily	Amitriptyline: increases the synaptic concentration of serotonin and/or norepinephrine in the CNS by inhibition of their reuptake Ketamine: noncompetitive NMDA receptor antagonist that blocks glutamate	Anticholinergic effects Postural hypotension Sedation	Formulations vary and can include other agents such as baclofen and lidocaine
Gabapentin	300 mg PO on day 1, followed by 300 mg PO twice daily on day 2, 300 mg PO three times a day on day 3, and thereafter	Modulates calcium channel activity by binding to the α2δ receptor site	Somnolence Dizziness Ataxia Confusion Disorientation	Do not discontinue abruptly
Pregabalin	150 mg PO daily in 2–3 divided doses; may increase to 300 mg daily in 2–3 divided doses	Modulates calcium channel activity by binding to the α2δ receptor site	Somnolence Dizziness Peripheral edema Xerostomia Ataxia Weight gain	Schedule V controlled substance Do not discontinue abruptly
Duloxetine	60 mg PO daily	Potent inhibitor of neuronal serotonin and norepinephrine reuptake and a weak inhibitor of dopamine reuptake	Fatigue Insomnia	Best evidence to support use in CIPN

CIPN chemotherapy-induced peripheral neuropathy, *CNS* central nervous system, *MOA* mechanism of action, *NMDA N*-methyl-D-aspartate receptor, *PO* by mouth

In a study evaluating topical baclofen 10 mg, amitriptyline 40 mg, and ketamine 20 mg in pluronic lecithin organogel vs. placebo for CIPN, the topical compound showed a trend toward improved outcomes with no toxicities reported [17]. In a pilot study of 75 cancer patients with CIPN, gabapentin led to statistically significant better responses compared to a control group of 35 patients who refused gabapentin [18]. Conversely, a trial of 115 patients who were randomly assigned to gabapentin or placebo showed no difference in outcomes [19]. Pregabalin was shown to improve outcomes in a group of 23 patients with oxaliplatin-induced peripheral neuropathy. The best result was achieved with a dose of 150 mg by mouth three times a day, and the benefit occurred between 2 and 6 weeks of therapy [20]. Duloxetine was evaluated in a randomized, double-blind, placebo-controlled crossover trial of 231 patients with CIPN. Patients in the duloxetine group experienced less pain as well as a greater decrease in the pain that interfered with daily functions [21]. Finally, combining agents may also increase the benefit seen from these agents. One case report showed that the combination of duloxetine and pregabalin was effective for CIPN induced by paclitaxel [22].

Hypertensive Crisis

Hypertension is the most common condition seen in the community, and it can lead to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately [23]. Hypertension has been reported to occur more frequently in patients with malignancy—37 % of the time versus 29 % in the general population [24].

Pathophysiology

The mechanism of worsening hypertension in patients with malignancy is not well known. It is hypothesized that certain chemotherapy or supportive agents are associated with hypertension and contribute to endothelial dysfunction with nitric oxide reduction, increase in vascular tone, decrease density of microvessels, renal thrombotic microangiopathy that leads to proteinuria, arterial vasoconstriction, sodium and fluid retention, and activation of the renin-angiotensin system [24].

Clinical Features

Just like the rest of the community, patients with malignancy are at risk for hypertensive crisis. Hypertensive crisis includes both urgencies and emergencies. Hypertensive emergencies are always associated with end-organ damage such as hypertensive encephalopathy, cerebral infarction or hemorrhage, myocardial ischemia or infarction, heart failure, aortic dissection, or renal failure. Hypertensive emergency is not related to any specific blood pressure (BP) number, but it usually involves an acute elevation of the systolic BP (SBP) greater than 180 mmHg or diastolic BP (DBP) above 120 mmHg [25]. Hypertensive urgency occurs when a patient presents with a significantly raised BP without evidence of end-organ damage. These patients need their BP reduced urgently but not emergently.

Chemotherapy Agents Implicated

The higher rate of hypertension in patients with malignancy can be contributed to the use of chemotherapy agents that can cause hypertension (angiogenesis inhibitors, 17–80 %; alkylating agents, 36–39 %; and immunosuppressants after stem cell transplantation, 30–80 %) [24, 26]. Anti-vascular endothelial growth factor agents, including bevacizumab, sunitinib, and sorafenib, have been associated with hypertension and have actually been reported to be a useful marker of efficacy for these agents [27]. Some of the end-organ effects (e.g., heart failure, stroke, or renal failure) of these chemotherapy agents can compound the hypertension or cause primary hypertensive crisis. See Table 4 for chemotherapy agents that have been associated with hypertension, heart failure, stroke and/or renal failure.

Treatment

There is no specific guideline for treating hypertension or specifying which agents to use in patients with malignancy. Patients with hypertensive urgency need to be treated, and this is usually achieved by administering oral agents followed by several hours of observation; see Table 5.

Aggressive blood pressure control is advised for patients with hypertensive emergency in order to minimize the risk of end-organ damage. Patients with hypertensive emergency require admission to an intensive care unit (ICU), intravenous (IV) antihypertensive agents, and continuous BP monitoring. Based on the Seventh Report of the Joint National Committee (JNC-7) guidelines, the generalized BP goal is to lower the mean arterial pressure (MAP) by 20–25 % within the first hour while avoiding excessive decreases in BP. When the patient is stable, the SBP can be lowered to 160 mmHg and DBP can be lowered to 100–110 mmHg within the next 2–6 h. If this level of BP control is tolerated and the patient is stable, a gradual reduction to the patient's baseline BP can be done over the next 24–48 h [28]. There are exceptions to the generalized BP goal for patients who have hypertensive emergencies. This includes patients with certain complications such as acute aortic dissection, acute intracerebral hem-

Table 4 Common chemotherapy, hormones, and immunosuppressants that have potential to cause hypertension[a], heart failure[b], stroke[c], or Renal Failure[d] [26]

Abiraterone[a,b]	Dasatinib[a,b,c,d]	Mitomycin[a,b,d]
Adalimumab[a,b]	Daunorubicin; liposomal[a,b]	Mitoxantrone[b,d]
Ado-Trastuzumab emtansine[a,b]	Decitabine[a,b,d]	Muromonab-CD3[a]
Afatinib[d]	Degarelix[a]	Mycophenolate[a,b,c,d]
Aldesleukin, IL-2[a,b,d]	Denileukin diftitox[a]	Nilotinib[a,d]
Alemtuzuma[a,b]	Dexamethasone[a,b]	Nilutamide[a]
Amifostine[a,d]	Docetaxel[a,b,d]	Obinutuzumab[a]
Anastrozole[a]	Enzalutamide[a]	Ofatumumab[a]
Arsenic Trioxide[a,b,d]	Epirubicin[b]	Oxaliplatin[a,d]
Axitinib[a,c]	Erlotinib[c,d]	Paclitaxel[a,d]
Azacitidine[a,b,d]	Estramustine[b]	Panitumumab[d]
Basiliximab[a,b]	Etoposide, VP-16[a]	Pazopanib[a,b,c]
Bendamustine[a,b,d]	Everolimus[a,b,d]	Peginterferon Alfa-2b[c,d]
Bevacizumab[a,b,c]	Exemestane[a]	Pemetrexed[a,d]
Bexarotene[a,b,c]	Fludarapine[b,d]	Pentostatin[a,b,d]
Bicalutamide[a,b]	Flutamide[a]	Pertuzumab[b]
Bleomycin[c]	Gemcitabine[a,b,c,d]	Ponatinib[a,b,c]
Bortezomib[a,b,c,d]	Gemtuzumab ozogamicin[a,d]	Prednisone[a,b,c]
Busulfan[a,b]	Hydrocortisone[a]	Ramucirumab[a,c]
Cabozantinib[a]	Hydroxyurea[d]	Regorafenib[a]
Capecitabine[a,b,c]	Ibritumomab tiuxetan[a]	Rituximab[a,b,d]
Carboplatin[a,b,c]	Ibrutinib[a,d]	Sirolimus[a]
Carfilzomib[a,d]	Idarubicin[b]	Sorafenib[a,b,c,d]
Carmustine, BCNU[d]	Ifosfamide[a,b,d]	Sunitinib[a,b,c,d]
Ceritinib[d]	Imatinib, STI-571[a,b,d]	Tacrolimus[a,d]
Cetuximab[a,b,d]	Interferon agents[a,b,d]	Tamoxifen[a,c]
Cisplatin[c,d]	Ipilimumab[d]	Temsirolimus[a]
Cladribine[d]	Irinotecan[c,d]	Thalidomide[c]
Clofarabine[a,d]	L-Asparaginase[a]	Trametinib[a,b,d]
Cyclophosphamide[a,b,d]	Lenalidomide[a,b,d]	Trastuzumab[a,b,c,d]
Cyclosporine[a,b]	Lomustine[d]	Tretinoin, ATRA[a,b,c,d]
Cytarabine; liposomal, ARA-C[a]	Mesalamine, 5-ASA[a,d]	Vandetanib[a,b,c]
Dabrafenib[a,d]	Methlyprednisolone[a,b]	Vinblastine[a,c]
Daclizumab[a]	Methotrexate[d]	Vincristine[a]
		Vinorelbine[a]

[a]Documented hypertension side effect
[b]Documented heart failure side effect
[c]Documented stroke side effect
[d]Documented renal failure side effect

Table 5 Common antihypertensive agents used for hypertensive urgencies [28, 29]

Agent	MOA	Dose	Onset	Duration	Adverse effects
Captopril	ACE inhibitor	12.5–25 mg PO every 1–2 h	15–30 min	4–6 h	Angioedema Cough Acute renal failure
Clonidine	Central α_2-agonist	0.1–0.2 mg PO every 1–2 h	30–60 min	6–8 h	Bradycardia Dry mouth Rebound hypertension after withdrawal Sedation
Labetalol	α_1, β_1&$_2$-blocker	200–400 mg PO every 2–3 h	30–120 min	6–8 h	Bronchoconstriction Heart block Heart failure Hypotension Vomiting
Furosemide	Loop diuretic	20–40 mg PO every 2–3 h	30–60 min	8–12 h	Hypokalemia Hyponatremia Volume depletion

ACE angiotensin-converting enzyme, *MOA* mechanism of action, *PO* by mouth

Table 6 Agents for treating hypertensive emergencies with comorbidities and blood pressure goals [25, 30–34]

Comorbidity	Preferred agent(s)[a]	Blood pressure goal
Acute aortic dissection	Esmolol[b]	SBP < 120 mmHg within 20 min; lowest BP possible that maintains end-organ perfusion
Acute heart failure (pulmonary edema)	Loop diuretics Nitroglycerin Nitroprusside	Generalized goal[c]
Acute ischemic stroke	Labetalol Nicardipine Nitroprusside	Ineligible for reperfusion therapy: <220/120 mmHg, decrease no more than 15 %
		Eligible for reperfusion therapy: ≤185/110 mmHg
		During and post-reperfusion therapy: ≤180/105 mmHg
Acute intracerebral hemorrhage	Labetalol Nicardipine	SBP 150–220 mmHg: Acute lowering of SBP to140 mmHg is probably safe
		SBP > 200 mmHg or MAP > 150 mmHg: Consider aggressive reduction
		Possible elevated ICP and SBP > 180 mmHg or MAP > 130 mmHg: consider monitoring ICP and reduce BP while maintaining CPP ≥ 60 mmHg
		No evidence of elevated ICP and SBP is > 180 mmHg or MAP > 130 mmHg: consider a modest reduction of BP; MAP of 110 mmHg or BP of 160/90 mmHg
Acute myocardial infarction	Clevidipine[d] Esmolol/labetalol Nicardipine[d] Nitroglycerin	Generalized goal[c]
Acute renal failure	Clevidipine Fenoldopam Nicardipine	Generalized goal[c]

BP blood pressure, *CPP* cerebral perfusion pressure, *ICP* intracranial pressure, *MAP* mean arterial pressure, *mmHg* millimeters of mercury, *SBP* systolic blood pressure

[a]Agents are listed in alphabetical order, not in preference

[b]β-Blockade must be used prior to other vasodilators

[c]Decrease MAP by 20–25 % during first hour, if patient is stable, decrease SBP to 160 mmHg and DBP to 100 mmHg over next 2–6 h, then a gradual reduction to the patient's baseline BP over the next 24–48 h

[d]May be used in patients with heart rate <70 beats/min

orrhage, and acute ischemic stroke with or without reperfusion therapy. The specific blood pressure goals are listed in Table 6.

Treatment decisions with parental agents should focus on the end-organ system at risk and associated side-effects caused by the specific agent used. See Tables 6 and 7 for BP goals and recommended intravenous agents per end-organ system.

Aortic Dissection

Acute aortic dissection has a high mortality rate of 1 % per hour over the first several hours [37]. Early diagnosis and treatment is crucial for survival. Intravenous and fast-acting β-blockers are the drug of choice due to their ability to lower the heart rate and stress on the aorta. If other agents are used for lowering the BP, β-blockers should always be used first to prevent reflex tachycardia [30, 37].

Heart Failure

Patients with heart failure, severe hypertension, and significant fluid overload should be initially treated with intravenous loop diuretics to reduce mortality [32]. Nitroglycerin and sodium nitroprusside are the most commonly used antihypertensive agents for this group of patients [31]. Nesiritide has also been used for decompensated heart failure, but its use is controversial due to a higher risk of renal failure and mortality when compared to nitroglycerin [38, 39].

Table 7 Common parenteral agents used for hypertensive emergencies [26, 28, 29, 35, 36]

Agent	MOA	Bolus dose	Continuous infusion dose	Dose titration	Onset	Duration	Adverse effects[a]
Clevidipine[b]	Calcium channel blocker	Not applicable	1–16 mg/h	1 mg/h every 2 min	2–4 min	5–15 min	Flushing Headache Heart failure Tachycardia
Esmolol	β_1-Blocker	250–500 µg over 1 min; may repeat after 5 min	25–300 µg/kg/min	25 µg/kg/min every 5 min	1–2 min	10–30 min	Bronchoconstriction Heart block Heart failure
Fenoldopam[c]	Dopamine-1 receptor agonist	Not applicable	0.1–1.6 µg/kg/min	0.05–0.1 µg/kg/min every 15 min	5–10 min	10–15 min	Flushing Headache Tachycardia
Labetalol	α_1, β_1&$_2$-blocker	20–80 mg over 2 min every 10 min	2–8 mg/min; max dose for bolus and infusion is 300 mg/24 h	Titrate by 0.5 mg/min every 60 min	5–10 min	2–6 h	Bronchoconstriction Heart block Heart failure Vomiting
Nicardipine	Calcium channel blocker	Not applicable	5–15 mg/h	2.5 mg/h every 5 min	5–10 min	2–4 h	Flushing Headache Reflex tachycardia
Nitroglycerin	Converts to NO and increases cGMP	Not applicable	5–200 µg/min	5–10 µg/min every 5 min	1–3 min	5–15 min	Headache Methemoglobinemia Tachycardia Vomiting
Sodium nitroprusside[d]	Increases cGMP, blocks intracellular calcium	Not applicable	0.25–10 µg/kg/min	Titrate by 0.5 µg/kg/min every 5 min	Immediate	1–2 min	Cerebral autoregulation impairment Coronary steal Cyanate toxicity Nausea/vomiting

cGMP cyclic guanosine monophosphate, *h* hour, *kg* kilogram, *µg* micrograms, *mg* milligrams, *min* minute, *MOA* mechanism of action, *NO* nitric oxide

[a]Hypotension may occur with all agents

[b]Caution with severe aortic stenosis and acute heart failure

[c]Caution with glaucoma and sulfite allergies

[d]Caution with high intracranial pressure, hepatic and renal failure

Ischemic Stroke

Appropriate management for ischemic stroke is very important. Studies have demonstrated a "U-shaped" relationship between BP and clinical outcome [31]. The concern with lowering the BP in patients with ischemic stroke is the expansion of the central ischemic core. Cerebral autoregulation can be lost after a stroke, leaving the core along with the surrounding ischemic penumbra prone to hypoperfusion and a potential worse outcome [36]. There are limited studies that have evaluated the optimal BP goal and appropriate pharmacotherapy. Modest lowering of the BP is recommended and dependent on the patient's eligibility for reperfusion therapy; see Table 6 [34]. The Stroke Council of the American Heart Association recommends the use of labetalol, nicardipine, and sodium nitroprusside.

Several small studies have compared labetalol and nicardipine to one another. In a meta-analysis, these two agents were found to have comparable side effects and efficacy for the treatment of hypertension in patients with several different types of strokes including acute ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage [40]. Nicardipine was found to lower the BP more consistently and predictably with less rescue agents than labetalol [40].

Hemorrhagic Stroke

The most acute concern after hemorrhagic stroke is hematoma volume expansion [41]. Hematoma expansion occurs very early (first 3 h), with limited expansion beyond 24 h [31]. Two studies have confirmed the feasibility and safety of early rapid BP lowering in patients with intracerebral hemorrhage (INTensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial [INTERACT] pilot study and the Antihypertensive Treatment of Acute Cerebral Hemorrhage [ATACH] trial) [42, 43]. Labetalol and nicardipine are used to control BP in patients with hemorrhagic stroke as mentioned in the ischemic stroke section. Several pilot studies have been published showing potential use of clevidipine in hemorrhagic stroke [44, 45].

Acute Coronary Syndromes

The goal for patients experiencing acute coronary syndrome is to decrease myocardial oxygen demand and improve coronary perfusion. For these patients experiencing hypertensive emergencies, both nitrates and β-blockers have been used to reach the above goal. If patients are unable to tolerate nitrates or β-blockers, calcium channel blockers have been used [25].

Renal Failure

Fenoldopam has an indication for hypertensive emergencies and has been demonstrated to improve creatinine clearance, urine flow rates, and sodium excretion in severely hypertensive patients with both normal and impaired renal function [46]. Therefore, it may be useful in patients with hypertensive emergencies and renal failure. Diuretic use in patients with severe hypertension and renal failure may be beneficial or harmful and is completely dependent on the patient's volume status.

It is absolutely crucial to recognize hypertensive emergencies as soon as possible. End-organ damage can be minimized by early diagnosis and treatment. Treatment and the BP goal are dependent on the end-organ involved.

Mucositis

Mucositis is a common adverse effect of several chemotherapy agents. A summary of the classification scales for mucositis can be seen in Table 8. The incidence of grade 3 or 4 oral mucositis is as high as 75 % in hematopoietic stem cell transplantation patients [48]. Defined as inflammatory and/or ulcerative lesions of the oral and/or gastrointestinal (GI) tract, mucositis can result in significant patient discomfort and delaying cancer therapy. The risk factors for developing mucositis include older age, female sex, poor oral care, saliva secretory dysfunction, malnourishment, renal dysfunction, smoking, and previous episodes of mucositis after cancer therapy [49].

Table 8 Summary of grading system for oral mucositis [47]

Grade	WHO	NCI-CTC
Grade 0 (none)	No mucositis present	No mucositis present
Grade 1 (mild)	Oral soreness, erythema	Painless ulcers, erythema, or mild soreness in the absence of lesions
Grade 2 (moderate)	Oral erythema, ulcers but able to eat solids	Painful erythema, edema, or ulcers but eating able to eat or swallow
Grade 3 (severe)	Oral ulcers and able to take liquids only	Painful erythema, edema, or ulcers requiring IV hydration
Grade 4 (life threatening)	Oral alimentation impossible	Severe ulceration or requiring parenteral or enteral nutritional support or prophylactic intubation
Grade 5 (death)	N/A	Death related to toxicity

WHO World Health Organization, *NCI-CTC* National Cancer Institute Common Toxicity Criteria, *N/A* not applicable

Pathophysiology

The first step of the process is the initiation phase in which reactive oxygen species are generated. Once generated, the reactive oxygen species as well as chemotherapy activate transcription factors (e.g., nuclear factor-κB), which causes upregulation of genes that result in the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. This activation of cytokines leads to tissue damage and apoptosis. In addition to direct damage, these cytokines also amplify other pathways which result in the production of pro-inflammatory cytokines. Next, during the ulcerative phase, the injury and damage that has previously occurred results in breakdown of the oral mucosa, and these ulcers serve as a site for bacterial colonization. This is followed by the healing phase in which the epithelial cells proliferate and differentiate, promoting tissue healing [47, 49].

Clinical Features

Many patients with mucositis often complain of a change in sensation, difficulty swallowing, mouth sores, mouth dryness, pain, bleeding, infection, and decreased oral intake [49]. Chemotherapy-induced mucositis is usually a transient event with an onset of about 3–5 days after drug administration, followed by ulceration a few days later and resolution within 2 weeks [50].

Chemotherapy Agents Implicated

The most common chemotherapy agents implicated in causing mucositis include 5-fluorouracil (5-FU), irinotecan, methotrexate, melphalan, anthracyclines (daunorubicin, doxorubicin, epirubicin, and idarubicin), taxanes (paclitaxel and docetaxel), and platinum compounds (cisplatin, carboplatin, and oxaliplatin). The rate of mucositis with anthracycline-based regimens is between 1 and 10 % except when combined with 5-FU and docetaxel, the risk is significantly higher. The rates with taxane-based and platinum-based therapy are similar, with an increased incidence when combined with 5-FU. When chemotherapy is combined with radiation therapy, the risk often exceeds 50 % [47].

Treatment

The first guideline for management of mucositis was published in 2004 by the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology and updated in 2007 and 2014 [51–53].

While the evidence to support basic oral care is lacking, it is generally recommended that good oral hygiene is necessary to maintain mucosal health. Chlorhexidine is an antimicrobial agent that can be used as part of an oral health plan; however, it should not be used to treat established oral mucositis. Chlorhexidine contains alcohol which can burn when it comes in contact with damaged mucosa. For pain control, the guidelines recommend a morphine patient-controlled analgesia (PCA) as the preferred treatment in patients undergoing stem cell transplantation; however, there is little evidence to recommend its use in other patient populations. The guidelines suggest the use of transdermal fentanyl, 2 % morphine mouthwash, and 0.5 % doxepin mouthwash as agents that may be effective for pain control. Avoiding liquid pain medications which include alcohol is necessary to prevent burning on ingestion. Topical preparations including ingredients such as lidocaine, benzocaine, diphenhydramine, nystatin, magnesium hydroxide, aluminum hydroxide, and occasionally corticosteroids are used frequently in the management of mucositis; however, currently there is no evidence to support their use. Several trials have shown bland saline rinses to be as effective as other topical preparations at a fraction of the cost. Sucralfate reacts with hydrochloric acid in the stomach and forms an adherent paste which binds to damaged GI mucosa. Based on the evidence, sucralfate is not recommended for the treatment or prevention of oral mucositis [51–55]. Topical agents such as Gelclair®, Caphosol®, and Biotene® may offer symptomatic relief, but data justifying the routine use of these agents is limited.

The National Comprehensive Cancer Network (NCCN) recommendations for management of mucositis support the use of lidocaine as a topical analgesic for pain and discomfort. Due to the risk of systemic absorption and reduction in the gag reflex, it is not recommended to swallow lidocaine solutions or gels [54].

One case series and another case report have been published on the use of ketamine mouthwash for mucositis pain [56, 57]. While the data is limited, this may be a potential option for management of pain associated with mucositis in the future.

Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV) is a debilitating side effect of chemotherapy, potentially impacting nutrition status, future treatment courses, quality of life, and overall cost of healthcare [58]. After the introduction of serotonin (5-HT_3) receptor antagonists, prophylactic antiemetic regimens for chemotherapy improved significantly, preventing many cases of CINV. However, breakthrough nausea and vomiting, refractory to these prophylactic regimens, still occurs commonly [59]. Unfortunately, there is a paucity of studies evaluating optimal regimens for the treatment of breakthrough CINV. This section will focus on management strategies for breakthrough CINV only.

Pathophysiology

CINV is initiated by the stimulation of enterochromaffin cells in the GI tract by chemotherapeutic agents. This causes a release of 5-HT_3, which sends information to the central nervous system [60]. These signals are received and processed by the vomiting center in the medulla oblongata and chemotherapy trigger zone, which are then converted to signals to promote emesis [61, 62]. Serotonin is the predominant neurotransmitter involved in the first 24 h of CINV, while signals from dopamine and substance P predominate after 24 h [63]. Other neurotransmitters involved include acetylcholine, corticosteroid, cannabinoid, and opiate [64].

Clinical Features

CINV is composed of both nausea and vomiting. Nausea is an unpleasant sensation in the back of the throat or epigastrium that may or may not result in emesis. Vomiting is a motor reflex which results in a forceful expulsion of the GI contents [61, 62]. CINV can be categorized into the acute and delayed phases. Acute CINV occurs within the first 24 h of chemotherapy, while delayed CINV occurs after 24 h and can last up to 7 days [61, 65]. Breakthrough CINV is any nausea or vomiting that occurs despite optimal prophylactic antiemetic regimens [66].

Chemotherapy Agents Implicated

Chemotherapeutic agents are classified into four different categories based on their emetogenicity risk. Highly emetogenic agents have a risk of greater than 90 %, moderately emetogenic agents have a risk of 30–90 %, agents with low emetogenicity have a risk of 10–30 %, and minimally emetogenic agents have a risk of less than 10 % for emesis [67]. See Table 9 for specific chemotherapy agents and their classifications.

Treatment

The treatment of breakthrough CINV is not well studied in clinical trials. There are currently three published guidelines from three different cancer organizations. The American Society of Clinical Oncology (ASCO) suggests using benzodiazepines, olanzapine, or dopamine antagonists [67]. NCCN recommends using an agent different from those included in

Table 9 Chemotherapy agents based on emetogenicity risk [60, 61]

Level	Agent	
High	Carmustine > 250 mg/m^2 Cisplatin ≥ 50 mg/m^2 Cyclophosphamide > 1500 mg/m^2 Cytarabine ≥ 2 g/m^2 Dacarbazine	Dactinomycin Lomustine Mechlorethamine Streptozotocin
Moderate	Aldesleukin > 12–15 million IU/m^2 Amifostine > 300 mg/m^2 Arsenic trioxide Azacitidine Carboplatin Carmustine ≤ 250 mg/m^2 Cisplatin < 50 mg/m^2 Clofarabine Cyclophosphamide ≤ 1500 mg/m^2 Cytarabine 1–2 g/m^2	Daunorubicin Decitabine Doxorubicin Epirubicin Idarubicin Ifosfamide Irinotecan Methotrexate ≥ 250 mg/m^2 Oxaliplatin
Low	Alemtuzumab Bortezomib 1 Cetuximab 1 Cytarabine ≤ 100 mg/m^2 Docetaxel Doxorubicin HCL liposome injection Etoposide 5-Fluorouracil Gemcitabine Ixabepilone Lapatinib	Methotrexate 50–250 mg/m^2 Mitomycin Mitoxantrone Paclitaxel Pemetrexed Temsirolimus Thiotepa Topotecan Trastuzumab Vorinostat
Minimal	Asparaginase Bevacizumab Bleomycin 1 Busulfan Cladribine Dasatinib Fludarabine	Methotrexate < 50 mg/m^2 Pegasparaginase Sunitinib Vinblastine Vincristine Vinorelbine

the prophylactic regimen and suggests that multiple agents with different mechanisms of action may be needed. NCCN recommends utilizing these agents on a scheduled, around-the-clock dosing strategy versus administering these agents on an as-needed basis. NCCN also states that no agent has been proven to be better than another [64]. Agents that have been recommended include benzodiazepines, dopamine antagonists, cannabinoids, antihistamines, corticosteroids, 5-HT_3 antagonists, and other agents such as olanzapine and scopolamine. See Table 10 for details on pharmacotherapeutic treat-

Table 10 Characteristics of agents used in the treatment of breakthrough CINV [59–61, 63–65, 68]

Agent	Dose	MOA	Adverse effects	Comments
Benzodiazepines				
Lorazepam	0.5–2 mg PO/IV every 4–6 h	Binds to benzodiazepine receptors in the postsynaptic GABA receptors	Sedation Respiratory depression Hypnosis/amnesia	Added benefit of reducing anxiety Not recommended as monotherapy
Dopamine antagonists				
Haloperidol	0.5–2 mg PO/IV every 4–6 h	Butyrophenone, most potent dopamine antagonist; weak anticholinergic and alpha-adrenergic blocking effects	Sedation QT_c prolongation Extrapyramidal symptoms	–
Metoclopramide	10–40 mg PO/IV every 4–6 h	Benzamide analog, peripheral dopamine antagonist; stimulates prokinesis via serotonin (5-HT_4) receptors	Dystonic reactions Akathisia Diarrhea Mild sedation Orthostatic hypotension	Increased efficacy at higher doses due to additional serotonin blockade
Prochlorperazine	10 mg PO/IV every 4 h (max 40 mg/day) or 25 mg PR twice daily	Phenothiazine, dopamine antagonist, some anticholinergic and alpha-adrenergic blocking effects, prochlorperazine with more predominant dopamine antagonism, promethazine with more antihistamine properties	Sedation Dystonia Extrapyramidal symptoms	-
Promethazine	12.5–25 mg PO/IV every 4 h			
Cannabinoids				
Dronabinol	5–10 mg PO every 3–6 h	Effects on the cannabinoid receptors in the CNS and peripheral receptors	Dizziness Dysphoria Postural hypotension Hallucinations	Use is limited by side effects
Nabilone	1–2 mg PO twice daily			
5-HT_3 receptor antagonists				
Ondansetron	16 mg PO/IV daily	Antagonistic effect at the 5-HT_3 receptor located in the GI tract, CTZ, and vomiting center	QTc prolongation Headache Constipation	PO and IV are equally effective All are equally effective/safe when given in biologically equal doses
Dolasetron	100 mg PO daily			
Granisetron	1–2 mg PO daily or 1 mg PO twice daily or 0.01 mg/kg IV (maximum 1 mg)			
Corticosteroids				
Dexamethasone	12 mg PO/IV daily	Not fully understood	Insomnia Increased appetite Hyperglycemia GI distress	Is more commonly used in prophylactic regimens for CINV
Other agents				
Olanzapine	2.5–5 mg PO twice daily (max 20 mg/day)	Effects on multiple receptors (serotonin, dopamine, acetylcholine, muscarinic)	Sedation Postural hypotension Increased appetite Weight gain	
Scopolamine patch	1.5 mg TD every 72 h	Antimuscarinic, anticholinergic	Drowsiness Fatigue Paradoxical CNS excitation Hallucinations Xerostomia	

CINV chemotherapy-induced nausea and vomiting, *CNS* central nervous system, *CTZ* chemotherapy trigger zone, *GABA* gamma-aminobutyric acid, *GI* gastrointestinal, *IV* intravenous, *kg* kilogram, *mg* milligrams, *MOA* mechanism of action, *PO* by mouth, *PR* per rectum or rectally, *TD* transdermal

ment options for CINV. Substance P/neurokinin 1 (NK-1) receptor antagonists such as aprepitant have only been studied as part of prophylactic regimens and have not been recommended by any of the three main guidelines from ASCO, NCCN, or the MASCC/European Society of Medical Oncology (ESMO) for the treatment of breakthrough CINV [64, 67, 69].

One retrospective study observed 33 patients who experienced breakthrough CINV that failed both benzodiazepines and dopamine antagonists and received at least one dose of olanzapine. Sixty-five to seventy percent of these patients had success with olanzapine. The typical dose given was 5–10 mg by mouth daily for a median of 4 days [63].

Another observational study evaluated medications received for breakthrough CINV. Of 39 patients who required rescue antiemetics, 88 % received prochlorperazine (dopamine antagonist) while 12 % received a 5-HT_3 antagonist. Both groups reported a 75 % reduction of nausea after 240 min. Both groups also noted significant symptom control within 30 min [58].

Navari et al. studied both olanzapine and metoclopramide in a double-blind, randomized trial that included 108 evaluable patients. Patients were included if they received highly emetogenic chemotherapy and appropriate prophylactic antiemetic regimens and developed breakthrough CINV. Olanzapine was given as a 10 mg dose orally every 24 h for 72 h, while metoclopramide was given as a 10 mg dose orally every 8 h for 72 h. Patients who received olanzapine had significantly better control of nausea and vomiting, and olanzapine was shown to be well tolerated [70].

CINV continues to be a significant adverse effect of chemotherapy that can impact the treatment of cancer. Utilizing the most effective prophylactic regimens based on the emetogenicity of the chemotherapy agent(s) is most important, but patients may still develop breakthrough CINV. In these cases, it is important to quickly control symptoms with scheduled antiemetics that have mechanisms differing from initial agents used for prophylaxis.

Nephrotoxicity

Acute kidney injury is defined as a sudden increase in serum creatinine level, a decrease in urine output, or the need for hemodialysis. It is classified into categories including prerenal, intrinsic damage, and postrenal depending on the cause. Prerenal kidney injury occurs secondary to renal hypoperfusion, intrinsic damage occurs after extended hypoperfusion or after direct injury to the renal vasculature by a medication, and postrenal kidney injury occurs due to urinary obstruction [71]. Exposure to concomitant nephrotoxic agents (Table 11) can increase the risk of chemotherapy-induced nephrotoxicity.

Chemotherapy Agents Implicated

Platinum-Based Compounds (Cisplatin, Carboplatin)

Cisplatin has a high incidence of acute kidney injury, and this is often the dose-limiting toxicity of this medication. The risk with carboplatin is not nearly as high, but when used in high doses (>1200 mg/m^2), renal dysfunction can occur. One of the most common sequelae of cisplatin renal toxicity is hypomagnesemia, which can continue for years following discontinuation of the medication. The cause of the kidney injury is related to proximal tubular damage [71]. Renal tubular epithelial cells/casts

Table 11 Drugs that can increase the risk of chemotherapy-induced nephrotoxicity

Medication	Renal toxicity mechanism
Acyclovir	Tubular obstruction
Allopurinol	Acute interstitial nephritis
Aminoglycosides	Acute tubular necrosis
Amphotericin B	Acute tubular necrosis
Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers	Inhibition of angiotensin II which causes efferent arteriole vasoconstriction
Contrast agents	Acute tubular necrosis
Diuretics	Acute interstitial nephritis
Foscarnet	Acute tubular necrosis, tubular obstruction
Ganciclovir	Tubular obstruction
Lithium	Chronic interstitial nephritis, glomerulonephritis
Nonsteroidal anti-inflammatory drugs	Inhibition of renal prostaglandins which causes afferent arteriole vasodilation, glomerulonephritis
Proton pump inhibitors	Acute interstitial nephritis
Sulfonamides	Tubular obstruction
Tacrolimus	Afferent arteriole vasoconstriction
Vancomycin	Acute interstitial nephritis

and/or granular casts can be seen in urine sediment analysis [72]. Another more rare adverse effect of cisplatin therapy is renal salt wasting which is often misdiagnosed as the syndrome of inappropriate antidiuretic hormone (SIADH) [73].

Ifosfamide

One of the dose-limiting side effects of ifosfamide is hemorrhagic cystitis which occurs when urinary excretion of reactive metabolites binds to sulfhydryl constituents in the proteins located in the bladder epithelium. In addition to hemorrhagic cystitis, ifosfamide can also induce nephrotoxicity by causing proximal tubular injury (Fanconi syndrome), and the greatest risk factors include exposure to cisplatin, underlying renal dysfunction, and cumulative doses greater than 90 g/m^2 [72]. Manifestations of Fanconi syndrome include hypophosphatemia, polyuria, acidosis, hypokalemia, glycosuria, and proteinuria [71]. Other chemotherapy agents that have been implicated in causing Fanconi syndrome include cisplatin, azacitidine, and imatinib [74]. The kidney injury can be reversible; however, permanent damage is possible [74]. Treatment includes replacement of fluids and electrolytes, to be elaborated on in the following section [73].

Gemcitabine

Rarely, gemcitabine may induce kidney injury though hemolytic uremic syndrome (HUS), resulting in thrombotic microangiopathy (TMA) which presents as anemia; thrombocytopenia; increased lactate dehydrogenase, bilirubin, and reticulocyte count; and decreased haptoglobin levels [75]. Risk factors for development of HUS include cumulative drug doses and previous therapy with mitomycin C [74]. Treatment is limited but has included plasmapheresis, corticosteroids, and fresh frozen plasma infusion [75].

Mitomycin

Renal toxicity with mitomycin manifests as HUS and can occur in 4–15 % of patients receiving the medication. Patients at higher risk of developing HUS include those with a cumulative dose greater than 60 mg [71]. Platelet transfusions should be avoided in HUS, unless there is massive bleeding because they may worsen the TMA [76].

Methotrexate

Acute renal failure can occur following high-dose methotrexate therapy which is defined as 1–12 g/m^2. The mechanism by which renal failure occurs is acute tubular necrosis secondary to the crystallization of the parent drug and metabolites within the kidney. Ensuring appropriate hydration and urinary alkalization is necessary in patients receiving high-dose methotrexate [71]. Leucovorin is often given with high-dose methotrexate to reduce toxicities. After converting to the active metabolite, 5-methyltetrahydrofolate, it restores the folate pool and continues the folic acid cycle. To treat renal toxicity, hemodialysis can be performed to decrease methotrexate levels; however, a post-dialysis plasma rebound often occurs [73, 74].

Cetuximab

Magnesium wasting is a major adverse effect of cetuximab therapy. The epidermal growth factor receptor in which cetuximab binds to is located on renal epithelium, and binding activates the magnesium channel in the distal convoluted tubule, causing reabsorption and subsequent wasting. To prevent adverse effects of hypomagnesemia, oral and/or intravenous replacement is necessary [72]. Further discussion on cetuximab-induced hypomagnesemia can be found in the next section.

Electrolyte Disorders

Cancer patients commonly develop electrolyte abnormalities whether due to nausea, vomiting, or diarrhea, leading to dehydration, kidney injury, tumor lysis syndrome, or even from the metabolic processes with cancer itself. In this section, we will highlight the predominant electrolyte disorders caused specifically by chemotherapy agents.

Chemotherapy Agents Implicated

Cisplatin

Cisplatin can cause a wide array of electrolyte abnormalities including hypomagnesemia, hypocalcemia, hypokalemia, and hyponatremia. The most common electrolyte disorder seen with cisplatin is hypomagnesemia. Most patients are asymptomatic, but symptoms can include muscle weakness and cramping, tetany, fatigue, seizures, and arrhythmias [77]. The incidence appears to be dose-related and was shown to reach 100 % after the sixth cycle of chemotherapy in one study [78]. Hypomagnesemia occurs due to proximal tubular necrosis caused by cisplatin at the site of magnesium reabsorption, which results in renal magnesium wasting [79].

Cisplatin-induced hypomagnesemia has been shown to persist in many patients, up to years after the discontinuation of cisplatin [77, 80]. Due to its high incidence of nephrotoxicity, cisplatin administration is usually preceded by judicious hydration with intravenous fluids. This induces an osmotic diuresis which increases urinary magnesium excretion and could worsen hypomagnesemia [81]. Though hypomagnesemia is often asymptomatic, it is important to treat because low serum magnesium can lead to refractory hypokalemia and hypocalcemia [81, 82].

Cyclophosphamide

Hyponatremia resembling the SIADH induced by cyclophosphamide was initially and is more commonly reported with high doses. Recently however, this adverse effect has been reported with moderate doses and doses as low as 500 mg/m^2 and 10 mg/kg [83]. SIADH seen with cyclophosphamide is postulated to be caused by either an antidiuretic hormone (ADH)-like metabolite or a direct toxic effect on the renal distal tubule by cyclophosphamide or one of its metabolites [83, 84]. Hyponatremia can present variably depending on the acuity and severity, causing symptoms ranging from headache, nausea, and vomiting to altered mental status, seizures, and coma [85]. Cyclophosphamide-induced SIADH generally occurs 4–12 h after drug administration and usually resolves within 24 h of drug discontinuation [84]. Treatment for SIADH centers around fluid restriction, but this may be challenging due to the recommendation for generous hydration to prevent cyclophosphamide-induced hemorrhagic cystitis [77].

Vinca Alkaloids

Of the vinca alkaloids, vincristine is the agent with the highest incidence of hyponatremia. This hyponatremia is thought to resemble SIADH and involves an inappropriate release of antidiuretic hormone in the setting of hypotonic hyponatremia [77]. The onset of hyponatremia usually occurs 1–2 weeks after the chemotherapy is administered and usually lasts for 2 weeks but can last up to 30 days. Hyponatremia induced by vinca alkaloids is also usually reversible with proper treatment, but fatality has been reported [84].

Ifosfamide

Fanconi syndrome is a well-known adverse effect of ifosfamide therapy as previously discussed. Fanconi syndrome involves damage to the proximal tubules which results in impairment of electrolyte reabsorption, including phosphorus, bicarbonate, and glucose. The predominant concern is hypophosphatemia, which can be severe enough to cause rickets in the pediatric population [86]. Other signs and symptoms of hypophosphatemia include respiratory distress, neurologic dysfunction, and seizures [85]. Several risk factors for ifosfamide nephrotoxicity that have been identified include high cumulative doses of ifosfamide, concomitant cisplatin use, and patients who have undergone nephrectomy [86].

Cetuximab

Cetuximab was shown to cause hypomagnesemia in over 11 % of patients in one retrospective study. Patients who received a concomitant platinum-based agent had a more rapid and more significant decrease in magnesium levels at the end of 12 weeks. The mechanism behind cetuximab-induced hypomagnesemia appears to be impaired reabsorption of magnesium from the loop of Henle, resulting in magnesium wasting. Although severe hypomagnesemia only occurred in approximately 11 % of patients, it has been shown that nearly half of patients who receive cetuximab develop some form of hypomagnesemia [87]. Oftentimes, hypomagnesemia due to cetuximab use is refractory to oral magnesium replacement and requires intravenous replacement. Another study showed variable rates of hypomagnesemia based on cancer type with non-small cell lung cancer with the highest risk and colorectal cancer with the lowest risk of developing hypomagnesemia [88].

Treatment

It is important to be cognizant of the common electrolyte disorders that can occur with chemotherapy in order to monitor serum electrolytes accordingly. Treatment of chemotherapy-induced electrolyte disorders requires vigilant monitoring and judicious replacement or correction when warranted. Oftentimes, the culprit for the electrolyte disorder is difficult to pinpoint due to confounders such as concomitant medications and disease processes, GI losses from vomiting or diarrhea, dehydration, or poor nutrition status. When identified, the treatment of these electrolyte disorders usually only requires replacement or correction (e.g., fluid restriction for SIADH hyponatremia) but may require alterations in therapy such as chemotherapy dose reductions, transitioning to alternative agents within the same class, changing the administration schedule, or even discontinuing the agent. When replacing electrolytes such as magnesium, potassium, phosphorus, and calcium, the clinician should be mindful of the patient's renal function and adjust replacement accordingly for impaired renal function. Electrolytes should be replaced orally if the patient is able to tolerate oral intake and if the patient is asymptomatic or mildly symptomatic. For acute, severe, or symptomatic electrolyte disturbances, electrolyte replacement should be given intravenously. See Table 12 for common electrolyte disorders and chemotherapy agents associated with these disorders. The reader is advised to refer to other references for a more detailed discussion of the treatment of electrolyte disorders [85, 90, 91].

Anaphylaxis

Patients with cancer are increasingly exposed to a wider range of chemotherapy agents and monoclonal antibodies that are new, powerful, and more targeted. Increased exposure leads to a higher opportunity to develop severe hypersensitivity reactions such as anaphylaxis.

Table 12 Electrolyte disorders and chemotherapy agents implicated [84, 89]

Electrolyte disorder	Agents	Mechanism	Clinical presentation	Treatment[a]
Hyponatremia (serum sodium <135 mEq/L)	Carboplatin Cisplatin Ifosfamide	Renal salt wasting or SIADH	Headache Nausea/vomiting Confusion Seizures Hypovolemic if renal salt wasting Euvolemic if SIADH	Renal salt wasting: PO/IV sodium chloride supplementation Hydration SIADH: Fluid restriction Can consider low-dose diuretics Can consider oral sodium chloride If severe or acute symptoms, consider initial management with hypertonic, 3 % sodium chloride infusion at a rate of 15–80 mL/h, or up to 1–2 mL/kg/h with frequent sodium monitoring
	Interferon Levamisole Melphalan Vinblastine Vincristine Vinorelbine	SIADH		
	Cyclophosphamide	SIADH or water intoxication		
	Methotrexate	Alteration in body fluid volumes		
Hypomagnesemia (serum magnesium < 1.5 mg/dL)	Cetuximab Cisplatin	Magnesium wasting (impaired reabsorption of magnesium in the kidneys)	Muscle cramps and weakness Paresthesia Tetany Tremulousness Arrhythmias Seizures	PO[b]/IV magnesium supplementation (e.g., magnesium oxide for PO, magnesium sulfate for IV) Mild to moderate hypomagnesemia (1.0–1.5 mg/dL): 8–32 mEq Severe hypomagnesemia (<1.0 mg/dL): 32–64 mEq
Hypokalemia	Azacytidine Cisplatin Ifosfamide Streptozocin	Renal losses via renal tubular acidosis, Fanconi syndrome, or secondary to hypomagnesemia	Weakness Constipation EKG changes Arrhythmias	PO/IV potassium supplementation (e.g., potassium chloride) Mild to moderate hypokalemia (2.5–3.4 mEq/L): 20–40 mEq Severe hypokalemia (<2.5 mEq/L): 40–80 mEq Ensure adequate repletion of magnesium
	Abiraterone	Excessive mineralocorticoid activity		
Hypophosphatemia (serum phosphorus < 2.7 mg/dL)	Azacytidine Ifosfamide Streptozocin	Proximal tubular damage impairing reabsorption of phosphorus, Fanconi syndrome	Respiratory distress Weakness Paresthesia Neurologic dysfunction Seizures	PO/IV phosphorus supplementation (i.e., sodium phosphate or potassium phosphate) Mild hypophosphatemia (2.3–2.7 mg/dL): 0.08–0.16 mmol/kg Moderate hypophosphatemia (1.5–2.2 mg/dL): 0.16–0.32 mmol/kg Severe hypophosphatemia (<1.5 mg/dL): 0.32–0.64 mmol/kg
Hypocalcemia (corrected serum calcium[c] < 8.6 mg/dL)	Cetuximab Cisplatin	Potentially secondary to hypomagnesemia (causing impaired parathyroid function) or via renal losses	Tetany	PO/IV calcium supplementation (e.g., calcium carbonate for PO, calcium gluconate for IV) Mild to moderate/asymptomatic: calcium gluconate 1–2 g IV or PO supplementation Severe/symptomatic: Calcium chloride[d] 1 g IV or calcium gluconate 3 g IV Ensure adequate repletion of magnesium

[a]Treatment recommendations are for patients with normal renal function; for patients with impaired renal function, administer 50 % or less of the recommended dose
[b]PO magnesium may cause diarrhea, especially in larger doses
[c]Corrected serum calcium = serum calcium + (0.8 × [4 − serum albumin])
[d]Requires administration via central IV access because extravasation may cause tissue necrosis

Table 13 Types of hypersensitivity reactions [92–94]

	Type I	Type II	Type III	Type IV
Mediated	IgE	IgG or IgM Destruction of cells	Antigen-antibody complexes	T cell ($CD4^+$ or $CD8^+$)
Timing	Seconds to minutes Can be delayed (1–72 h)	Days	Hours to days	Delayed (2–3 days)
Reactions	Anaphylaxis Laryngeal edema Bronchospasms Cutaneous reactions Nausea Vomiting	Hemolytic anemia Thrombocytopenia	Inflammation Serum sickness Vasculitis	Dermatologic
Causes	Hay fever Food IV contrast dye Latex Vaccines Insect bites/stings Medications *Chemotherapy agents* L-Asparaginase Paclitaxel Docetaxel Teniposide Procarbazine Cytarabine	Transfusion reactions Methylene blue Heparin	Beta-lactams Quinidine Minocycline	Organ transplant rejection Poison ivy

Pathophysiology

The exact mechanism by which hypersensitivity reactions occur is often unclear and may vary among agents [92]. Most reactions to chemotherapy agents are consistent with type I hypersensitivity based on the Gell and Coombs immunopathologic mechanism; see Table 13 [92, 93].

Clinical Features

Anaphylaxis is an allergic reaction characterized by multisystem involvement and is considered a type I mediated reaction that is seen with certain chemotherapy agents listed below. The initial symptoms of anaphylaxis are often nonspecific and include tachycardia, faintness, cutaneous flushing, urticaria, diffuse or localized pruritus, and a sensation of impending doom. These symptoms are usually within minutes of administering the offending agent, but reactions may develop later. Biphasic or late-phase reactions that occur 1–72 h after the initial attack have been reported [95].

Chemotherapy Agents Implicated

Hypersensitivity reactions are frequently associated with certain chemotherapeutic classes/agents such as taxanes, platinum-containing compounds, epipodophyllotoxins, asparaginase, procarbazine, monoclonal antibodies, and, occasionally, doxorubicin and 6-mercaptopurine [94, 96]. Immediate, acute reactions from monoclonal antibodies have been reported in 5–10 % for rituximab, 2–3 % for infliximab, and 0.6–5 % for trastuzumab and reported with omalizumab, natalizumab, basiliximab, abciximab, and cetuximab [96]. Hypersensitivity symptoms to taxanes usually develop in the first few minutes of the infusion and mostly occur on the first or second exposure. Platinum-containing compound reactions usually occur at the time of cancer reoccurrence or after the patient has been exposed for at least six cycles [96].

Treatment

Early and rapid assessment is crucial and every minute counts. If a patient is unresponsive and pulseless, cardiopulmonary resuscitation should begin and the appropriate Advanced Cardiovascular Life Support (ACLS) algorithm should be used. Advanced airway management with oxygen should be established and maintained without any delay. Circulation should be supported initially with a rapid fluid challenge of 500–2000 mL of 0.9 % sodium chloride [97, 98].

Epinephrine treatment is also used to help maintain circulation in patients experiencing anaphylaxis. In a Cochrane systematic review, no randomized controlled trials using epinephrine were identified. The widespread use of epinephrine

in anaphylaxis is based off of other types of studies and expert opinion and recommended in all anaphylaxis guidelines published to date [98–100]. Other types of studies include fatality studies with strong evidence; most people who died from anaphylaxis did not receive an epinephrine injection before cardiac arrest [99].

The adult dose of epinephrine has been published with weight-based dosing at 0.01 mg/kg, to a maximum dose of 0.5 mg and fixed doses ranging from 0.2 to 0.5 mg. The route of each dose is either intramuscularly (IM) or subcutaneously (SC) and repeated every 3–5 min as needed for unresolved anaphylaxis symptoms [99]. Epinephrine IM injections into the lateral aspect of the thigh have been reported to provide more rapid absorption and higher plasma epinephrine levels than IM or SC administration in the arm. There are no studies comparing IM and SC being administered in the thigh [98]. Epinephrine SC injection may need to be considered in patients post-chemotherapy or radiation treatment without a known platelet count status to prevent a hematoma from an IM injection. When anaphylaxis is not responding to repeated epinephrine IM or SC doses, intravenous epinephrine should be considered [98].

Adjunctive therapy has been seen with H_1-antihistamines, H_2-antihistamines, and glucocorticoids. None of these modalities of therapy have any evidence to support their use and have been pushed to second-line therapy in most guidelines. The first-generation, H_1-antihistamine diphenhydramine has been used because of its availability in IV formulation and its ability to relieve urticaria and itching within minutes after oral or IV administration. Due to its ability to cross the blood–brain barrier readily, diphenhydramine causes drowsiness and impaired cognitive function. Concerns with its potential harmful effects have minimized its use during anaphylaxis. Diphenhydramine given orally, IM, or slow IV in a dose of 25–50 mg has been suggested [98].

There are no studies supporting administration of H_2-antihistamines or recommending one over another. However, this class of drugs has a low potential to harm and may be helpful in the management of anaphylaxis. Giving it with a H_1-antihistamine may decrease urticaria, flushing, headache, hypotension, and rhinorrhea [99].

There is no definitive conclusion supporting the use of glucocorticoids in this group of patients. The onset of the glucocorticoid action can take anywhere from 4 to 6 h to take effect. They are traditionally given to help reduce the symptoms and to prevent the biphasic anaphylactic reaction that may occur [95, 99, 100]. They are not the drug of choice for the initial phase of anaphylaxis, and if given, it should only be after initial resuscitation. Do not delay the administration of IV fluid or epinephrine. If given, intravenous methylprednisolone has been recommended in an old published guideline using 1–2 mg/kg/day divided in four daily doses. Oral prednisone is recommended for milder attacks at 0.5 mg/kg/day [101]. In another guideline published in 2008, IM/IV hydrocortisone was recommended at an adult dose of 200 mg. Of note, all glucocorticoid dosing for anaphylaxis is extrapolated from acute asthma treatment dosing [99, 102]. Figure 1 is an algorithm that goes through the steps for treating patients with signs and symptoms of anaphylaxis.

Early recognition and treatment of anaphylaxis saves lives. There is little to no supporting evidence for the treatment of anaphylaxis, but epinephrine has shown to be a benefit, and death has been seen without its use.

Extravasation

Extravasation is a well-recognized complication of intravenous chemotherapy [103]. The incidence of accidental extravasation of intravenous drugs into the tissue can be anywhere from 0.1 to 6.5 % [103, 104].

Clinical Features

Extravasation is the unintentional instillation, leakage, passage, or escape of fluid or drug out of a blood vessel into surrounding tissue. This may result in varying degrees of impairment including pain, necrosis, and tissue sloughing. The degree of tissue damage is related to the properties of the drug that is extravasated, the duration of the tissue expose, and the amount of drug that was infiltrated. Chemotherapy drugs can be classified into three categories according to their potential cause of tissue damage: vesicant, irritant, and non-vesicant. A vesicant is any agent that has potential to cause tissue destruction, blistering, severe injury, or tissue necrosis when extravasated. An irritant is any agent that can cause inflammation or irritation characterized by aching, tightness, and phlebitis but without necrosis. Non-vesicants are drugs that rarely produce acute reactions or destroy the tissue when they infiltrate.

Chemotherapy Agents Implicated

Chemotherapy agents are often classified into the above three categories (Table 14). Every attempt should be made to minimize the risk of chemotherapy agents from extravasation. This attempt is viewed as a collaborative practice between the physicians, nurses, pharmacists, patient, and patient's caregivers. All healthcare professionals should adhere to policies and procedures at their institution to prevent extravasation. Unfortunately, not all chemotherapy extravasations are preventable. Healthcare professionals, patients, and caregivers should know the patient's associated and other risk factors for extravasation; see Table 15. All

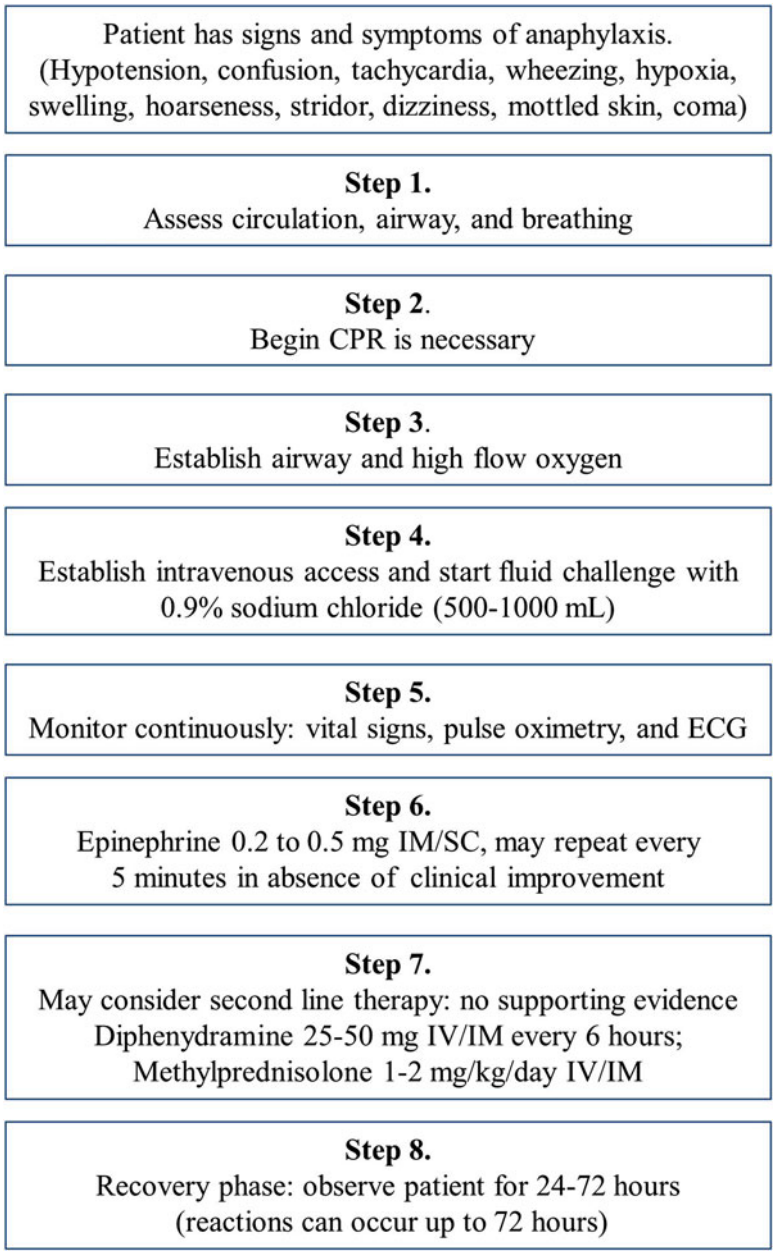

Fig. 1 Anaphylaxis treatment algorithm for adults [95, 97, 98, 100]

parties involved also need to be cognizant of the signs and symptoms of chemotherapy extravasation, see Table 16.

Chemotherapy extravasation reactions may not manifest until several hours, days, or even months after the infusion has been stopped or completed [109].

Treatment: Pharmacologic and Non-pharmacologic

Extravasation of chemotherapy is considered a true medical emergency. Regardless of the chemotherapy agent, early treatment is the key to minimizing tissue damage. If treatment is left to the EC, it may be too late. Figure 2 walks through all the treatment steps that should be completed if a patient presents with signs and symptoms of chemotherapy extravasation. As part of the institution's policies and procedures in providing early intervention for chemotherapy agent extravasations, an extravasation kit should be available in or near the infusion center of chemotherapy agents. Extravasation kits should contain a pen, disposable syringes, small-gauged needles, cold-hot packs, gauze pads, adhesive plaster, sterile and protective gloves, and medications (e.g., dexrazoxane, dimethyl sulfoxide (DMSO) 50–99 %, hyaluronidase). By the time a patient is seen in the EC, steps one through four if not all in Fig. 2 should be completed. If the

Table 14 Classification of chemotherapy agents according to their vascular damage potential [103–106]

Vesicants	Irritants	Non-vesicants
Cisplatin[a] (if >20 mL of 0.5 mg/mL)	Arsenic trioxide[b]	Arsenic trioxide[b]
Docetaxel[a]	Bleomycin[b]	Asparaginase
Dactinomycin	Bortezomib[b]	Bleomycin[b]
Daunorubicin	Busulfan	Bortezomib[b]
Doxorubicin	Carmustine	Cladribine[b]
Epirubicin	Carboplatin	Cyclophosphamide
Idarubicin	Cladribine[b]	Cytarabine
Mechlorethamine	Cisplatin[a] (if concentration less than 0.5 mg/mL)	Fludarabine
Mitomycin C	Dacarbazine	Gemcitabine[b]
Mitoxantrone	Docetaxel[a]	Ifosfamide[b]
Oxaliplatin[a]	Etoposide	Interferons
Paclitaxel[a]	Fluorouracil	Interleukin-2
Vinblastine	Gemcitabine[b]	Melphalan[b]
Vincristine	Ifosfamide[b]	Methotrexate
Vindesine	Irinotecan	Monoclonal antibodies
Vinorelbine	Ixabepilone	Pemetrexed
	Liposomal cytarabine	Pentostatin
	Liposomal daunorubicin	Raltitrexed
	Liposomal doxorubicin	Temsirolimus
	Liposomal vincristine	Thiotepa[b]
	Melphalan[b]	
	Mitoxantrone[a]	
	Oxaliplatin[a]	
	Paclitaxel[a]	
	Paclitaxel, nanoparticle albumin bound	
	Plicamycin	
	Streptozocin[a]	
	Teniposide	
	Thiotepa[b]	
	Topotecan	

[a]Has been described as both an irritant and vesicant in the literature
[b]Has been described as both irritant and non-vesicant in the literature

steps have not been completed prior to the EC, it is crucial that treatment starts right away.

Various non-pharmacological and pharmacological treatments have been utilized in the past to help minimize the damage of chemotherapy agent extravasations. The studies that are available vary in the degree of success in treating extravasations. It should be noted that only a handful of treatment options or "antidotes" exist that can be injected or topically applied to the affected area(s).

Vesicant chemotherapy agents can be divided into two categories: DNA binding versus non-DNA binding, see Table 17. This is important to keep in mind when deciding on treatment options for chemotherapy agent extravasations. Vesicants that bind to nucleic acids in DNA such as anthracyclines bind to the DNA in the cells of healthy tissue and promote cell death. DNA-chemotherapy complexes are released from the dead cells in the tissue and taken up by adjacent healthy cells by endocytosis. This process is a continued cycle for a long period of time and has been seen weeks to months after the incident [103]. Unfortunately, if left untreated, the cell damage spreads larger and deeper which becomes more painful with time. Localizing the offending agent can be done by cooling the area with ice or cold gel packs. This procedure may help with the pain by constricting vessels and potentially preventing the offending agent from spreading to healthy tissue. There is insufficient published evidence that supports the efficacy of this treatment, but it may be beneficial in reducing discomfort caused by any burning sensations and tenderness [107]. The next step is to neutralize the offending agent, and this will depend on the chemotherapy agent that was extravasated; see Table 18 for dosing.

Vesicants that do not bind to DNA such as vinca alkaloids have an indirect effect on healthy tissue. Non-DNA-binding chemotherapy agents are metabolized in the tissue and are

Table 15 Patient risk factors for extravasation [105, 107, 108]

Patient associated	Others
Small and fragile veins	Insufficient training of staff, poor technique
Vascular disease, Raynaud's disease; peripheral neuropathies; peripheral vascular disease such as diabetes	Butterfly, metal, or large-gauged needles
Impaired lymph flow and venous circulation	Inadequate secured needle
Superior vena cava syndrome	Veins used adjacent to tendons, nerves, or arteries
Locally infiltrating tumors	Needle location (e.g., antecubital fossa, wrist or dorsum of hand)
Age—elderly and young at the highest risk	Inappropriate needle length
Restlessness or confusion	Catheter failure
Cerebral vascular accident	Multiple attempts at cannulation
Coagulation abnormalities	Irritant and vesicant drugs
Obesity	Prolonged infusions
	Multiple treatments of chemotherapy agents
	Previous vinca alkaloids administration
	Radiation therapy – current or past

Table 16 Signs and symptoms of extravasation [105]

Blister or vesicle formation	Stinging
Induration	Pain
Erythema	Alteration of the rate of flow or increased resistance that can't be explained
Venous discoloration	No blood return
Swelling at the site of infusion	Leakage of fluid from around injection site
Burning	

more easily neutralized [103]. The injury caused by these agents is usually more localized, mildly to moderately painful, and improve over time [115]. Local warming is preferred with this group of agents to increase blood flow to the area, which helps distribute the chemotherapy agent and promotes its absorption [104]. However, controversies have arisen with this technique [106]. Pharmacological treatment used for these agents helps dilute the offending chemotherapy agent; see Table 18 for dosing.

DNA-Binding Agents

Dexrazoxane has been used for many years to help minimize anthracycline cardiotoxicity. More recently, it has been used for anthracycline extravasations. The mechanism behind its use includes its ability to inhibit DNA topoisomerase II—the target of anthracyclines—and its ability to act as an iron binder, minimizing oxidative damage in the tissue that can be caused by these agents. Two pivotal multicenter studies and several case reports have shown dexrazoxane to be well tolerated and highly effective in preventing surgical resection after anthracycline extravasation [110, 111]. Mouridsen et al. reported that dexrazoxane prevented 53 out of 54 patients' extravasations (confirmed by fluorescence-positive tissue biopsy) from having to undergo surgery debridement. Seventy-one percent of the patients were able to continue with their scheduled treatment plan. Overall, treatment was well tolerated with bone marrow suppression (underlying disease and chemotherapy), mild transient elevation of liver

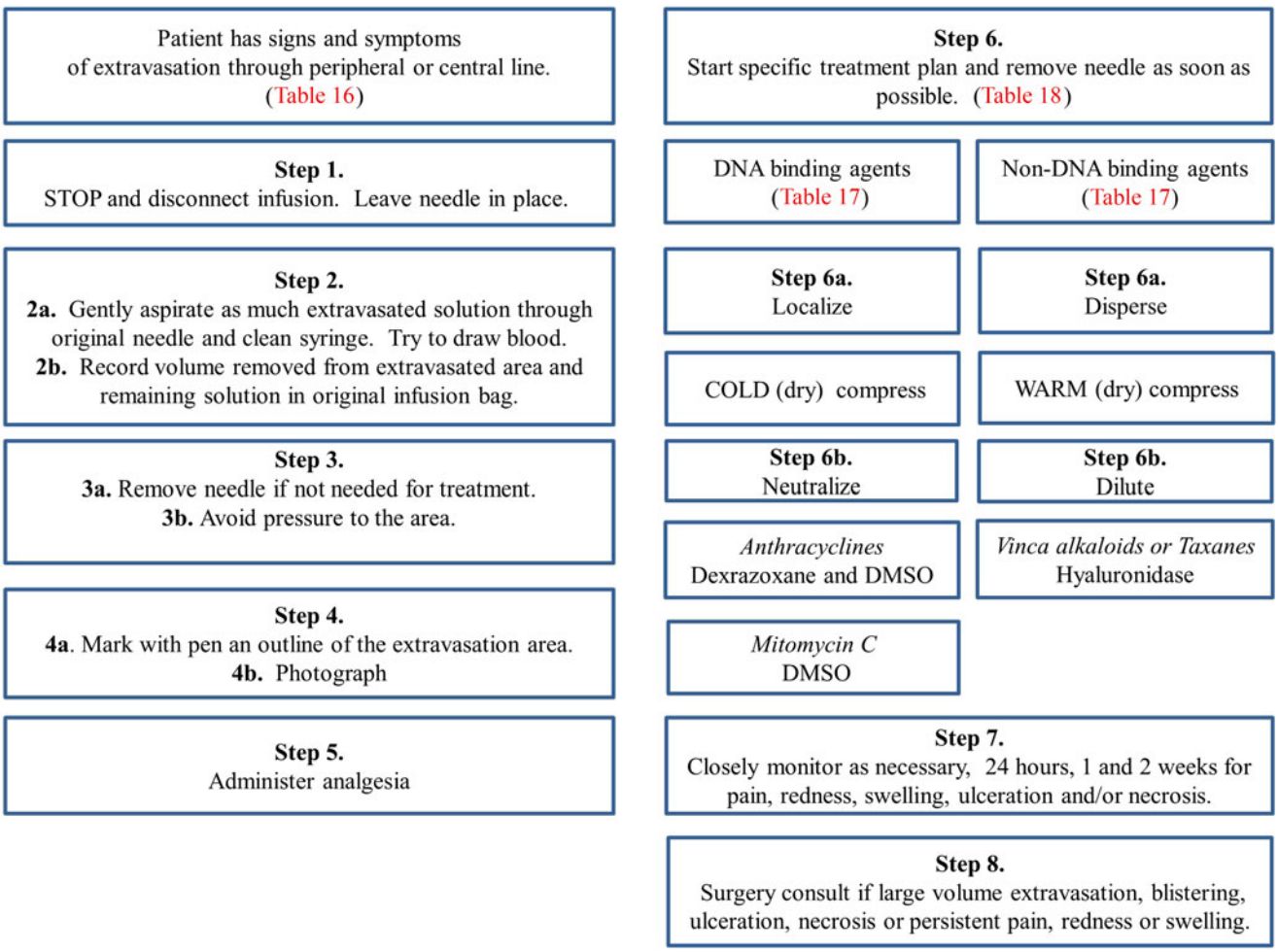

Fig. 2 Extravasation treatment steps for vesicants [103, 105]

Table 17 Classification of vesicant chemotherapy agents [103]

Classification	Examples
DNA binding	
Alkylating agents	Mechlorethamine
Anthracycline antibiotics	Daunorubicin, doxorubicin, epirubicin, idarubicin
Other	Mitoxantrone
Non-DNA binding	
Vinca alkaloids	Vinblastine, vincristine, vindesine, vinorelbine
Taxanes	Docetaxel, paclitaxel

Table 18 Treatment after extravasation [105, 110–114]

Drug	Non-pharmacologic treatment	Pharmacologic treatment
Anthracyclines	Dry cold compress (3-day course)	Dexrazoxane (3-day course)
Daunorubicin Doxorubicin Epirubicin Idarubicin	Immediately for 20 min and 4 times daily—do not apply 15 min prior to or during dexrazoxane infusion	Within 6 h: 1000 mg/m^2 (max 2000 mg) IV Day 2: 1000 mg/m^2 (max 2000 mg) IV Day 3: 500 mg/m^2 (max 1000 mg) IV Doses are 24 h apart and infused over 1–2 h in opposite arm If CrCl is less than 40 mL/min – decrease dose by 50 % or Topical DMSO 50–99 %
		Immediately apply topically 1–2 mL with cotton swab over area twice the size of that affected and allow to air dry every 6–8 h for 7–14 days; do not apply if using dexrazoxane
Cisplatin	Dry cold compress	Sodium thiosulfate 1/6 M
		1/6 M = 4 mL 10 % sodium thiosulfate + 6 mL water
		Inject 2 mL for each 100 mg of extravasated cisplatin through existing needle; if needle has been removed, inject 1 mL SC [0.1 mL doses clockwise around extravasation using small-gauge (25 or less) needle]; may repeat SC dose several times over the next 3–4 h
Mechlorethamine	None	Sodium thiosulfate 1/6 M
		1/6 M = 4 mL 10 % sodium thiosulfate + 6 mL water
		Inject 2 mL for each 1 mL of extravasated mechlorethamine into existing needle; if needle has been removed, inject 1 mL SC [0.1 mL doses clockwise around extravasation using small-gauge (25 or less) needle] may repeat SC dose several times over the next 3–4 h
Mitomycin C Mitoxantrone	Dry cold compress (3-day course)	Topical DMSO 50–99 %
	Immediately for 20 min and 4 times daily	Immediately apply topically 1–2 mL with cotton swab over area twice the size of that affected and allow to air dry every 6–8 h for 7–14 days
Taxanes	Dry warm[a] compress (3-day course)	Hyaluronidase
Docetaxel Paclitaxel	Immediately for 20 min and 4 times daily	Inject 1–6 mL of 150 units/mL solution through the existing needle; if needle has been removed, inject 1 mL of solution per 1 mL of extravasated chemotherapy agent SC in a clockwise manner into multiple sites of the extravasation area using small-gauge (25 or less) needle; may repeat SC dose several times over the next 3–4 h
Vinca alkaloids		
Vincristine Vinblastine Vindesine Vinorelbine		

CrCl creatinine clearance, *DMSO* dimethyl sulfoxide, *IV* intravenous, *mg* milligrams, *SC* subcutaneous

[a]Some literature suggests using cold compresses with taxanes

enzymes occurring in approximately 25 % of patients, nausea in 20 %, and some reported local infusion site pain [110]. Controversies still surround this agent due to multiple reasons—it is the only drug licensed for the treatment of anthracycline extravasation—there is a lack of comparison trials to other agents, high cost of a single treatment, and position statements of societies and other organizations not supporting the use of dexrazoxane [110].

Dimethyl sulfoxide (DMSO) is a topically applied solvent that increases skin permeability, promotes absorption of extravasated vesicants, and scavenges free radicals. DMSO has been studied in various amounts and concentrations

(50–100 %), various application frequencies (every 2–8 h), various durations of treatment (2–14 days), and for several different types of chemotherapy extravasations [108]. In a prospective study, 20 patients were treated topically with DMSO 99 % after removal of the anthracyclines and the needle. It was applied immediately in most cases with a median of 25 min after recognition and reapplied every 6 h for 14 days. One patient received it 7 days after extravasation. No ulcerations were noted and surgical debridement was not needed. Some patients reported mild pigmented area, mild discomfort at the injection site, and a characteristic garlic breath odor [112]. Local DMSO in combination with dexrazoxane should be avoided. DMSO combination did not protect against injury and may lessen the effects of dexrazoxane [106]. Toxicity of mitomycin C can also be prevented with DMSO topically [113, 116]. The use of DMSO in the USA is limited by its availability; medical-grade DMSO at concentrations greater than 50 % is difficult to find [108].

Sodium thiosulfate 1/6 M (0.17 M) solution is the only antidote currently available and recommended for extravasation of mechlorethamine or concentrated cisplatin (>20 mL of greater than 0.5 mg/mL); see Table 18 for dosing [106].

Non-DNA-Binding Agents

Evidence from animal and human studies supports the efficacy of hyaluronidase for vinca alkaloids or taxane extravasation [106, 114, 117]. Hyaluronidase is a protein enzyme that helps degrade hyaluronic acid that holds tissue planes together, rapidly dilutes, and enhances drug absorption. Bertelli et al. used hyaluronidase after extravasation of vinca alkaloids in seven patients. They administered 250 units of hyaluronidase directly into the indwelling catheter still in place or six subcutaneous injections with a 25-G needle around the extravasation area. They avoided steroids, cold packs, pressure, and dressing. None of the patients suffered from skin necrosis [114].

Surgical Intervention

The optimal timing of surgical intervention is unknown. Only one third of vesicant extravasation in the extremities actually results in ulceration. Therefore, routine surgical intervention should not be the initial treatment [118]. A plastic surgical consultation is recommended if the patient experiences a large volume vesicant extravasations (not defined); severe pain, if healing has not occurred 1–3 weeks after extravasation; or if there is early necrosis present [106].

Saline flushing or washout/flush-out techniques have been described in the literature. There is some evidence that this may be beneficial. Several techniques have been used and in combination with other treatments [107]. The flush-out technique is usually performed by plastic surgeons, and the most recent technique published is making several small-stab incisions and administering large volumes of 0.9 % sodium chloride to flush out the extravasated drug [119].

Extravasation is a medical emergency. Preventative care or early intervention is the key to successful treatment.

Conclusion

Patients with malignancy have their own set of unique emergencies. The emergency can be derived from the malignancy itself, adverse reactions from their treatment regimens, or supportive care regimens. Having a multidisciplinary team that understands these unique emergencies can save lives. Therefore, it is crucial for all that are involved to be knowledgeable of oncologic emergencies and chemotherapy toxicities to promptly diagnosis and treat the cancer patient.

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Treatment Toxicity: Radiation

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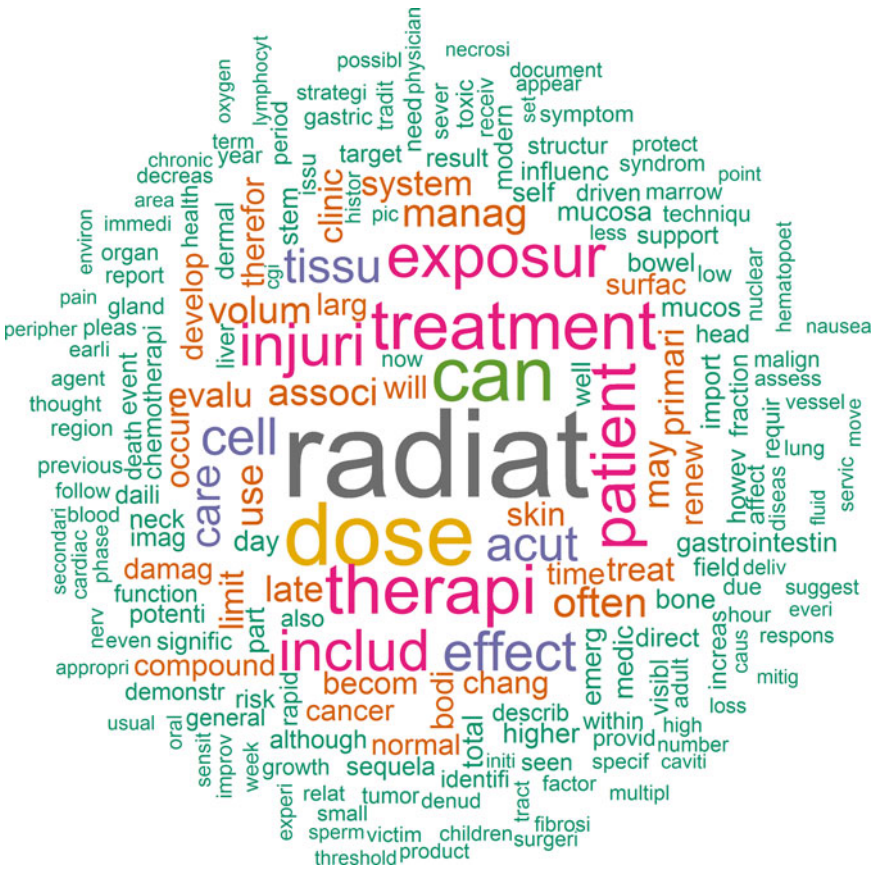

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Introduction

Exposure to radiation can include diagnosis and primary management of a malignancy or an unintended event as seen in nuclear accidents and acts of terrorism. More than 60 % of cancer patients will have radiation therapy as part of their primary treatment portfolio, and the visible accelerated risk of nuclear events increases our collective need for education of health-care providers in the evaluation of radiation exposure and injury [1–8]. Although effects on tissue may not be visible or clinically apparent during an evaluation for emergency service, exposure is an important aspect to the medical history of the patient as it leaves an invisible clinical footprint which may be relevant to medical situations at a later time point, even decades after exposure. Intentional exposure is usually well documented with dose/volume precision in the radiation oncology treatment record. However at the time of an unanticipated emergency department visit, hospital record documentation is often limited to a few words describing treatment total dose and volume in a brief qualitative manner as the shadow radiation therapy record is often not directly linked to the hospital informatics systems. Therefore, information valuable to the emergency health-care team may be cursory, incomplete, or even inaccurate if obtained from a service unfamiliar with radiation treatment and exposure to normal tissue.

Unintentional exposure is more challenging to document and often limited to mathematical models of duration and distance from the primary incident as victims are often unmonitored. While the models may be helpful, they often can be less accurate, especially in computation of the integral or total body dose [1, 6, 8]. Fluoroscopy during interventional radiology/cardiology procedures can lead to a surprisingly high-radiation dose to underlying structures, that is often not or poorly documented, again a relatively hidden risk in patient care [2–4].

With an increasing number of cancer survivors including transition of survivors from pediatrics to adult physicians, there is a developing knowledge gap both at the primary care and emergency medicine levels concerning both acute and late effects of radiation exposure and how these interrelate with patient health care in the acute care setting moving forward. It will be incumbent on the radiation oncology community and radiation exposure experts to improve documentation and communication to health-care staff in order to better prepare both patients and physicians for identifying contributing factors and strategies of short- and long-term normal tissue-driven processes that affect patients after radiation treatment and exposure.

Acute Radiation Toxicity: Unintended Exposure

Normal tissue toxicity from radiation exposure can be divided into acute (up to 90 days from exposure), subacute (from 90 days to 2 years from exposure), and chronic or late (>2 years from exposure) phases of injury. Although acute intentional injuries are traditionally managed by the responsible treating physicians during primary management of a malignancy, accelerated normal tissue damage that affects hydration balance and nutrition can often require evaluation by emergency services for triage and disposition. Unintentional exposure uniformly requires evaluation by emergency services with appropriate support from experts trained in managing acute radiation effects and radiation safety officers trained in assessing the nature of the exposure and possible radiation dose received by the victims. This would also include the evaluation of risk to personnel caring for the victim. The acute phase of injury can affect many cell systems including toxicity to tissues of both limited and rapid self-renewal potential. These include, but are not limited to, the central nervous system, bone marrow, skin, and mucosal surfaces lining the head/neck and gastrointestinal (GI) system.

Knowledge of the effects of radiation damage to the body has been acquired through animal models as well as events in history documenting human exposure. These events include atomic bomb survivors and people affected through unintended nuclear fallout and nuclear accidents. Symptoms associated with unintended radiation exposure vary with the severity of the exposure. At very high single-fraction total body doses (>10 Gy), death will occur through cerebrovascular syndrome in spite of support within 24–48 h. The syndrome is due to uncontrollable swelling within the central nervous system associated with compromise of all neuromuscular processes. At total body doses of 5–12 Gy, death without support will occur in 1–2 weeks due to denudation and destruction of the gastrointestinal system associated with profound fluid loss and diarrhea. These cells have a self-renewal capacity measured within a few days; thus, a single total body dose of 10 Gy will eliminate a large portion of the stem cells within the gastrointestinal crypts. Although this dose does not affect differentiated adult cells, the exposure eliminates self-renewal potential of the stem cell; therefore, the mucosal surface of the GI tract becomes denuded with no barrier for fluid and blood loss within a short period of time, measured in days. At total body exposure doses of 2–5 Gy, death will occur from damage to the hematopoietic system with primary damage to progenitor cells inhibiting

self-renewal. Lymphocytes may die an intermitotic death, and this finding may be a surrogate biomarker for acute exposure within the first few hours to days of an incident [1, 5–8]. However, by day 30, most circulating blood elements are depleted with death often attributed to infection. The term, LD 50/30, is borrowed from our pharmacology colleagues and reflects the lethal dose (LD) of an agent that will cause 50 % mortality in 30 days. Although radiation is not a drug, the LD 50/30 is now generally thought to be 5 Gy with modern hospital support [1].

At the time of exposure, victims will develop symptoms consistent with a radiation syndrome that can be visible as early as 15 min from the time of exposure [1, 6, 8]. The reaction may last several days until symptoms merge with other events associated with the exposure. Symptoms are generally gastrointestinal and neuromuscular. At lower doses, victims experience anorexia, nausea, and vomiting associated with lassitude. The degree of symptoms is commensurate with dose. At higher doses, patients can experience severe diarrhea, fever, and hypotension suggesting more immediate toxicity including more pronounced neural damage. Usually at low doses, the prodromal phase is followed by a latent period where the victim may appear and feel well for a period of days to weeks. At that point gastrointestinal and hematopoietic damage becomes more evident and requires intervention [1, 5, 6, 8].

If the total body exposure is less than 4–5 Gy, the majority of experts recommend no immediate intervention other than symptomatic treatment as needed. This would include hydration and antiemetic therapy for nausea/vomiting. Antibiotics can be given for infection as needed. If the exposure is greater than 5 Gy, then death associated with the hematopoietic syndrome becomes a real concern. Intervention with isolation and barrier nursing with appropriate blood product support may improve survival. Experience from Chernobyl suggests that efforts to limit infection, bleeding, and physical trauma during the time of blood count nadir may improve the LD 50/30 to and possibly beyond 7 Gy. To the best of our current knowledge, no human being has survived a single total body exposure beyond 10 Gy. The use of bone marrow transplant in this setting remains controversial with strong advocates on both sides of the question [7].

Injuries to the gastrointestinal system and hematopoietic systems may be accompanied by dermal injury. Often in particle exposure including low-energy photons, there is significant asymmetry in dose as often the event is triggered by an accident involving the hands. Dermal injuries can be primitive biomarkers for dose with epilation/erythema at doses of 3–6 Gy and wet desquamation, bullae, ulceration, and necrosis seen at higher doses [1, 9]. These injuries can be life threatening due on part to concomitant infection and should be managed with the same support offered to burn victims.

In the triage of victims with unintended exposure, it is most important to develop as accurate an assessment of dose as possible. Health-care workers will likely be monitored; however, the general public will not, and therefore experts trained in radiation exposure and dose assessment are crucial in the early phase of the evaluation. There are several basic tools to use as part of the initial evaluation. The time to emesis decreases with increasing radiation dose. The rapid onset of nausea and vomiting in the evaluation suggests a higher exposure. A decline in lymphocyte count can be associated with an exposure dose of best relative estimate occurring within 48 h of exposure. This is often hampered because the preexposure lymphocyte count is unknown. If a laboratory for cytogenetic evaluation is available, another surrogate evaluation is to assess the number of chromosomal aberrations in peripheral lymphocytes when they are stimulated to divide. This technique has more value at lower doses as lymphocytes die quickly at high doses [1, 7, 8].

There have been numerous nuclear accidents over the past 50 years with people exposed to total body or partial body radiation. These include nuclear events as well as unintentional exposure to victims unaware of the immediate risk [6, 8]. The Medical Sciences Division of the Oak Ridge Institute for Science and Education operates a Radiation Emergency Assistance Center for the US Department of Energy. The center is a 24-h consultation service with medical and health physics support for issues associated with radiation events and exposure. Resources include expertise for radiation dose assessment, computation of dose from radionucleotides, and laboratory facilities for dose assessment. The 24-h emergency telephone number is 865.576.3131, and the website is http://www.orau.gov/reacts.

Since the development of nuclear weapons, there has been a keen scientific interest in identifying chemical compounds that can protect normal tissues from the effects of radiation exposure. Radiation protectors are elements that are given prior to exposure or in some cases, shortly thereafter, to limit the effect of exposure on normal tissue. Radiation mitigators are compounds that have the potential of influencing the effect and impact of the exposure. Therapeutic compounds are applied once the injury has occurred. There have been more than 4000 compounds synthesized to address this point. Sulfhydryl compounds (SHs) have been shown to be effective radioprotectors with the simplest compound being cysteine, which contains a natural amino acid. It was shown in 1949 that this compound could protect animals from lethal doses of total body radiation if injected or injected in large amounts (equivalent of 150 mg/kg) [10, 11]. The toxicity of sulfhydryl compounds can be limited by the addition of a phosphate group [10]. Once the compound becomes intracellular, the compound loses the phosphate group, and the compound is thought to serve as a free radical scavenger limiting

intracellular damage. The only compound approved by the US Food and Drug Administration (FDA) is amifostine (WR-2721). It is sold as Ethyol and has been used to prevent xerostomia in patients undergoing radiation therapy for head/neck carcinoma [12]. Amifostine has been used in several clinical trials evaluating effectiveness in protecting multiple mucosal surfaces as well as a protectant for pulmonary injury in patients undergoing total body radiation therapy as part of bone marrow transplant [12]. In a Radiation Therapy Oncology Group (RTOG) clinical trial, amifostine was associated with an improvement in patient assessment of mouth dryness and swallowing [12, 13]. In this trial, there was no difference in tumor control between patients receiving amifostine or placebo. Citrin and colleagues [10] have identified nitroxides as agents for radioprotection in clinical development. Stable nitroxide free radicals and their specific electron reduction products, hydroxylamines, protect cells when exposed to oxidative stress; therefore, compounds such as these are under evaluation. Other antioxidants, including alpha tocopherol and beta-carotene, have not yet been shown to be of clinical benefit [14, 15]. The issue of simultaneous tumor protection has been a concern of the clinical use of radioprotectors. This is the reason these compounds have not been easily integrated into clinical management. Investigators have explored the use of intracellular superoxide dismutase (SOD) using gene therapy vectors to enhance the intracellular component of SOD to limit damage caused by superoxide radicals [16, 17].

Mitigators are compounds that can limit damage associated with radiation exposure once an event has occurred but prior to the clinical manifestation of both acute and late toxicity of radiation exposure and treatment. These compounds are generally thought to influence the metabolic cascade of events that occur after exposure and in turn limit damage associated with radiation. To date, most of the compounds are cytokines and growth factors directed to stimulate stem cell proliferation and balance the inhibition of stem cell growth induced by radiation to the hematopoietic and gastrointestinal system. These include granulocyte colony-stimulating factor (G-CSF) and keratinocyte growth factor (KGF) [18]. These factors contribute to many aspects of cell recovery. KGF has positive influence in the recovery of mucosal surfaces during the acute phase of toxicity as well as limit the late effects of radiotherapy, including xerostomia [10]. Mitigators of late toxicity are largely directed to limit fibrosis, which is thought to be a primary factor in late pulmonary injury and other tissues of more limited self-renewal potential [10, 14–17, 19–23]. The primary target for this strategy is thought to be transforming growth factor beta (TGF B), which appears to play an important role in the development of fibrosis associated with radiation [24–26]. Accordingly, many compounds in development to prevent late effects either directly or indirectly target the TGF B signaling pathway including receptor inhibition [24–26]. Tumor protection is also a concern in the evaluation of treatments associated with this parallel pathway.

Investigators at the University of Massachusetts Medical School have evaluated the use of interleukin-1 alpha (IL-1α) as a mitigator to dermal damage associated with radiation exposure. Interleukin-1 (IL-1) inhibits neutrophil infiltration into the initial inflammatory response to radiation damage. Dermal injury was induced with electron particle therapy. Knockout mice deficient in IL-1α or the IL-1 receptor demonstrated both decreased dermal injury and more rapid healing suggesting the importance of this cytokine in the generation of radiation-associated skin damage. Neutrophil inhibition generated subsequent to radiation-induced tissue injury influences the pathogenesis of radiodermatitis. In a separate group of experiments, investigators from the same institution demonstrated that hyperspectral optical imaging (HSI) can demonstrate both acute and late oxygenation and perfusion changes in dermal tissue with changes occurring as early as 12 h after radiation exposure using a strontium 90 applicator [27, 28]. Imaging changes in oxygenation and perfusion predated clinical visible skin change by 14 days [28]. Unpublished data sets from this group as part of a human IRB clinical trial in breast cancer patients undergoing radiation therapy have shown that changes in imaging correlate very well with radiation dose and dose asymmetry in the treated volume.

In summary, with the increased risk of nuclear radioterrorism and increased radiation exposure identified during air and space travel, there is a renewed sense of urgency to better define and refine our response to a nuclear event. It is important to acknowledge that dose and particle contamination become essential points during the initial triage of the patient. The best supportive care has the potential of improving patient survival which may include hydration and blood product support with barrier nursing added as needed. There is renewed interest in developing a targeted pharmacologic response to both protect and mitigate issues surrounding radiation exposure.

Normal Tissue Effects of Radiation Therapy

Often oncology patients under active treatment are seen in evaluation by emergency physicians particularly during non-primary clinic times including evenings and weekends. In large academic centers, this practice is under change as outpatient weekend service is becoming more important to clinical oncology as more primary patient care management, including bone marrow transplantation, moves to the outpatient setting. Nevertheless, often emergency personnel are involved with patient care matters that are directly or indirectly associated with the management of the malignancy or

the sequelae of management including triage of acute care problems that may be related in part to previous therapy delivered years and decades in the past. In the following sections, we will address sequelae of management and how this influences patient care for modern emergency medicine.

Management of Acute Effects of Radiation Therapy

Sequelae to normal tissue are mostly attributed to cell death from radiation therapy. The balance between stem cell development and cell death is driven in a large part by tissue organization, stem cell proliferation, stem cell number, and cytokine response for growth stimulus. Acute effects from therapeutic radiation therapy are associated with cell systems that have rapid self-renewal potential including bone marrow progenitors and mucosal surfaces. These sequelae are driven by several factors including the concomitant use of cytotoxic chemotherapy and the volume of mucosal tissue in the radiation therapy treatment field. Acute effects generally occur during the course of radiation therapy and can affect multiple organ systems largely associated with mucosal surfaces including the skin, head/neck, gastrointestinal tract, and bone marrow. Acute effects are exacerbated by the use of chemotherapeutic and/or molecularly targeted small molecule agents delivered both before and during radiation therapy. Although not well validated through mechanism, patients can experience dramatic acute effects from low-dose radiation therapy to the skin and mucosa if they have received prior sensitizing medications including low-dose chemotherapy for autoimmune disease (methotrexate for rheumatoid arthritis) and selected antibiotics (tetracycline) [9]. The phenomenon, referred to as radiation recall, can even be seen in patients who received medications years in the past [9]. Although acute effects mostly impact tissues of rapid self-renewal potential, there can be selected circumstances where near-immediate changes occur that are often not anticipated by the primary providers of care. Patients treated in the head and neck region can experience swelling of the parotid glands with 24 h of exposure of 200 cGy. The adventitia of the parotid gland is tight with limited capacity for expansion from swelling; therefore, rare patients can experience severe pain and discomfort from low-dose therapy. There is often a need to urgently treat patients with significant tumor burdens, particularly in the mediastinum. Radiation to tumors of the mediastinum particularly sensitive to treatment (lymphoma, small cell lung cancer, or germ cell neoplasm) can trigger both nausea and metabolic crisis (hyperkalemia, hypercalcemia, etc.) from rapid tumor lysis [see Chapter]. Symptomatic treatment including fluids and medication to counter metabolic by-products is essential for a good outcome.

Acute effects to tissues of rapid self-renewal potential are influenced by total radiation dose, daily treatment dose (fractionation), and volume of tissue treated. This information is often not immediately available to emergency departments when patients present for evaluation as specific treatment documentation is often in the department shadow record and not directly integrated into electronic health-care records. The Affordable Care Act provides incentives to rectify this problem. The volume of the treatment target influences the number of stem cells directly affected from daily treatment. Daily treatment dose also influences injury to stem cells. Hence, total and daily doses as well as target volume are all directly related to the development of sequelae from the treatment. Specific acute injuries to organ systems are discussed in the following section.

Skin

The epidermis is the site of many acute reactions to radiation exposure. The dermal stem cells abut the basement membrane and are the active proliferating cell component covered by layers of keratinized cells, which are desquamated. The stem cells are the target for injury. The time for dermal cell division and migration is between 14 and 21 days depending on the area of the body under evaluation. Single doses of 5 Gy will generate early erythema followed by vasodilation, fluid exudation, cellular migration, and loss of proteins and other constituents of plasma products [9, 29, 30]. Investigators have shown that this process can be identified on hyperspectral imaging within 12 h of exposure with evidence that the evaluation on imaging can be dose specific in spite of the fact that clinical expression of change may not become apparent for 2–3 weeks [27, 28]. Fluoroscopy procedures use orthovoltage (low-energy) X-rays which deliver higher percentages of radiation dose to the skin surface [2, 3]. Complicated procedures in interventional radiology requiring significant fluoroscopy time can create acute dermal injury even in the modern era as acute injuries are influenced by fractionation (daily dose) and total dose (Fig. 1). With hypofractionation protocols using high daily dose with compressed treatment schedules including stereotactic therapy for the lung and liver, we are again witnessing injuries to the skin that were traditionally seen in a historical context [31]. The treatment for acute injury is driven in a large part by radiation dose and treatment volume. Modern accelerators deliver the majority of the radiation dose below the skin surface; therefore, with traditional fractionation, it is unusual to have patients to demonstrate significant dermal sequela with conservative measures, including various skin creams and ointments. Radiation beams resonate on skin surfaces within dermal folds; therefore, these intertriginous areas are more vulnerable to injury during treatment. Hypofractionation protocols may deliver a higher dose frac-

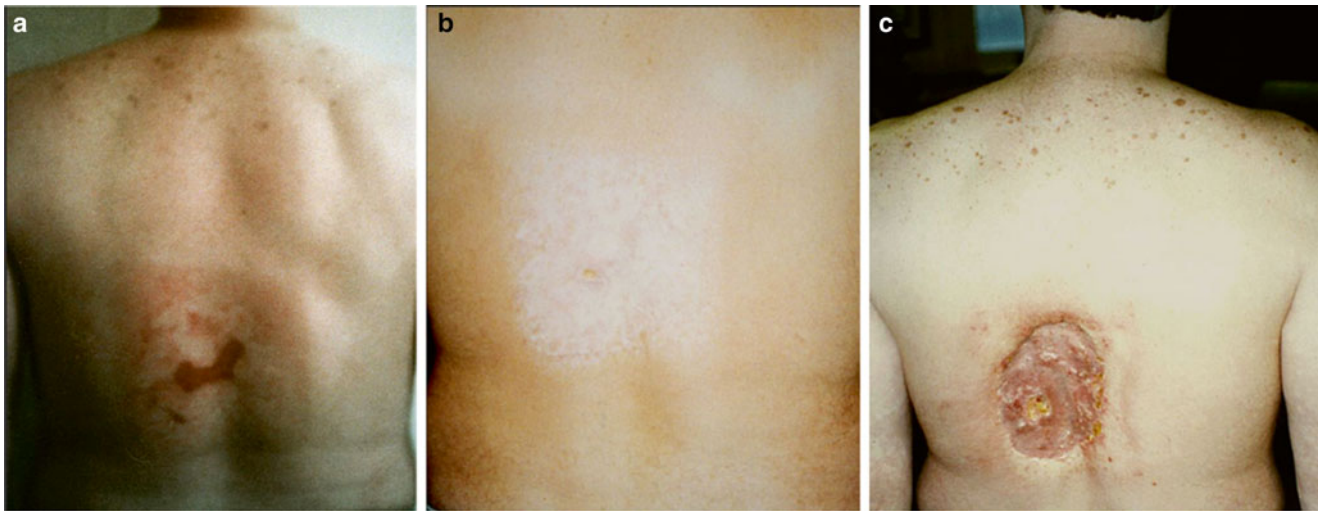

Fig. 1 Skin injury, attributed to radiation, of a 40-year-old male who underwent multiple coronary angiography and angioplasty procedures. (**a**) At 6–8 weeks after the procedures. (**b**) At approximately 16–21 weeks following the procedures with small ulcerated area present. (**c**) At approximately 18–21 months following the procedures, with evidence of tissue necrosis [4]. Reprinted with permission from fda.gov

tionation to dermal surfaces if treatment planning is not optimal. There are reported soft tissue injuries to the skin during stereotactic body radiosurgery when immobilization devices unintentionally functioned as bolus devices augmenting radiation dose to skin surfaces [31]. As information matures on molecularly targeted therapies, there is increasing evidence of skin toxicity to multiple new agents including EGFR inhibitors (rash 2–4 weeks into therapy), BRAF inhibitors (rash/photosensitivity), BCR-ABL inhibitors (keratosis pilaris/maculopapular rash), and m-TOR inhibitors (rash/pruritis) [10].

Hematopoietic System

The effects on the hematopoietic system are driven by the volume of the bone marrow and lymphoid system treated, previous chemotherapy and radiation treatment, and radiation dose. Total body exposure will result in a near-immediate decrease in circulating B and T lymphocytes, and a total body dose of 3.0–4.0 Gy likely inhibits the ability to respond to new antigen stimuli. Most patients treated for a malignancy with radiation therapy are treated to a partial body, and usually partial organ, volume that would have a limited effect on the immune response unless the patient is neutropenic from concurrent chemotherapy primary disease [32].

Gastrointestinal Tract

The mucosa of the gastrointestinal tract has similar organization to the tissues of the skin as stem cells reside at the basal layer and migrate to the surface at varied time points during their life cycle. In general, the cells that line segments of the gastrointestinal tract possess a shorter life span that their counterparts in the skin. The mucosa of the head and neck and large bowel self-renew every 2 weeks, the mucosa of the gastric region renews nearly every day, and the small intestine renews every 3 days. This explains, in part, why nausea from therapy directed to the gastric region and small bowel can be apparent very early postexposure.

Because the mucosal systems have rapid self-renewal potential, acute sequela from management can be substantial and is driven by radiation dose, daily treatment fraction, and volume of mucosa in the treatment field. By the second week of treatment, the mucosa of the head and neck becomes denuded with increasing pain. Secondary tissues including salivary glands and taste buds also display limited function driven in a large part by the volume of mucosa in the treatment field. By week 4, the mucosa will slough and be replaced by confluence of white cells and fibrin exudate. The impact on secondary tissues becomes more pronounced with severe xerostomia and loss of taste. This creates challenges with maintaining adequate dental hygiene and nutrition. Often patients treated to substantial mucosal volumes require supplemental nutrition for extended periods of time during and beyond treatment completion. These patients can be cured on their primary malignancy; therefore, adopting an aggressive approach to the management of the acute effects from the treatment is reasonable and medically appropriate. Symptomatic pain management with topical and enteral medications are important management vehicles for care during this period of time [32].

The epidemiology of carcinoma of the esophagus has changed during the past 30 years in North America. Squamous cell carcinomas associated with alcohol and

tobacco use have been replaced by primary adenocarcinomas, largely of the distal esophagus associated with gastric surface gland migration (Barrett's esophagus). This has been seen in multiple countries and is now the great majority of esophageal cancers. The mucosa of the esophagus will self-renew in a time frame similar to head and neck mucosa; therefore, 2 weeks into a treatment course, the patient will begin to develop swallowing discomfort related to treatment. Often these patients initially feel improved due to tumor response; however, mucosal denudation from treatment also becomes apparent during this time course, and symptoms associated with dehydration and nutritional imbalance become more visible during this time frame. Symptomatic management with pain medication and fluid support is an important adjunct during this period of time.

Treatment of the gastric mucosa can cause near-immediate nausea/vomiting due in a large part to the rapid self-renewal capacity of gastric stem cells. During a treatment course of radiation therapy, delayed gastric emptying can be observed due to edema in the bowel wall as well as the development of ulceration during treatment due to limited stem cell renewal capacity.

Early complications of the small and large bowel are similarly driven by radiation dose, treatment fractionation, volumes of bowel in the radiation therapy treatment field, and previous abdominal surgery. Previous abdominal surgery can result in adhesions which can fix segments of bowel into a specific location, potentially exacerbating acute injury due to limitation of blood supply and repeated high-dose treatment [15, 33]. The small bowel absorbs protein, carbohydrate, fat, and water. If the mucosal surface is denuded, foodstuffs cannot be absorbed. Carbohydrate and fat function as a micelle and draw more water into the gastrointestinal tract resulting in increased bowel movement frequency and symptoms consistent with malabsorption. The large bowel mainly absorbs water; therefore, if generous segments of the large bowel are included in the therapy field, increased bowel frequency may occur with risk of dehydration and electrolyte loss often exacerbated with the concurrent use of chemotherapy. Although some of these issues can be anticipated and addressed through daily clinical care with fluid and electrolytes, often, these patients present for emergency department evaluation during evenings and weekends for symptom management. Therefore, up-to-date clinical information can often facilitate and support emergency services when needed including the risk of secondary infections associated with therapy. From a clinical perspective, patients being treated for recurrent disease often have more acute and potentially more serious sequela than patients being treated on an adjuvant basis. The root cause for this phenomenon is multifactorial, likely driven in part by tumor compromise of normal tissue function and vasculature prior to the initiation of therapy [32].

Subacute and Late (Delayed) Effects of Treatment

For both primary and emergency health-care providers, the late effects of cancer management can be less visible to casual observation but become a highly visible component to patient care years and decades after primary management. As patients are cured of their primary malignancy, secondary effects of therapy on normal tissue structure and function are now important for follow up and preventative care as needed. As children treated for malignancy grow and become adults, adult physicians will need to embrace previous therapy as a significant component to their past medical history and treat accordingly. Acute effects of treatment are not always a predictive indicator of late effects, specifically patients without acute effects during the primary management phase of treatment remain at identifiable risk for late effects.

Usually acute effects of radiation management affect cells that have a rapid self-renewal capacity. Nearly every cell system in both adults and children is at risk for late effects driven in a large part by the total radiation dose and volume of normal tissue treated. Late effects are also influenced by daily treatment dose. Children remain at significant lifetime risk as growth and development of all cell systems is directly affected by therapy [15].

The relationship of chemotherapy to delayed effects from radiation therapy to normal tissue is less well described [15]. Although it is recognized in a qualitative manner that chemotherapy exacerbates acute effects of radiation therapy to tissues of rapid self-renewal potential, the impact of chemotherapy on late effects of treatment is not understood. To date, most radiation oncologists have not made adjustments in dose to normal tissue targets; however, our volumetric dose volume tools are now providing metrics through histogram analysis. The quantitative analysis of normal tissue effects in the clinic (QUANTEC) is a significant effort by radiation oncologists to define dose volumetrics for thresholds for normal tissue injury [34]. This effort reviewed most of the available and relevant published data to date and provides guidelines for physicians to follow for prevention of injury [34]. Because of modern computer metrics, the guidelines are driven by both radiation dose and volume exposed to treatment. When treatment is developed through three-dimensional planning and executed through conformal delivery systems, including intensity modulation, normal tissue volumetric are available for analysis through dose-volume histogram tools.

In this section, the late effects of radiotherapy will be described. This is important for emergency physicians as often this information is not available as part of the past medical history of the patient during an acute care evaluation and triage for advanced medical care. Improved knowledge of late effects will influence management and evaluation

including the evaluation strategy in the acute care setting. Understanding these effects will improve patient care and evaluation moving forward.

Skin

Acute effects (described previously) of radiation injury to the skin generally resolve within 1 month of completion of therapy. With traditional fractionation to radiation doses of 7000 cGy, there can be thinning of the epidermis with deceptive prominence of the vascular pattern (telangiectasia) in the dermis. The degree of vascularity is decreased; however, thinning of the epidermis can make the vessels in the dermis appear more prominent [9]. With hypofractionation protocols now in clinical use, there can be more visible injury associated with varying degrees of fibrosis [31]. Hyperspectral imaging demonstrates that oxygenation is decreased, therefore providing an explanation to limitations in wound healing when there is secondary injury and infection [10, 27]. Local immunity and moisture glands significantly diminish; therefore, injury to irradiated tissue can result in significant delay in healing with persistent ulceration and damage possibly requiring aggressive surgical care including hyperbaric oxygen therapy in extreme situations [9]. To date there has been little progress on specific therapies that can be applied to radiation injury once it is clinically apparent. The current standard of care is to follow optimal wound care strategies.

Skin tissue can also demonstrate a phenomenon called "recall." There are chemotherapy agents and antibiotic agents that can cause acute erythema and skin breakdown in areas that were previously irradiated. This can occur years after primary radiation therapy management.

Patients with autoimmune disorders including lupus and scleroderma may be vulnerable to accelerated fibrosis from traditional radiation therapy. This creates issues for wound healing for secondary injury as well as limitations in function of organs requiring coordinated muscle function including the esophagus [9].

Bone Marrow

Although the primary focus of attention is with acute effects, bone marrow can remain fragile years after therapy and vulnerable to various medications and external agents after radiation therapy. This is especially true for white cell elements and platelets. If there is a diminution in red cell count, this is usually not associated directly with radiation therapy and will require more extended evaluation for blood loss and anemia. Pancytopenia and bone marrow aplasia is becoming a more common consequence of cancer therapy and often is first identified in an acute care environment. This often influences both choice and duration of treatment of infections and other late sequelae of management. Secondary blood dyscrasias including secondary blood malignancies are associated with primary management and are often first identified in the acute care setting [15, 32].

Gastrointestinal Tract

There are substantial late effects of management to be considered in the acute care environment. These are issues that can significantly complicate patient management and often require adjustments in management in the acute care environment.

The mucosa of the oral cavity recovers in a manner similar to the skin; however, there is residual compromise of the environment of the oral cavity, which is long standing in nature. The floor of the mouth is taut and lacks mucosal redundancy; therefore, it is susceptible to injury that heals less well than other structures in the oral cavity. If ulceration occurs, debris and particles can sequester in the open space and cause necrosis of underlying structures including the mandible. This requires careful management including hyperbaric therapy and surgery. These issues are challenging and may become more frequent as radiation therapy moves to more hypofractionation protocols for head and neck cancer. Patients have dry mouth due to radiation dose to the parotid glands, the submandibular glands, and the often overlooked submucosal gland structures that provide moisture to the mucosal surface. These microscopic glands are ubiquitous in distribution throughout the mucosal surface. This creates secondary issues for dentition for both adults and children. Although teeth do not self-renew and by default are not directly affected by radiation, treatment affects the environment of the oral cavity and both the growth and development of teeth in children and the oral cavity environment for adults. The saliva becomes more acidic and prone to fungal overgrowth. The mucosa of the gingival becomes thin and denuded. These changes can lead to chronic decay and demineralization of teeth. Fluoride mouthwash with periodic use of baking soda/water rinses helps de-acidify the oral cavity and promotes more optimal oral hygiene; however, these changes are often unrelenting and difficult to control. Optimal radiation planning strategies with intensity modulation may help mitigate these changes moving forward. Building a strong relationship with dental medicine helps facilitate optimal patient care [15, 32].

Motility of the gastrointestinal tract is not a well-described side effect of radiation management; however, this is becoming a more visible issue in the management of head and neck malignancies and esophageal cancers [35]. Contractility of the medial constrictor muscles of the hypopharynx are now

described and appear to mimic swallowing issues often seen in patients with neurodegenerative disorders [35]. At times these changes are related to treatment-associated dermal and interstitial edema, and addressing the edema through lymphedema clinics can be very helpful. As more patients survive their primary malignancy, these issues are becoming more frequent and impose significant restrictions on patient recovery from treatment. Delayed gastrointestinal emptying associated with antral fibrosis and denudement of the mucosa of the gastric lining cells can be seen in patients treated to the gastric region, usually at doses of greater than 45 Gy to the gastric region or the gastric resection site.

Late effects to both small and large bowel include every tissue component. There is atrophy of the mucosa resulting in limited absorption of protein, carbohydrate, and fat. This contributes to various degrees of malabsorption syndromes and inconsistent bowel function. If there is previous abdominal surgery, bowel may be fixed in position resulting in stenosis and ulceration requiring surgery. Relatively little is known about effects to the exocrine and endocrine pancreas although atrophy of the pancreas can be seen on imaging years after treatment of an upper abdominal malignancy [15, 32].

Liver

There is renewed interest in defining radiation dose effects to the liver as stereotactic body radiosurgery techniques have been effective in the treatment of both metastatic disease to the liver and primary hepatocellular carcinoma. Sequela to the liver, known as radiation-induced liver disease (RILD), is driven by the volume of the liver treated and the functional status of the liver at the time of therapy. Both primary and metastatic disease can impose varying degrees of veno-occlusive changes in the parenchyma, and treatment can induce scar tissue that can limit the functional status of the remaining liver. Magnetic resonance imaging has become a valuable tool in validating the degree of veno-occlusive changes and has evolved into a quantitative metric in predicting possible radiation-associated liver injury prior to the administration of radiation therapy [36]. Investigators are using metrics identified on dynamic contrast imaging to establish the appropriate radiation dose to target. The threshold of injury to the liver is significantly decreased when the entire organ volume is treated. Sioshansi et al. have demonstrated injury to the diaphragm without changes in the chest wall resulting in chronic pleuritic pain among patients undergoing stereotactic body radiosurgery [37]. The liver is sensitive to interactions with chemotherapy perhaps best demonstrated in the pediatric population when radiation therapy is delivered with actinomycin D chemotherapy for Wilm's tumor. Sequela can include a dramatic decrease in blood counts as well as changes consistent with liver failure including coagulation disorders [32].

Kidney

The kidney, similar to the liver, is a relatively late-responding radiosensitive critical organ. Radiation doses of greater than 20 Gy in 2 Gy fractions can result in renal damage with anemia and hypertension. Although not yet validated through clinical trials, the threshold for injury is thought to be lower when nephrotoxic chemotherapy is used with radiation therapy. Via the use of intensity modulation, radiation oncologists can be creative with partial volume therapy and spare as much renal parenchyma as possible. Nevertheless, in comparison with siblings, there is an increased risk of renal failure in the cancer survivor; therefore, investigators should attempt to limit renal dose to as little as possible during the planning of treatment. To date this issue has not yet been defined as a point of interest for imaging and delivery of contrast agents; however, this may become an important issue in the clinic moving forward [15, 32, 33].

Lung

As with the liver and kidney, the lung is a very sensitive intermediate to late-responding tissue. In extreme situations, injury to the therapeutic lung can be life threatening. There are generally two periods of damage that can be identified. Pneumonitis (period of active inflammation) can occur 2–6 months after completion of radiation therapy, and fibrosis can occur years after treatment delivery. During the pneumonitis phase of injury, there is active inflammation often visible on thoracic imaging. If the patient is asymptomatic, observation is a reasonable approach. Symptoms including cough and shortness of breath associated with these imaged changes are often managed by corticosteroids and antibiotics as appropriate [38]. There are reports of radiation injury to the lung tissue outside of the radiation treatment field. Although felt to be spurious at initial review, investigators have suggested that production of nitric oxide gas as a by-product of radiation-induced injury may play a role in generating injury in other parts of pulmonary parenchyma not directly in the radiation therapy treatment region [39]. Fibrosis as a late change can result in parenchymal scar as well as pleural and pericardial effusions resulting in limitation of pulmonary reserve and chronic need for supplemental oxygen. Modern radiation techniques including the use of motion management and intensity modulation may limit the risk of injury by limiting the volume of parenchyma receiving higher doses. Dose-volume histogram analysis also suggests that it is likewise important to limit the volume of

normal lung parenchyma receiving 20 Gy. Modern radiation therapy techniques seek to limit both the volume of lung receiving both high and low doses. Interactions with other pulmonary toxic agents such as bleomycin play a key role in evaluating the dose-volume effect of radiation therapy. This is especially important in patients treated for Hodgkin lymphoma. Recent studies do reveal an increased risk of chronic pulmonary disease in cancer survivors in comparison to siblings [15, 24, 25, 40].

Heart and Peripheral Vessels

Historically the heart was considered to be a late-responding tissue with exception of pericarditis, which could occur during or shortly following radiation therapy, especially in patients with generous cardiac volumes in the treatment field. Patients typically present with sharp, anterior chest pain with pericardial fluid causing shortness of breath and a low-grade fever. Anti-inflammatory medication and treatment interruption alleviate symptoms. With modern cardiology evaluation techniques including magnetic resonance and nuclear medicine studies, we can now identify previously unforeseen cardiac events. This is important as studies are suggesting an association between radiation therapy and the development of cardiovascular disease when the heart is an unintended target of treatment. Tangential irradiation to the left breast as treatment for breast cancer can deliver a measureable mean dose to the heart even with intensity modulation techniques [41].

Anterior-posterior treatment techniques used to treat Hodgkin lymphoma with historical nonimage-guided techniques resulted in full-dose radiation therapy to multiple critical cardiac structures. In reviewing the anterior posterior cardiac anatomy using traditional radiation therapy treatment fields for Hodgkin lymphoma, multiple critical structures reside in the parallax of the vertebral body including the primary cardiac vessels, the electrical conduction nodes, and the aortic valve. The mitral valve resides generally 2 cm lateral to the left edge of the vertebral body in patients without chronic lung disease. Therefore traditional radiation treatment for Hodgkin lymphoma included many cardiac structures treated at high dose, placing these tissues at risk for the lifetime of the patient. Modern cardiac imaging using multiple platforms reveals segments of myocardium, which can demonstrate dyskinesis in small segments of the cardiac myocardium (apex) after tangential radiation therapy for breast cancer. The clinical importance of these findings is uncertain. Intensity modulation decreases radiation dose to the heart; however, there is a population at risk treated with radiation therapy in the preintensity modulation era that will be at risk for the next several decades for heart disease. Recent studies demonstrate a significant risk of heart disease in the cancer survivor compared to their siblings [29, 37, 40–54].

Large peripheral vessels were historically viewed as resistant to radiation therapy; however, as we begin to move forward with hypofractionation protocols, reports of injury are being reported. During historical times when treatment was delivered with orthovoltage therapy, carotid injury was described recognizing that dose to carotid was likely much higher than the reported tumor dose. Pathology of injury includes intimal hyperplasia and weakening of the carotid muscle. There are reports of fistula formation and sudden death due to rupture of the carotid vessels [29, 51]. Reports of injury to other large vessels (subclavian, femoral, etc.) were reported when there was overlap with radiation therapy treatment fields necessitating large radiation dose to a tubular structure [51]. With modern radiation therapy and traditional fractionation strategies, radiation injury to large vessels is uncommon. However, with higher daily doses to tubular structures, late injury can result and become clinically important. Symptomatic injury to veins is less common, and injury to capillaries can be visible at radiation doses of 50 Gy. This is an area, however, where retreatment of second cancers may predispose to injury in future patients.

Central and Peripheral Nervous System

The brain has several categories of cells susceptible to injury including the glia (support cells), primary neurons, and blood vessels. All of these tissues are generally considered as late-responding tissues; therefore, most sequelae occur as late events. The most important sequela is necrosis, which can occur within 6 months of radiation therapy; however, reports of late injury indicate that events can occur several years after treatment. Necrosis is seen more often now that radiosurgery techniques are used more commonly in patient care. Rarely, demyelinating syndromes can occur in the central nervous system. These syndromes can also occur in the spinal cord. Reversible syndromes can occur in the spinal cord in doses as low as 35 Gy; however, irreversible changes including myelitis begin to occur at doses of 45–50 Gy with traditional fractionation and appear to incrementally increase with larger radiation dose and larger volume of the spinal cord included in the treatment field. Toxicity may be increased with the addition of neurotoxic chemotherapy including *cis*-platinum, vinblastine, Ara-C, gemcitabine, and methotrexate. Peripheral nerves can likely tolerate a higher dose of radiation therapy as the cauda equina, and larger nerves appear to tolerate radiation doses in excess of 55 Gy without evidence of injury [55]. Visual field changes are seen in radiation doses higher than 5400 cGy to the optic nerve and chiasm [56]. It is thought that the chiasm is sensitive to radiation therapy as it has an end-arterial blood supply. This was first described in patients

treated to the pituitary gland for pituitary adenomas using daily treatment fractions of greater than 200 cGy/day [57]. Therefore, with modern-day image guidance and partial volume therapy, some investigators believe that tolerance of these structures may be higher than described in the historical literature. The cochlea can be affected by radiation, and this effect can be more pronounced at lower doses with the use chemotherapy including *cis*-platinum. Historically the lens is very sensitive to radiation therapy with cataract formation identified at very low dose (500 cGy) [9, 58].

Brachial plexopathy has been described in breast cancer patients treated to peripheral lymph nodes. Although the radiation dose threshold is thought to be 5400 cGy for injury, this is an uncommon side effect for patients treated for head and neck cancer with higher doses of radiation. The prevailing thought is that the more sensitive part of the plexus is the region where the nerve bundles coalesce immediately inferior to the lateral third of the clavicle. In the early days of radiation therapy, this area was calculated using an anterior field to a depth of 5 cm. The nerves can be as superficial as 1 cm below the skin surface; therefore, the nerve region received a higher percent dose and in some case would have received the equivalent of a high daily fraction (>120 % of the prescribed dose). This is compounded further by the use of posterior axillary boosts, which were often viewed and calculated as separate fields with exit overlap at the egress points of the brachial plexus into the upper extremity. Therefore it is entirely possible that the threshold dose for brachial plexus injury may be higher than described in historical literature due to unintentional overlap of radiation field volumes and unspecified increases in daily fraction size to a critical target. In the modern world using three-dimensional volumetrics, the axilla is a volume, and modern planning permits more uniform radiation dose distribution through a volume than two-dimensional treatment planning constructs [59].

Reproductive Organs, Genitalia, and Endocrine

Spermatogonia are among the few cell systems that can die an intermitotic death; therefore, the absolute number of sperm cells markedly decreases with modest doses of radiation. The period of development of stem cell to spermatozoa is 75 days; therefore, exposure to radiation can induce damage to mature sperm. In regions of nuclear events such as Chernobyl, there are reports of increased neurocognitive and developmental abnormalities in children born to survivors of these events [6]. Most oncologists offer sperm banking to patients with known direct exposure to radiation therapy. Indirect exposure with scatter radiation dose will often require use of birth control for two cycles of sperm development (6 months) to lessen risk of damaged sperm in the ejaculate. Leydig cells secrete testosterone, and their specific function is regulated by pituitary gonadotropins, prolactin, and luteinizing hormone. Treatment to the pituitary gland may impose secondary events to gonadal function. Although Leydig cells are more resistant to radiation exposure, there is an incremental decrease in testosterone in doses exceeding 20 Gy. Various chemotherapy agents including vincristine and mechlorethamine (mustargen) influence sterility. Oocytes are very sensitive to radiation and as sperm die an intermitotic death. Because hormonal secretion is associated with follicular maturation, unlike the testicle, treatment of the ovaries results in more immediate suppression of hormonal function. Female genitalia can demonstrate mucosal atrophy and loss of moisture [15, 32, 60]. Radiation therapy to children for pelvic malignancies including rhabdomyosarcoma can result in significant atrophy and maldevelopment of gonadal organs and pelvic anatomy. Cardiovascular health as well as other medical comorbidities including problems associated with growth can be significantly influenced by diminution of hormonal function at a young age.

Hypothyroidism is a common sequela associated with both surgery and radiation therapy to the low neck. This is quite prevalent in patients treated for head/neck cancer and Hodgkin lymphoma. For patients treated for head and neck cancer, neck dissection and primary surgery also influence the incidence of hypothyroidism. Pituitary therapy creates panhypopituitary syndrome with need for replacement therapies as appropriate. This can have significant health issues in multiple endocrine organs. Interestingly, there is little data for adrenal function; however, there are reported cases of adrenal malfunction and decreased cortisol with high-dose radiation therapy. More often, adrenal malfunction occurs in patients as a secondary bystander effect to pituitary therapy [15, 32, 61].

Pediatrics

Treatment of children is unique as every cell system has self-renewal potential; therefore, unlike adults, sequelae are visible and identified in all tissues due to growth and development. The bone and cartilage are key areas that distinguish adults from children. In general terms, with radiation doses of 20 Gy, growth deficits in bone may be irreversible [32, 62]. The deficits in bone and cartilage development are more visible with higher radiation doses and younger age. In adults, the threshold dose for bone necrosis may be 55 Gy with traditional fractionation strategies; however, there are interesting reports of the use of advanced technology imaging including MR demonstrating sacral fractures in gynecological patients receiving less than 50 Gy to the bone [62]. Radiosurgery techniques, particularly to targets in close approximation to the chest wall, are reinviting injury to the rib and chest wall that is often non-healing. Treatment techniques including volume-modulated

arc therapy [63] appear to play an essential role in decreasing this risk.

Recent studies have demonstrated that long-term survivors of cancer therapy including radiation are frailer than their counterparts and acquire chronic diseases at a higher rate. They may also be susceptible to premature death than their sibling counterparts [40].

Conclusion

Intentional and unintentional radiation exposures have a powerful impact on normal tissue function and can induce both short-term and long-term injury to all cell systems. In the evaluation of acute phase management, assessing radiation dose and exposure is essential to management strategy. Appropriate support can be given to those at risk for serious acute injury. The effects of radiation treatment and exposure, however, last for the lifetime of the patient and can have implications for all organ systems. A broad understanding of these effects is essential for the modern acute healthcare provider in the emergency department setting.

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Emergency Radiology

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Introduction

Oncologic emergencies encompass a wide spectrum of pathology and can affect any organ system. Etiologically, these can be divided into metabolic, hematologic, and structural emergencies [1]. Metabolic and hematologic conditions are frequently diagnosed based on clinical and laboratory findings, often with only incidental imaging support. Structural emergencies are those arising from mass effect, tissue infiltration, tumor hemorrhage, vascular invasion with resulting occlusion or hemorrhage, and organ drainage pathway obstruction. Diagnostic imaging can also provide a "road map" for subsequent image-guided interventional and noninvasive therapies.

Imaging Modalities

There is an increasing array of diagnostic imaging options available in evaluating oncologic emergencies. Selecting the appropriate imaging modality requires consideration of availability, speed, patient-specific factors, and anticipated diagnostic yield.

Plain radiography: It is a rapid, universally available, low-cost screening modality. Its core utility is for osseous and pulmonary evaluation and for screening for intestinal obstruction and pneumoperitoneum. It is particularly useful in trauma to the appendicular skeleton and less sensitive in the diagnosis of axial and spinal trauma, although still used as a screening tool.

Multidetector computed tomography (*CT*): It is rapid and highly available. It is the mainstay in the emergent evaluation of the head, neck, chest, abdomen, and pelvis. Modern CT technology allows for thin X-ray beam collimation to 0.625 mm, allowing for isotropic image acquisition and elegant post-processing capabilities, including orthogonal and curved planar reformations and 3D surface rendering [2].

The diagnostic value of CT derives from its ability to discriminate tissues based on physical density, which is measured in Hounsfield units (HU) and displayed in grayscale on a picturing and archiving communication system (PACS) workstation. By convention, water has a density of 0 HU and appears intermediate in grayscale. Air has a density of approximately −1000 HU and appears relatively dark (hypodense or hypoattenuating). The bone and calcium have densities in the range of +1000 HU and appear relatively bright (hyperdense or hyperattenuating). Intravascular or unclotted extravascular blood, for example, has a density of around 30–45 HU but increases in attenuation to 45–70 HU as clot matures [3]. Administration of iodine-based nonionic intravenous (IV) contrast increases soft tissue and vascular conspicuity, further improving diagnostic yield. Most malignancies display predictable enhancement characteristics, and the use of IV contrast often permits accurate diagnosis. In oncologic emergencies, routine use of IV contrast is suggested for the neck, chest, abdomen, and pelvis, primarily for soft tissue evaluation. For the evaluation of osseous pathology, IV contrast is not usually necessary. Most intracranial emergencies are imaged with head CT without IV contrast, as opacified intracranial vessels may obscure extra-axial hemorrhage. Optimizing arterial or venous enhancement by adjusting the timing of image acquisition allows for an assessment of vascular abnormalities, such as dural venous sinus thrombosis (CT venogram) or vasospasm (CT angiogram).

Magnetic resonance imaging (*MRI*): It may not be accessible after hours at many centers. MRI requires a greater degree of patient stability and compliance than does CT and entails longer imaging times. Core utility in the emergent setting is for intracranial (e.g., acute stroke, tumor burden, dural venous sinus thrombosis) and spine (e.g., cord compression, cord edema, epidural tumor, and osseous involvement) evaluation. Gadolinium-based IV contrast aids in quantifying the extent of malignant disease and can potentially characterize soft tissue tumors. As with CT, IV contrast is not typically essential for osseous evaluation. Commonly performed MR imaging sequences for the brain include T1-weighted (T1), T2-weighted (T2), fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI). For spinal imaging, typical sequences are acquired in the sagittal plane and include T1, T2, and either T2 fat-saturated or short-tau inversion recovery (STIR) images, as well as post-contrast sequences. Axial image sequences for the s)pine are institution dependent but typically include T1 and T2 images. If contrast is administered, post-contrast T1 images are obtained using fat saturation techniques. Signal from fat is bright, or hyperintense, on MRI. When background fat signal is suppressed, it appears hypointense, increasing the conspicuity of contrast-enhanced malignant tissue. MRI imaging of the long bones often employs proton density (PD) sequences as an alternative to fat-saturated T2 images. As with CT angiography (CTA) or venography (CTV), MR angiography (MRA) and venography (MRV) can be used to assess for vascular pathology, although IV contrast is not always necessary.

Ultrasonography (*US*): It is rapid, universally available, mobile, and accessible for clinician bedside usage. This sound-based modality is limited by image degradation that occurs at tissue interfaces with bone or air. Doppler US is ideally suited for the assessment of blood vessels and soft tissue vascularity. It is highly useful in procedural guidance owing to its portability and the absence of radiation. It is also a good tool for extremity soft tissue disease, ascites, pleural effusions, vessel patency, and biliary pathology.

Nuclear medicine: In the emergent setting, only ventilation/perfusion (V/Q) imaging is used with any frequency to evaluate for pulmonary embolism. V/Q studies are reserved for patients with contraindications to CT pulmonary angiogram (CTPA), such as a history of significant adverse reaction to iodinated IV contrast agents or renal insufficiency. Positron emission tomography (PET) has minimal value in the emergent oncologic patient due to increased patient preparation requirements, lengthy acquisition time, and limited availability. Other nuclear medicine exams have established utility in imaging oncology patients (e.g., whole-body bone scintigraphy); however, these are infrequently used in the emergent setting and fall outside the scope of this review.

Fluoroscopy: It is useful for esophagography and provides procedural guidance for lumbar puncture, myelogram injection, joint aspiration, and tube/drain placement.

Interventional radiologic procedures can provide further diagnostic information as well as guide therapies in the acute setting, most commonly with the use of conventional catheter angiography, embolization for acute hemorrhage, and tube or drain placement for relieving obstruction or abscess drainage.

In the following pages, we provide a concise review of the imaging evaluation of oncologic emergencies. Due to space constraints, this is not intended as a comprehensive review. Rather we seek to highlight important imaging characteristics of key malignancy-related conditions across a range of organ systems to serve primarily as a reference to clinicians involved in cancer care or as a primer for radiology trainees, who will invariably encounter oncologic emergencies during training and beyond.

Neurologic Emergencies

Intracranial Mass Effect, Edema, and Hemorrhage

Fundamentally, malignant tumors are space-occupying masses that compete with normal anatomical structures for limited real estate in the brain and spinal canal. Intracranial mass effect derives from a combination of actual tumor volume and peritumoral edema, which together are responsible for causing various cerebral herniation patterns and hydrocephalus. Effective tumor volume can change rapidly as a consequence of necrosis, hemorrhage, and cyst formation, which contribute to mass effect (Fig. 1).

On unenhanced head CT, the appearance of malignant tissue is variable, depending on its histological composition. Generally, malignant tumors are slightly hyperdense relative to white matter, and hemorrhagic or melanin-containing components are considerably denser (e.g., malignant melanoma). Cystic and necrotic components generally measure near-water attenuation depending on the presence of cellular debris or blood products. Perilesional edema results in relative hypodensity of the surrounding brain parenchyma. Especially on unenhanced CT, the presence of edema may be the only indication of underlying malignancy, and further evaluation with a contrast-enhanced study, ideally MRI, is indicated. Edema from malignancy is a reactive process, and the amount of edema is proportional to tumor size and rate of growth. Accordingly, a small but rapidly growing mass may present as precipitously as a larger but more indolent mass. Tumor cell lysis and treatment-related neurotoxicity represent important additional sources of edema and mass effect, which can be anticipated and prospectively managed with systemic corticosteroid administration.

Intracranial herniation resulting from mass effect can be classified as subfalcine, transtentorial, transalar, and tonsillar [4]. Transtentorial herniation can be further characterized as ascending (originating from the posterior fossa), descending (cerebral hemispheres), or uncal (temporal lobes), depending on the location of the tumor [1]. Ascending transalar herniation results from middle cranial fossa mass effect and causes superior and anterior temporal lobe displacement across the sphenoid ridge [4]. Descending transalar herniation results from frontal lobe mass effect and causes posterior and inferior displacement across the sphenoid wing [4]. Masses located in tightly confined structures, such as the posterior fossa, can result in the rapid development of clinically significant herniation.

Patients with hypervascular metastases, including renal cell carcinoma, melanoma, thyroid, and choriocarcinoma, are at highest risk for both intra-axial (within the brain substance) and extra-axial (within the epidural, subdural, or subarachnoid space) hemorrhages [5, 6]. Intracranial hemorrhage can also result from acute disseminated intravascular coagulation (DIC), to which patients with hematologic tumors are particularly predisposed [7]. Regardless of cause, intra-axial hemorrhage appears as a hyperdense mass with a variable degree of circumferential edema on unenhanced head CT. Hyperdensity in the subarachnoid, subdural, or epidural spaces indicates extra-axial hemorrhage. Contrast-enhanced brain MRI is essential for further characterizing the underlying malignancy.

Hydrocephalus

Hydrocephalus is classified as noncommunicating (obstructive) and communicating (nonobstructive). Noncommunicating hydrocephalus results from obstruction of CSF flow, while communicating hydrocephalus is the result of excess CSF production or decreased resorption at the arachnoid villi. The foramen of Monro, aqueduct of Sylvius, and the fourth

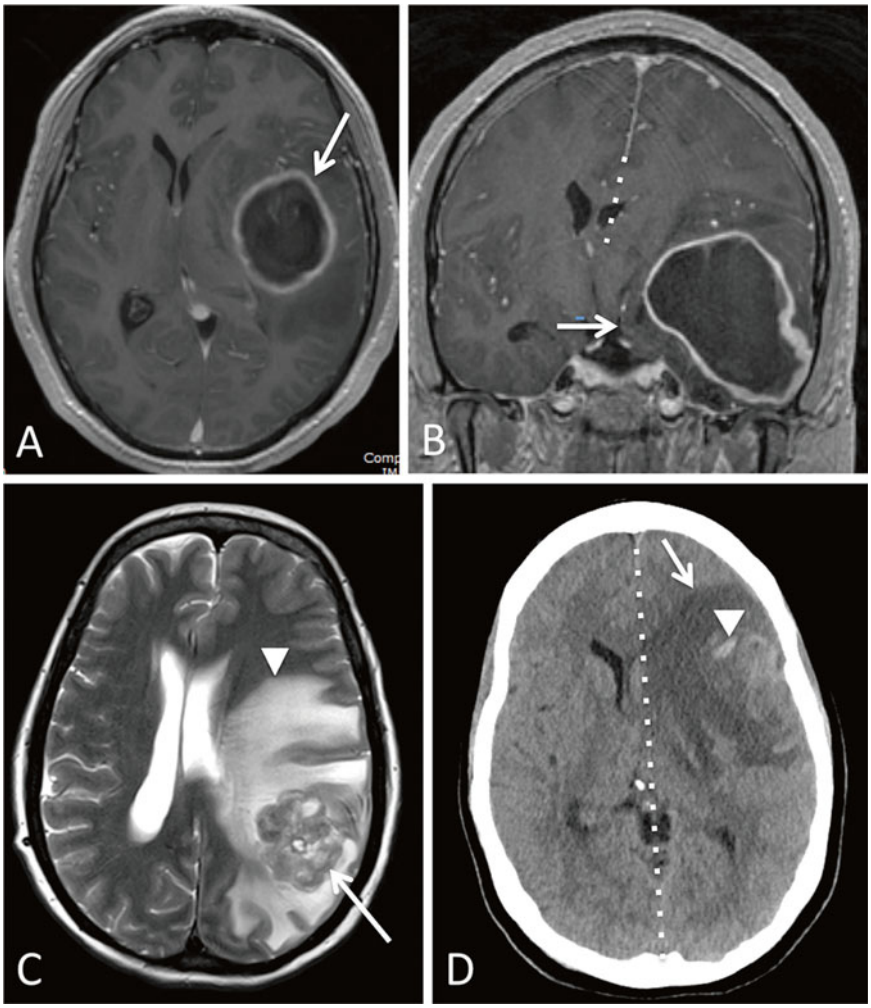

Fig. 1 Intracranial mass effect. (**a**) Axial post-contrast T1 brain MR image demonstrates a rim-enhancing intraparenchymal cavitary metastatic mass (*arrow*). (**b**) Coronal contrast-enhanced T1 MR image in the same patient demonstrates left-to-right midline shift (*dotted line*), compatible with subfalcine herniation. Uncal herniation is also shown by an *arrow* on image **b**. (**c**) T2 axial brain MR image depicts marked T2-hyperintense edema surrounding a cystic intraparenchymal metastatic lesion in the left parietal lobe (*arrow*). Note extent of edema beyond the actual mass (*arrowhead*). (**d**) Unenhanced head CT image demonstrates a left frontal lobe mass with marked surrounding hypodense edema (*arrow*), local sulcal effacement, and left-to-right midline shift (*dotted line*). There is small-volume intra-tumoral hemorrhage (*arrowhead*), which may have caused this patient's acute presentation

ventricle are anatomically prone to obstruction by the presence of an adjacent primary or metastatic mass [6]. Specifically, pineal metastases or primary neoplasms have a particular association with hydrocephalus [8]. The primary feature of communicating hydrocephalus on unenhanced CT is global ventricular enlargement. In noncommunicating hydrocephalus, there is disproportionate enlargement of the lateral ventricles; the third ventricle may also be disproportionately enlarged depending on the anatomic level of obstruction. In acute obstructive (noncommunicating) hydrocephalus, increased ventricular pressure can result in transependymal CSF accumulation, resulting in a low-density appearance to the immediate periventricular white matter.

Leptomeningeal Carcinomatosis

The pia and arachnoid maters are interconnected, thin, and weblike cerebral coverings and together comprise the leptomeninges; leptomeningeal carcinomatosis (LMC) is characterized by the deposition of tumor along these membranes. These tumoral cells can subsequently impede CSF resorption by obstructing the arachnoid villi, leading to communicating hydrocephalus [6]. LMC portends a dim prognosis, with median survival in the range of 2–3 months [9]. It is important to note that up to 40 % of patients with LMC may have normal unenhanced CT, and in an additional 25 % of cases, LMC is indistinguishable from intraparenchymal disease [10]. Up to 2/3 of patients with LMC demonstrate abnormal findings at contrast-enhanced MRI, however. Unenhanced MRI findings include high FLAIR signal within the cerebral sulci, cerebellar folia and cisterns, and communicating hydrocephalus [11]. Contrast-enhanced MRI findings include linear or nodular enhancement within the sulci, cisterns, ventricles, and along the cranial nerves [1]. The most common primary solid malignancies associated with LMC are breast and lung [9, 10].

Dural Venous Sinus Thrombosis

There are many benign causes of dural venous sinus thrombosis (DVST), including oral contraceptive use, pregnancy, thrombophilic disorders (such as factor V Leiden, protein

C/S deficiency), recent immobilization, and infection, such as meningitis or mastoiditis [12]; however, patients with malignancy have a particularly elevated risk for developing DVST related to dehydration, chemotherapy effects, and hypercoagulable state [13, 14]. Tumor involvement of the cranium or skull base, dura, or leptomeninges may result in local venous stasis secondary to mass effect on a dural venous sinus, representing an additional mechanism for DVST formation. Specific cancer chemotherapeutic agents that have known association with the development of DVST include asparaginase, thalidomide, dexamethasone, and tamoxifen [14].

Unenhanced head CT is often the initial imaging modality used to evaluate patients suspected of having DVST, who may present with signs and symptoms of increased intracranial pressure [14]. The classic unenhanced head CT finding in uncomplicated DVST is hyperdensity within the affected dural venous sinus, although this is not invariably present (Fig. 2). The superior sagittal and transverse sinuses are most frequently affected overall in DSVT [13]. The diagnosis is confirmed with CTV or MRV, both of which will depict an intraluminal filling defect within the affected sinus. CTV is faster, and usually more accessible after hours, while MRV is performed alongside MRI of the brain, providing a more sensitive assessment for early venous ischemia or congestion resulting from the DVST. In cases of venous infarct, edema or hemorrhage in a non-arterial distribution is common. Treatment of tumor-related DSVT is typically brain irradiation or chemotherapy, depending on tumor histology [7].

Stroke

The hypercoagulable state of malignancy constitutes the primary risk factor for the development of cerebral vascular accidents (CVA) in oncologic patients [7]. As noted above, this population is at elevated risk for DVST, which can lead to ischemia and hemorrhagic infarction. Leptomeningeal infiltration of the Virchow–Robin perivascular spaces can result in arterial ischemia secondary to thrombosis or vasospasm [7].

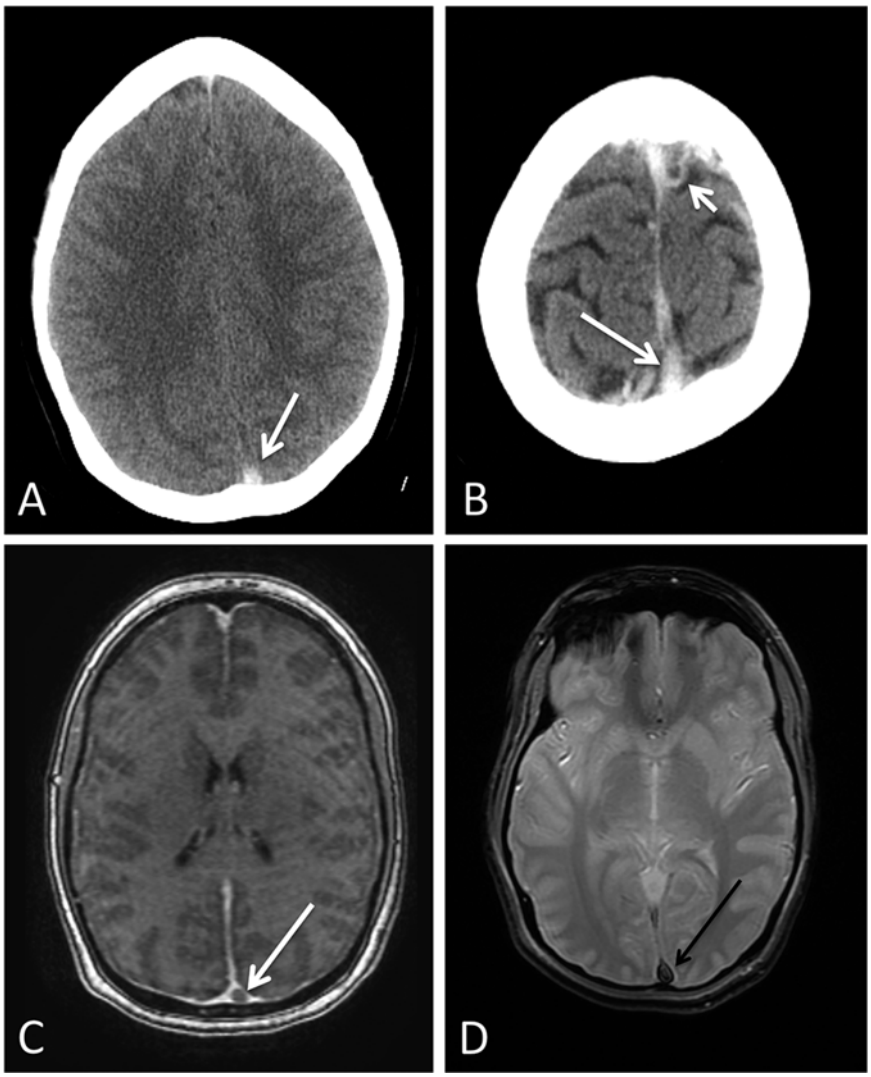

Fig. 2 Dural venous sinus thrombosis. (**a**) Axial unenhanced head CT image in a patient with lymphoma and headache demonstrates a hyperdense superior sagittal sinus (*white arrow*), suggesting superior sagittal sinus thrombosis. (**b**) A more superior unenhanced axial head CT image in the same patient near the vertex demonstrates continued superior sagittal sinus hyperdensity (*long arrow*) and multiple adjacent hyperdense cortical veins, suggesting thrombosis of these superficial veins as well (*short arrow*). (**c**) Post-contrast T1 axial brain MR image in the same patient illustrates a hypointense filling defect in the superior sagittal sinus, compatible with thrombus (*white arrow*). (**d**) Gradient echo axial brain MR image demonstrates "blooming" in the superior sagittal sinus, indicative of extracellular blood products (*black arrow*)

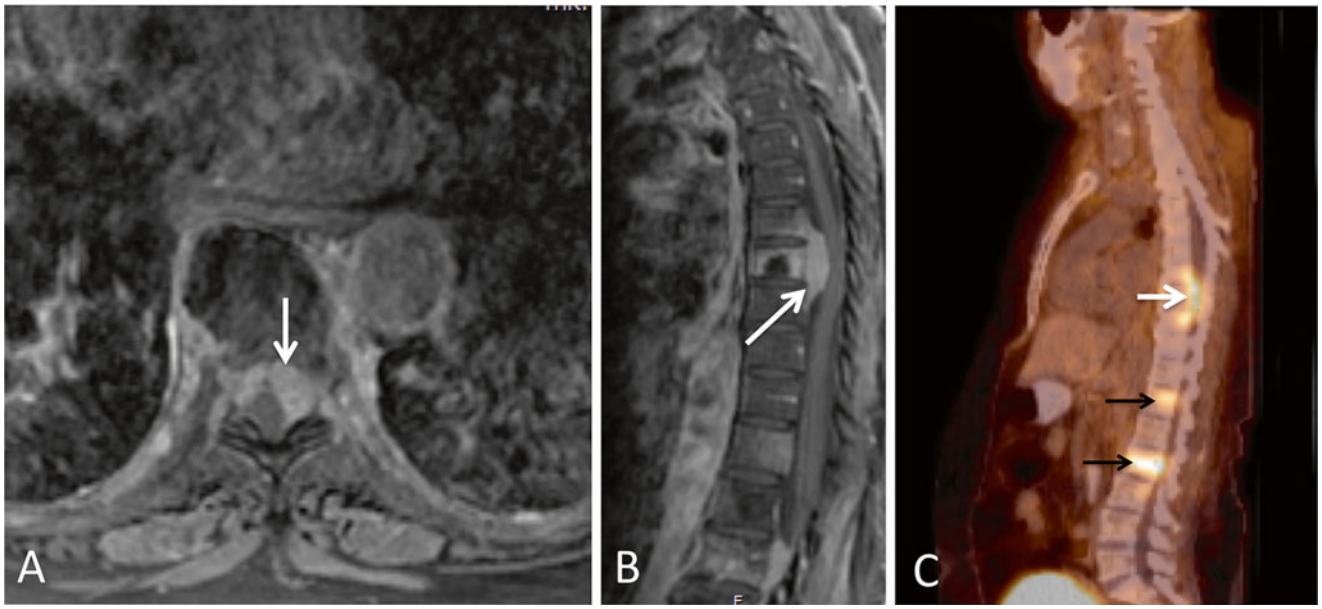

Fig. 3 Post-contrast axial T1 MR image (**a**) and sagittal post-contrast T1 MR image of the thoracic spine (**b**) depict an enhancing mass arising from the T7 vertebra and extending into the epidural space (*white arrows*). There is associated severe cord compression. A single-fused sagittal FDG-PET/CT image of the entire spine (**c**) demonstrates robust metabolic activity in the tumor at the T7 vertebral level (*white arrow*) and at several other remote vertebral levels (*black arrows*)

Additionally, arterial infarction can occur secondary to herniation as a consequence of compression of large arteries against rigid intracranial structures, such as the cerebral falx or tentorium. For instance, transfalcine herniation can result in anterior cerebral artery (ACA) compression and ipsilateral ACA-territory infarct [1, 5]. Similarly, transtentorial herniation can result in compression of the posterior cerebral artery (PCA) and, thereby, result in PCA-territory infarct [5]. Less commonly, transalar herniation can result in compression of the carotid terminus and lead to infarction in both the ACA and MCA territories.

Although the initial imaging evaluation of stroke patients regardless of cause is with unenhanced head CT, MRI provides optimal evaluation of tumor location and extent (including leptomeningeal disease) and is more sensitive in the identification of early ischemia as compared to CT. Areas of acute ischemia are markedly hyperintense on DWI and are typically associated with increased T2 signal. Conventional MRI can provide an overall assessment of vessel caliber and enhancement, but dedicated MRA or MRV sequences provide better detail of arterial and venous pathology.

Spinal Pathology

For the purposes of this emergency radiology chapter, spinal disease is divided into pathology involving the osseous spine and that contained within the spinal canal (most commonly epidural or intramedullary involvement). Osseous spine disease is also addressed in the musculoskeletal subsection. Here, we focus primarily on epidural and intramedullary spinal diseases, which can both present as oncologic emergencies. Metastatic disease of the spinal epidural space occurs in 5–10 % of patients with cancer, most commonly from prostate, breast, and lung primaries [15]. When epidural tumor volume is advanced, it compresses the thecal sac and can result in malignant spinal cord compression (Fig. 3). In addition to metastatic disease, spinal cord compression can result from mass effect from primary bone tumors, osseous lymphoma, or multiple myeloma. Spinal epidural metastases localize to the thoracic region in 60 % of cases and lumbosacral area in 30 % of cases. Cervical spine involvement is less common [15].

Plain radiography is often the initial modality used in the evaluation of spinal cord compression despite its poor predictive value in determining which patients will have spinal tumor involvement [16]. Vertebral body height loss secondary to pathologic compression is one of the most easily identifiable findings on plain radiography. Compression fractures resulting in loss of vertebral body height ≥50 % are associated with spinal epidural disease in nearly 85 % [15]. Erosion of the osseous margins of the spine may be the earliest radiographic sign of intraspinal extension of disease, but this finding is not sensitive [17]. Vertebral pedicle erosion, in particular, may be the most specific finding of epidural disease [15]. CT is superior to plain radiography in accurately depicting bone erosion and assessing compression fractures. A further advantage of CT over plain radiography is that nonosseous disease can often be identified, although MRI is better suited for soft tissue pathology. CT can also be helpful in planning for interventional procedures or surgery.

MRI provides the most sensitive and specific evaluation of bone marrow pathology, epidural tumor, spinal cord compression, and intramedullary spinal disease. Spinal cord compression is discussed in detail in a separate chapter. Metastatic involvement of the spinal cord parenchyma is referred to as intramedullary spinal cord metastatis (ISCM) [15, 18]. Although ISCM has become much more frequently recognized in the era of MRI, spinal epidural disease is still nearly 20 times more common [15]. ISCM affects the cervical, thoracic, and lumbar cords equally and is most often solitary [15]. Bronchogenic carcinoma, particularly small-cell carcinoma, accounts for the majority of cases (54 %) [15]. MRI with IV contrast is necessary for the diagnosis of ISCM and can effectively discriminate spinal cord edema from enhancing tumor. Intravenous contrast also helps in differentiating tumor with surrounding edema from transverse myelitis.

Additional Acute Neurologic Complications of Malignancy

Neurologic complications of cancer treatment include chemotherapy- or irradiation-induced brain edema, attendant intracranial hypertension, and opportunistic infection from systemic immunosuppression [5]. Infectious meningitis is often undetectable at unenhanced head CT; however, entities such as invasive fungal sinusitis or herpes encephalitis can be apparent on unenhanced head CT and further characterized with brain MRI. Paraneoplastic limbic encephalitis, which can present with acute onset confusion, short-term memory loss, hallucinations, and mood changes, is particularly difficult to diagnose clinically as it can be confused with primary psychiatric conditions. Furthermore, limbic encephalitis can have a similar imaging appearance to herpes encephalitis [5]. In 70–80 % of patients with limbic encephalitis, MRI FLAIR or T2 sequences show hyperintense signal in one or both medial temporal lobes (Fig. 4) [19]. The tumors most frequently implicated are small-cell lung cancer, testicular germ cell neoplasms, thymoma, Hodgkin lymphoma, and teratoma [19].

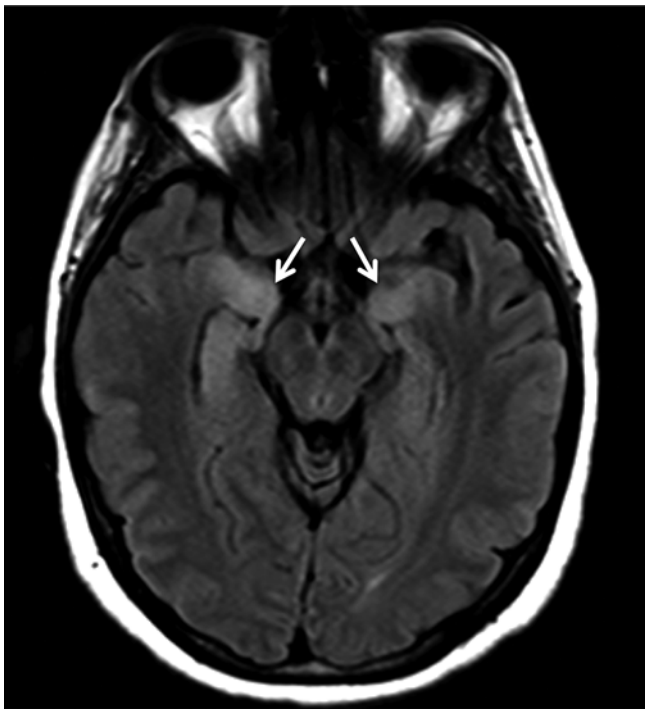

Fig. 4 Single FLAIR axial brain MR image in an emergency department patient with small-cell lung cancer and altered mental status depicts bilateral medial temporal hyperintensity (*arrows*). Diagnosis of paraneoplastic limbic encephalitis was based on clinical and imaging characteristics

Chest Emergencies

Central Airway Obstruction

Airway compromise necessitating palliative treatment occurs in 20–30 % of patients with lung cancer over the course of their lifetime [20, 21]. Airway narrowing can result from intrinsic tracheobronchial disease, extraluminal compression by tumor, or a combination of both [2, 20]. Anatomical distortion of the airways as a result of surgery for lung cancer can also lead to airway compromise [20]. Chest radiography is often the initial imaging test in these patients and may reveal a mass involving the lung parenchyma, hilum, or mediastinum with associated post-obstructive atelectasis or pneumonia [2]. Tracheal deviation or airway narrowing may be present [22].

The imaging gold standard for the assessment of the central airway obstruction is contrast-enhanced CT chest and neck (above the thoracic inlet) (Fig. 5) [20]. CT accurately depicts the severity and extent of airway stenosis and helps differentiate intrinsic from extrinsic disease. CT also helps separate primary malignancy from metastases and distinguish tumor from atelectasis or post-obstructive pneumonia [2, 23]. Post-processed images, such as virtual bronchoscopy, can render the tracheobronchial tree in a visual format familiar to the clinician for planning palliative interventions, such as stenting or ablative therapies, complementing conventional bronchoscopy to improve the technical success of airway recanalization (Fig. 6) [2]. FDG-PET will accurately discriminate a malignant hilar mass from adjacent post-obstructive atelectasis; however, patient preparation, imaging acquisition time, and availability limit its usefulness in the emergent setting [1].

Esophagorespiratory Fistula

Esophagorespiratory fistula formation is a relatively rare, but potentially devastating, complication of esophageal and bronchogenic carcinoma, occurring in up to 22 % of esophageal malignancy and around 1 % of bronchogenic carcinoma

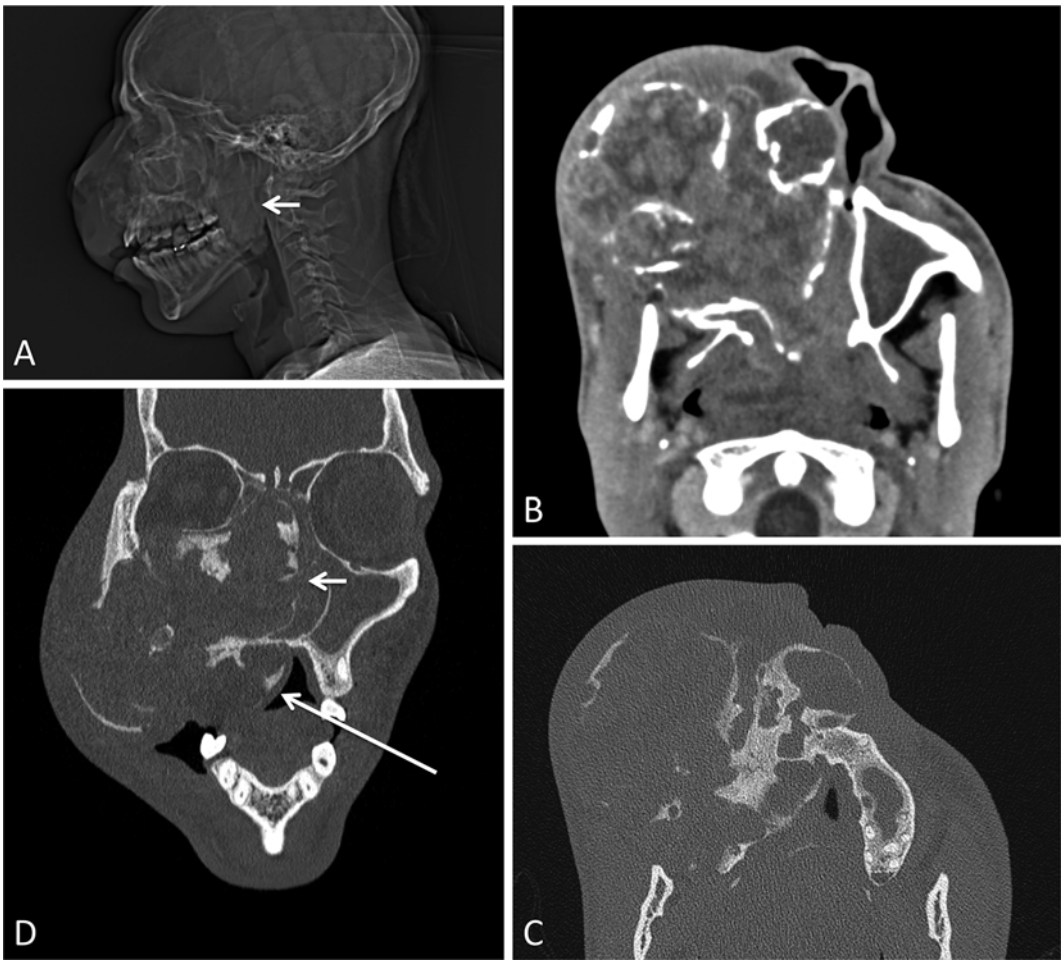

Fig. 5 This patient had a progressive feeling of "not getting enough air" and presented to the emergency department. This case of advanced ameloblastoma of the right maxillary alveolar ridge in a young man demonstrates tumor mass effect involving the face and upper airway. The lateral scout image from head CT (**a**) depicts facial deformity as well as tumor replacing much of the nasopharynx (*white arrow*). Axial contrast-enhanced facial CT using soft tissue window (**b**) and bone window (**c**) depicts substantial mass effect in the right lower face and widespread local bone destruction. Coronal image (**d**) demonstrates the complete occlusion of the nasal cavity from tumor invasion and mass effect (*short arrow*) and also substantial mass effect on the oral cavity (*long white arrow*)

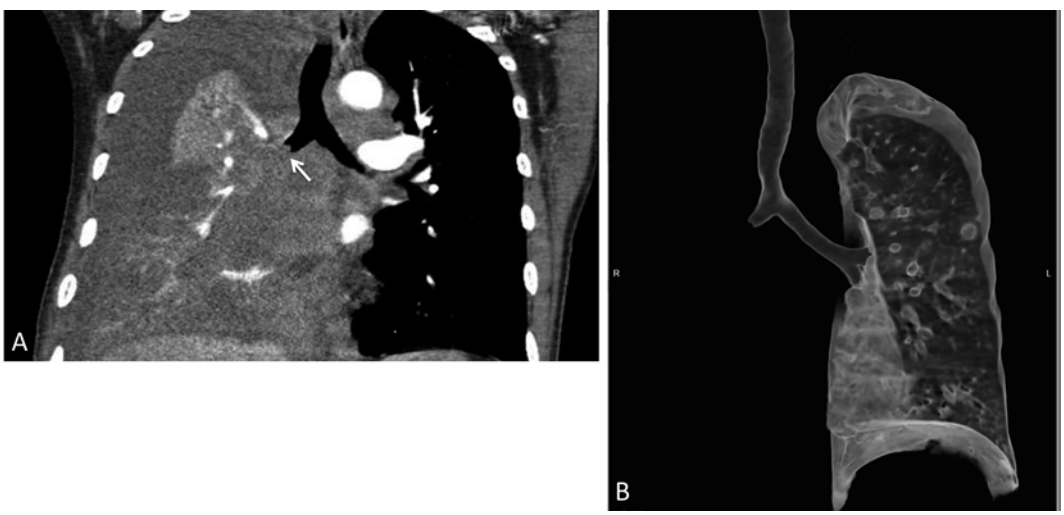

Fig. 6 Coronal contrast-enhanced chest CT (**a**) in a patient with squamous-cell carcinoma demonstrates soft tissue occluding the right main bronchus (*arrow*) with total collapse of the right lung, inseparable from malignant tissue. Volume-rendered virtual bronchoscopy was created from the original contrast-enhanced chest CT dataset (**b**)

[24, 25]. Nodal metastases and lymphoma can erode into the esophagus and airways and have also been implicated in esophagorespiratory fistula development [25, 26]. The risk of death is related to sepsis from repeated episodes of aspiration or from overwhelming lung infection [24]. Chest radiography findings are nonspecific and can include airspace consolidation, lung abscess, and pleural effusion resulting from aspiration of secretions and ingested material [26].

Fluoroscopic evaluation of the aerodigestive tract during the administration of an oral contrast agent will depict simultaneous opacification of the esophagus and tracheobronchial tree distal to the fistula. This procedure is best performed using a low-osmolar, water-soluble, iodinated contrast agent (iohexol), as large volumes of aspirated barium can compromise alveolar oxygen exchange and extravasated barium can incite an inflammatory response in the mediastinal soft tissues. Aspiration of high-osmolar, water-soluble contrast agents can lead to pulmonary edema and should likewise be avoided [27]. Chest CT performed after orally ingested contrast (CT esophagography) may demonstrate a direct communication between the respiratory tract and esophagus at the site of fistula formation with additional findings of ingested contrast agent within the respiratory tract distal to the fistula [26]. Abnormal soft tissue is often identified in the region of the fistula, indicating the site of malignancy [28]. CT is helpful in evaluating the extent and number of fistulas and the presence of a possible esophagopulmonary fistulous communication [26]. Virtual bronchoscopy or esophagography can enhance diagnostic confidence and serve as a component of treatment planning for emergent intervention [26].

Superior Vena Cava Syndrome

Malignancy is responsible for 90 % of cases of superior vena cava syndrome (SVCS) [29]. Benign causes of SVCS include thrombosis from indwelling catheters, fibrosing mediastinitis due to immune response to *Histoplasma capsulatum* or tuberculosis, prior radiotherapy, cardiac pacer wires, and Behçet disease [24, 29, 30]. The clinical features of SVCS relate to venous congestion due to obstruction of the SVC from extrinsic compression by tumor or intraluminal occlusion from bland or tumor thrombus. Primary malignancy involving the superior vena cava resulting in SVCS is exceptionally rare [31]. Because bronchogenic carcinoma accounts for the majority of malignancy-related SVCS, chest radiography may reveal a lung mass with possible associated hilar or mediastinal involvement; however, cross-sectional imaging is necessary to confirm the diagnosis and identify the underlying etiology. Conventional venography was previously the imaging gold standard for diagnosing SVCS, but in contemporary practice, it is employed solely during endovascular intervention [31].

Contrast-enhanced chest CT is currently the preferred imaging modality for the assessment of SVCS. If this condition is suspected on the basis of clinical presentation, CT image acquisition following a 60-s delay optimally opacifies the systemic venous system and ideally characterizes the level (above or below the azygos arch) and extent of SVC obstruction [31]. Practically speaking, however, the diagnosis is often made on routine chest CT or CTPA protocol with shorter time delays [31]. Features of contrast-enhanced chest CT include complete occlusion of the SVC, an intraluminal filling defect within the SVC, marked narrowing of the SVC from surrounding soft tissue, and opacification of mediastinal or chest wall venous collateral vessels (Fig. 7) [31]. Included images of the upper abdomen may demonstrate intense enhancement of the medial segment of the left hepatic lobe ("quadrate lobe"), reflecting collateralization of the superficial epigastric veins and the left portal vein [31]. CT imaging findings of SVC obstruction may precede the development of the clinically apparent syndrome and present an opportunity for early intervention [29]. The underlying cause of the obstruction, most commonly bronchogenic

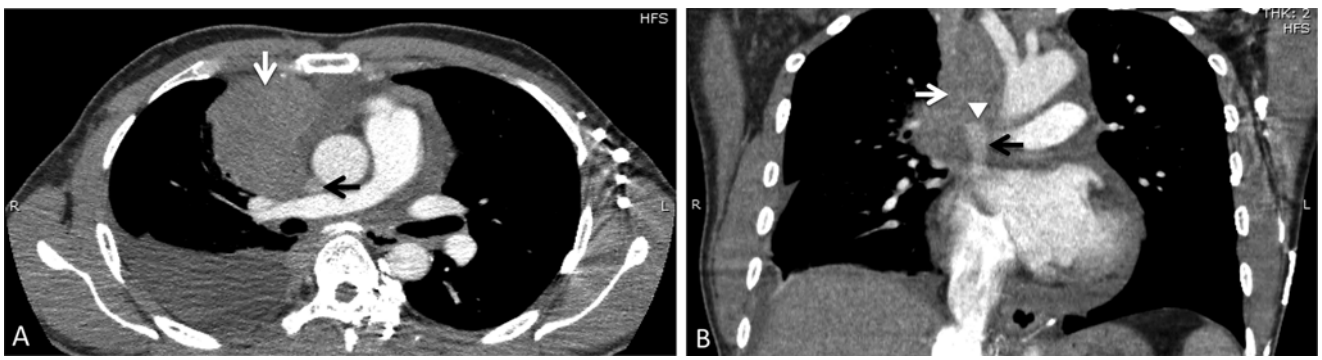

Fig. 7 Axial (**a**) and coronal (**b**) contrast-enhanced chest CT images demonstrate malignant SVC occlusion in this patient presenting with clinical SVC syndrome. Bulky enhancing soft tissue mass (*short arrows*) obliterates the expected location of the SVC. The inferior portion of the SVC is narrowed and displaced medially on the coronal image (**b**), superior to which SVC cutoff from tumor involvement is noted (*arrow head*). Tissue sampling revealed bronchogenic carcinoma. A right pleural effusion is also present

carcinoma, lymphoma, or extrathoracic metastatic disease when considering malignant etiologies, will also be depicted at CT, representing a critical diagnostic advantage over catheter venography [28]. Although enhancement of soft tissue within the SVC represents intraluminal tumor, presumptive soft tissue enhancement without pre-contrast images for reference can be misleading. CT axial images and post-processed coronal and sagittal reformatted images also assist in planning for endovascular interventions. MRI approaches 100 % sensitivity and specificity in the diagnosis of SVCS but is rarely used in the emergency setting due to limited scanner availability and patient characteristics [29].

Endovascular stenting has replaced chemotherapy and radiation therapy as the treatment of first resort in malignant SVCS, except in the case of chemotherapy-sensitive lymphoma, due to rapid clinical response and established long-term patency [29]. SVC stenting is carried out in the angiography suite. Under ultrasound guidance, the internal jugular, femoral, or subclavian vein is accessed, and superior vena cavography is performed to confirm the extent of disease and inform stent selection and placement. Using guidewires, the obstruction is traversed and progressive dilatation of the obstructed lumen is optionally preformed prior to stent placement. In addition, local thrombolysis and mechanical thrombectomy may reduce the length of obstruction and risk of pulmonary emboli; however, thrombolysis has been associated with an increased risk of periprocedural bleeding [29]. A self-expanding endoprosthesis is deployed across the obstruction, taking care to not apply excessive pressure, which can result in SVC rupture and cardiac tamponade [29]. A chest radiograph is usually obtained following the procedure to confirm satisfactory stent placement and to serve as a baseline reference for future imaging. Reduction in symptoms is immediate and clinical response to stenting is around 95 % in bronchogenic carcinoma [32]. Recurrence of obstruction has been reported with an incidence of 0–40 % [33]. Repeat stent placement is indicated in these cases and is associated with a high success rate [33].

Massive Hemoptysis

Massive hemoptysis is generally defined as expectoration of ≥300–600 mL of blood within a 24-h period and is associated with a 9–38 % mortality rate [34, 35]. While pulmonary tuberculosis is the leading cause of hemoptysis worldwide, bronchogenic carcinoma is the most common malignant etiology [35]. Unstable patients presenting with massive hemoptysis are usually initially managed with bronchoscopy, which localizes the site of bleeding into the airways with a 73–93 % diagnostic yield and can be used for hemostasis [34]. Chest CTA performs equally well in determining the site of hemorrhage but is superior to bronchoscopy in identifying the underlying cause [34]. Chest radiography may reveal a lung mass, cavitary lesion, consolidation, or mediastinal mass, but up to ¼ of patients with malignancy as the cause for hemoptysis may have a normal chest radiograph [36]. In most patients, chest CTA with post-processing is the diagnostic study of choice and can identify the site, underlying cause, and vascular origin of bleeding with a high degree of accuracy [35]. In 90 % of patients with massive hemoptysis, a bronchial artery source is implicated [34]. On chest CTA, an abnormally dilated (≥2 mm diameter) or tortuous bronchial artery is suspicious for source of bleeding and targeted for embolization (Fig. 8) [35]. Active extravasation of contrast, while highly specific, is relatively rare, present in only 3.6–10.9 % of cases [35].

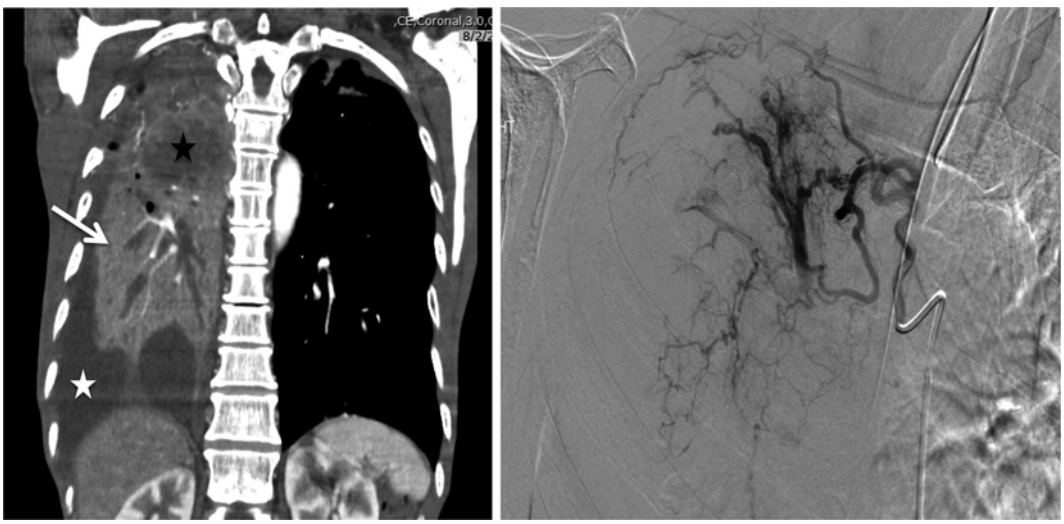

Fig. 8 (**a**) Coronal contrast-enhanced chest CT in a patient with massive hemoptysis depicts a hypodense right suprahilar mass (*black asterisk*) and subtotal right lung collapse (*arrow*). Pleural fluid is also seen adjacent to the collapsed lung (*white asterisk*). (**b**) Accompanying bronchial artery angiography with dilated and tortuous bronchial arteries, which were subsequently embolized, resulting in hemostasis

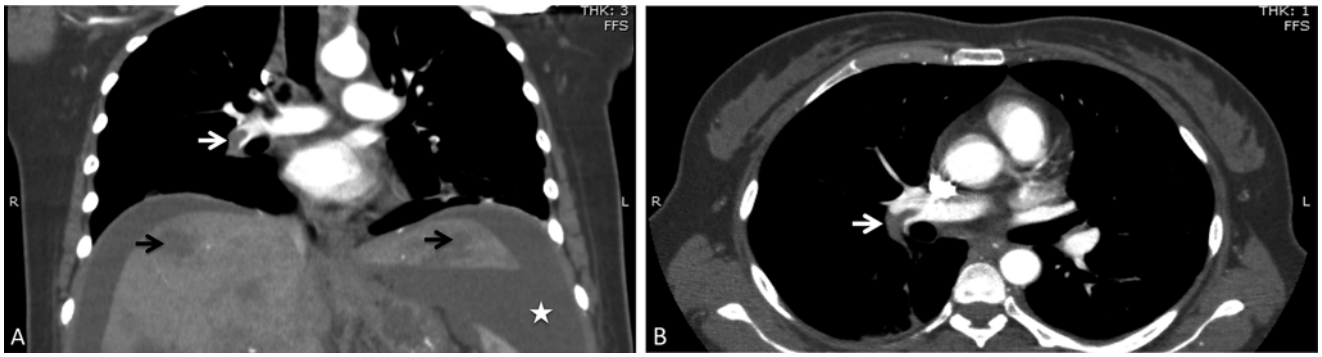

Fig. 9 Coronal (**a**) and axial (**b**) contrast-enhanced chest CT images demonstrate a hypodense filling defect in the contrast-opacified lumen of the right main pulmonary artery, with extension into the interlobar pulmonary artery, compatible with acute pulmonary embolism (*white arrows*). Also visible in the upper abdomen are multiple hepatic metastatic lesions (*black arrows*) and malignant ascites (*asterisk*)

In addition to high diagnostic yield, chest CTA aids in planning the approach to catheter angiography and has been shown to decrease procedure time and technical success rate of subsequent embolotherapy [34, 35]. Bronchial artery embolization is an effective and safe treatment for massive hemoptysis with documented 73–99 % success in effecting immediate control of bleeding [35]. Recurrence occurs in 10–29 % in the first month and relates to incomplete embolization due to extensive disease or an occult non-bronchial or pulmonary arterial source [35]. These patients are usually effectively retreated with embolization.

Pulmonary Embolism

Acute pulmonary embolism (PE) is a leading diagnostic consideration in the oncologic patient presenting with acute chest pain. Left untreated, acute PE can be fatal [37]. Cancer patients are at particularly heightened risk for thromboembolic disease due to hypercoagulability. Used in conjunction with various clinical decision instruments and D-dimer values to measure pretest probability, imaging plays an essential role in the diagnosis. As with any patient presenting with acute chest pain, chest radiography is used as an initial screening modality, although most patients with acute PE will have a normal chest radiograph [37]. The Westermark sign (geographic lucency related to pulmonary arterial obstruction) and Hampton hump (wedge-shaped, peripheral consolidation representing infarcted lung tissue), though classically associated with acute PE, are rarely seen in practice. More commonly, atelectasis or airspace consolidation may be present in a minority of patients, but these findings are not specific [37]. The chief utility of chest radiography is to exclude other etiologies for chest pain, including pneumonia, pneumothorax, or pleural effusion [37]. In addition, chest radiography is helpful in interpreting ventilation/perfusion (V/Q) scintigraphy.

After excluding other causes of acute chest pain, CTPA is the imaging modality of first resort for diagnosis of acute PE. CTPA has well-established diagnostic accuracy, with 86 % positive predictive value and 95 % negative predictive value, having surpassed catheter pulmonary arteriography as the imaging gold standard [37, 38]. On CTPA, a centrally located hypodense intraluminal filling defect within the densely opacified pulmonary arterial system is seen in acute PE (Fig. 9) [37, 38]. Suboptimal vascular opacification and respiratory motion can reduce the diagnostic accuracy of CTPA, with a nondiagnostic rate of around 6 %, whereas V/Q scintigraphy is inconclusive in over 25 % of cases [37]. Incidental, but important, additional findings can be detected with CTPA, such as pulmonary nodules and mediastinal lymphadenopathy [38].

Doppler and grayscale sonography of the deep venous system in the extremities is frequently employed as an adjunct to CTPA, since 36–45 % of patients with acute PE have proximal deep venous thrombosis (DVT) [38]. Features of DVT on sonography include visualization of intraluminal thrombus, loss of venous compressibility, venous distention, and the absence or diminution of Doppler color or spectral signal [37]. Serial negative extremity ultrasound examinations may obviate the need for additional investigative procedures or treatment in patients who are not candidates for CTPA related to renal insufficiency or adverse reaction to iodinated contrast or for whom CTPA or V/Q imaging is indeterminate [37]. By the same token, patients with evidence of extremity DVT by ultrasound and high pretest clinical suspicion for acute PE can be treated empirically without confirmatory imaging [38]. MR pulmonary angiography (MRPA) with and without gadolinium-based contrast agents has been studied in the evaluation of acute PE. Despite good documented diagnostic performance in technically adequate examinations, MRPA is currently not recommended for routine use due to limited availability and expertise in interpretation and suboptimal technical success [38].

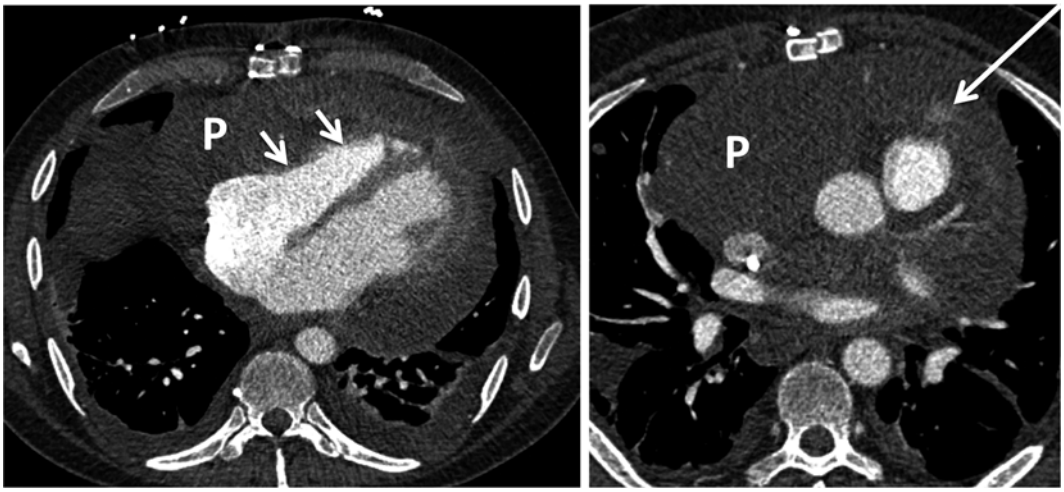

Fig. 10 Contrast-enhanced axial chest CT in a patient with metastatic melanoma depicts a large pericardial effusion (P). Findings are compatible with malignant effusion by CT given the effusion density and the nodular-enhancing tumor foci (*long arrow*). Flattening of the right ventricular wall is suggestive of cardiac tamponade physiology (*short arrows*)

Pericardial Effusion and Pericardial Tamponade

Pericardial effusion and tamponade can be caused by primary malignancy in the chest, metastatic disease from a remote primary location, and following treatment for malignancy [39]. Common primary malignancies associated with pericardial effusion include bronchogenic carcinoma, breast carcinoma, lymphoma, and leukemia [39]. Lymphatic obstruction by tumor deposits is the predominant mechanism responsible for the development of malignant pericardial effusion, although direct contiguous extension (bronchogenic, esophageal, and breast) and hematogenous spread of tumor (lymphoma and leukemia) are other notable pathways for pericardial malignant disease [40]. Primary pericardial malignancies, such as mesothelioma or fibrosarcoma, are exceptionally rare etiologies for pericardial effusion [41, 42]. If accumulation of pericardial fluid is rapid, as little as 200–250 mL can result in tamponade physiology due to the relative inextensibility of the parietal pericardium [40, 43].

A large pericardial effusion will result in an enlarged cardiac silhouette with a "water bottle" conformation on chest radiography [43]. On echocardiography, a pericardial effusion is readily apparent, and prolonged right atrial collapse during late diastole and right ventricular collapse in early diastole are characteristic for cardiac tamponade [43]. In the emergency setting, contrast-enhanced chest CT is ideally suited to establish the presence, extent, and possible cause of a pericardial effusion leading to tamponade. Fluid measuring near-water attenuation suggests a simple effusion, whereas higher density fluid caused by hemorrhagic tumor deposits and cellular debris is often seen in malignant pericardial effusion [44]. An irregularly thickened (≥2 mm) pericardial lining with enhancing nodularity is highly suspicious for a malignant etiology in the appropriate setting, although mycobacterial infection can also have this appearance (Fig. 10) [44]. If a lung or chest wall mass and/or mediastinal adenopathy is present on CT, these findings would lend support to a malignant cause of a pericardial effusion. Definitive diagnosis is made by cytological examination of aspirated fluid. Treatment by pericardiocentesis with or without drain placement is performed with CT or echocardiography guidance [22, 28].

Abdominopelvic Emergencies

Bowel Emergencies

Bowel obstruction in patients with abdominal or pelvic malignancy results from impingent on the bowel lumen from intrinsic mural disease or from extramural compression, usually from serosal implants (Fig. 11). In addition, many oncologic patients have undergone prior abdominal or pelvic surgery, which predisposes to bowel obstruction secondary to adhesions [45]. Colorectal carcinoma (10–30 %) and ovarian malignancy (20–50 %) are the most common cancers associated with bowel obstruction. Metastatic disease is more commonly implicated than primary malignancy in small-bowel obstruction, as it is usually secondary to compressive effects from peritoneal metastases; however, primary gastrointestinal malignancy can rarely result in obstruction (Fig. 12). Additional primary cancers that can present with peritoneal metastases, and predispose to small-bowel obstruction, include gastric, pancreatic, breast, and lung [45].

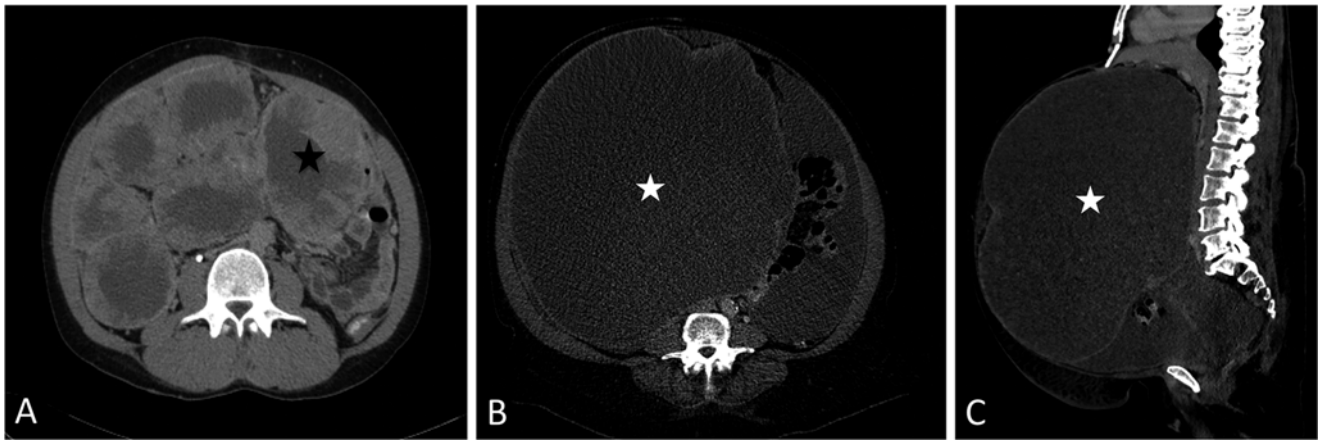

Fig. 11 Certain tumors, particularly late in a patient's disease course, can exert tremendous mass effect in the peritoneal cavity. By virtue of this mass effect, they can compress the GI or GU tracts and result in early satiety, nausea, vomiting, and bowel or ureteral obstruction, respectively. A contrast-enhanced axial CT image of the abdomen and pelvis (**a**) demonstrates multiple large peripherally enhancing peritoneal implants from choriocarcinoma (representative lesion indicated by a black asterisk), which significantly displace normal structures. In a different patient, axial (**b**) and sagittal (**c**) contrast-enhanced CT images of the abdomen and pelvis demonstrate bulky multicystic masses (*white asterisks*) with very thin walls arising from a mucinous ovarian cystadenoma

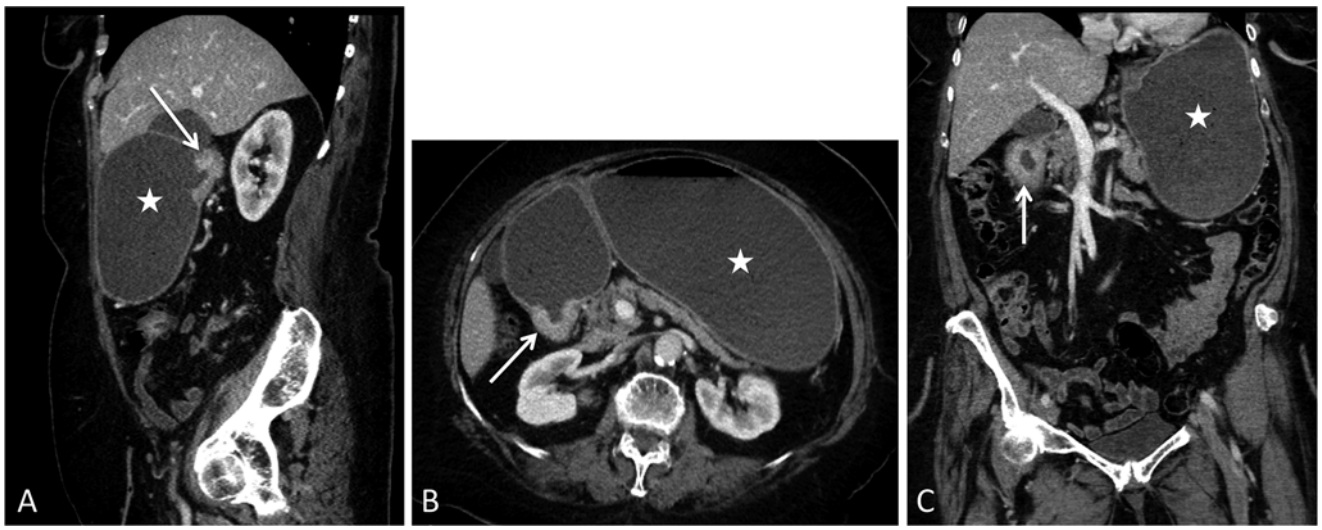

Fig. 12 57-year-old presented to the emergency department with nausea and vomiting. Sagittal (**a**), axial (**b**), and coronal (**c**) contrast-enhanced CT images of the abdomen and pelvis demonstrate a dilated fluid-filled stomach (*asterisk*). At the gastric antrum, there is irregular, enhancing wall thickening resulting in gastric outlet obstruction (*arrows*). Pathology revealed poorly differentiated gastric adenocarcinoma of the distal stomach and pylorus

In the emergency setting, suspected bowel obstruction is often initially assessed with abdominal radiography. Supine abdominal radiographs may demonstrate abnormally dilated small bowel (≥2.5 cm in diameter) in small-bowel obstruction and small bowel and colon in colonic obstruction [46]. Upright abdominal radiographs may show multiple air-fluid levels or, in the case of viscus perforation, free-air accumulation under the diaphragms. Plain radiography is only around 50–60 % accurate in the evaluation of small-bowel obstruction and does not adequately predict the site of obstruction [46, 47]. Contrast-enhanced CT of the abdomen and pelvis is the imaging of choice when evaluating for bowel obstruction, with far superior accuracy in securing the diagnosis (95 %) and locating the site of obstruction [47]. On CT, dilated small bowel ≥2.5 cm (outer wall-to-outer wall) is seen proximal to a discrete transition point, distal to which the remainder of the small bowel and the colon are relatively decompressed (Fig. 13) [46]. Abnormal enhancing or necrotic soft tissue may be seen in the region of the transition point, representing peritoneal metastatic disease or, rarely, primary bowel malignancy. In contradistinction to small-bowel obstruction, large-bowel obstruction is most often caused by primary colorectal malignancy as opposed to metastatic disease [48]. Large-bowel obstruction is diagnosed when both small bowel and

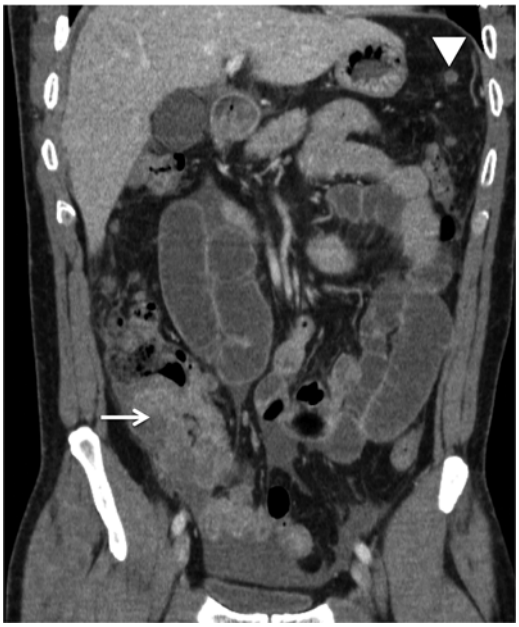

Fig. 13 Single coronal contrast-enhanced CT image of the abdomen and pelvis in a patient presenting with nausea and vomiting demonstrates a heterogeneously enhancing cecal-region mass (*arrow*). There are dilated, fluid-filled segments of small bowel, compatible with small-bowel obstruction. Pathology revealed appendiceal carcinoma. Note serosal metastatic implants (*arrowhead*)

colon (≥9 cm for cecum, otherwise ≥6 cm) are dilated proximal to a transition point within the colon [49]. Differentiating a transition point from a post-inflammatory or ischemic stricture in large-bowel obstruction on CT can be difficult given similar imaging appearances. The presence of enlarged local lymph nodes may suggest a malignant etiology. Oral or rectal contrast is typically not administered except for suspected bowel complications, such as perforation or fistula or sinus tract formation [47, 50]. MRI is generally not used for evaluating bowel obstruction and is often reserved for pregnant or pediatric patients, in whom ionization radiation exposure is of particular concern.

Among patients with spontaneous pneumoperitoneum secondary to bowel perforation, 14 % are attributable to malignancy [51]. Plain radiography is diagnostic in only 30–59 % of cases of free intraperitoneal gas but approaches 100 % accuracy in large-volume pneumoperitoneum [51]. Radiographic signs include free air under the diaphragms, increased bowel wall visualization from the presence of extraluminal and intraluminal gas (Rigler sign), lucency outlining the falciform ligament (falciform ligament sign), air outlining the entire abdominal cavity (football sign), and a hyperlucent liver [51]. Abdominal radiography cannot predict the site of perforation. CT, however, is exceedingly sensitive for the detection of free peritoneal gas (96–100 %) and can correctly identify the site of perforation with 80–90 % accuracy [51]. CT features of bowel perforation include discrete bowel wall defect and extraluminal gas, oral or rectal contrast, or bowel contents [51]. Both colorectal carcinoma and gastrointestinal lymphoma are complicated by perforation with a prevalence of up to 9 %, and systemic chemotherapy has been observed to further increase the risk of perforation in bowel lymphoma [52].

Ischemic colitis can coexist with colonic malignancy with an incidence of up to 7 %, and 20 % of patients with ischemic colitis have an underlying colorectal cancer [53, 54]. Ischemic colitis secondary to malignancy can result from increased intraluminal pressure and subsequent diminished blood flow in the dilated colon proximal to site of primary malignancy. In cases without mechanical obstruction, bacterial overgrowth in stagnant segments of colon has been implicated in ischemic colitis [55]. Pancreatic adenocarcinoma can compress the superior mesenteric artery and vein, resulting in critically diminished perfusion and subsequent bowel ischemia [55]. Metastases to the mesenteric root, including colon, breast, ovarian, and lung primaries, can similarly result in bowel obstruction by direct vascular impingement [1]. In ischemic bowel, contrast-enhanced CT of the abdomen and pelvis is the imaging modality of choice, and features include mural thickening, submucosal edema (low attenuation) or hemorrhage (high attenuation), engorgement of mesenteric vessels, mesenteric edema, altered or absent mucosal enhancement, intramural gas, or portal venous gas. Permeation of intraluminal gas across damaged mucosa causes intramural gas and appears as focal or circumferential locules of air within the colonic wall. Gas can then propagate into the mesenteric and portal veins, giving the appearance of air-attenuation filling defects within these vessels.

Intussusception is characterized by telescoping of a segment of bowel along with its corresponding mesentery into an adjacent segment of bowel. Whereas 95 % of cases of intussusception are idiopathic in children, 80–90 % of adult cases are associated with underlying mass lesions, referred to as "lead points," and are most commonly polypoid bowel neoplasms [56, 57]. In 30 % of small bowel and 60 % of colonic intussusceptions, an intramural or extrinsic lead point will be malignant [56]. At CT, intussusception is characterized by a "bowel-within-bowel" appearance with direct visualization of an inner bowel segment and surrounding fat (intussusceptum) enveloped by an adjacent outer segment of bowel (intussuscipiens), with or without accompanying vessels, rendering a targetoid or sausage-like appearance [48, 57]. Intussusception can be complicated by bowel obstruction or ischemia, the features of which are described above.

Spontaneous Intra-abdominal Hemorrhage

Spontaneous hemorrhage from visceral organ malignancy is a rare, but potentially catastrophic, oncologic emergency. Ten to fifteen percent of patients with hepatocellular carcinoma

will present to the emergency department with tumor rupture leading to intraparenchymal hematoma, subcapsular hematoma, hemoperitoneum, or some combination. Risk factors for spontaneous hemorrhage of hepatocellular carcinoma include peripheral or subcapsular location and large tumor size [58]. Hypervascular metastases to the liver, such as melanoma, renal cell carcinoma, and lung cancer, are at particularly heightened risk for spontaneous hemorrhage. Reports of spontaneous hemorrhage from primary angiosarcoma of the liver have been documented [3]. Although spontaneous splenic rupture is more commonly reported in infection, notably *Cytomegalovirus*, Epstein–Barr virus, or malaria, lymphomatous or leukemic splenic involvement can also give rise to severe hemorrhage, necessitating immediate endovascular treatment or splenectomy [59].

Spontaneous tumor rupture is evaluated with contrast-enhanced CT of the abdomen and pelvis in order to confirm the presence of rupture, identify the site of involvement, and determine the extent of hemorrhage (Fig. 14). The appearance of extravascular blood on CT varies in a time-dependent manner. Acute blood products will demonstrate an attenuation in the range of 30–45 HU, whereas clotted blood has attenuation values from 45 to 70 HU [3]. When a focal area of high-density clotted blood is seen in the abdomen or pelvis on a background of lower-density, more acute-appearing hemorrhage, it is referred to as the "sentinel clot" and points to the site of primary source of bleeding [3, 48]. On occasion, ongoing bleeding can be seen during the acquisition of CT images as "active extravasation of contrast," with focal areas of high-density (85–370 HU) extraluminal IV contrast material and surrounding clotted hematoma [60]. Ongoing bleeding requires emergent surgical or endovascular interventions to control blood loss. In this setting, particularly with unstable patients, catheter angiography and catheter-directed embolization can aid in management.

Urinary and Biliary Obstruction

Approximately one-quarter of patients with pelvic or retroperitoneal malignancy will develop life-threatening urinary obstruction [1]. Progressive urinary tract obstruction most often results from compression or invasion of the ureters, most commonly the distal 1/3 of the ureters below the level of the common iliac arteries, by primary malignancies, such as prostate, urinary bladder, cervix, ovarian, or colorectal [1, 61]. Lymphoma, sarcoma, and, less likely, retroperitoneal metastatic disease from primary cancers, such as cervix, urinary bladder, prostate, colorectal, ovary, and testes, can likewise result in ureteric obstruction by direct tumor invasion or compression [1, 61].

Hydronephrosis and hydroureter can be identified by ultrasound as expansion of the renal collecting systems and ureters with anechoic urine. The obstructing mass may not be evident at ultrasound, and advanced cross-sectional imaging is usually required to assess for the presence, size, and location of the malignancy. In the emergency setting, CT is often initially employed, either as standard single-phase post-contrast CT or formal CT urography. In single-phase CT, both the obstructed urinary tract and offending lesion are clearly depicted. A delayed enhancement pattern of the ipsilateral kidney may be present, reflecting compromised excretion of contrast due to downstream obstruction (Fig. 15). CT urography is not often employed in the acute setting but would consist of an unenhanced image set, followed by nephrogenic phase (100 s after IV contrast administration) and excretory phase (3 min post-contrast) imaging [62]. The urographic component, however, may be limited in severe obstruction, which would inhibit excretion of contrast. Treatment of malignant urinary obstruction is palliative, as median survival is measured in months [61, 63]. Nephroureteral stent and percutaneous nephrostomy tube

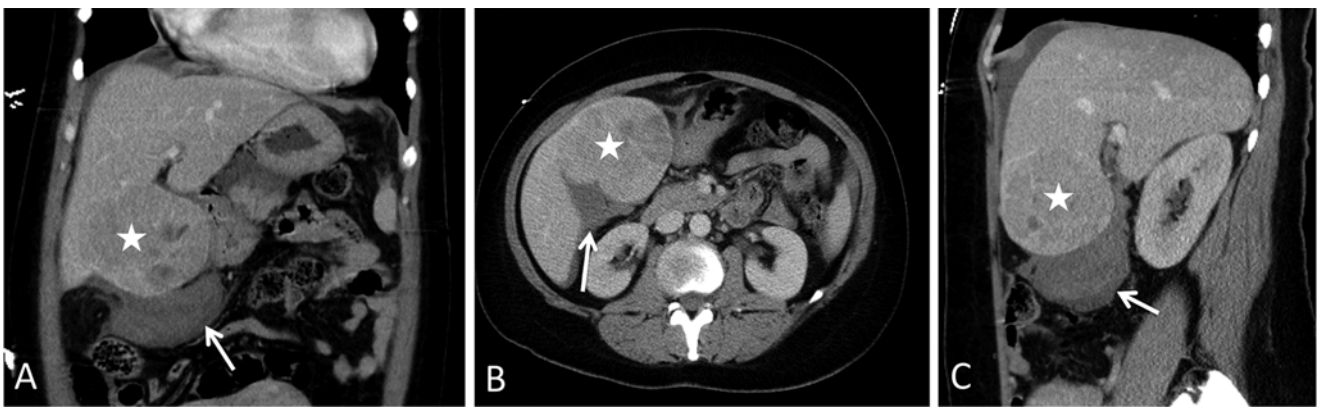

Fig. 14 A 47-year-old patient presented to the emergency department with acute onset right upper quadrant pain. Coronal (**a**), axial (**b**), and sagittal (**c**) contrast-enhanced CT images of the abdomen reveal a heterogeneously enhancing exophytic hepatic mass (*asterisk*) arising from the right hepatic lobe. There is surrounding high-density fluid, compatible with blood products (*arrows*). Pathology revealed hemorrhagic hepatocellular carcinoma

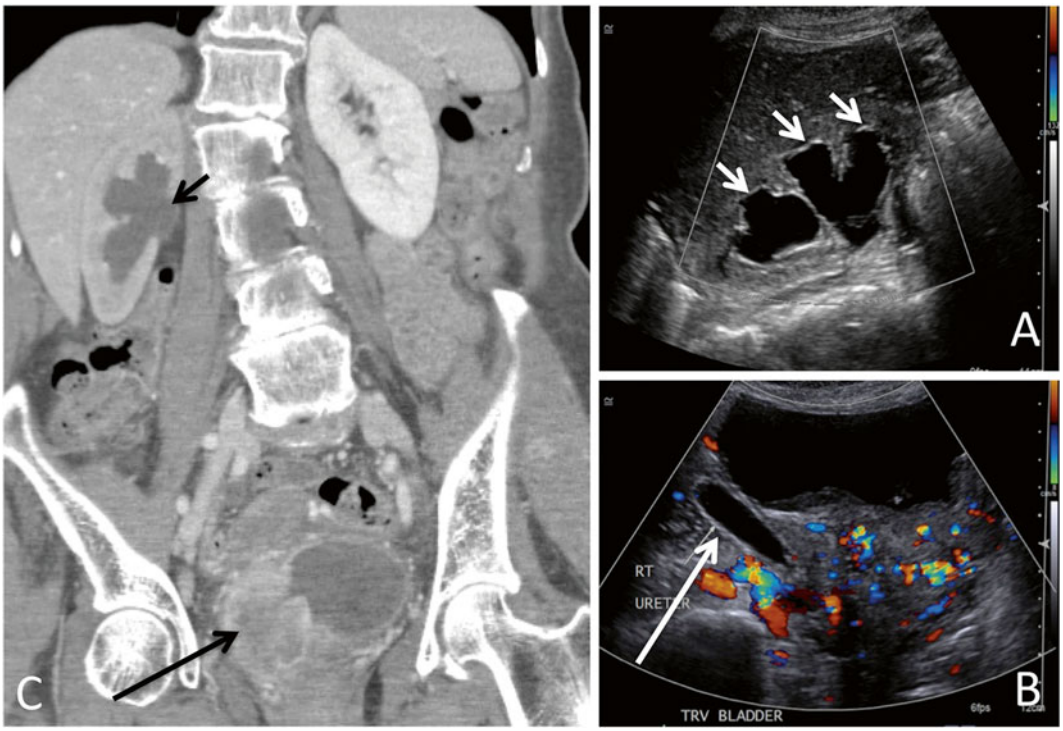

Fig. 15 A 70-year-old female with urinary bladder urothelial carcinoma. (**a** and **b**) Initial sonographic image shows dilation of the renal collecting system with calyceal blunting (*short white arrows*). Subsequent sonographic image of the pelvis shows dilation of the distal ureter (*long white arrow*), with vascularized soft tissue mass in the urinary bladder. Coronal CT image (**c**) redemonstrates hydronephrosis (*short black arrow*) and confirms the enhancing mass in the right aspect of the urinary bladder (*long black arrow*). Also present is relative hypoenhancement of the right kidney compared to the left kidney, termed a "delayed nephrogram," a finding often seen with higher-grade ureteral obstruction

placement are the most common interventions for palliative urinary diversion [61].

Obstruction of the biliary system from primary tumor invasion or compression of the bile ducts by hilar nodal metastases can result in significant mortality and morbidity [64]. Pancreatic adenocarcinoma, periampullary malignancy, and cholangiocarcinoma are most the most commonly implicated primary malignancies associated with biliary obstruction [64, 65]. In patients presenting with jaundice, abdominal pain and/or laboratory evidence of biliary obstruction, with known or suspected malignancy, abdominal ultrasound, CT, or MRI will confirm the obstruction and frequently identify the obstructing malignancy. CT and MRI offer the additional advantage of preprocedural planning and staging [66]. MR cholangiopancreatography (MRCP), which is always acquired in combination with conventional MRI of the abdomen, is a noninvasive imaging technique that provides exquisite anatomic detail of the dilated biliary tree and can often exclude choledocholithiasis as a cause of obstruction [67]. Endoscopic ultrasound can be complementary to CT and MRI/MRCP in difficult cases [66]. Pancreatic adenocarcinoma is typically characterized as an ill-defined, infiltrative mass, which is hypoattenuating with respect to normal pancreatic parenchyma on CT. In rare cases, pancreatic adenocarcinoma is indistinguishable from normal pancreatic tissue. When this occurs, the presence of malignancy in the pancreatic head can be inferred by the "double duct" sign, representing simultaneous common biliary and main pancreatic ductal dilatation [64]. Cholangiocarcinoma is classified as intrahepatic, hilar, and extrahepatic, and most occur at the bifurcation of the hepatic ducts (Klatskin tumor) [64]. At the time of presentation, the common imaging appearance of cholangiocarcinoma is biliary ductal dilatation, which can be focal or diffuse. On cross-sectional imaging, infiltrative hilar cholangiocarcinoma is further characterized by an ill-defined soft tissue mass with associated by bile wall thickening or complete duct luminal obliteration (Fig. 16). Intrahepatic (mass-forming) cholangiocarcinoma is hypovascular and demonstrates gradual centripetal enhancement in a time-dependent manner following IV contrast administration [64].

In patients with advanced malignant biliary obstruction, palliative biliary diversion can be performed surgically, endoscopically, or via a percutaneous approach. A surgical approach results in significant reduction in recurrent obstruction but is associated with a higher complication rate [65]. Endoscopic and percutaneous stenting using both plastic and metallic stents is associated with lower complication rates but higher re-occlusion rates and need for repeat procedures [65, 68]. In general practice, bypassing distal biliary obstruction is usually initially attempted with ERCP and

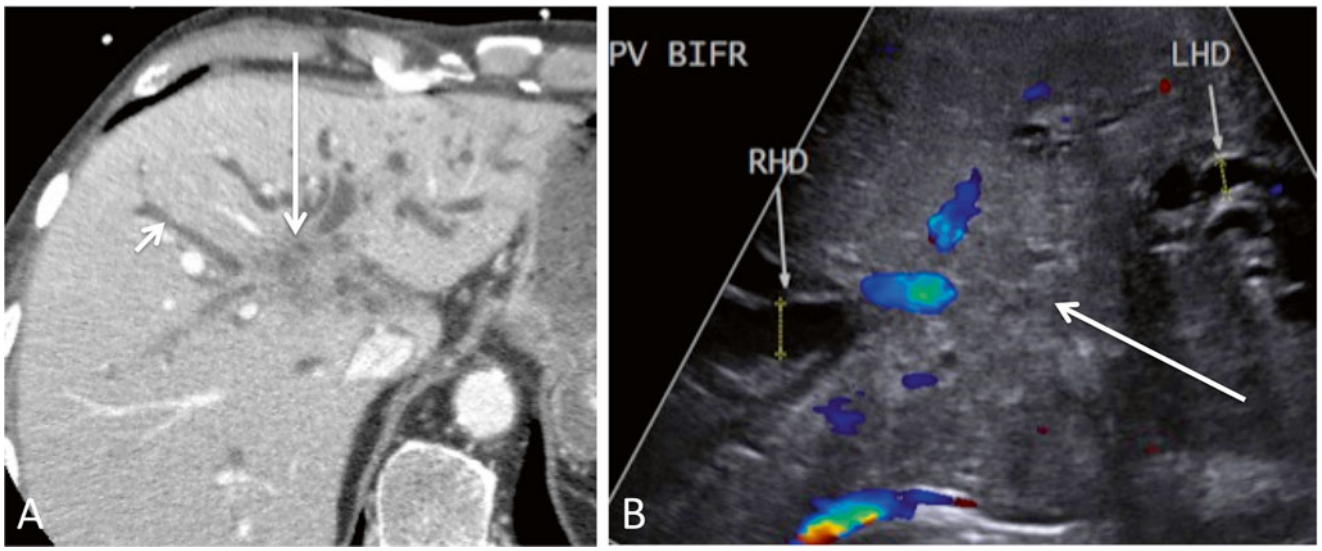

Fig. 16 Contrast-enhanced axial CT image of the abdomen (**a**) and transverse sonographic image centered at the hepatic hilum in a patient presenting to the ED with jaundice and right upper quadrant pain. The CT image depicts intrahepatic biliary ductal dilation (*short arrow*) and a hypoenhancing hepatic hilar mass, typical of cholangiocarcinoma (Klatskin tumor). Sonographic image of the right upper abdominal quadrant (**b**) demonstrates biliary ductal dilation and an ill-defined heterogeneous mass with Doppler signal, indicating vascularity. *RHD* right hepatic duct, *LHD* left hepatic duct

percutaneous biliary drainage and stenting reserved for endoscopic technical failure [68]. For proximal obstruction, both approaches can be taken, sometimes in combination, but a percutaneous approach, which is usually carried out in the interventional radiology suite, may be more appropriate when drainage of segmentally dilated bile ducts is desired, as percutaneous ultrasound can first identify these structures, allowing for a more targeted subsequent intervention using fluoroscopic guidance [68].

Musculoskeletal Emergencies

Pathologic Fractures

The musculoskeletal system is comprised of the axial and appendicular skeleton as well as the supporting muscles and soft tissues. Oncologic emergencies can affect both structural components, but skeletal complications are much more frequently encountered. Bone is the most common site for metastatic disease [69]. At postmortem examination, the incidence of metastatic bone disease was 73 % in breast cancer, followed in frequency by prostate (68 %), thyroid (42 %), lung (36 %), and renal (35 %) [69]. The burden of osseous metastatic disease correlates to the frequency of skeletal-related events (SREs), which include fractures, surgical or therapeutic intervention for bone lesions, spinal cord compression, and hypercalcemia of malignancy [70].

The destruction of trabecular and cortical bone by primary or metastatic tumor degrades the intrinsic structural stability and, therefore, weight-bearing capabilities of the bone and predisposes patients to pathologic fractures. These fractures occur in both the axial and appendicular skeleton but are most debilitating in the vertebra, pelvis, or lower extremities (Fig. 17).

Appendicular Skeleton

Regarding the long bones, plain radiographs provide rapid initial screening. When fractured, subsequent orthopedic consultation and stabilization of a pathologic fracture restores functionality and decreases pain. If plain radiographs are not revealing, but there remains a high clinical concern for fracture, further imaging may be warranted. Specifically, in patients with low bone mineral density, nondisplaced fractures can be occult by plain radiography, and if the patient cannot bear weight or has unexplained pain, further evaluation with cross-sectional imaging may be warranted. Unenhanced MRI provides very sensitive evaluation for both metastatic involvement of the bone and acute fracture; however, after-hours availability is not widespread. Normal bone marrow varies by location within the bone and patient age; however, in general, normal marrow can be categorized as hematopoietic or fatty. Fatty marrow is T1-hyperintense and T2-hyperintense, while hematopoietic marrow is slightly hypointense on both sequences. The proportion of hematopoietic marrow decreases with patient age. Marrow can be replaced or infiltrated by metastases, leukemia, or lymphoma, resulting in T1 signal that is hypointense relative to skeletal muscle (which serves as an internal frame of reference) [71]. On T2 fat-saturated and STIR imaging,

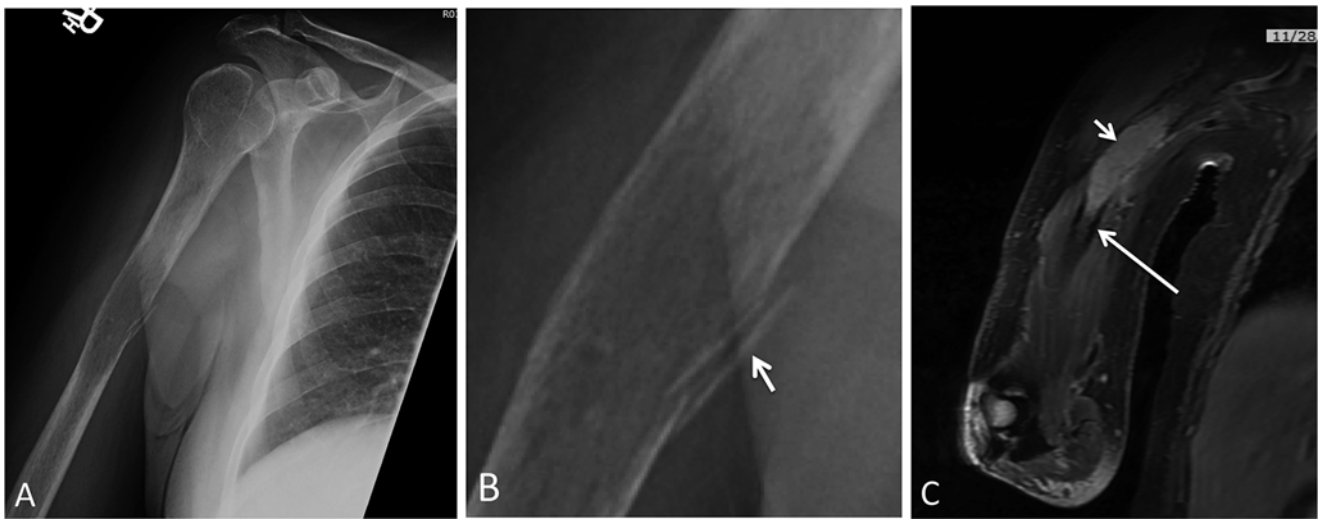

Fig. 17 AP radiograph of the humerus demonstrates a geographic, moth-eaten, lytic, destructive lesion, with cortical endosteal thinning and mild marrow cavity expansion (**a**). Image **b** is a magnified image of the associated pathologic fracture with adjacent cortical fragments (*arrows*). Coronal T1 post-contrast fat-saturated MR image (**c**) demonstrates enhancing soft tissue mass replacing the normal fatty marrow cavity (*short arrow*) and obliterating the T1-hypointense cortex (normal cortex shown with *long arrow*). Diagnosis is plasmacytoma with pathologic fracture

malignancy is usually hyperintense, resulting from intrinsically higher water content and reactive edema [71]. In the case of fracture, fluid-sensitive MRI sequences (T2 and T2 or PD with fat saturation) will demonstrate robust marrow edema, while T1 sequences are used to localize the site of cortical disruption. Unenhanced CT can be used in the emergent setting to identify and characterize fractures. The primary limitations of unenhanced CT in the evaluation of malignant involvement include diminished sensitivity for malignant soft tissue and early marrow metastatic disease.

Vertebral Fractures

Metastatic disease to the spine is the most common form of skeletal malignancy, and osteolytic bone destruction may occur in up to 2/3 of patients [69]. As previously noted, plain radiography is widely available and rapid, but relatively insensitive for pathologic vertebral body fractures. In the setting of trauma in cancer patients, if there is clinical concern for fracture, unenhanced CT is the imaging modality of choice for identification and characterization of fractures. At MRI, the presence of bone marrow edema (T2 or STIR hyperintensity) indicates an acute time course. The addition of IV contrast to an MR examination provides a more sensitive evaluation of epidural tumor extension but will not further characterize the underlying osseous malignancy and is not necessary in diagnosing fracture. This is because bone metastases do not always enhance after the administration of gadolinium. Sclerotic metastatic disease and treated or partially treated tumor foci, for example, typically do not enhance but will still be detected on MRI without IV contrast [71]. CT-guided vertebroplasty can help reduce pain in a wide variety of osteolytic vertebral lesions [72].

In the setting of vertebral fracture, spinal cord compression can result from retropulsion of bone fragments or soft tissue tumor into the spinal canal. Additionally, local hemorrhage resulting from the fracture can cause local mass effect and exacerbate spinal canal narrowing. MRI provides the optimal assessment of the spinal cord, including the degree and cause of narrowing and the presence or absence of spinal cord edema. For further information on this topic, please see the dedicated chapter on spinal cord compression. Image-guided treatment of this entity is discussed in the section on neuroradiologic emergencies.

Impending Fractures

The Mirels classification system provides an overview of the risk of impending fracture in long bones, with a score ≥8 suggesting prophylactic surgical fixation [73–75]. The calculation of the Mirels score incorporates lesion site, nature of the osseous lesion, lesion size relative to cortical thickness, and pain. Location: upper limb (one point), lower limb (two points), and trochanteric region in the proximal femur (three points). Location: blastic (one point), mixed (two points), and lytic (three points) lesions. The size of lesion expressed as a proportion of cortical involvement: less than 1/3 (one point), 1/3 to 2/3 (two points), and greater than 2/3 (three points) [73, 75]. Pain is the final component necessary to assemble the Mirels score, with pain subjectively classified as mild (one point), moderate (two points), or functional (three points). Imaging, usually consisting of both CT and plain radiography, is necessary in computing a Mirels score and can inform patient management by suggesting fixation prior to fracture.

Pain

Bone metastases are the most common cause of cancer-related pain, although the majority of individual metastatic bone lesions are not painful [69]. Radiographs can identify lytic bone lesions as an area of radiolucency, but only after a loss of 30 % or more of bone mineral density; radiographs can be used as a screening tool, but continued clinical concern for a metastatic lesion in the presence of normal radiographs may warrant cross-sectional imaging. Unenhanced CT provides detailed bone anatomy and can be useful in the assessment of impending fracture risk or in preoperative planning. MRI provides very sensitive evaluation, identifying smaller nondestructive regions of marrow infiltration or metastatic disease [71]. Image-guided percutaneous cryoablation has proven effective for bone pain management. Radiofrequency ablation is an additional treatment option but may cause a temporary pain exacerbation.

Hypercalcemia

Hypercalcemia of malignancy comprises more than 1/3 of all cases of hypercalcemia presenting to the emergency department [43]. As many as 1/3 of cancer patients will experience hypercalcemia at some point in their disease course [22]. Hypercalcemia of malignancy can result from tumoral or systemic release of parathyroid hormone-related peptide (PTHrP), osseous metastatisis resulting in direct osteoclastic stimulation and osteolysis, and secretion of vitamin D analogs by the tumor [22, 43]. Radiologic manifestations of hypercalcemia of malignancy can include osteopenia and osteoporosis and resorption of the bone at the distal clavicle and about the sacroiliac joints, as well as nephrocalcinosis and nephrolithiasis.

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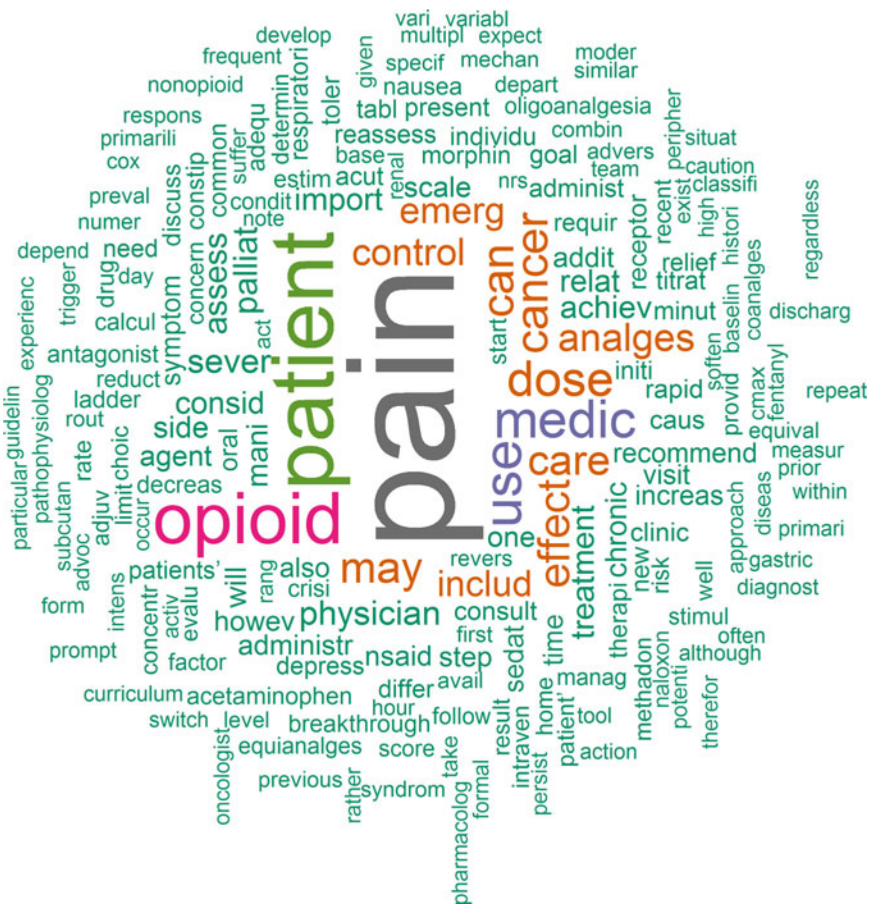
Part IV

Palliative Care

Pain Management

Danielle M. McCarthy



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Introduction

Pain is one of the most common symptoms experienced by patients with cancer. Prevalence estimates (pooling patients with multiple types of cancer and in various stages of treatment) suggest that >50 % of cancer patients experience pain [1]. The prevalence of pain is higher for patients who have metastatic or advanced stage disease, and nearly a third of cancer patients rate their pain as moderate or severe [1]. The prevalence of pain in the subset of cancer patients visiting the emergency department is less well defined; estimates of cancer patients presenting with pain as their primary complaint range from 10 to 41 % of cancer patients' ED visits for all causes [2]. Regardless of the chief complaint that prompted the ED visit (e.g., presenting primarily for pain crisis or presenting for infectious symptoms), giving analgesics is among the most frequent treatments provided to cancer patients in the ED. The severity of patient self-reported symptoms, including pain, is a reliable predictor of emergency department visits [3, 4].

Classification of Pain

The National Comprehensive Cancer Institute states that a "pain emergency" is an occasion on which a patient is experiencing severe pain (at least a numerical rating of 7 on a 10-point scale) [5]. Such a pain emergency may arise from inadequate control of a patient's baseline persistent pain or may be a more acute pain crisis superimposed on a well-established history of chronic pain. Such pain is commonly referred to as "breakthrough pain." Similar to the more general pain prevalence estimates detailed above, nearly two-thirds of patients with chronic cancer pain syndromes experience breakthrough pain episodes [6]. In general, it is accepted that a patients' baseline persistent pain must be well controlled before attributing the pain episode to "breakthrough pain" [7].

Such pain emergencies require a rapid response from emergency physicians to administer analgesics to obtain pain control. The approach to a pain emergency should be similar to the emergency physician's approach to any other emergency and include an assessment of the history, severity, timing, and location of the pain in addition to a thorough physical exam. In addition to classifying pain in cancer patients as baseline pain or breakthrough pain, other important considerations when assessing pain in cancer patients include: awareness of the pain mechanism or pathophysiology, consideration of the triggers of the pain crisis, and discussion of the goals of care.

Pain Severity

Many tools are available to assess pain severity and thereby quantify pain. Examples of such pain severity assessment tools include numerical rating scales (NRS), visual analogue scales (VAS), and picture scales (e.g., Faces Pain Scale). More in-depth assessments, which often incorporate numerical or visual analogue rating scales, are also available and include the Brief Pain Inventory, the McGill Pain Questionnaire, and the Memorial Pain Assessment Card. Pain is subjective, and at times in the ED, high pain scores are greeted with skepticism; therefore, it is important to use one of these validated measures to assess patients' pain. This is particularly important for patients with chronic pain who may not exhibit more objective signs (e.g., grimacing) or vital sign changes such as tachycardia [8]. Using a pain score measure, and applying it consistently, will help to add a more objective means of reproducibly tracking patients' pain and response to treatment over time. Although any of the above-mentioned measures are validated and can be useful if applied consistently, for purposes of ED evaluation of cancer pain, a numerical rating scale (NRS) is preferred [9, 10]. Specifically, in cancer patients, a NRS has better capability to distinguish between a patient's background or chronic pain and breakthrough pain [10]. The NRS is an 11-point scale ranging from 0 to 10. When asking patients to rate their pain on this scale, it is important to provide consistent verbal anchors to the scale [11]. Most commonly, the anchors are "0 = no pain" and "10 = worst pain possible" or "=pain as intense as you can imagine" [9].

In addition to pain ratings, it is important to ask patients their expectations regarding pain relief. Asking "At what level of pain do you feel comfortable?" recognizes that patients with chronic pain, including those with chronic cancer pain, do not necessarily expect pain intensity scores to reach zero [12]. Use of such personalized pain goals may allow adequate analgesia while avoiding the overtreatment of pain and resultant adverse effects.

Pain Mechanisms

In addition to assessing pain intensity, the pathophysiology and trigger of the pain should be considered. No universally accepted system for classifying cancer pain exists [13]. Nonetheless, cancer pain is often described in terms of the pathophysiology of the pain and is broadly divided into nociceptive or neuropathic pain. Nociceptive pain is caused by tissue injury and can be further subdivided into visceral pain (from organs) or somatic pain (related to bones, joints, soft

tissue). Visceral pain (e.g., peritoneal carcinomatosis) is more poorly localized than somatic pain (e.g., bone metastases). Neuropathic pain is related to dysfunction of nerves; this dysfunction may be central or peripheral and has many possible etiologies, including direct compression of a nerve or related to treatment (e.g., inflammation post-radiation). Often, those with cancer suffer from complex pain states combining both nociceptive and neuropathic mechanisms. Considering the pathophysiology of the pain is important because different types of pain may respond to treatments differently. Additionally, patients with cancer may suffer from non-cancer-related pain syndromes such as pre-existing diabetic neuropathy or arthritis pain. Although these pain syndromes are not directly related to the cancer, they can nonetheless contribute to patients' psychological distress and suffering.

Other historical factors, such as recent treatments and the stage of the cancer, can also aid the emergency physician in defining a trigger for the pain. This information can help the physician determine if the pain represents a reversible pain crisis, an anticipated worsening related to recent treatment, or a worsening related to progression of disease. A new pain or pain in a new location may represent disease progression and as such may require more extensive diagnostic evaluation than an increase in intensity of a known chronic pain.

Before beginning an extensive diagnostic search for the cause of a new pain and before starting a patient on a new analgesic, it is important to discuss the goals of care with the patient as part of a shared decision approach to care. These conversations can be difficult because of the lack of a pre-existing relationship but are nonetheless important. The extent of the patients' diagnostic evaluation will depend on their goals of care and should take into consideration of the risk or discomfort of diagnostic tests and what action would be taken with different results of those tests.

Oligoanalgesia

Any discussion of pain control in emergency medicine should include a discussion of oligoanalgesia. Oligoanalgesia, defined as the underuse of analgesics, has been increasingly described in the literature over the past decade. In the context of cancer patients, a recent review found that 43 % of cancer patients did not receive adequate pain treatment [14]. This estimate implies that many patients seeking care in the ED for breakthrough pain may have had inadequate baseline pain control. The problem of oligoanalgesia for these patients is then compounded by a well-established history of oligoanalgesia in the ED itself. Specifically, recent studies have found that pain is undertreated in the ED and that disparities in pain treatment exist related to age and race [15–17]. Many factors likely contribute to oligoanalgesia in the ED. One concern in particular relates to significant tension between providing adequate analgesia and ongoing concerns drug misuse, addiction, and deaths from prescription opioids in the USA [18]. In the context of the cancer patient in the ED, the immediate focus should be on controlling the breakthrough pain during the ED visit. Decisions about new prescription analgesics from the ED can be made in conjunction with the treating oncologist or palliative care physician.

Treatment Options

Treatment of cancer pain should be individualized. There are many treatment modalities available to the cancer patient, including pharmacologic, interventional (e.g., injection therapies, neural blockade), rehabilitative (e.g., therapy for lymphedema), psychological (e.g., cognitive behavioral therapy), neurostimulation, or integrative (e.g., massage) [19]. Those modalities may be applied singularly or in a combined modality fashion. Most of these therapies are not immediately accessible to the emergency physician; thus, while an awareness of these therapies is important, the primary tools at the emergency physician's disposal to improve pain are pharmacologic.

WHO Analgesic Ladder

Nearly 30 years ago, in 1986, the World Health Organization published recommendations for the management of cancer pain. These recommendations included a three-step analgesic "ladder" intended to guide the selection and escalation of analgesics [20] (Fig. 1). This model has been frequently used for not only cancer pain, but for other painful syndromes. Over the intervening 30 years, modifications to the existing ladder have been suggested, including eliminating the second step of the ladder, adding a fourth step, or "fast tracking" patients to the top of the ladder [21, 22]. When considering the individual patient, it is important to reconcile evidence-based clinical guidelines and new information (e.g., new medications, importance of risk assessment) with the original WHO consensus-based guidelines [19]. However, the WHO analgesic ladder provides a good framework for the discussion of the different types of analgesics and the rationale that analgesic choice should be given commensurate to the patients' pain intensity, as measured by a pain scale.

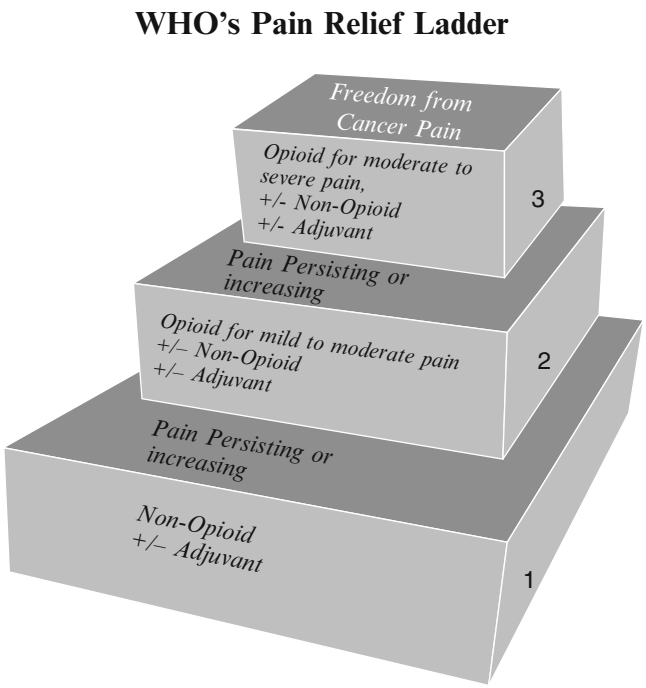

Fig. 1 WHO analgesic ladder (Reprinted with permission of The World Health Organization: http://www.who.int/cancer/palliative/pain-ladder/en/ accessed: October 15, 2015)

Non-opioid Analgesics

Non-opioid analgesics include nonsteroidal anti-inflammatory medications (NSAIDs) and acetaminophen. These medications are useful in the management of acute and chronic pain. One limitation of both NSAIDs and acetaminophen is a "ceiling effect" wherein increasing the dose above a certain level does not provide any additional pain relief. The ceiling effect therefore limits the ability of these medications to be titrated for severe pain; however, even when NSAIDs and acetaminophen alone are insufficient for pain control, they should be considered as a co-analgesic to opioid treatment because they may reduce the dose of opioid needed to achieve pain control.

Acetaminophen is a non-salicylate analgesic that does not have any antiplatelet activity. It does not have clinically detectable anti-inflammatory effects; however, it may be a useful analgesic for some conditions. One concern with acetaminophen is potential hepatotoxicity; doses should not exceed 4000 mg/day.

NSAID medications possess both anti-inflammatory and analgesic properties. These medications act by inhibiting isoforms of an enzyme called cyclooxygenase (COX); inhibition of this enzyme results in decreased synthesis of prostaglandins. Different classes of NSAIDs have varying selectivity for the isoforms of the COX enzyme (COX-1 and COX-2). Depending on the source of the patient's pain and comorbidities, a choice of a nonselective or selective NSAID can be made. Patients who respond to one of the NSAIDs may not respond as well to others. NSAID medications also have significant side effects that should be considered prior to administration. All NSAIDs cause a reversible decreased platelet aggregation (while the drug is at therapeutic serum concentrations). If patients already have a high risk of bleeding, the use of NSAIDs should be carefully considered. All NSAIDs can cause gastrointestinal (GI) adverse effects, ranging from dyspepsia to bleeding gastric ulcers. Medications to protect the gastric mucosa, such as a proton-pump inhibitor (PPI), should be considered to minimize the risk. NSAIDs can also lead to renal insufficiency through multiple mechanisms, and caution should be used when patients have risk factors for renal impairment, including advanced age, dehydration, diuretic use, or multiple myeloma.

Opioid Analgesics

When patients' pain is not adequately controlled by non-opioid analgesics, opioid analgesics represent the next step on the WHO analgesic ladder. Opioid medications can be classified as naturally occurring opioids (e.g., morphine, codeine) and semisynthetic (e.g., dihydromorphone, oxycodone) or synthetic compounds (e.g., fentanyl, methadone). Opioids can further be classified by their action at the opioid receptor (agonist, partial agonist, or antagonist) and by the receptor where they primarily function (mu, delta, or kappa). Opioid receptors exist in both the central nervous system and the peripheral tissues; however, the clinical effects of opioids are thought to be related primarily to the opioid action on central rather than peripheral receptors [23].

Opioids can be administered by multiple means, including oral, rectal, transdermal, intranasal, subcutaneous, or intravenous routes. The intramuscular route provides no pharmacologic advantage over subcutaneous administration and has the disadvantage of causing additional pain. If time permits, the oral route of administration is preferred [20]; however, for patients in a severe pain crisis, more rapid pain control may necessitate the use of intravenous opioids. Opioids, with the exception of methadone, follow first-order kinetics and achieve their peak plasma concentration (and maximal analgesic effect) along a similar timeline: 60–90 min for oral administration, 30 min for subcutaneous or rectal administration, and 6–10 min for intravenous administration [24].

If time permits the administration of an oral opioid, it is also important to remember that many oral opioids are combination pills with a non-opioid analgesic (e.g., acetaminophen). The presence of the non-opioid limits titration of the medication orally to avoid toxicity from the co-analgesic (e.g., maximum of 4000 mg/day of acetaminophen).

For those patients in more severe pain, or requiring intravenous dosing for other reasons (difficulty swallowing), there are many available intravenous opioids. For the opioid-naïve patient, morphine is a safe, standard drug to start therapy [5, 25]. However, morphine should be used with caution in patients with renal impairment because one of the active metabolites (morphine-6-glucoronide) can accumulate with renal dysfunction. For intravenous dosing of the opioid-naïve patient, a starting dose of 2–5 mg of morphine (or equivalent) is recommended. This dose should be followed by a reassessment at 15 min, and if the pain score remains unchanged or increased, the initial dose given should be increased by 50–100 %. If the pain score is decreased but still moderate (e.g., 4–6), the same initial dose should be repeated [5].

For the opioid tolerant patient, the drug choice will likely be informed by their home medications and prior opioid use. Patients may be on a combination of opioid medications at home (e.g., transdermal and oral preparations or long-acting and immediate release preparations). In order to identify the approximate opioid use of a patient at home, and thereby to more accurately estimate their pain control needs in the ED, equianalgesic dosing tables can be used (Table 1).

Equianalgesic dosing tables were first constructed in the 1960s and 1970s to codify the relative potency of different opioid formulations. These tables can be used to calculate patients' baseline outpatient opioid use. Recently, experts have expressed concerns over the limitations of the data used to construct the dosing tables and their applicability in the clinical realm [26, 27]. Specifically, the studies used to construct these tables were primarily acute rather than chronic pain. Research also suggests that there is significant variability in the dose needed to achieve pain relief between individuals which may be influenced not only by prior exposure to opioids, but also by age, gender, and genetic polymorphisms that affect opioid binding [8]. Given this potential for wide variability in dose response, the equianalgesic dosing recommendations as well as the starting doses noted above should be considered a guideline, to be individualized by the practicing physician.

Table 1 Equianalgesic dosing table[a]

Opioid	Oral dose	Parenteral dose	Duration of action (h)
Morphine	10 mg	30 mg	3–4
Hydrocodone	–	30 mg	4–8
Hydromorphone	1.5 mg	7.5 mg	3–4
Oxycodone	15–20 mg	–	3–6
Fentanyl[b]	–	50–100 μg	1–2

[a]This table is a guide only. Equianalgesic dosing tables vary subtly and this table should not replace more in-depth review of dosing

[b]Applies to IV conversion only. For transdermal fentanyl conversion, see package insert

When using the equianalgesic dosing tables, the first step is to calculate the patient's "equianalgesic dose equivalent" based on the analgesic use over the previous 24 h. After choosing the opioid to administer, the dose initial IV dose will be determined by converting the previous 24-h requirement to a total IV equivalent. Once a 24-h IV equivalent has been calculated, the first dose should be 10–20 % of that total dose [5]. After the first dose is given, a reassessment should occur within 15 min, and, similar to opioid-naïve patients, if the pain level remains >7, the dose should be escalated by 50–100 %. If the pain is moderate (e.g., 4–6), the same initial dose should be repeated, and if the pain level is low (e.g., 0–3), then the initial dose can be used as needed.

Another reason to exercise caution when switching opioids is because of opioid cross-tolerance. Patients on opioids will develop tolerance; this is expected. One of the signs of tolerance is achieving less pain relief from the same dose of the medication. One approach to optimize pain control when tolerance is present is to switch (or rotate) the opioid being used. In other clinical situations, opioid rotation may be useful to minimize adverse effects. Although there is some cross-tolerance between opioids, it is not complete. This incomplete cross-tolerance is due to many factors, including individual variations in metabolism, concurrent medications that impact metabolisms, and individual variations in opioid receptors. Due to this variability in individual response when switching opioids, it is recommended to first calculate the equianalgesic dose and then to decrease the calculated dose by 25–50 % [8, 26]. Ultimately, the clinical situation should be considered when choosing a 25 % reduction vs. a 50 % reduction, including factors such as the patient's pain control and individual adverse effect profile. Two medications with exceptions to the 25–50 % automatic reduction are methadone and fentanyl. When switching to methadone, larger automatic dose reductions are recommended (75–90 %) [19]. Converting to transdermal fentanyl should follow the calculated equianalgesic dose in the package insert and does not require an automatic dose reduction [19]. Conversions to methadone and fentanyl are complex and should typically be done in consultation with the treating oncologist, pain specialist, or palliative care team rather than by the emergency physician independently.

Opioid Side Effects

Opioid analgesics have many potential side effects that may make patients or prescribers reluctant to use the medications or use them in adequate doses to achieve pain control. Patients can develop a tolerance to certain side effects (e.g., nausea or respiratory depression); however, other side effects (e.g., constipation) are not decreased with chronic use (Table 2). Several symptoms including pruritus and rash may result

Table 2 Adverse effects of opioids

Adverse effect	Develop tolerance	Treatment
Constipation	No	Use laxative prophylactically
Pruritus	No	Opioid rotation
Nausea	Often	Opioid rotation Anti-nausea medications
Sedation	Yes	Decrease or rotate opioid Discontinue other medications that can cause sedation
Respiratory depression	No	Decrease or rotate opioid Discontinue other medications that can cause sedation Sedation will precede respiratory depression
Delirium	No	Decrease or rotate opioid Discontinue other medications that can cause delirium Avoid sedating medications unless necessary and consider the use of antipsychotic medications

from either allergy or direct opioid effects from mast-cell degeneration and histamine release. True anaphylaxis to opioids is rare, but can occur. Care must also be taken to distinguish between opioid side effects and underlying the clinical manifestations of comorbidities such as dehydration or drug interactions [28].

Respiratory depression is one of the most feared side effects of opioids; however, tolerance can develop in a period of days to weeks of being on opioids, and it is rare in patients taking opioids chronically. Respiratory depression occurs in a dose-dependent fashion due to opioid action at the brain stem respiratory centers. Concomitant use with other sedating medications, such as benzodiazepines, may increase the risk for respiratory depression. Sedation precedes respiratory depression. If there is a concern for respiratory depression (from either home medications or medications administered in the ED), naloxone can be administered. Naloxone is an opioid receptor antagonist which will reverse the effects of the opioid; however, the half-life of naloxone is shorter than the half-lives of many opioids, so patients need continued observation if there was a concern for respiratory depression. Naloxone can precipitate acute and severe withdrawal symptoms in the patient taking chronic opioids and should be administered cautiously. Diluting 1 mL of the standard 0.4 mg/mL concentration of naloxone in 10 mL of normal saline and administering 2 mL every few minutes allow reversal of respiratory depression while minimizing withdrawal symptoms.

Nausea is one of the most common side effects of opioids with estimates ranging from 10 to 40 % of patients experiencing nausea [29]. The opioid causes nausea through several mechanisms including stimulation of the chemoreceptor trigger zone, slowed gastric emptying, and effects on the vestibular system. Depending on the source of the nausea, different antiemetics will have variable efficacy. Dopamine receptor antagonists (e.g., prochlorperazine or haloperidol) or serotonin antagonists (e.g., ondansetron) will be the most useful for nausea related to the chemoreceptor trigger zone, whereas promotility agents (e.g., metoclopramide) may have more impact when gastric stasis is causing the nausea.

Constipation is another common side effect that emergency physicians should anticipate in patients for whom they prescribe opioids. Among cancer patients on chronic opioids, the prevalence of constipation is as high as 90 % [30]. Opioids slow bowel transit time and peristalsis and tolerance does not develop to constipation over time.

Pharmacologic agents to ease constipation are typically divided into five categories: bulk-forming agents, softeners, stimulants, osmotic agents, and peripheral mu-opioid receptor antagonists. Bulk-forming agents increased fecal mass to stimulate peristalsis. Stimulants act by increasing intestinal motility, whereas osmotic agents (e.g., polyethylene glycol, lactulose) act by increasing water content in the large bowel. Typically, both a stool softener and a stimulant (or prokinetic) agent are required to counteract the effect of the opioids. Bulk-forming agents and stool softeners are unlikely to be effective in isolation. If constipation is not relieved by a combination of stool softener and stimulant agent, an osmotic agent can be used. A recent Cochrane review recommended the use of polyethylene glycol over lactulose for chronic constipation because of better outcomes related to stool frequency, form, associated abdominal pain and use of additional products [31]. Two new peripherally acting mu-opioid receptor antagonists may be considered if laxative therapy has failed. Both methylnaltrexone, administered subcutaneously, and alvimopan, an orally active agent, have demonstrated efficacy in reversing opioid-induced constipation [32, 33].

Adjuvants (Co-analgesics)

Adjuvant medications, also known as co-analgesics, are a diverse group of drugs that may have a primary indication other than pain; however, they work to enhance the effects of traditional analgesics, "have independent analgesic activity in certain painful conditions, or counteract the adverse effects of analgesics" [8, 34]. The emergency physician may not be starting these medications in the ED to achieve pain relief in the acute setting; however, it is important to have a familiarity with these medications both when taking the patients history and when discussing future treatment options with their outpatient oncologist or palliative care team.

Adjuvant medications are on every step of the WHO pain ladder, and they encompass many drug classes, including antidepressants, corticosteroids, anticonvulsants, local

Table 3 Adjuvant drugs for use during ED cancer pain crisis[a]

Category	Example	Indication	Comments
Corticosteroids	Dexamethasone Methylprednisolone	Spinal cord compression Bone metastases	Often used to treat emergencies associated with cancer progression (e.g., spinal cord compression), but also have utility for other painful conditions including bone metastases
Benzodiazepines	Lorazepam Diazepam	Anxiety Muscle spasm	Use with opioids can be limited because of sedation
Anesthetics			
Local	Topical lidocaine 5 % patch	Neuropathic pain	FDA approved to be worn for 12 h and then removed for 12 h
Systemic	Ketamine	Intractable pain	Dissociative anesthetic without significant respiratory depression

[a]Other adjuvant drugs include anticonvulsants, antidepressants, stimulants, bisphosphonates, and cannabinoids; these drugs are not included in the table because they are less likely to be used in the acute pain setting in the ED

anesthetics, muscle relaxants, and benzodiazepines. The addition of some of these medications may result in a better balance of patient safety and efficacy of pain relief. However, caution must be used to avoid oversedation or other side effects related to polypharmacy as many co-analgesics are potentially sedating.

Specific adjuvant medications that may be useful to emergency physicians for use in patients with pain crises are outlined in Table 3.

EPEC-EM

The Education for Physicians on End-of-Life Care (EPEC™) curriculum is intended to teach the core competencies of palliative care and is a useful resource for physicians wanting to learn more about this topic [35]. Supported by the National Institutes of Health, the EPEC-Emergency Medicine curriculum is an adaptation of the original EPEC curriculum designed for those who work in the emergency department. One of the tenets of care advocated by EPEC™-EM curriculum and others is the rapid titration of opioids to achieve pain control.

Rapid Titration

Rapid titration of opioids has been advocated to achieve adequate pain control for patients presenting to the ED rather than traditional outpatient oral medication titration which can require several days to achieve analgesia [36]. Several different protocols, utilizing various opioids, have been evaluated in the literature and found to be safe [37–39]. The commonalities between the recommended protocols include having a formal numerical assessment of pain followed by administration of medications based on severity of pain and a formal reassessment of pain at a scheduled interval (ranging from 5 to 30 min). This cycle or reassessment and medication administration continues until either pain control is achieved or unwanted side effects limit further opioid use.

EPEC-EM advocates the following approach to the rapid assessment of cancer pain [24, 40]:

Step 1: Assess the patient and history.

This assessment should include discussion of the home medication use and dosing of both opioids and adjuvants. Additionally, the responsiveness of the pain to opioids should be estimated.

Step 2: Administer treatment.

For patients with severe pain (>7/10), IV medications should be given. For those with mild to moderate pain, the best route and choice of medication can be individualized based on the assessment and goals of care.

- For opioid-naïve patients: 0.1 mg/kg of IV morphine equivalent (less if patient is elderly or high risk)
- For opioid tolerant patients: 5 % of the previous 24-h IV morphine equivalents

These recommended starting doses are slightly lower than the doses advocated by the National Comprehensive Cancer Network noted above (10 % bolus vs. 5 % bolus). Both of these recommendations are guidelines and should be customized to the clinical scenario and take into account the patients' presentation, polypharmacy, and goals of care.

Step 3: Reassess the patient's pain and reassess for unwanted side effects (somnolence or confusion) when C_{max} has been achieved.

The timing of the reassessment can vary based on when the maximum concentration (C_{max}) of the medication is reached (calculated by route of administration, e.g., approximately 15 min for IV administration). This timing is chosen because the maximum side effects will be experienced at the time of C_{max} [24]. Although parental agents will reach C_{max} faster than orally or subcutaneously dosed opioids, there is some variation within parental agents as to the speed of achieving peak plasma concentrations. Fentanyl, which is more lipophilic than morphine, can achieve peak plasma concentrations within 5 min and therefore may be particularly useful for rapid titration [36, 39].

Step 4: Achieve adequate pain control by redosing the medication if necessary.

For patients with persistent severe pain (>7/10) in whom no unwanted side effects have been noted, the initial opioid dose can be doubled. For those in whom there has been an improvement in pain control, but an unacceptable level of pain persists, the initial dose can be repeated. Both of these strategies will increase the effective C_{max} and thereby decrease pain.

Steps 3 and 4 should be repeated until pain control is achieved or side effects limit further administration of opioids. Additionally, adjuvant medications should be considered.

Step 5: Determine the plan for disposition, discharge instructions, and follow-up.

Patients whose pain cannot be adequately controlled in the ED should be considered for admission. Similarly, patients may have other medication conditions aside from pain that prompted their ED visit and should be admitted if further evaluation or treatment is needed. In the case that a patient presented solely for pain and the rapid titration of pain medication in the ED has controlled their pain, discharge can be considered. Adjustments to the patients long-acting and breakthrough opioids can be determined based on patients' previous medication use, allergies, and tolerance of medications in the past. Methadone should not be started in the ED without consultation because of its complicated dosing. Communication with the patients' treating primary care physician, oncologist, or palliative care specialist is important, as is ensuring follow-up for the discharged patient.

Palliative Sedation

Distinct from the rapid titration of medications, another strategy that can be considered in the ED for pain control in cancer patients with intractable pain is "palliative sedation." A commonly accepted definition for palliative sedation therapy is "the use of specific medications to relieve intolerable suffering from refractory symptoms by a reduction in patient consciousness" [41]. The goal of palliative sedation is to relieve distress and not to speed the dying process and therefore is distinct from euthanasia or physician-assisted suicide. Morphine has been used for the relief of dyspnea but is not effective at achieving sedation. Ketamine, a short-acting NMDA receptor antagonist, preserves respiration, but can effectively achieve sedation and be used for intractable pain or agitation [42]. Emergency physicians will likely have some familiarity with ketamine from procedural sedations, but when initiating it for palliative sedation, consultation with the palliative care team may be useful.

Consultation

Consultation with the cancer patients treating physicians is not only useful in coordinating discharge, but also in determining their treatment in the ED [43]. Additionally, some patients presenting to the ED may not have previously interacted with a palliative care physician; the emergency physician can and should consider consulting with palliative care if deemed necessary after an evaluation of the patient and discussion of wishes regardless of patients' prior engagement with palliative care. The "Improving Palliative Care in Emergency Medicine" project has recommended the use of a screening tool to assist in the decision to consult palliative care from the ED [44]. If the patient has a serious, life-threatening illness (in the case of cancer, this includes patients with metastatic or locally advanced incurable disease) and any one of the following conditions, palliative care consultation should be considered:

- Not surprised: You would not be surprised if the patient died in the next 12 months.
- Bounce backs: The patient has had >1 ED visit or hospital admission for the same condition within several months.
- Uncontrolled symptoms: The current ED visit prompted by difficult-to-control physical or emotional symptoms.
- Functional decline: Their presentation reveals a decline in function, feeding intolerance, unintentional weight loss, or caregiver distress.
- Increasingly complicated: There exist complex long-term care needs that require more support.

Consultation of palliative care from the ED may not only result in more expeditious relief of suffering for the patients, but has also been noted to decrease the length of time that the patient spends in the hospital by 3.6 days, compared to patients for whom palliative care consults were initiated post-admission [45].

Summary

Patients with cancer often seek care in the emergency department, for both pain related to their condition and for other symptoms. Regardless of the symptom prompting the visit, it is important to assess and manage pain in this population. Multiple classes of medication to acutely control pain are available to the emergency physician has many medications to acutely control pain. It is important to assess the pain formally, using pain scales, and to discern if the pain crisis is related to progression of disease or expected breakthrough pain or if a search for a new pain precipitant is needed.

Regardless of the cause, pain should be managed quickly and the patients' pain score should be frequently reassessed. The exact choice of medications will vary depending on the clinical situation and should be determined after reviewing the patients' home medications, comorbidities, and goals of care.

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Substance Abuse Issues in Oncology: What the ED Professional Needs to Know

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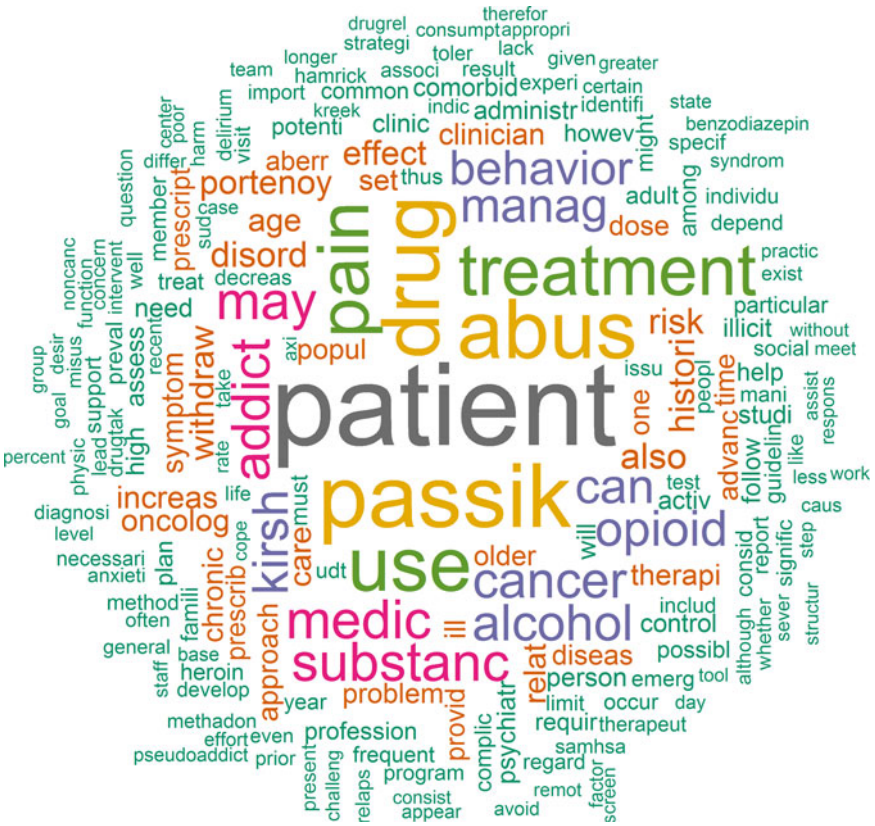

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Introduction

Until very recently, discussing the problem of substance abuse in people with cancer might have been seen as having only minor clinical relevance. Certainly, the relief of anxiety, pain, and other distressing symptoms has been identified as a top priority for oncologic clinicians, and the use of medications, even those with abuse potential, has been deemed essential. Much of the literature on this subject suggests that problems of substance abuse are only infrequently encountered in oncology. Perhaps this underestimation of the problem stems from the fact that much of this academic work has come from tertiary care settings—where those with histories of addiction are less frequently encountered because of barriers to care in the form of economic issues, lack of insurance coverage, and estrangement from healthcare providers who might diagnose and refer patients to such centers. Or perhaps it has been that cancer typically remains a disease of the sixth decade of life and beyond, whereas addiction overwhelmingly manifests earlier in life, making it unlikely to emerge de novo in a person first exposed to substances with abuse potential when they are older and ill [1, 2]. Or perhaps it has been because cancer used to follow an almost uniformly fast and fatal trajectory, and so any exposure to controlled substances was likely to be brief and occur during a period of time that the person was becoming increasingly disabled and less likely to engage in practices related to the obtaining and use of illicit drugs. Thus, even if the exposure to such drugs might trigger a relapse in a person who suffered with the disease of addiction before they became ill with cancer, the dysfunctional behaviors that might have been set in motion would be mediated and limited by the relentless impact of the cancer itself. Or perhaps it was simply the trivialization of addiction that characterized the early rhetoric accompanying the increase in opioid prescribing that led to this being such a neglected topic [3].

During recent years, in response to the public health crisis that is chronic pain in our aging society, the prescribing of opioids and other controlled substances has increased dramatically. Unfortunately, a parallel set of public health crises has arisen: the problems of prescription drug abuse, diversion, overdose, and death. Now that people with cancer are living longer at all stages of disease, including those with painful but stable disease and those who go onto remission but are left with chronic pain issues from chemotherapy and other factors, exposures to controlled substances are considerably longer than they once were, and thus there is greater opportunity for those who come to the disease with a history of substance use disorder (SUD) to lose control, overuse, or even have the problem of addiction fully rekindled [4, 5]. Finally, of additional concern for those prescribing controlled substances and treating pain, anxiety, and other symptoms in people with cancer including older patients, their medications are increasingly sought after by younger drug abusers in their family or environment (including grandchildren and caregivers). Thus, it is not only important for oncologic professionals of every stripe to have a working knowledge of addiction medicine principles and practices, but particularly the oncologic emergency department (ED) professional. In the ED, consequences of drug abuse—from the older person with cancer presenting in withdrawal because family members have stolen their medication to the younger person whose addiction has been rekindled by the need for pain medication—are likely to be common. Common doesn't mean obvious however, and it is important to dispel myths about the relative absence of addiction issues in cancer to help emergency care providers anticipate such problems and learn to manage them.

The increasing use of opioids in non-cancer pain grew out of recognition that people with cancer pain (at least those seeking treatment at tertiary care facilities) appeared to be able to take these medications with generally positive results. That is, their pain was controlled, side effects manageable, functional status improved or stabilized, and problems of misuse or addiction minimal. Opioid prescribing then increased dramatically, particularly in North America, to the much more diverse population of those with chronic pain—more diverse in terms of age, psychiatric, and addiction histories and comorbidities, as well as in duration of exposure [6]. Not surprisingly, the results of this effort were mixed. Cancer pain management with opioids follows a basically self-titration model consistent with an assumption that risk of misuse and addiction is uniformly minimal across patients. When this method of delivering opioid therapy in non-cancer pain began to meet with problems of abuse and diversion, a risk stratification model began to emerge. Younger age, personal or family history of addiction, history of sexual trauma, and active psychiatric comorbidity were seen as risks for a poor outcome in opioid therapy, unless the delivery of this therapy was tailored to the needs of the individual (with the employment of safeguards such as urine drug testing, prescription monitoring programs and the like, as well as consultations with psychiatric and addiction professionals to assure safety). There is a certain irony in the fact that oncologic pain management must now take a page from the non-cancer pain "playbook." This type of risk stratification is somewhat foreign to oncology pain management, but it seems that the time is right to close the loop and for the therapy that initially influenced non-cancer pain practice to adopt strategies developed therein, especially now that many of the differences between cancer and non-cancer pain patients have narrowed [7].

Pain and anxiety management are not the only aspects of cancer care affected by the presence of a SUD. Indeed, because unchecked drug or alcohol abuse can cause spotty or complete nonadherence to potentially lifesaving cancer

treatments, virtually every step along the disease trajectory, from diagnosis to palliative care, can be threatened. Thus, the "downstream" complications of substance abuse can lead to a person with cancer presenting in the ED with problems related to nonadherence of every variety. A question is whether the ED professional will recognize them as such. And if the ED professional is working outside of a tertiary care academic center, the frequency with which they will be confronted with SUDs is shockingly high, due to the high base rate of these disorders in this population which is so much more reflective of the population as a whole. Particularly when one considers that substance use can be a risk factor for cancer, one would expect substance abusers to be over- not under-represented in the oncology population. Many oncologic ED professionals from nearly all of the disciplines represented in this group of practitioners are lacking in their knowledge of addictions. There is an enormous gap between the prevalence of these problems and the expertise available to care for cancer patients who are struggling with them. It is hoped that this chapter helps bridge this gap for oncologic emergency medicine.

Major Issues

Prevalence

Substance use disorders are a consistent phenomenon in the USA over time, with estimated base rates of 6–15 % [8–12]. This prevalence of drug abuse certainly touches medically ill patients and can negatively influence how patients are treated. Although few studies have been conducted to evaluate the epidemiology of substance abuse in patients with advanced illness, these disorders reported to be relatively rare within the tertiary care population with cancer and other advanced diseases ([13–15]). However, the prevalence of alcoholism in major cancer centers is most likely underestimated. A study by Bruera and colleagues [16] of 100 terminally ill alcoholic cancer patients found that despite multiple hospital admissions and screenings, only one-third had documentation of alcoholism in their medical records. How then would the ED professional know to anticipate and plan for emergent problems related to alcohol abuse in a person presenting in their setting?

The belief that aging drug habits diminish and vanish with age is no longer held with the certainty of past belief. An early study supporting this belief reported that 50 % of individuals addicted to narcotics were no longer active drug users by age 32 and over 99 % were no longer users by age 67 [17]. However, as the "baby boom" cohort ages, the extent of alcohol and medication misuse is predicted to increase significantly because of the combined effect of the growing population of older adults and cohort-related differences in lifestyles and attitudes [18]. One study suggested that the number of illicit drug users aged 50 years or older will double from the year 2000 to the year 2020 because of an anticipated 52 % increase in this segment of the population and the attendant shift in attitudes and historical experiences with substance use in this cohort [19].

Prescription Drug Abuse

The use of illicit drugs and the nonmedical use of prescription opioids have increased significantly in the general population over the last decade, with the highest prevalence among younger adult men [20, 21]. Such estimates, however, belie alarming trends emerging among older adults. Among adults aged 50 or older, nearly five million, roughly 5 % of that age group, report using illicit drugs in the past year [12]. Marijuana is the most abused drug in the USA, but among adults aged 60 or older, the abuse of prescription drugs is equally common. A changing pattern of cannabis use among older adults suggests that as an individual ages, the social incentive to smoke marijuana decreases, while the attempt to use it medicinally increases [22]. In the oncology setting, this might include an attempt to self-medicate for nausea, anorexia, pain, anxiety, or combinations of these common symptoms [23]. More alarming than rates of cannabis use, ED visits related to pharmaceutical abuse more than doubled from 2004 to 2008 among adults aged 50 or older, and a fifth of these was among adults aged 70 or older [24]. Prescription opioids were the most common culprit, followed by benzodiazepines. Although ED visits in 2008 related to illicit drug use among adults 50 and older were a little less than half that of pharmaceuticals (118,495 vs. 256,097 visits), they were not uncommon [24, 25]. The majority of those visits were related to cocaine, followed by heroin. Consistent with this, one study demonstrated marijuana, cocaine, and opioid use in 2.4 %, 1.9 %, and 11.6 % of elderly men, respectively [26]. Substance use treatment admissions among adults aged 50 and older have nearly doubled in recent years, from 6.6 % of all admissions in 1992 to 12.7 % in 2009 [27]. During this same time period, alcohol as the only substance of abuse being treated decreased from 87.6 to 58.0 %, while the addition of other drugs to alcohol increased from 12.4 to 42.0 %. Also around this time, treatment admissions involving heroin more than doubled, from 7.2 to 16.0 %, and those reporting multiple drugs of abuse nearly tripled [28].

Even as the baby boomer population ages and more frequently experiences pain, there is a paucity of information on older patients and the risk of comorbid pain and SUDs. A survey in Denmark revealed that 22.5 % of men and 27.8 % of women aged 65 and older reported chronic pain [29]. Of these men and women, 35 % of them were not satisfied with their pain treatment. This can lead to alternative

methods for relieving pain such as taking non-prescribed medications. In one study of 100 patients with chronic pain (average age near 50), 23 tested positive for illicit drugs, and 12 tested positive for opioids, even though they had no prescription and denied taking opioids [30]. In another study of primary care patients in a Veterans Affairs facility who were receiving opioids for the treatment of chronic pain (average age 59), 78 % reported at least one indicator of medication misuse during the prior year, with significantly more of those who misused pain medications reporting comorbid SUD [31]. This is consistent with a more recent examination of a subset of data from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system's finding that though severe chronic pain is common in adults entering treatment for prescription opioid abuse, it is exponentially more prevalent in adults older than 45 years (70 %) relative to the 18–24-year age group (45 %) [1]. Clearly, to the extent that chronic pain and SUDs are comorbid or mutually exacerbating problems, older adults are a particularly vulnerable population. This might be especially true in the oncology culture, wherein performing a risk assessment has been historically uncommon and decreasing patients' wariness about using opioids aggressively when needed has been the biggest concern.

Thus the emerging pattern, consistent with the aging of the "baby boom" generation and their greater likelihood of exposure to various types of drugs, is that illicit and prescription drug misuse and abuse, along with the need for treatment, is expected to double by 2020 (relative to 1990s prevalence estimates) among older adults [19, 32], with the greatest changes reflecting the increasing rates of ED visits and treatment admissions related to prescription opioids, benzodiazepines, heroin, and cocaine. Knowledge of these trends should assist oncology providers in identifying and managing problems in a more age-appropriate manner.

Alcohol

There have been relatively few studies examining the prevalence of alcoholism in an oncology population. The prevalence likely varies widely from one cancer to another with the highest rate in the head and neck cancer population. One study found that greater than 25 % of patients admitted to a palliative care unit had problems with alcohol abuse [16]. Socioeconomic barriers such as low income or unemployment, lack of health insurance, and possibly even attempts to self-medicate early symptoms of cancer may preclude patients from seeking care at tertiary care centers. Alcohol abuse obviously complicates cancer care. For example, postsurgical withdrawal and delirium tremens (DTs) can be life threatening. Unfortunately many patients are unrecognized prior to undergoing surgery. Integrating screening for alcoholism and offering detoxification ahead of surgery are underutilized opportunities.

Defining Abuse and Addiction in the Medically Ill

It is difficult to define substance abuse and addiction in patients with cancer, as the definitions of both terms have been adopted from addicted populations without medical illness. Furthermore, the pharmacological phenomena of tolerance and physical dependence continue to be confused with abuse and addiction. The use of these terms is so strongly influenced by sociocultural considerations that it may lead to confusion in the clinical setting. Therefore, the clarification of this terminology is necessary to improve the diagnosis and management of substance abuse when treating patients with advanced disease [33, 34].

Substance abuse: psychosocial, physical, and vocational harm that occurs from drug taking

- Identifying harmful drug-taking behaviors is more difficult when patients are receiving potentially abusable drugs for legitimate purposes.

Substance dependence: a normal phenomenon for many patients taking medication for chronic conditions

- "Tolerance" occurs when a higher dosage of a drug is required to achieve the same effect.
- "Physical dependence" occurs when a patient begins to require a drug in order to function normally and can lead to withdrawal symptoms when medication administration ceases.

Because substance abuse is increasingly widespread in the population at large, patients with cancer who have used illicit drugs are more frequently encountered in medical settings. Illicit drug use, actual or suspected misuse of prescribed medication, or actual SUDs create the most serious difficulties in the clinical setting, complicating the treatment of pain management. However, the management of substance abuse is fundamental to medical therapy adherence and safety during treatment. Also, adverse interactions between illicit drugs and medications prescribed as part of the patient's treatment can be dangerous. Continuous substance abuse may alienate or weaken an already tenuous social support network that is crucial for alleviating the chronic stressors associated with advanced disease and its treatment. Therefore, a history of substance abuse can impede treatment and pain management and increase the risk of hastening morbidity and mortality among those with advanced cancer, which can only be alleviated by a therapeutic approach that addresses drug-taking behavior while expediting the treatment of the malignancy and distressing symptoms, as well as addiction [13, 14].

Important factors when assessing drug-taking behavior in cancer patients

- Undertreatment of associated issues, particularly pain disorders
- Sociocultural differences in defining "aberrant" drug taking

Pseudoaddiction

Various studies have provided compelling evidence that pain is poorly treated in many oncology patients [35–37]. Clinical experience indicates that the inadequate management of symptoms and related pain may be the motivation for aberrant drug-taking behaviors.

Pseudoaddiction: distress and aberrant drug-seeking behaviors that produce a similar pattern as addicts; however these behaviors actually stem from the patient seeking relief from untreated pain [38].

- Patients are often attempting to "self-medicate," and behaviors can be considered pseudoaddictive if sufficient pain relief eliminates these behaviors.
- Physical dependence can often lead to pseudoaddictive behaviors, as clinicians do not compensate for growing tolerance to medications and therefore underdose patients.

More recent scientific advances have also provided new insight into behaviors that may be considered pseudoaddiction. Pharmacogenetic variances in the enzymes that metabolize pain medications help to explain individual differences in medication response and side effects experienced. If a patient is an ultrarapid metabolizer, they may complain that the medication is effective for a shorter period of time than is common for that medication. If a patient is a poor metabolizer, they may complain that the medication is not working or possibly continue to ask for increased amount of medication. Pharmacogenetic variations should be considered and pharmacogenetic testing implemented when a patient has an unusual response to a medication, more than expected side effect profile, and/or inefficacy at usual dosages [39].

The potential for pseudoaddiction creates a challenge for the assessment of a known substance abuser with an advanced illness. Clinical evidence indicates that aberrant behaviors impelled by unrelieved pain can become so dramatic in this population that some patients appear to return to illicit drug use as a means of self-medication. Others use more covert patterns of behavior, which may also cause concerns regarding the possibility of true addiction. Although it may not be obvious that drug-related behaviors are aberrant, the meaning of these behaviors may be difficult to discern in the context of unrelieved symptoms ([13–15]). This can be a particularly vexing issue when the person with cancer presents in the ED. Is the presentation related to poor pain control, substance abuse, or both?

Aberrant Drug-Taking Behaviors

When a drug is prescribed for a medically diagnosed purpose, less assuredness exists as to the behaviors that could be deemed aberrant, thereby increasing the potential for a diagnosis of drug abuse or addiction. The ability to categorize these questionable behaviors as apart from social or cultural norms is also based on the assumption that certain parameters of normative behavior exist. Although it is useful to consider the degree of aberrancy of a given behavior, it is important to recognize that these behaviors exist along a continuum, with certain behaviors being less aberrant (such as aggressively requesting medication) and other behaviors more aberrant (such as injection of oral formulations) (see Table 1). If a large portion of patients were found to engage in a certain behavior, it may be normative, and judgments regarding aberrancy should be influenced accordingly ([13–15]).

We know more scientifically about aberrant behaviors, their prevalence, and meaning today than we did in the mid-1990s. We know that many patients will have at least a few aberrant behaviors in a 6-month period (Passik et al. [85]). We also know that once a patient has demonstrated four behaviors in their lifetime, they have an 85 % likelihood of meeting diagnostic criteria for substance use disorder [40]. But there is still much to be learned, confirmed, replicated, and studied.

Disease-Related Variables

Changes caused by progressive diseases, such as cancer, also challenge the principal concepts used to define addiction. Alterations in physical and psychosocial functioning caused by advanced illness and its treatment may be difficult to distinguish from the morbidity associated with drug abuse. In particular, alterations in functioning may complicate the ability to evaluate a concept that is vital to the diagnosis of addiction: "use despite harm." For example, discerning the questionable behaviors can be difficult in a patient who develops social withdrawal or cognitive changes after brain irradiation for metastases. Even if diminished cognition is clearly related to pain medication used in treatment, this effect might only reflect a narrow therapeutic window rather

Table 1 Examples of aberrant drug-taking behaviors and severity

Examples of clearly aberrant behaviors	Examples of potentially aberrant behaviors
Illicit drug use	Requests for early medication refills
Intravenous injection of oral formulations	Requesting specific medications
Recurrent prescription "losses"	Patient taking extra doses of medication

than the patient's use of analgesic to acquire these psychic effects [33, 34, 41]. To accurately assess drug-related behaviors in patients with advanced disease, explicit information is usually required regarding the role of the drug in the patient's life. Therefore, the presence of mild mental clouding or the time spent out of bed may have less meaning than other outcomes, such as noncompliance with primary therapy related to drug use or behaviors that threaten relationships with physicians, other healthcare professionals, and family members [33, 34, 41].

Definitions of Abuse and Addiction for Advanced Illness

Abuse: use of an illicit drug or prescription medication with medical indication

Addiction: the compulsive use of a substance resulting in physical, psychological, or social harm to the user and continued use despite the harm" [42]

- This definition of addiction emphasizes the psychological and behavioral nature of this syndrome [33, 34, 41].

A differential diagnosis should also be considered if questionable behaviors occur during treatment. A true addiction (substance dependence) is only one of many possible interpretations. A diagnosis of pseudoaddiction should also be taken into account if the patient is reporting distress associated with unrelieved symptoms. Impulsive drug use may also be indicative of another psychiatric disorder, the diagnosis of which may have therapeutic implications. On occasion, aberrant drug-related behaviors appear to be causally remotely related to a mild encephalopathy, with perplexity concerning the appropriate therapeutic regimen. On rare occasions, questionable behaviors imply criminal intent. These diagnoses are not mutually exclusive [33, 34, 41].

Varied and repeated observations over a period of time may be necessary to categorize questionable behaviors properly (see Table 2). Perceptive psychiatric assessment is crucial and may require evaluation by consultants who can elucidate the complex interactions among personality factors and psychiatric illness.

Patients with borderline personality disorders, for example, may impulsively use prescription medications that regulate inner tension or improve chronic emptiness or boredom and express anger at physicians, friends, or family. Psychiatric assessment is vitally important for both the population without a prior history of substance abuse and the population of known substance abusers who have a high incidence of psychiatric comorbidity [43].

Table 2 Differential diagnoses to consider when interpreting aberrant drug-taking behaviors

Possible alternate diagnoses for aberrant drug-taking behaviors
Anxiety
Depression
Insomnia
Problems of adjustment (such as boredom caused by decreased ability to engage in usual activities)
Borderline personality disorder

Risks in Patients with Current or Remote Histories of Drug Abuse

There is a lack of information regarding the risk of abuse or addiction during or subsequent to the therapeutic administration of potentially abusable drugs to medically ill patients with a current or remote history of abuse or addiction [33, 34]. The possibility of successful long-term opioid therapy in patients with cancer or chronic nonmalignant pain has been indicated by anecdotal reports, particularly if the abuse or addiction is remote [44–46].

Because it is commonly accepted that the likelihood of aberrant drug-related behavior occurring during treatment for medical illness will be greater for those with a remote or current history of substance abuse, it is reasonable to consider the possibility of abuse behaviors occurring when using different therapies. For example, although no clinical evidence exists to support the notion that the use of short-acting drugs or the parenteral route is more likely to cause questionable drug-related behaviors than other therapeutic strategies, it may be prudent to avoid such therapies in patients with histories of drug abuse [33, 34].

Clinical Management of Substance Use Disorders in Oncology

The most challenging issues in caring for patients with advanced disease typically arise from patients who are actively abusing alcohol or other drugs. This is in part because patients who are actively abusing drugs experience more difficulty in managing pain [47]. Patients may become caught in a cycle where pain functions as a barrier to seeking treatment for addiction possibly complicating treatment for chronic pain [48]. Also, because pain is undertreated, the risk of binging with prescription medications and/or other substances increases for drug-abusing patients [47]. The implementation of a more comprehensive treatment plan for such patients may indeed only be initiated after ED visit(s) bring the need for such a labor intensive program to light.

General Guidelines

The following guidelines can be beneficial, whether the patient is actively abusing drugs or has a history of substance abuse. The principles outlined assist clinicians in establishing

structure, control, and monitoring of addiction-related behaviors, which may be helpful and necessary at times in all pain treatment [13].

Recommendations for the long-term administration of potentially abusable drugs, such as opioids, to patients with a history of substance abuse are based exclusively on clinical experience. Research is needed to ascertain the most effective strategies and to empirically identify patient subgroups which may be most responsive to different approaches. The following guidelines broadly reflect the types of interventions that might be considered in this clinical context [33, 41, 49].

Multidisciplinary Approach

Pain and symptom management is often complicated by various medical, psychosocial, and administrative issues in the population of advanced patients with a substance use disorder. The most effective team may include a physician with expertise in pain/palliative care, nurses, social workers, and, when possible, a mental healthcare provider with expertise in the area of addiction medicine [13, 14].

Assessment of Substance Use History

In an effort to not offend, threaten, or anger patients, clinicians frequently avoid asking patients about drug abuse. There is also often the expectation that patients will not answer truthfully. However, obtaining a detailed history of duration, frequency, and desired effect of drug use is vital. Adopting a nonjudgmental position and communicating in an empathetic and truthful manner is the best strategy when taking patients' substance abuse histories ([13–15]).

In anticipating defensiveness on part of the patient, it can be helpful for clinicians to mention that patients often misrepresent their drug use for logical reasons, such as stigmatization, mistrust of the interviewer, or concerns regarding fears of undertreatment. It is also wise for clinicians to explain that in an effort to keep the patient as comfortable as possible, by preventing withdrawal states and prescribing sufficient medication for pain and symptom control, an accurate account of drug use is necessary ([13–15]).

Taking an accurate, detailed history from the patient is essential for the proper assessment and treatment of alcohol and drug abuse as well as any comorbid psychiatric disorders. It is also important to ask about the duration, frequency, and desired effect of drug or alcohol consumption. In the wake of current pressures to treat the majority of patients in ambulatory settings and to admit patients on the morning of major surgery, the quick identification of alcoholism and initiation of plans for social, medical, and physiological needs of the patient must begin upon initial contact.

The use of a careful, graduated-style interview can be beneficial in slowly introducing the assessment of drug abuse. This approach begins with broad and general inquiries regarding the role of drugs in the patient's life, such as caffeine and nicotine, and gradually proceeds to more specific questions regarding illicit drugs. This interview style can also assist in discerning any coexisting psychiatric disorders, which can significantly contribute to aberrant drug-taking behavior. Once identified, treatment of comorbid psychiatric disorders can greatly enhance management strategies and decrease the risk of relapse ([13–15]).

Use of Risk Assessment Tools

As stated above, potential opioid use must be accompanied by risk stratification and management. Given time constraints, a full psychiatric interview may not be feasible, and thus time-sensitive measures are clearly needed to help in this endeavor. Many screening tools contain items on personal and family history of addiction as well as other history-related risk factors, such as preadolescent sexual abuse, age, and psychological disease. These are tools for clinical decision-making and should not be viewed as necessarily diagnostically accurate [50, 51]. Whatever tool the clinician chooses, it is advised that the screening process be presented to the patient with the assurance that no answers will negatively influence effective treatment. One risk factor unique to the oncology setting is the economic pressure that accompanies the disease and its treatment. The depletion of savings over time can be a huge stress, and for some the temptation to divert medications with a street value may be seen as a matter of survival.

Setting Realistic Goals for Therapy

The rate of recurrence for drug abuse and addiction is high in general. The stress associated with cancer and the easy availability of centrally acting drugs increase this risk. Therefore, total prevention of relapse may be impossible in this type of setting. Gaining an understanding that compliance and abstinence are not realistic goals may decrease conflicts with staff members in terms of management goals. Instead, the goals might be perceived as the creation of a structure for therapy that includes ample social/emotional support and limit setting to control the harm done by relapse ([13–15]).

There may be some subgroups of patients who are unable to comply with the requirements of therapy because of severe substance use disorders and comorbid psychiatric diagnoses. In these instances, clinicians must modify limits on various occasions and endeavor to develop a greater variety and intensity of supports. This may necessitate frequent team meetings

and consultations with other clinicians; however, pertinent expectations must be clarified, and therapy that is not successful should be modified ([13–15]).

Evaluation and Treatment of Comorbid Psychiatric Disorders

Extremely high comorbidities of personality disorders, depression, and anxiety disorders exist in alcoholics and other patients with substance abuse histories [43]. Individuals with a history of alcohol abuse have been found to be at higher risk for other psychiatric disorders (Helzer and Pryzbeck [86]). The most common comorbid mental disorders associated with alcoholism are anxiety disorders (19.4 %), antisocial personality disorder (14.3 %), affective disorder (13.4 %), and schizophrenia (3.8 %) (Regier et al. [87]). The occurrence of comorbid mental disorders in alcoholics may contribute to poor treatment compliance and success due to cognitive limitations and premorbid (in relation to the diagnosis of cancer) pain and neurological deficits. The same is true of opioid abuse where 85 % of addicts have a comorbid, non-drug abuse-related psychological disorder [43]. Thus, the ED professional assessing the cancer patient with addiction or alcoholism must anticipate and identify for treatment or referral any comorbid disorders present. The treatment of depression and anxiety can increase patient comfort and decrease the risk of relapse or aberrant drug taking ([13–15]).

Alcohol Withdrawal Syndrome

Alcohol withdrawal is dangerous and can seriously complicate cancer treatment. In some instances, it is fatal. The first symptoms of withdrawal typically appear in the first few hours following the cessation of alcohol consumption and may consist of tremors, agitation, and insomnia. In cases of mild to moderate withdrawal, these symptoms tend to dissipate within 1–2 days without recurrence. However, in cases of severe withdrawal, autonomic hyperactivity, hallucinations, and disorientation may follow. The onset of delirium tremens marks the individual's progression from the withdrawal state to a state of delirium that represents a serious medical emergency.

Delirium tremens (*DTs*): characterized by agitation, hallucination, delusions, incoherence, and disorientation, typically within the first 72–96 h of withdrawal

- Occurs in approximately 5–15 % of patients with alcohol withdrawal [52].
- Is self-limiting and often ends with the patient entering a deep sleep with amnesia for most of the episode.
- DTs can increase the risk of further complications in medically ill patients.

Wernicke-Korsakoff's syndrome: indicative of thiamine deficiency that causes permanent cognitive impairment

- Frequently underdiagnosed
- Symptoms
  - Fixed upward gaze
  - Alcoholic neuropathy
  - "Stocking-glove" paresthesia
  - Autonomic instability
  - Delirium encephalopathy

Medical Treatment of Withdrawal

While a full discussion of the pharmacological approach to alcohol withdrawal is beyond the scope of this chapter, a basic approach to its treatment is given. The use of hydration, benzodiazepines, and, in some cases, neuroleptics is appropriate for the management of alcohol withdrawal syndrome (see Table 3). The administration of a vitamin-mineral solution is indicated to counteract the effects of malnutrition that results from the alcohol itself and poor eating habits. Thiamine 100 mg administered intramuscularly or intravenously for 3 days before switching to oral administration for the duration of treatment will prevent the development of Korsakoff's syndrome and alcoholic dementia. A daily oral dose of folate 1 mg should also be given throughout the course of treatment. In cases of mild withdrawal, hydration alone may be sufficient. Benzodiazepines (lorazepam, midazolam, diazepam, and chlordiazepoxide) are the drugs of choice for the management of alcohol withdrawal because of their sedative effects (see Table 4) [53, 54]. Careful consideration must be given to route, absorption, potency, and dose of benzodiazepine prescribed. Dose should be based upon estimated alcohol consumption and the type of detoxification setting (see below). Insufficient administration of benzodiazepines (too low dose or too rapid taper) may allow the progression of withdrawal to a state of delirium tremens. The development of seizures is life threatening, and they

Table 3 Guidelines for the treatment of alcohol withdrawal

• Continual close monitoring of withdrawal status
• Utilization of benzodiazepines
• Taper dose slowly (generally not by more than 25 % per 24-h period)
• Administration of thiamine 100 mg IM or IV qid
• Administration of folate 1 mg po qid
• Monitor for signs of the potential onset of delirium tremens
• Consideration should be given to a loading dose of phenytoin for patients with a history of withdrawal seizures or for patients in whom seizures are likely (i.e., patients with brain metastases)

Table 4 Types and characteristics of benzodiazepines for treatment of alcohol withdrawal

Drug	Dose	Duration of action	Half-life (h)
Chlordiazepoxide	25–100 mg every 3 h IV	Short	5–30
Diazepam	10–20 mg every 1–4 h IV	Short	20–100
Lorazepam	1–2 mg every 1–4 h IV	Intermediate	10–20
Midazolam	1–5 mg every 1–2 h IV	Very short	1–4

may repeatedly recur in the patient while unconscious. The non-benzodiazepine anticonvulsants are not prescribed prophylactically. In cases of severe withdrawal and confusion, neuroleptics (i.e., haloperidol 0.5–5.0 mg IV every 8 h) are added to the treatment regimen. Commonly, alcoholic patients report to the hospital either intoxicated or in the early stages of withdrawal. From a surgical perspective, serious complications can arise from the presence of alcohol withdrawal, and its acute management is the primary treatment goal. Unfortunately, clinicians are frequently provided insufficient lead time to properly detoxify the patient prior to surgery (typically less than 24 h), and the patient is at an increased risk for the postoperative development of organic mental disorders, seizure, and delirium tremens. Since alcoholic cancer patients are already at high risk for delirium postoperatively due to poor nutrition, prior head trauma, and brain injury from excessive alcohol consumption, the development of seizures and delirium tremens adds to the risk of fatality. It is important to note that since it is desirable for the patient to be alert postoperatively for ambulation and use of pulmonary toilet, the amount of sedation required for detoxification is much lower than the desired level of sedation in a nonsurgical alcoholic patient.

Preventing and Minimizing Withdrawal Symptoms

Because patients with drug abuse histories often use multiple drugs, it is necessary to conduct a complete drug-use history to prepare for the possibility of withdrawal. Delayed abstinence syndromes, such as those that may occur after abuse of some benzodiazepine drugs, can be particularly diagnostically challenging ([13–15]).

Considering the Therapeutic Impact of Tolerance

Patients who are active substance abusers may be tolerant to drugs administered for therapy, making pain management more difficult. The magnitude of this tolerance is never known. Therefore, it is best to begin with a conservative dose of therapeutic drug and then rapidly titrate the dose, with frequent reassessments, until the patient is comfortable [33, 34, 46]. Also, it must be remembered that opioids, pharmacologically speaking, still have no ceiling [55]. Cancer patients and those with progressive disease can be treated with gradually increasing doses, and opioids can still be titrated to effect or toxicity with no arbitrary number of milligrams constituting a limit. Tolerance to a variety of opioid effects can be reliably observed in animal models [56], and tolerance to non-analgesic effects, such as respiratory depression and cognitive impairment [57], occurs regularly in the clinical setting. However, analgesic tolerance does not appear to routinely interfere with the clinical efficacy of opioid drugs.

Psychopharmacology Approaches

Disulfiram (Antabuse) is a pharmacological agent that has been approved by the Food and Drug Administration (FDA) since 1951 for the treatment of alcoholism. Antabuse serves as a deterrent by inducing an unpleasant physical state characterized by nausea or vomiting when alcohol is consumed, thus ideally leading to alcohol cessation [58]. The practicality and effectiveness of Antabuse is questionable however, since its use has been limited by difficulties with patient adherence for continued use of the drug [59].

There have been a number of studies shedding light on subgroups of patients who have been shown to benefit the most from treatment with Antabuse. The findings have shown that patients with the following characteristics generally experience the most long-term benefits from Antabuse: (1) older than 40 years of age, (2) longer drinking histories, (3) socially stable, (4) highly motivated, (5) prior attendance of Alcoholics Anonymous, (6) cognitively intact, and (7) able to maintain and tolerate dependent or treatment relationships [60–62]. Further research is needed to ascertain what factors and patient characteristics will increase the likelihood of successful treatment. A greater understanding has the potential to significantly enhance clinicians' ability to select those patients who will experience optimal effectiveness.

Methadone Maintenance

Methadone maintenance therapy (MMT) is superior to illegal heroin use, in part, because the extreme highs and lows felt by heroin users (related to the waxing and waning of serum

heroin levels) are avoided by the long-acting properties of methadone. The term "agonist blockade" was coined to describe the phenomenon of significantly limited or blunted effects after administration of "usual" doses of mu-opioid agonists to subjects on high-dose methadone (e.g., 80–120 mg/day).

In humans, all opiates suppress the hypothalamic-pituitary-adrenal (HPA) axis when given acutely, and this effect persists during chronic, intermittent exposure to short-acting opioids during chronic cycles of heroin addiction [63].

The endogenous mu-opioid receptor-mediated opioid system in humans appears to constitutively provide tonic inhibition of the HPA axis [63, 64]. Thus, administration of mu-opioid receptor antagonists to healthy human volunteers leads to activation of the HPA axis [64–68]. Similarly, the HPA axis is activated in opioid withdrawal, or with administration of mu-opioid receptor antagonists to opioid-dependent individuals, or during acute cocaine or alcohol consumption [64, 67].

Kreek and colleagues (Kreek et al. 2004; [69]) proposed that suppression of the HPA axis through administration of intermittent or binge-type short-acting opioids (e.g., heroin) and then with repeated alternating short cycling of suppression (e.g., with heroin administration), followed by activation (e.g., with heroin withdrawal [i.e., just before next dose]), may lead to and/or exacerbate atypical responsivity to stress/stressors, as well as addictive-type behavior (with resultant self-administration/relapse). Adequate methadone maintenance treatment permits normalization of the HPA axis—including response to a chemically induced stress of metyrapone challenge [70, 71]. In an optimal situation, stabilized methadone-maintained former heroin addicts treated in high-quality methadone maintenance treatment programs (e.g., associated with psychosocial interventions) with effective methadone doses experience the following: markedly reduced drug craving, reduced or eliminated heroin use, improved or normalized stress-responsive hypothalamic-pituitary-adrenal axis, as well as reproductive, gastrointestinal, and immunologic functions with relatively normal responses to acute pain [72, 73].

Buprenorphine and Naltrexone

Two other therapies used in the medication-assisted treatment (MAT) of those with opioid addiction and alcoholism are not without their complexities if they are to be used in people with cancer.

Buprenorphine is a partial opioid agonist that has significantly advanced MAT for opioid addiction on an international level. Available as a pill, sublingual film (with and without naltrexone), and as an implant for addiction treatment, its use in people with cancer can complicate the treatment of pain in the setting of disease progression and require dose escalation that could "bump up against" the drug's ceiling effect or in the treatment of acute pain requiring the use of a pure mu agonist. However, there are also reports of the successful use of oral and transdermal buprenorphine for chronic and breakthrough cancer pain in nonaddicts [74]. If a person with cancer also has a history of opioid addiction and is to be managed with continuation of their buprenorphine treatment, consultation should be sought from an addiction medicine expert (who also has the appropriate certification to prescribe it where necessary).

The oral opioid antagonist naltrexone is used to treat alcohol cravings and opioid addiction and is also available as a monthly depot injection for addiction treatment. While ultralow-dose naltrexone has been used to augment opioids for cancer-related pain and for the treatment of side effects such as constipation, little has been written about the use of this therapy for addiction treatment in people with cancer. While one can imagine antagonist therapy having a role in, for example, people surviving cancer who struggle with addiction (and in whom pain severe enough to require opioids is not part of the clinical picture), in those with pain and with active disease, its role is limited. There is a paucity of data and direct clinical experience on which specific recommendations might be made. These medications can cause difficulties for the ED professionals as they might, for instance, need to intervene for acute pain in the ED setting, the management of which is complex in persons on antagonist therapy.

Selecting Appropriate Drugs and Route of Administration for the Symptom and Setting

The use of long-acting analgesics in sufficient amounts may help to minimize the number of rescue doses needed, lessen cravings, and decrease the risk of abuse of prescribed medications, given the possible difficulty of using short-acting formulations in patients with substance abuse histories. Rather than being overly concerned regarding the choice of drug or route of administration, the prescription of opioids and other potentially abusable drugs should be carried out with limits and guidelines ([13–15]).

Many clinicians now respond to particularly high opioid dose requirements with rotation to another opioid. This practice capitalizes on incomplete cross-tolerance, or the unique pharmacology of methadone in particular, to bring doses down while maintaining or improving efficacy and changing the balance of efficacy to toxicity [75, 76]. Some clinicians set arbitrary dose limits for the various opioids. Others stop using certain opioids they perceive as of higher risk or street value. Still others became so disillusioned as to stop using opioids altogether.

Recognizing Specific Drug Abuse Behaviors

In an effort to monitor the development of aberrant drug-taking behaviors, all patients who are prescribed potentially abusable drugs must be evaluated over time. This is particularly true for those patients with a remote or current history of drug abuse, including alcohol abuse. Should a high level of concern exist regarding such behaviors, frequent visits and regular assessments of significant others who can contribute information regarding the patient's drug use may be required. To promote early recognition of aberrant drug-related behaviors, it may also be necessary to have patients with histories of recent active abuse to submit urine specimens for regular screening of illicit, or licit but non-prescribed, drugs. When informing the patient of this approach, explain that it is a method of monitoring that can reassure the clinician and provide a foundation for aggressive symptom-oriented treatment, thus enhancing the therapeutic alliance with the patient ([13–15]).

Using Nondrug Approaches as Appropriate

The most effective psychotherapeutic treatment approach with medically ill people appears to be one that focuses on the development of effective coping skills, relapse prevention, and, most importantly, treatment compliance. Alcohol or the specific substance being abused represents one of the dependent patient's primary, albeit maladaptive, coping tools. As a result, the improvement of coping skills in these individuals is critical. When compounded with the stress associated with cancer, substance abuse cessation can be overwhelming and contribute to noncompliance and discontinuation of treatment. Teaching specific, illness-related coping methods with an emphasis upon containing episodes of consumption is essential. Further, the recognition and treatment of anxiety and depression may decrease the patients' need and desire for alcohol or substances. As an alternative to the abstinence approach, a harm reduction with crisis intervention as a central component should be utilized. The fundamental aims of this approach are enhancement of social support, maximization of treatment compliance, and containing harm associated with episodic relapses. Further, minimizing the frequency and intensity of the patients' use and consumption is the broad goal of treatment. Thereby, further damage to the patient will be reduced as well as the facilitation of treatment compliance.

Other psychotherapeutic approaches beneficial for this population are support groups and 12-step programs. The problem lies in that traditional 12-step groups are based on an abstinence-only policy. This poses a problem for patients who are being treated with opioids for pain-related syndromes. More recently, support groups have been tailored for this specific population.

Many nondrug approaches exist to assist patients in coping with chronic pain in advanced illness. Such educational interventions may include relaxation techniques, ways of thinking of and describing the experience of pain, and methods of communicating physical and emotional distress to staff members. Although nondrug interventions are adjuvants to management, they should not be perceived as substitutes for drugs targeting pain or other physical or psychological symptoms ([13–15]).

Inpatient Management Plan

In designing the inpatient management of an actively abusing patient with advanced illness, it is helpful to use structured treatment guidelines. Although the applicability of these guidelines may vary from setting to setting, they provide a set of strategies that can ensure the safety of the patient and staff, control possible manipulative behaviors, allow for supervision of illicit drug use, enhance appropriate use of medications for pain and symptom control, and communicate an understanding of pain and substance abuse management ([13–15]).

Under certain circumstances, such as actively abusing patients who are scheduled for surgery, patients should be admitted several days in advance, when possible, to allow for stabilization of the drug regimen. This time can also be used to avoid withdrawal and to provide an opportunity to assess whether modifications of an established plan are necessary [13, 14].

Once established, the structured treatment plan for the management of active abuse must proceed conscientiously. In an effort to assess and manage symptoms, frequent visits are usually necessary. It is also important to avoid drug withdrawal, and to the extent possible, prescribed drugs for symptom control should be administered on a regularly scheduled basis. This helps to eliminate repetitive encounters with staff that center on the desire to obtain drugs ([13–15]).

Treatment management plans must be designed to represent the clinician's assessment of the severity of drug abuse. Open and honest communication between clinician and patient to stress that the guidelines were established in the best interest of the patient is often helpful. However, in cases where patients are unable to follow these guidelines despite repeated interventions from the staff, discharge should be considered. Clinicians should discuss this decision for patient discharge with the staff and administration, while considering the ethical and legal ramifications of this action ([13–15]).

Outpatient Management Plan

Alternative guidelines may be used in the management of the actively abusing patient with advanced illness who is being treated on an outpatient basis. In some instances, the treatment plan can be coordinated with referral to a drug rehabilitation program. However, patients who are facing end-of-life issues may have difficulty participating in such programs. Using the following approaches may be helpful for managing the complex and more difficult-to-control aspects of care.

Case Study A 36-year-old white male with stage IV lung cancer (Pancoast tumor) that was locally advanced and widely metastatic presented late after a 35-lb weight loss. His sister had died of the same disease at age 35, and he had a history of significant substance abuse and drug dealing. The patient complained of out of control pain and lack of willingness of any local providers to prescribe pain medication. The patient was inflexible about acceptance of any other treatments (i.e., nerve block, epidural) other than OxyContin™. The patient's pain was 10/10 from brachial plexopathy with mixed neuropathic/somatic/visceral components.

Patient was titrated to effect over time. The maximum dose reached 800 mg bid at the time of death with 100 mg liquid MS04 q1h rescues. Although the patient was dying, structured management was required because of his history. The structured management plan was as follows: hospice nurses delivered one-day supply, unscheduled visits for pill counts, urine screens, and a reliable family member was identified to lock up pain medication supply.

The patient settled down and with renewed trust was willing to add nortriptyline, which helped with neuropathic pain, as well as steroids for nausea, cachexia, and fatigue.

Guidelines for Prescribing

Patients who are actively abusing must be seen weekly to build a good rapport with staff and afford evaluation of symptom control and addiction-related concerns. Frequent visits allow the opportunity to prescribe small quantities of drugs, which may decrease the temptation to divert and provide a motive for not missing appointments ([13–15]).

Procedures for prescription loss or replacement should be explicitly explained to the patient, with the stipulation that no renewals will be given if appointments are missed. The patient should also be informed that any dose changes require prior communication with the clinician. Additionally, clinicians who are covering for the primary care provider must be advised of the guidelines that have been established for each patient with a substance abuse history to avoid conflict and disruption of the treatment plan ([13–15]).

Twelve-Step Programs

Depending on the patient's stage of advanced illness and functional status, the clinician may consider referring the patient to a 12-step program with the stipulation that attendance be documented for ongoing prescription purposes. If the patient has one, the clinician may contact the patient's sponsor, depending on the stage of illness and individual capabilities, in an effort to disclose the patient's illness, and that medication is required in the treatment of the illness. This contact will also help decrease the risk of stigmatizing the patient as being noncompliant with the ideals of the 12-step program ([13–15]). If the patient is unable to participate in a 12-step program, other psychosocial and/or spiritual team members can provide care that supports sobriety.

Urine Medication Monitoring

One of the most commonly utilized risk management tools in chronic non-cancer pain management and adherence monitoring/sobriety in addiction treatment is urine drug testing (UDT). Depending upon the method employed, UDT can be used to gauge whether the patient is adherent to their prescribed medication, whether or not they are also taking non-prescribed licit medications, and/or whether they are using illicit drugs and alcohol [77]. Indeed, one study in which primary care doctors were taught to employ a "menu" of risk management techniques including UDT and then studied over time to exam their use of them found that UDT was the most commonly retained practice element on 6-month follow-up [78].

It is safe to say UDT is underutilized both in the treatment cancer and addiction and in the management of cancer-related pain with opioids. Perhaps oncologic ED professionals, due to their lack of familiarity with the evolution in methods and mind-set that had occurred in the laboratory and clinic in the last decade, think of UDT in only its forensic incarnation. In that view, UDT is a means out of finding if "bad people" are "doing bad things," as seen in a prior chart review study [79]. Thus they are fearful that introducing UDT to their patients and integrating it into patient management will be offensive. Providers may also fear their lack of a vocabulary for discussing results with patients. The forensic method, from which more modern clinical testing sprung, tends to rely on immunoassay (IA) testing which offers fast but only class-level (not drug-specific) results with high cutoffs. It is meant to detect recent use of classes of drugs that would impair, for example, a truck driver from driving. Cutoffs are high because of the legal and other consequences that could follow and to avoid falsely accusing people. In recent years, gas chromatography and liquid chro-

matography with mass spectrometry have become capable of giving highly accurate drug-specific results and return them in a timely fashion (1–2 days as opposed to 10 days–2 weeks). Such results can be used to determine whether a patient is misusing a range of drugs or alcohol and gauge their adherence with specific medication and controlled substance regimens. A paucity of data exists as to how such techniques might influence the management of cancer patients, and more data is needed in this arena, but the use of UDT for those with pain and/or substance use disorder is well documented [80–84].

Family Sessions and Meetings

The clinician, in an effort to increase support and function, should involve family members and friends in the treatment plan. These meetings allow the clinician and other team members to become familiar with the family and additionally help the team identify family members who are using illicit drugs. Offering referral of these identified family members to drug treatment can be portrayed as a method of gathering support for the patient. The patient should also be prepared to cope with family members or friends who may attempt to buy or sell the patient's medications. These meetings will also assist the team in identifying dependable individuals who can serve as a source of strength and support for the patient during treatment ([13–15]). These published guidelines generally advocate an approach to UDT based on risk stratification (i.e., frequency of testing and choice of methods are aimed at matching the approach to the level of risk of abuse, addiction, and diversion in an individualized way to each patient). Such an approach seeks to maximize the benefit of testing while also managing cost. As oncology professionals learn to integrate UDT into treatment of the person with cancer and addiction or the management of chronic opioid therapy, there is no reason to think that the adaptation of a similar approach might not be a reasonable way to proceed.

Conclusion

Treating oncology patients with chronic pain and substance use disorders is both complicated and challenging, as each can significantly complicate the other. Whether our patients respond to cancer treatments or have life-limiting disease, we can no longer justify high-dose opioid therapy in a vacuum without trying to assess and manage addiction and abuse behaviors. Using a treatment plan that involves a team approach to recognize and respond to these complex needs is the optimum treatment strategy. While pain management may remain challenging even when all treatment plan procedures are implemented, the healthcare team's goal should be providing the highest level of pain management for all patients with substance use disorders.

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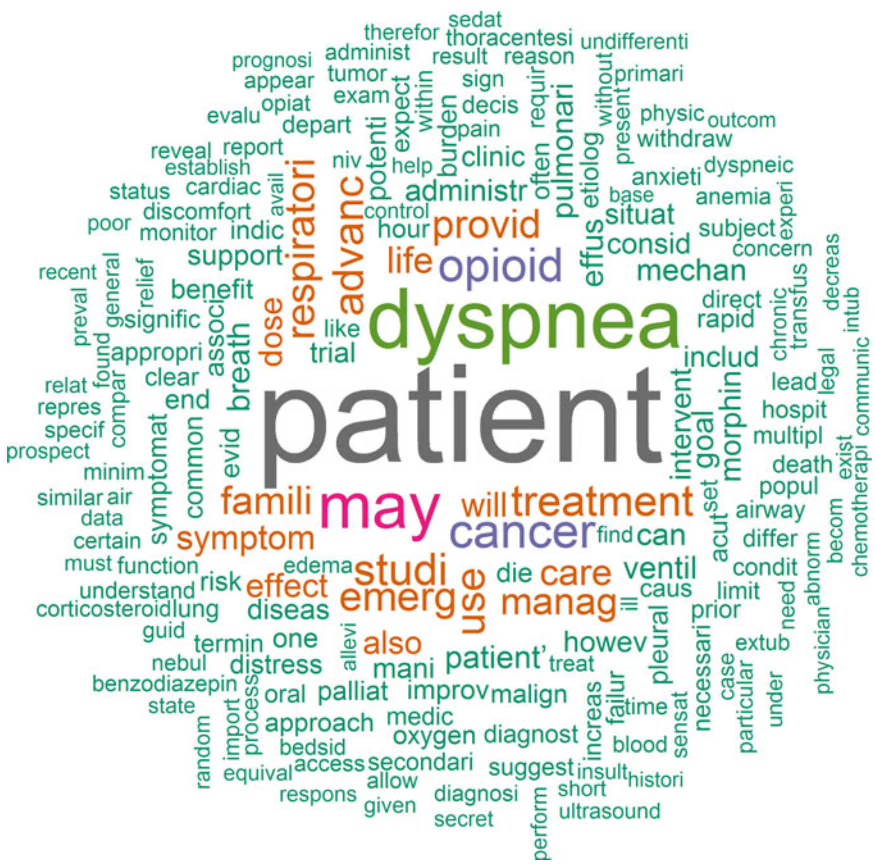
Dyspnea in the Dying Patient

Trevor Pour and Ashley Shreves



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Introduction

Dyspnea is a broad, general term used to characterize any sensation of respiratory discomfort. In a statement by the American Thoracic Society from 2012, dyspnea was appropriately defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [1]. It is important to emphasize that dyspnea is indeed subjective and thus a *symptom*; this contrasts to classic *signs* of respiratory distress including tachypnea, nasal flaring, and accessory muscle activation. As such, a variety of language may be used to describe the sensation: terms such as breathlessness, shortness of breath, tightness, air hunger, difficulty breathing, labored breathing, and heavy breathing. All of these descriptors relate to an increased awareness of the breathing process—normally an unconscious physiologic activity—caused by any number of insults to be described later in this chapter.

As a common endpoint for multiple disease processes, dyspnea is remarkably prevalent in the advanced cancer population at the end of life. Some degree of dyspnea has been reported in up to one third of all older adults living at home, approximately half of all patients admitted to tertiary care hospitals, 70–80 % of patients with terminal cancer in the last 6 weeks of life, and up to 94 % of patients with chronic lung disease at some point in the last year of life [2–6]. It is both debilitating for patients and emotionally upsetting for their families and caregivers. It also ranks among the most distressing symptoms at the end of life, leading to a marked reduction in the quality of life and a source of both fear and anxiety for all parties involved [7].

Derangements of the pulmonary/respiratory system have long been recognized by emergency providers as an indicator of serious illness and of the potential need for prompt intervention. Patients who present to the emergency department in respiratory distress appear extremely ill and receive rapid attention, in many cases leading to intubation and the use of mechanical ventilation. When caring for a patient with end-of-life/terminal dyspnea, however, for whom these aggressive interventions may be misaligned with patient's goals of care, the necessity for rapid treatment is no less imperative. In these situations, a focused and patient-centric plan coupled with an empiric approach to symptom management is necessary. This chapter will present a structured approach to the management of dyspneic patient at the end of life whose goals are not purely curative and for whom comfort and quality of life are of primary importance. As emergency providers are well aware, responding to acute symptomatology often requires treatment prior to definitive diagnosis, and the management of terminal dyspnea is no different. In some instances, however—namely, those with reversible causes—diagnosis is worth pursuing, and those instances will be discussed herein.

Neurophysiology

The pathophysiology of dyspnea is complex and remains poorly understood compared to other common clinical phenomena such as pain or nausea. The best current evidence counters the traditional model of dyspnea as a singular entity, instead suggesting multiple neurophysiologically distinct afferent pathways each replete with a unique subjective experience and a different set of predisposing stimuli [8, 9]. To illustrate, one such multifaceted model subdivides dyspnea into (1) air hunger, which is the urge to breathe characterized by an increased ventilatory drive secondary to hypercapnia; (2) increased work of breathing, associated with exhaustion due to effortful breathing; and (3) tightness, a sensation most associated with bronchoconstriction and asthma [10]. While the details of this particular multidimensional model of dyspnea are beyond the necessary scope of knowledge for the emergency provider, it is worth noting that data will continue to emerge on these discrete neurologic pathways, with potential implications for specifically targeted therapeutic options in the future. It also highlights the need for careful appraisal of the literature concerning dyspnea and potential for conflicting study outcomes, as the majority of evidence to date is based on the assumption a single unified perception of dyspnea.

A more practical understanding of dyspnea as it relates to oncologic etiologies focuses primarily on the brainstem respiratory complex and its relation to the most common variant of dyspnea, air hunger [11]. Through direct action on medullary chemoreceptors, $PaCO_2$, PaO_2, and pH act to regulate respiratory drive by modulating both rate and effort [12]. When an insult causes disruption in homeostasis of any of these variables, an appropriate motor response is elicited to correct this imbalance. The end result of these physiologic insults, whether they be mechanical, metabolic, or neuromuscular, is often a failure to match ventilation with brainstem-mediated respiratory drive. Once this mismatch occurs, the patient develops a sensation of breathlessness and air hunger, which may then exacerbate the predisposing condition through increased metabolic demand. Anxiety and fear, sensations which both precipitate *and* are exacerbated by dyspnea, are cortically mediated (primarily limbic and paralimbic) and are distinct from those initial sensations mediated by the brainstem respiratory motor drive [13]. This neurologic distinction allows for multiple therapeutic approaches to be discussed.

Etiology and Prevalence

Dyspnea is widely prevalent in advanced cancer, with a marked increase in symptoms as patients near the end of life [4]. While primary lung cancer conveys the highest risk of all malignancies

for developing shortness of breath—affecting up to 84 % in one large cross-sectional study—all primary cancers are associated with some increased incidence of dyspnea [3, 14]. There are many specific conditions associated with respiratory compromise which disproportionately affect patients with active malignancies. Below is a partial list of these diagnoses with particular emphasis on cancer-related etiologies and common comorbid conditions. Many are reversible, and these will be explored individually later in this chapter [15].

- Airway obstruction: foreign body/aspiration and tumor burden.
- Anaphylaxis and angioedema.
- Asthma/reactive airway disease.
- Anemia: blood loss, nutritional deficiency, and chemotherapy induced.
- Behavioral/emotional: anxiety and panic attack.
- Chronic obstructive pulmonary disease/emphysema.
- Deconditioning/cachexia/muscle weakness.
- Decreased cardiac output: myocardial ischemia, arrhythmia, tamponade, and hypovolemia.
- Decreased chest wall compliance: hepatosplenomegaly, ascites, obesity, and tumor burden.
- Diaphragmatic/respiratory muscle weakness: neuromuscular disorders and fatigue.
- Metabolic acidosis: renal failure, sepsis, and toxic ingestions.
- Pneumonia.
- Pneumothorax.
- Pulmonary edema/congestive heart failure.
- Pulmonary effusion: malignant and infectious.
- Pulmonary embolism.
- Pulmonary hypertension.
- Pulmonary fibrosis/interstitial lung disease: autoimmune, environmental, and secondary to radiation or chemotherapy.
- Pulmonary receptor stimulation: environmental irritants.
- Ventilation/perfusion mismatch.

Complicating diagnosis and treatment, most patients will present with multiple, coexisting etiologies of dyspnea; a study of one hundred advanced cancer patients revealed a median of five different abnormalities that could have contributed to their shortness of breath [16]. The most frequent cause for symptoms in this cohort was a direct pulmonary pathology related to disease progression; this was followed by treatment-related pathologies secondary to chemotherapy or radiation and then by nonmalignant etiologies such as underlying chronic lung disease. There were, in up to 30 % of patients with dyspnea and advanced cancer, no clear identifiable causes for their dyspnea [16].

Evaluation

Arrival in ED/History

Evaluation of the undifferentiated patient with respiratory distress may be challenging in the emergency setting. Frequently, providers face an acutely unstable patient with limited access to complete medical history. Patients may arrive initially unaccompanied by family or caregivers to provide historical context to the hospital visit. In these situations, management should proceed as with any other emergency patient: with focus on stabilization of the airway, breathing, and circulation, as represented through legal advance directives. In many states, the increasingly utilized POLST (Physician Orders for Life-Sustaining Interventions) advanced directive contains the only legally recognized out-of-hospital Do Not Intubate (DNI) order and can provide critical guidance in the early management of unstable patients with advanced cancer. If the situation arises in which an intervention was made—such as endotracheal intubation—and it later becomes clear that this was misaligned with the patient's stated goals of care, there is no legal or ethical barrier to withdrawing these life-sustaining treatments in the emergency department [17].

Physical Exam

There are many elements of the physical exam in the dyspneic cancer patient which can aid in both prognostication and diagnosis. As patients may be unable to communicate either secondary to their chronic disease process or from their dyspnea, exam findings must be used to guide acute medical management. Classic signs associated with respiratory distress include gasping, accessory muscle activation, tachypnea, shallow respirations, and poor air movement on lung auscultation. Facial expressions should also be noted, as grimacing may suggest pain or discomfort from dyspnea [15]. Family members or caregivers may be especially helpful in this regard, as they may be more skilled at distinguishing specific nonverbal cues or changes from baseline appearance [18]. Chest auscultation for abnormal breath sounds may also guide management—diffuse wheezing may suggest an obstructive process such as asthma/COPD, while bibasilar or focal rales may be more indicative of pulmonary edema or pneumonia. Stridor is concerning for upper airway obstruction or allergic reaction. A focal or asymmetric decrease in breath sounds could indicate pulmonary effusion, pneumothorax, or hemothorax. Distant cardiac sounds or a cardiac rub is concerning for pericardial effusion. In patients with notable skin pallor, anemia may be contributing

to dyspnea, while peripheral cyanosis would suggest a more significant hypoxic state. Abdominal distention may represent underlying malignant ascites, which may cause restriction in lung expansion and subsequent respiratory distress. Peripheral edema, especially a change from baseline, may indicate worsening heart or renal failure, while asymmetric extremity edema may be concerning for deep vein thrombosis and pulmonary embolism.

There is prognostic value in certain physical exam findings at the end of life. For example, the inability to clear oral secretions, colloquially known as a "death rattle," has been associated with a median time from onset to death of 23 h [19]. Other physical exam findings to guide expectations include respirations with mandibular movements (median time 2.5 h), extremity cyanosis (1 h), and inability to palpate radial pulse (1 h) [19]. A retrospective chart review of advanced cancer patients revealed the following historical and vital sign abnormalities as predictors of death within 2 weeks: triage respirations >28 (RR 12.7), pulse >110 (RR 4.9), history of uncontrolled progressive disease despite treatment (RR 21.9), and history of metastatic disease (RR 3.9) [20].

Laboratory Studies

There is no strong evidence to guide the decision to send laboratory studies in the acute emergency setting for the terminal cancer population. Consider sending labs if they could provide diagnostic clues which will lead to action consistent with the patient's stated goals. In some patients, the placement of an intravenous line alone is an unwelcome burden.

If mechanical ventilation is an option, assessment of $PaCO_2$ may be of clinical utility. If the patient wishes to receive blood transfusions, a complete blood count should be checked, along with a type and screen. While lactate levels have been shown to correlate with mortality and thus could theoretically be used as a prognostic tool, a study on patients with advanced cancer found that arterial blood gas could not help differentiate between patients who died imminently and those who did not [20, 21].

EKG

An electrocardiogram is a noninvasive intervention which provides rich diagnostic information and minimal patient burden. An EKG can provide diagnostic clues to indicate myocardial infarction, dysrhythmia, pericarditis/myocarditis, pericardial effusion, pulmonary embolism/heart strain, electrolyte abnormalities, or digoxin effect. In the absence of any compelling reason not to, or if refused by the patient, obtaining a 12-lead EKG should be part of the ED evaluation of the dying patient with dyspnea.

Imaging

Chest x-ray is similar to the electrocardiogram in terms of great diagnostic value compared to minimal burden. Common etiologies of dyspnea may be diagnosed rapidly in the emergency setting with chest radiography: pleural effusions, pneumothoraces, and pulmonary infiltrates/edema are all easily identifiable and may allow for target therapies to relieve symptoms. For patients with limited functional status, portable films may be shot at the bedside. As an adjunct, or even a potential replacement, for chest radiography is bedside ultrasound. Emergency physicians are becoming more adept at using ultrasound as a diagnostic tool and as a procedural aide, and the noninvasive nature of the modality allows for high-quality images to be collected with a minimum burden to the patient. Recent studies have shown that thoracic ultrasound can differentiate between cardiac and pulmonary causes of dyspnea and accurately diagnose free or loculated pleural effusions, pneumothoraces, and lung consolidations [22, 23].

Generally, there is limited value in computed tomography (CT) for the diagnosis and treatment of dyspnea in terminal cancer patients. While CT represents the gold standard for detection of pulmonary embolus (PE) and therefore should be used if the patient's goals of care and functional status align with PE treatment protocols, this test requires that the patient briefly leave their monitored bed and move to a radiology suite where close symptom management is challenging and onto a flat exam table which may exacerbate dyspnea [24]. Also, since it is reasonable to discontinue or hold anticoagulation for treatment of venous thromboembolism when advanced cancer patients enter the dying phase, it extends that withholding anticoagulation for acute PE is also reasonable; these patients are unlikely to see significant long-term benefit from anticoagulation and are at higher risk for complications [25]. Symptomatic management can and should continue despite the lack of a concrete diagnosis, so if PE is suspected, the decision to pursue advanced imaging should come only after a frank discussion with patient and family about the risks of harm and benefit of the proposed treatment course.

Cardiac Monitoring/Telemetry/Vital Signs

Cardiac monitoring provides real-time information to providers and can also help to identify transient dysrhythmias. However, it also provides a noisy and oftentimes fear-producing distraction for patients and their families. Unless there is a clear and convincing reason to keep patients on cardiac monitoring, consider changing alarm limits, turning off in-room monitor screens, or removing the patient entirely to minimize physical barriers between patient and family.

Vital sign abnormalities should be expected in the dying patient, and unless the rapid identification of these vital signs will make a meaningful impact in patient care, it may be best to keep them off. This will allow the family to focus on their loved one without distractions and remind providers that treatment of the patient should come before treatment of vital sign abnormalities in this population.

General Management

There exist two approaches to the alleviation of dyspnea, as there are with most acute symptoms: One approach is to correct the underlying disorder responsible for the insult in physiologic hemostasis. For example, this may include the drainage of a symptomatic pleural effusion or pericardial effusion. It may involve provision of supplemental inhaled oxygen to a hypoxic patient or bronchodilators to an asthmatic. In the acute setting, however, diagnostic uncertainty exists and a direct approach is not always possible. And in some scenarios, the medical treatment necessary for correction of a primary insult may either be futile or come with an unacceptable side effect profile or burden to the patient being treated. In these situations, a second approach is necessary to alleviate dyspnea by interfering with the downstream cortical pathway. This is not a departure from standard emergency practice—many patients present to the ED with undifferentiated pain or nausea, which requires prompt symptomatic treatment prior to availability of diagnostic testing.

Opioids

The general approach to nonspecific, terminal dyspnea primarily consists of systemic opioid administration. Opioids are safe, effective, largely predictable, and fall well within the comfort zone of the emergency provider. The majority of laboratory and clinical trials to date suggest a benefit of opioids for the treatment of symptomatic breathlessness in advanced illness [11, 26]. But similar to the pathophysiology of dyspnea itself, the exact mechanisms by which opioids exert their influence and alleviate dyspnea are not entirely understood. Leading theories based on current experimental evidence indicates that opioids likely function to modulate the effect of chemoreceptor-activated central respiratory drive on actual ventilation rate and effort [27]. By reducing this reaction to insult and the subsequent compensatory physiologic changes, an increased subjective tolerance may be reached. In addition, the established presence of opioid receptors in bronchial epithelial cells indicates a potential function in both central feedback and local inflammatory response [28, 29]. Finally, there exists a strong emotional component of anxiety which is commonly reported alongside dyspnea and acts to exacerbate the subjective experience. Though it is unclear whether there exists a direct or indirect effect, opioid administration has been shown to measurably decrease reported anxiety in dyspneic patients [30].

In 2011, Banzett and colleagues performed a well-controlled randomized trial using morphine for the relief of dyspnea [30]. This study artificially stimulated air hunger by limiting minute ventilation in healthy patients while inducing hypercapnia. Using patient-reported dyspnea scores on the validated VAS as their primary outcome, IV morphine was compared to IV saline with a significant benefit in both dyspnea scores and anxiety in the morphine study arm. While this study was performed on young and healthy subjects and therefore is less representative of the typical cancer patient, it provides insight into the mechanics of dyspnea and offers valuable data from a controlled environment.

Larger analyses of clinical data have also revealed similar findings. Although there are only a few randomized controlled trials of opioids for dyspnea in terminally ill cancer patients, a 2008 systemic review of available literature examined seven trials of cancer patients receiving either subcutaneous or nebulized morphine versus placebo [31]. The authors concluded that subcutaneous morphine was effective at reducing dyspnea in this population, although nebulized treatments did not reveal a significant difference compared to a saline placebo.

The choice of opioid medication for the relief of breathlessness is based on provider preference and departmental availability, similar to the treatment of pain. The literature bears this to be true, as dyspnea studies often use different but generally equivalent opioid regimen. There have been clinically significant results shown in trials with oral dihydrocodeine [32], oral hydromorphone [33], IV morphine [34], oral morphine [35], and multiple studies on subcutaneous morphine [36]. Renal dysfunction has been cited as a justification for caution in morphine administration secondary to the theoretical risk of limited renal clearance of toxic metabolites, although the data for this is not robust [37]. Fentanyl has no clinically significant active toxic metabolites and may be effectively used if there is provider concern [38].

Route of administration should be based on patient specifics' parameters; in patients with intravenous access, for whom peripheral IV placement is within their established goals of care and does not represent and unwelcome burden, IV administration is straightforward and rapid. These medications can also be delivered subcutaneously in patients without IV access with minimal discomfort and may also be given orally for those patients able to safely swallow. As was described earlier, there is no strong data to support the use of nebulized opioid formulations, despite the potential for benefit given the known presence of local opioid receptors

within lung epithelial cells [29]. However, it has been suggested that many of these nebulized trials have failed to show a difference against placebo due to the fact that nebulized saline could also be an effective treatment modality [26]. Finally, there have been no randomized controlled trials on formulations other than morphine for nebulized delivery, so additional investigation must be performed prior to ruling out nebulized opioids altogether [36].

In terms of dosing and escalation, providers should treat opioid administration for dyspnea similar to pain, by giving a reasonable starting dose and reassessing symptom progression in 10–15 min, up-titrating as needed [15]. Recent prospective trials have used mean doses of 2.5 mg of PO hydromorphone (equivalent to 0.4 mg IV) and 9.4 ± 8.8 mg of PO morphine (equivalent to 0.8 mg IV) to achieve a desired level of patient comfort. Reasonable starting doses for opioid-naïve patients, therefore, should be approximately 1–2 mg IV morphine equivalent or 0.2–0.4 mg IV hydromorphone. If symptoms are unchanged after 10–15 min, consider re-dosing an equivalent or increased amount. If symptoms are improved, but not fully controlled, consider giving another 50 % of the starting dose and continue to reassess. Be aware that higher doses may be necessary in patients who are opioid tolerant; many advanced cancer patients will be on chronic standing and/or breakthrough opioids for chronic pain. In these situations, start by administering approximately 10 % of the patient's total daily opioid dose. For example, if a patient takes 15 mg of oral morphine every 4 h around the clock, their total daily dose equals 90 mg. An appropriate initial dose would be 9 mg PO morphine (equivalent to 3 mg IV). If the patient is taking multiple formulations of opioids, a conversion table should be employed to ensure safe dosing practices. Complicated dosing or high-dose opioid regimens should warrant a consultation with the palliative care service, if available.

Measure improvement in dyspnea through direct patient report, if possible. Again, similar to pain management, the patient's subjective experience of their symptoms is the best indicator of improvement. A visual analog scale (VAS) is usually used for these purposes in both research and clinical use. However, as patients near the end of life are oftentimes unable to effectively communicate, providers will often be forced to rely on elements of the physical exam and family gestalt to gauge response to treatment. It has been suggested to use simple "yes/no" questioning for symptom relief in patients struggling to communicate, as many patients who are unable to provide a scaled response to symptom improvement are still able to indicate yes/no responses [18]. There has also been a respiratory distress observation scale developed for these clinical scenarios, which involves heart rate, respiratory rate, degree of restlessness, accessory muscle use, end-expiratory grunting, nasal flaring, and a "look of fear" [39]. These tools are necessary to prevent undertreatment of a patient's symptoms due to communication challenges.

It is important to consider the potential side effects associated with opioid administration, chief among them being constipation. For this reason, any patient placed on scheduled opioid treatment should be managed expectantly with a bowel regimen. Common prophylactic regimens include a stool softener (e.g. docusate, polyethylene glycol, magnesium) with a stimulant laxative (e.g. senna, bisacodyl) [40]. Other side effects to consider include nausea, vomiting, sedation, pruritus, and allergy/anaphylaxis. These can be managed supportively.

There is understandable hesitation on the part of emergency physicians when considering the use of opiates in patients with dyspnea. In sufficient doses, opiates can lead to respiratory depression and even apnea, so administering these medications to a patient with respiratory compromise can seem dangerous. Fortunately, there is evidence to support the safety of these agents in cancer populations suffering from dyspnea, particularly those patients at the EOL. In several small prospective observational studies, mostly comprised of patients with advanced cancers, carefully administered opiates, even when given to opiate-naïve patients, did not result in clinically important respiratory depression or hypercapnia [41–43]. Furthermore, two large observational studies of hospice patients found minimal to no association with opiate usage, dosage, and life expectancy [44]. The key to safe, effective opiate administration, as stated earlier, is to "start low, go slow" carefully targeting symptomatic relief, titrating up doses in appropriate intervals, and with appropriate clinical monitoring.

Benzodiazepines

In select clinical scenarios, administration of benzodiazepines may be considered as a second- or third-line pharmacologic agent. The primary indication for this medication is when anxiety appears to be playing a significant role in the patient's discomfort and when other interventions have failed to alleviate symptoms. As briefly stated earlier, there is a physiologic justification for benzodiazepines despite the current lack of strong supporting clinical evidence. In current neurophysiologic models of dyspnea, there appears to be a distinct emotional component of dyspnea, which may be modulated by opioids but may theoretically benefit more from the anxiolysis associated with benzodiazepine administration [10].

There is, however, a very weak clinical evidence base for this intervention with few studies indicating effectiveness. The largest review to date published in 2010 examined seven independent trials composed of 200 subjects and found a

slight but nonsignificant trend toward a beneficial effect compared to placebo [45]. Since that time, other studies have been performed; one prospective trial assessed the safety profile of administration of 1 mg lorazepam in conjunction with opioids (morphine and hydromorphone) to palliative care unit patients with dyspnea and anxiety. No adverse events, hypoxia, or respiratory depression was noted. Patients all reported relief from their admission/baseline dyspnea, but no control group was included in the study [13]. Another open-label prospective trial examined the use of clonazepam 0.5 mg with oral morphine in an outpatient palliative care opioid/benzodiazepine-naïve population and found no respiratory depression, no change in end tidal CO_2 measurements, and no hospitalizations during the study period [46].

Given limited evidence for efficacy but without evidence for harm when used in small doses, benzodiazepines should be considered as an adjunct to opioids in situations where anxiety appears to be playing a role in symptomatology.

Corticosteroids

Corticosteroids represent a treatment for certain conditions associated with advanced cancers and should not be applied generally in the same fashion as opioids and benzodiazepines. There is limited data on their use, but case studies report temporary symptomatic improvement for specific conditions such as lymphangitic malignant spread and chemotherapy/radiation-induced pneumonitis [47]. Corticosteroids are the mainstay of treatment for radiation-induced lung injury, typically treated with a taper starting with 60–100 mf of daily oral prednisone [48]. There are also case reports of rapid improvement in dyspnea associated with upper airway tumor obstruction after administration of steroids, likely secondary to reduction in airway edema [49]. Reported doses include 10 mg IV dexamethasone and 125 mg IV methylprednisolone, administered every 6 h. Significant side effects exist and must be considered. These include hyperglycemia, infection risk, fluid retention, and potential psychomotor agitation [50]. In patients with life expectancies of days to weeks, however, long-term side effects are less concerning and therefore should be balanced against potential benefit.

Supplemental Oxygen

Supplemental oxygen is often reflexively administered to patients presenting to the ED with dyspnea, particularly those patients suffering from hypoxia. While oxygen has been demonstrated to improve the QOL and longevity of patients with severe COPD, its use in patients with dyspnea at the EOL is more controversial [51, 52]. In one large randomized trial of patients with advanced illnesses and dyspnea, about 15 % of whom had cancer, home oxygen resulted in no symptomatic improvements when compared to room air [53]. Surprisingly, in a prospective cohort study of patients admitted to a palliative care unit with advanced cancers, hypoxia and dyspnea showed little correlation. Furthermore, patients in this study had more dyspnea relief with opioid rather than oxygen administration [41]. As hypoxia is likely just one of the many factors contributing to dyspnea at the EOL, these results are somewhat predictable. Regardless, certain oxygen delivery devices like nasal cannula are minimally burdensome, so a time-limited trial in hypoxic, dyspneic patients can be considered, even those endorsing comfort-oriented goals. More caution should be used, however, when applying more burdensome devices like a non-rebreather mask, if the goals are comfort-oriented, as this may actually contribute to discomfort without clear evidence of efficacy.

Noninvasive Ventilation (NIV)/Mechanical Ventilation

NIV has been well studied and its efficacy well demonstrated in patients with CHF and COPD [54]. In recent years, this tool has been applied to a broader range of patients, even those with advanced cancers. A recent high-quality randomized trial evaluated the use of NIV when compared to oxygen (via venture or non-rebreather mask) for patients with advanced cancers presenting with acute respiratory failure. Patients receiving NIV had greater improvements in dyspnea scores and needed less opiates; however, about 10 % of patients randomized to this group discontinued therapy secondary to issues like mask intolerance (compared to none in the oxygen group). Mean survival was the same in both groups, 4–5 days, however, seemed to favor the use of NIV in those patients with concomitant hypercapnia [55]. In an observational study of patients with advanced cancer and respiratory failure, over half of patients treated with NIV actually survived their acute illness and were discharged alive from the hospital [56]. These studies suggest that for select patients with advanced cancer and a potentially reversible cause of acute dyspnea/respiratory failure, NIV can be a useful tool that improves symptoms and meaningfully prolongs life. In other patients, however, particularly those with respiratory failure secondary to progression of underlying disease, NIV simply artificially prolongs dying and can worsen suffering [57]. Prior to initiation of this therapy, it is recommended that clear, time-specific goals be established with the patient and/or key decision-makers. For example, if there is no marked improvement in the patient's mental

status and/or the mask seems to be causing discomfort in the next 24 h, NIV should be transitioned off and opiates used exclusively to alleviate dyspnea.

Intubation is often considered, particularly in the ED, in advanced cancer patients with dyspnea and respiratory failure. Counseling patients and their families about the risks and benefits of this invasive intervention is critical. A recent study of cancer patients admitted to the ICU requiring ventilatory support demonstrated the importance of contextualizing the respiratory failure within a broader understanding of the overall illness. In the subgroup of patients with relapsed cancer and poor performance status (poor baseline function), hospital mortality was high, approaching 90 % [58]. Patients and families should be counseled that the use of mechanical ventilation is very unlikely to meaningfully prolong life in patients dying from an advanced cancer and is likely to lead to a burdensome death within the ICU setting.

Management of Specific Conditions

Pleural Effusion

Malignant pleural effusion is a challenging entity in the emergency setting, particularly in symptomatic patients with guarded prognoses. It is a common condition, with an estimated 150,000 cases in the USA annually and a prevalence in advanced cancer of approximately 15 % [59, 60]. Most pleural effusions will not become symptomatic until they reach over 500 cc in volume, and they can expand to over 2000 cc in volume. Practice guidelines for malignant effusions have traditionally recommended drainage with bedside thoracentesis, with consideration of pleurodesis—typically with talc—for prevention of recurrence and re-accumulation [61]. Talc pleurodesis, however, requires inpatient hospitalization and surgery, may be distressing and painful, and may lead to further complications including pneumothorax or empyema. Increasingly, indwelling pleural catheter drainage is being employed for either permanent or temporary management of re-accumulation, thus diverting patients away from the traditional and burdensome pleurodesis [59]. Of note, palliative chemotherapy may actually benefit patients with recurrent effusions who have chemotherapeutic-responsive tumors [60]. This does not represent an emergency intervention but should be known when discussing the full range of therapeutic options with a family.

Functional status and patient prognosis should guide treatment, along with patient and family values and goals of care. In general, therapeutic thoracentesis alone is typically recommended in patients with a short expected prognosis or poor functional status, which allows for temporary evacuation of pleural fluid without necessitating hospital admission. Effusions may re-accumulate rapidly within days or slowly, on the order of months. There are no good predictors to help determine which patients are at a higher risk for rapid re-accumulation [59]. The potential for rapid recurrence is an important detail to share with patients' families who may have very different expectations of this procedure. Most, but not all, patients will experience relief in dyspnea following a thoracentesis, but given that dyspnea is multifactorial in advanced cancer, families should also understand that thoracentesis is not necessarily a definitive treatment for an individual patient's symptoms. For those patients with frequent recurrent pleural effusions or for those with predicted longer life expectancies, it may be more appropriate to refer for pleurodesis or tunneled catheter placement.

If performed in the emergency setting, thoracentesis should be done by an experienced provider utilizing ultrasound guidance. A retrospective study on 445 patients undergoing thoracentesis for malignant pleural effusion revealed a 0.97 % pneumothorax rate with ultrasound guidance and 8.89 % without [62]. Re-expansion pulmonary edema is a known potential complication and may occur if greater than 1.5 L are removed at once, although the incidence of this is uncommon, around 0.5 % in a series of 185 cases [63, 64].

Anemia

Advanced cancer patients have a high prevalence of anemia, with studies suggesting up to 70 % of these patients live with a hemoglobin concentration below 12 g/dL. While the majority of anemia in this population is of unclear etiology, many are thought to have anemia of chronic disease or nutritional deficiencies, notably of folic acid [65]. In a study aimed at establishing the cause of dyspnea in advanced cancer patients, up to 20 % of enrollees were found to have a hemoglobin level which was low enough to have effected tissue perfusion [16]. In these situations, transfusion should be considered. Major elements impacting this decision include prognosis, functional status, and goals of care. There are risks and burden associated with transfusion, including additional time spent in the hospital, necessarily placement of intravenous access, and the risks of transfusion reaction, infection, or fluid overload. A prospective study of outpatient palliative care patients with cancer found that by using a transfusion cutoff of 8 g/dL, patients had a significant improvement in both self-reported dyspnea and fatigue, but these effects began to decrease approximately 2 weeks after transfusion [66]. The decision to transfuse should be left up to the treatment team in conjunction with the patient and family, though they should be aware that the subjective benefit in dyspnea relief is likely temporary and does carry some limited risk.

Oral Secretions

As death approaches, secretions pool in the posterior oropharynx and patients become too weak to swallow or clear them. Anticholinergic agents are commonly used to address the noisy breathing that many patients experience as a result. Most patients are unconscious at this point and thus unlikely to be bothered by what is known as the "death rattle" [19]. Family members, however, can find the noise distressing, so treatment is often considered. Unfortunately, there is a lack of high-quality evidence on this topic to guide management. In a Cochrane review evaluating interventions for noisy breathing near the end of life, only one small study met criteria for inclusion with no benefit found to any treatments evaluated.

For patients with intravenous access, glycopyrrolate 0.2 mg IV or atropine 0.1 mg IV can be administered. For those without IV access, drops of atropine 1 % ophthalmic solution can be given by mouth [67]. More important than medication choice, however, is educating family and caregivers that this is a normal part of the dying process unlikely to be distressing to the patient. It is also an established prognostic sign that life expectancy is likely hours to days.

Tumor Burden

Lymphangitis carcinomatosis (LC), a condition involving hilar/mediastinal lymphatic inflammation secondary to malignant spread, affects between 6 and 8 % of patients with intrathoracic metastases with the most common underlying primary tumors being breast, stomach, and lung [68]. LC manifests as nonspecific, nonproductive cough with associated dyspnea and may be definitively diagnosed by CT scan or bronchoscopy/biopsy [69]. As a late finding in advanced cancer, it carries a poor prognosis, with 50 % survival at three months after first respiratory symptom. Corticosteroids have a palliative role by decreasing inflammation and should be considered in patients who carry this diagnosis [47]. In certain cases, palliative chemotherapy may also be offered and may give temporary improvement in symptoms over time.

Palliative Extubation

Establishing goals of care can be a time-intensive and arduous process. Oftentimes, a patient will present profoundly dyspneic to the emergency department alone or with EMS and with no ability to communicate their goals of care. In these situations, unless emergent airway management appears futile, patients will appropriately be intubated and placed on mechanical ventilation. After medical stabilization, when it is possible to clarify a patient's wishes with family or supporting documentation, it may become clear that the patient did not want to be placed on a ventilator. The appropriate management in these situations will vary—some families prefer to wait until they leave the emergency department into a more controlled environment (a hospital room or on a palliative care floor) prior to withdrawal of mechanical ventilation. In other situations, the emergency provider may withdraw support in the emergency department.

There may be hesitation on the part of the healthcare provider regarding the ramifications of withdrawal in the emergency department. A public health survey of medical attending physicians in 1993 revealed that only 43 % agreed that "there is no ethical difference between forgoing a life support measure and stopping it once it has been started" [70]. But from both an ethical and legal standpoint, there is no difference between these two actions [71]. The ethical principle of *autonomy*, which dictates that a patient has the right to make his or her own decisions, must be honored. In situations such as these, there must be evidence of the patient's prior wishes; this may be supported by written documentation such as an advanced directive or POLST or the decision may be made by a legally designated healthcare proxy [72]. There may also be situations in which the physician deems ongoing care to be *futile*. In these cases, there is no ethical or legal obligation to continue providing support, and life support may be withdrawn. This decision should be made with the support of family or loved ones, but the legal requirement of proxy designation or advance directives is less imperative.

To prepare for withdrawal of mechanical ventilation, first ensure that the family understands the prognosis and potential outcomes following withdrawal. There is a common expectation that death is imminent after endotracheal tube removal, so appropriate counseling on expected outcomes should be set prior to the procedure. Document the relevant conversation with the patient's proxy decision-makers along with relevant clinical findings prior to withdrawal; this should support the decision to withdraw care. Allow family to make any necessary spiritual arrangement, ensure a relatively quiet space around the patient's bedside, and turn off monitors and unnecessary equipment including blood pressure cuffs and pulse oximeters. It is best to keep IV access in place for rapid administration of sedatives if necessary.

Prior to extubation, give a dose of glycopyrrolate (0.2 mg IV, may be repeated every 6 h) to minimize respiratory secretions. Pushing a dose of sedative prior to extubation is also helpful to prevent patient discomfort. Reasonable choices include morphine, midazolam, pentobarbital, or propofol, along with an infusion if necessary to keep the patient comfortable. At the time of extubation, deflate the tube cuff and

ensure that there is plenty of support staff at the bedside to clean secretions from the patient's airway, with suctioning if needed, and to administer any necessary sedatives. Turn off the ventilator to prevent alarming. The goal of sedation is to minimize tachypnea and prevent agitation [72]. Families may be concerned with sedative administration, but similar to the management of undifferentiated dyspnea without airway management, provision of opioids after palliative extubation does not appear to have any effect on hastening death [73, 74]. Be available to the family, as they will often have questions during the dying process and may ask for frequent reexaminations of their loved one.

Regarding prognostication, one study of mechanically ventilated ICU patients who were terminally extubated revealed that half died within 1 h of withdrawal, with the majority dying within 10 h [75]. Factors that were predictive of an earlier time to death included a high oxygen requirement ($FIO_2 > 70$ %) and the use of vasopressors. Note that over half of this study group had been mechanically ventilated for over 10 days, and therefore these results may not be entirely reflective of the acute/emergency population.

After the patient dies, ensure that the family is able to spend time around the bedside and provide bereavement support as needed.

Summary

Dyspnea in advanced cancer is distressing, complex, and often multifactorial. As patients approach the end of life, dyspnea becomes a common endpoint for multiple disease processes, with many factors simultaneously contributing to a patient's underlying shortness of breath. Many of these patients will seek care in the emergency department, necessitating emergency providers to have a strong understanding of the pathophysiology and management of terminal dyspnea. Above all, clear and open communication will help guide the diagnostic workup and treatment course for a patient with dyspnea near the end of life. Patient's goals may range from purely symptomatic treatment to aggressive extension of life, and therefore each patient will need to receive truly customized care from the onset of their emergency department visit.

Fortunately, while the neurophysiology of dyspnea is complex, the treatments are not. Opioids are the clear mainstay of symptomatic management. The proper titration of opioids will often be sufficient to adequately treat dyspnea at the end of life, but in certain situations a patient may require or request more intensive treatment. These interventions range from blood transfusions to noninvasive ventilation to bedside thoracentesis. By developing a keen understanding of the risks, benefits, and long-term outcomes of these interventions, the emergency provider is better able to equip the patient and family with the information they require to decide whether the intervention aligns with their goals and values.

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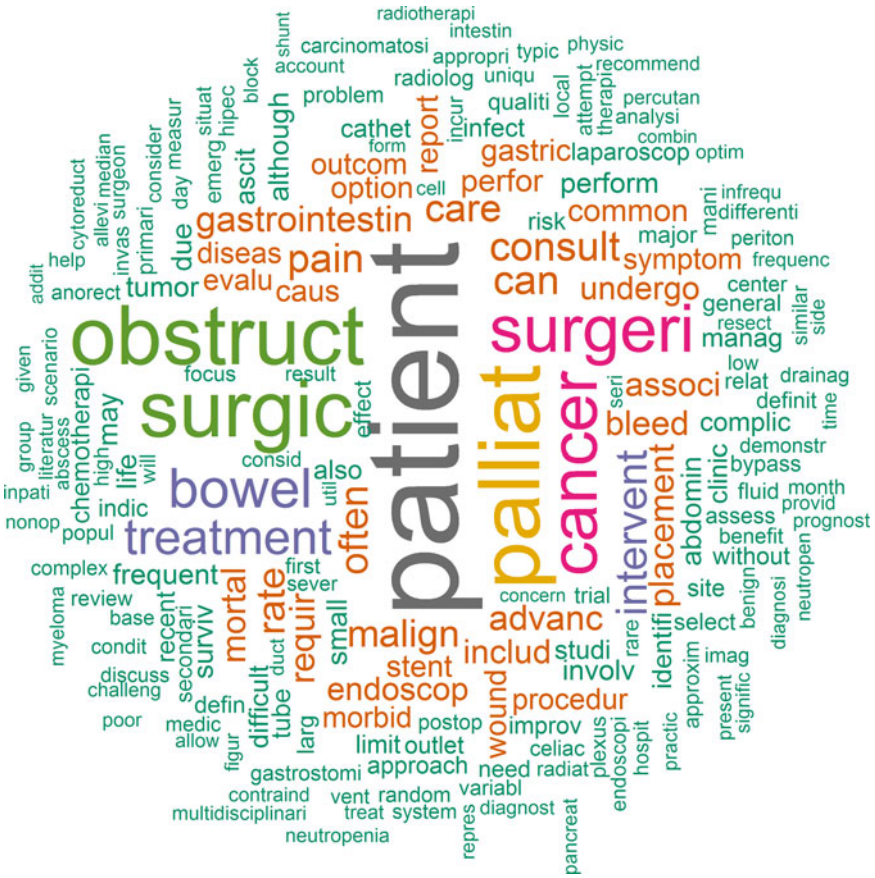
Palliative Surgery

Brian Badgwell



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Introduction

Palliative care, defined by the World Health Organization, is care to improve the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering [1]. Palliative care involves the assessment and treatment of pain and other physical, psychosocial, and spiritual problems. The first distinction that must be made in addressing palliative surgery is differentiating surgical palliative care from medical palliative care. Medical palliative care is the management of symptoms such as pain, nausea, cachexia, delirium, and fatigue. Surgical palliative care can broadly be separated into two main categories. The first is operative palliative surgical care in which surgical interventions are the treatment modality utilized to palliate patients with advanced or incurable illness. Palliative surgery is defined as surgery performed with the purpose of alleviating symptoms and improving quality of life [2]. This form of palliative surgical care is often encountered during surgical consultation or in the emergency department. The second form of palliative surgical care involves nonoperative care and decisions about the appropriate level of care in postoperative or trauma patients with life-threatening conditions or postoperative complications. This form of palliative surgical care is most often encountered in the intensive care unit or postoperative inpatient unit.

The focus of this chapter on palliative surgery will be clinical diagnoses evaluated for potential surgical intervention. Palliative surgical consultation is a frequent occurrence in hospitals that treat cancer patients. Approximately half of all inpatients undergoing surgical consultation at major cancer centers meet the criteria for palliative care. In a study at MD Anderson of over 1000 inpatient surgical consultations, 40 % met the criteria for surgical palliative evaluation [3]. The low overall median survival of all patients (2.9 months) highlights the need for a selective approach to patients undergoing palliative surgical consultation. Attempts to identify variables associated with poor survival, and perhaps identify patients that should be managed without surgery, were largely unsuccessful in this study, although patients with two or more radiologic sites of disease and carcinomatosis had poorer survival. The risks of palliative surgery are significant as palliative surgical procedures were performed in 27 % of patients with a 90-day morbidity and mortality rate of 40 % and 7 %. Risk-benefit discussions during the consent process for palliative surgery are difficult owing to several limitations in existing data and research. First, the benefits of palliative surgery are largely unknown due to a paucity of high-quality, prospective, patient-reported outcome studies. Second, prognostication is difficult for advanced cancer patients, and the risks of surgery must be balanced against the estimated remaining length of life for patients undergoing palliative surgical consultation. Lastly, randomized clinical trials are difficult to perform in palliative populations and particularly in palliative surgical populations [4].

Despite a selective practice of surgical intervention, palliative surgery can still account for approximately 20 % of a surgical oncologists practice and over 1000 procedures per year at cancer centers [5, 6]. The frequency of palliative surgical consultation and intervention aids in the identification of common diagnoses and treatment patterns. Gastrointestinal obstruction is the most common indication for palliative surgical consultation at approximately 40 % [3]. Gastrointestinal bleeding and wound complications/infections each account for 10 % of palliative surgical consultations. Abdominal pain of unclear etiology is also common and often includes patients with constipation, ileus, carcinomatosis with resultant gastrointestinal dysfunction, and medication or treatment-related side effects. The common theme throughout many of these palliative surgical consultations is the acute presentation of symptoms as these patients are often evaluated in the hospital or emergency department. Although acute in nature, palliative surgical consultations rarely require urgent surgical intervention and allow for time to engage in multidisciplinary care discussions and a thorough evaluation of the associated risks and benefits.

Gastrointestinal Obstruction

Gastrointestinal obstruction is one of the most common indications for surgical consultation, even in patients without cancer. The standard approach by general surgeons in the evaluation of patients with obstruction includes a history to identify the anatomic site and degree of obstruction. Past surgical history is an important component of the subjective assessment for patients with obstruction as adhesions and hernias are the two most common causes of obstruction. Cancer is notably the third most common cause in the bowel obstruction differential diagnosis in patients undergoing general surgery evaluation. The objective assessment should first focus on vital signs to evaluate for hemodynamic instability. Fever and tachycardia are findings worrisome for ischemia. A complete physical examination should be performed. A focused assessment of the abdomen is necessary to evaluate for strangulated incisional or inguinal hernias, the degree of abdominal distention, and peritoneal signs. Laboratory analysis is necessary to manage electrolyte abnormalities and evaluate for leukocytosis, which could also indicate ischemia. Imaging is frequently obtained, first with plain films but computed tomography imaging is often required in cancer patients to determine not only the site of obstruction but also to evaluate for sites of metastasis within the abdomen, multifocal obstruction, and ascites. Treatment should begin during the evaluation of patients with bowel obstruction

and may include nasogastric tube decompression, intravenous fluid resuscitation, and Foley catheter placement.

There are various definitions for gastrointestinal obstruction in cancer patients. Definitions include malignant bowel obstruction, patients with bowel obstruction secondary to recurrent cancer, patients with stage IV cancer and obstruction, and definitions based on anatomic site of obstruction [7–9]. A definition formulated during an international multi-institutional and multidisciplinary conference tasked with creating a definition for subsequent palliative trials defined malignant bowel obstruction as (1) clinical evidence of a bowel obstruction via history, physical exam, or radiographic examination; (2) bowel obstruction beyond the ligament of Treitz; (3) intra-abdominal primary cancer with incurable disease; or (4) non-intra-abdominal primary cancer with clear intraperitoneal disease [10]. A simplified definition for malignant bowel obstruction is blockage of the small or large intestine in a patient with advanced cancer [11]. As treatment varies depending on the anatomic site of obstruction, defining the obstruction as gastric outlet, small bowel, or large bowel can help identify differences in the utilization of endoscopic or surgical procedures and also identify differences in outcomes such as survival or symptom improvement [9]. Regardless of the definition, bowel obstruction in patients with advanced cancer is common with reported rates of up to 42 % of patients with advanced ovarian cancer and up to 24 % of patients with advanced colorectal cancer developing obstruction during their lifetime [12]. Adding to the complexity of defining bowel obstruction in cancer patients is that somewhere between 3 and 40 % of obstructions may have a benign etiology and are caused by adhesions or strictures not associated with malignancy [13].

Emesis and abdominal distention in patients with incurable cancer can be due to a myriad of factors other than mechanical obstruction. Patients with advanced cancer can suffer from electrolyte abnormalities, cachexia with metabolic derangements, pain medication side effects, constipation, autonomic dysfunction due to plexus involvement from malignancies with a tendency for perineural invasion, and chemotherapy/radiotherapy side effects. There are many surgical consultations for bowel obstruction that are ultimately found to have gastroparesis, ileus, or constipation.

Bowel obstruction in patients with advanced cancer is rarely a surgical emergency and typically allows time to consider multidisciplinary aspects of the patient's condition. Previous treatment, cancer stage, and prognosis are unique variables to consider in cancer patients with gastrointestinal obstruction. Although accurate prognostication is difficult, it is helpful to attempt to determine if a patient can recover from abdominal surgery and obtain a meaningful quality of life prior to death from their malignancy. The next aspect of surgical decision-making to consider is morbidity and mortality rates, which are considerable in patients undergoing palliative surgery. Morbidity and mortality rates are widely variable in the literature with a range of morbidity from 9 to 90 % and a range of mortality from 9 to 40 % [12]. A recent series from our institution demonstrated morbidity and mortality rates for surgical intervention of 44 % and 5 %, respectively [9].

Recognizing the lack of randomized trials and limited data from observational and retrospective studies of patients with advanced malignancy and bowel obstruction, various groups have attempted to provide consensus statements and treatment algorithms for these difficult clinical scenarios. The Working Group of the European Association for Palliative Care has provided clinical practice recommendations that state surgery should not be routinely undertaken and will only benefit selected patients with end-stage cancer and mechanical obstruction [12]. The working group went on to recommend absolute contraindications to surgery such as previous abdominal surgery which showed diffuse metastatic cancer, involvement of the proximal stomach, and ascites which recurs rapidly after drainage. Relative contraindications include poor general performance status, poor nutritional status, and extra-abdominal metastases producing symptoms which are difficult to control. Many investigators have sought to identify variables associated with adverse outcomes. Ascites and carcinomatosis are frequently reported as independent indicators of poor survival and also diminished ability to tolerate oral intake after palliative surgical intervention [14–16]. The combination of ascites and carcinomatosis creates a situation which is rarely palliated with surgery, other than venting gastrostomy tube placement.

Gastric Outlet Obstruction. Gastric outlet obstruction is defined as obstruction of the distal stomach or proximal duodenum and is most often associated with gastric, duodenal, or pancreatic malignancy. Figure 1 demonstrates a CT image

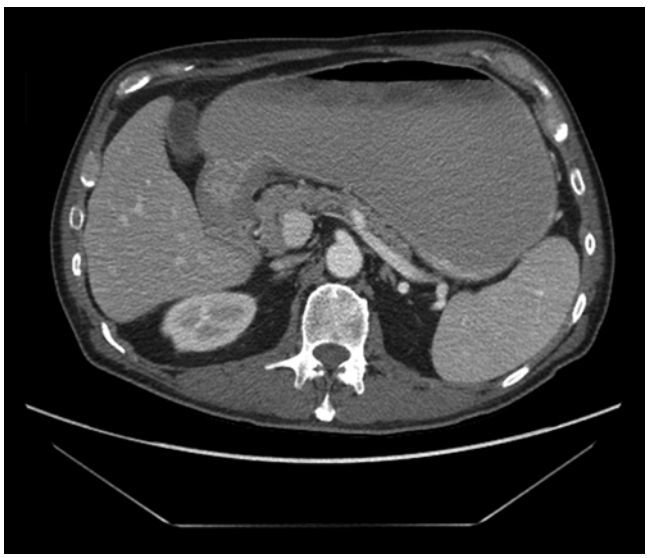

Fig. 1 CT image demonstrating gastric outlet obstruction

of a patient with gastric outlet obstruction secondary to gastric cancer involving the pylorus. Gastric outlet obstruction only accounts for approximately 20 % of palliative surgical consultations for gastrointestinal obstruction but has an associated low median survival of 3 months, highlighting the need for selective use of surgical intervention [9]. The surgical option for palliation is most often a loop gastrojejunostomy. Although technically simple, morbidity and mortality rates are significant and temporary delayed gastric emptying can occur after surgery [17]. The other option for palliation of gastric outlet obstruction is endoscopic stent placement. Endoscopic stents have less risk of morbidity and mortality but lack the durability of a surgical bypass [18, 19]. Stents are prone to occlusion and migration and often require patients to remain on a liquid diet. As the majority of cancers that cause gastric outlet obstruction are associated with limited survival, prognostication plays a role in treatment selection. A small multicenter randomized trial of stent placement versus gastrojejunostomy demonstrated an improvement in oral intake of only 3 days for patients undergoing stent placement compared to surgery [20]. In addition, more recurrent obstructive symptoms and reinterventions were observed in the stent group, leading the authors to recommend that gastrojejunostomy should be considered the preferred treatment in patients with a life expectancy of 2 months or longer. A systemic review of case series, comparative studies, and randomized trials similarly recommended stents for patients with a predicted short life expectancy and surgery for patients with anticipated longer survival [21].

Venting gastrostomy tubes are another option for patients with symptoms of nausea and emesis and contraindications to surgical or endoscopic palliation. Gastrostomy tube placement may be performed through open surgery, laparoscopic surgery, endoscopy, or interventional radiology, although preference is given to the least invasive procedure possible as median post-procedure survival rates are reported as 13–17 days [22, 23]. A common decision point in patients with advanced disease requiring a venting gastrostomy tube is whether to proceed with endoscopic or interventional radiologic placement. Although complications for either technique include tube migration, leakage, and infections of the tube site, review articles suggest endoscopic placement has fewer complications [24].

Small Bowel Obstruction. Small bowel obstruction is defined as obstruction from the third portion of the duodenum to the ileocecal valve. Small bowel obstruction represents the most common indication for palliative surgical consultation in patients with gastrointestinal obstruction (64 %), but has a similar median survival (3.5 months) to gastric outlet obstruction [9]. Only 25 % of patients with small bowel obstruction undergo surgical intervention with the majority (52 %) undergoing nonoperative/nonprocedural management and 24 % undergoing endoscopic/interventional procedures. The majority of endoscopic or interventional radiologic procedures in this population are venting gastrostomy tubes as stents are typically not an option for small bowel obstructions. Many patients with advanced cancer and bowel obstruction have had previous surgery, adding difficulty in the differentiation of an obstruction due to malignancy from an obstruction due to benign adhesive disease. The surgical procedure is often not decided upon until completing exploration of the abdomen, and the two most common approaches are either bowel resection or intestinal bypass. A venting gastrostomy tube can be placed at surgery for patients with disease prohibiting resection or bypass and conditions felt to be at high risk for early re-obstruction.

Large Bowel Obstruction. Consultations for large bowel obstruction represent a minority of consultations for gastrointestinal obstruction, although the frequency is dependent on local referral patterns and expertise for endoscopic palliation. Colorectal stent placement technical success rates are often reported to exceed 90 % with symptom improvement in the majority of patients. Although the risks of perforation with stent placement are low, stent migration or re-obstruction can each occur at a frequency of approximately 25 % [25]. Patients deemed most appropriate for surgery may undergo bypass, bowel resection, or diverting ostomy placement.

Gastrointestinal Bleeding

Similar to bowel obstruction, gastrointestinal bleeding in patients with cancer can be due to benign or malignant causes. The initial evaluation focuses on determining the severity of bleeding and assessing for hemodynamic instability. Utilizing the same initial approach taught through advanced trauma and life support training, surgeons assess the airway, breathing, and circulation of patients with gastrointestinal bleeding while ensuring adequate intravenous access. During this time, laboratory analysis should begin to include a complete blood count, coagulation factors, and electrolytes with BUN and creatinine. A nasogastric tube and Foley catheter are often required for patients with active bleeding. Most patients are hemodynamically stable which allows time for medical management and diagnostic workup. Endoscopy is the primary modality utilized in gastrointestinal bleeding for diagnosis and therapy. Other less commonly required tests include tagged red blood cell scans, arteriography, and capsule endoscopy. As patients with advanced cancer are often best treated without surgical intervention, therapeutic options also frequently involve embolization performed by interventional radiologists.

Bleeding secondary to tumor or treatment-related complications can involve many site-specific diagnostic and treatment issues. Tumors of the gastroesophageal junction and

stomach often account for anemia through a slow rate of gastrointestinal hemorrhage and rarely require urgent surgery. In a recent review of 289 patients with advanced gastric cancer from the Massachusetts General Hospital, only 3.5 % required emergent surgery at presentation, of which none were performed for bleeding [26]. In addition, 233 patients in this series were managed without resection of the primary tumor, of which only 6 patients required subsequent emergency surgery for obstruction or perforation and no patient required surgery for bleeding. The low rate of surgical intervention for gastric hemorrhage is likely due to the many options available for bleeding secondary to tumor involvement such as endoscopic interventions, chemotherapy, and radiotherapy. Again using the example of gastric cancer, palliative radiotherapy can control bleeding in 70 % of patients with a low rate of requirement for additional interventions during the patient's remaining life [27].

Bleeding from small bowel tumors can be secondary to primary or metastatic malignancy. The small intestine can be a difficult diagnostic challenge as endoscopy will typically only assess the duodenum from above and terminal ileum from below. The remainder of the small bowel may involve arteriography or capsule endoscopy to accurately localize the site of bleeding. Bleeding from the large intestine and rectum can often be localized with colonoscopy, with the majority of cases attributable to primary colon and rectal cancer. Primary tumor response rates to palliative chemotherapy and radiation (for rectal cancer) are good and infrequently require emergent surgery.

Wound Problems and Infections

Palliative wound care can be a challenging clinical scenario that is of extreme importance to the patient. Problems related to wounds include bleeding, exudate, odor, pain, and limitations in function. Wound complications and infections are a frequent indication for palliative surgical consultation, representing 10 % of palliative surgical inpatient consults at MD Anderson Cancer Center [3]. Treatment approaches include local wound care, excision, amputation, systemic therapy, and radiation. Traditional wound care management strategies are limited by the impaired healing of patients with advanced malignancy or patients that have received recent immunosuppressive therapy. Malignant fungating wounds are a unique challenge due to malodor and discharge that can affect up to 5 % of people with cancer [28]. Figure 2 demonstrates a malignant fungating squamous cell cancer of the posterior scalp. Systematic reviews have identified few high-quality studies or effective therapies to guide the topical treatment of malodor and discharge in fungating wounds. Surgery is rarely an option but may be a last resort in patients that have wounds refractory to other therapy and are appropriate surgical candidates. Involvement of plastic surgery for advanced wound closure techniques is frequently required in patients undergoing surgery for wound problems. An emerging technology, electrochemotherapy, has shown early promise through the application of chemotherapy by electroporation pulses [28].

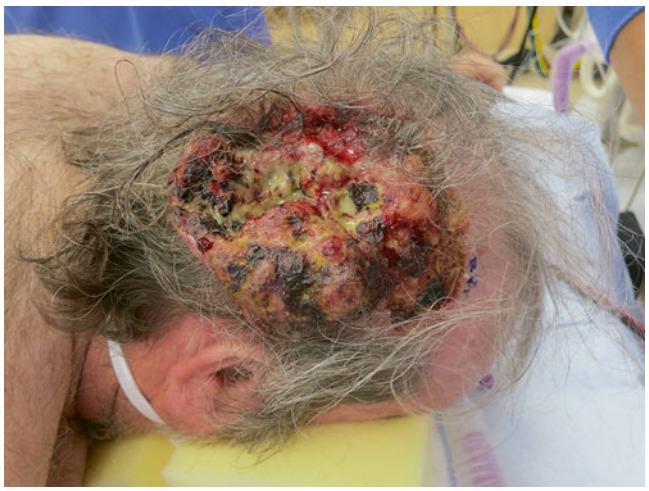

Fig. 2 Fungating malignant wound of the posterior scalp

Obstructive Jaundice

Options for treating biliary obstruction in patients with cancer include endoscopic stent placement, percutaneous catheter placement, or surgical bypass. Prognostication, although difficult and often inaccurate, can help identify the optimal treatment method. Endoscopic stent placement is often the best treatment modality as it is safe and effective. Recurrent obstruction can occur but may be decreased with the use of self-expanding metallic stents. Percutaneous catheter placement by interventional radiology is often reserved for patients that fail endoscopic stent placement as percutaneous procedures have a higher complication rate and are more invasive. Surgery is required in a fraction of patients but should be considered in patients that fail endoscopic attempts, live far away from referral centers with endoscopic expertise, or have other indications for surgical intervention such as concomitant gastric outlet obstruction. Figure 3 shows a CT image of a patient with concomitant bile duct obstruction and duodenal narrowing secondary to a locally invasive pancreatic neuroendocrine tumor. Roux-en-Y hepaticojejunostomy/choledochojejunostomy is the most frequently performed method of palliation and involves anastomosis of a 40–60 cm Roux limb to the bile duct in an end-to-side or side-to-side fashion. Anastomosis of the bowel to the gallbladder (cholecystojejunostomy) is a simpler method of biliary bypass but has not been embraced due to concerns over cystic duct patency. There has been

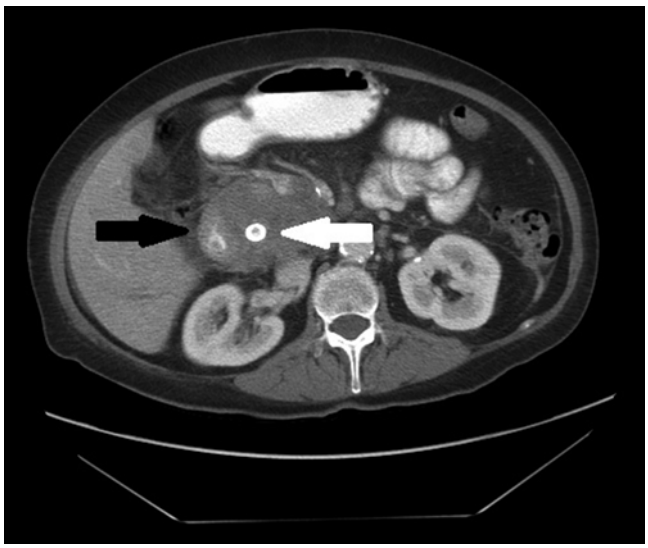

Fig. 3 CT image demonstrating a locally invasive pancreatic cancer causing narrowing of the duodenum (*black arrow*) and bile duct obstruction requiring metallic stent placement (*white arrow*)

renewed interest in cholecystojejunostomy as the ease of the procedure is conducive to a laparoscopic approach with acceptable results in small series [29]. However, a large population-based analysis of the SEER Medicare data found a biliary intervention rate of 7.5 % for patients undergoing cholecystojejunostomy and only 2.9 % for patients undergoing bile duct bypass [30]. A laparoscopic hepaticojejunostomy/choledochojejunostomy would alleviate the concerns over re-obstruction but is an advanced, complex laparoscopic procedure limited to a few centers.

Bowel Perforation

As with gastrointestinal bleeding and obstruction, there are benign and tumor-related causes of bowel perforation. Common benign causes of perforation include peptic ulcer disease and diverticulitis. Tumor-related causes include direct tumor invasion with perforation but also the side effects of cancer treatment such as immunosuppression, radiation effects, steroid administration, and the direct effects of chemotherapy that may render cancer patients more prone to bowel perforation. Cancer patients may also be more prone to iatrogenic bowel perforation due to the need for frequent endoscopic and interventional radiology procedures. As many cancer patients with bowel perforation have advanced or incurable disease, the optimal treatment is often based on a balance between the clinical presentation and oncologic prognosis. The majority of cancer patients with bowel perforation are treated with surgery with a 30-day mortality rate of 15 % and morbidity rate of 46 % [31]. Nonoperative care is another option, particularly in patients with incurable disease, and may have similar outcomes in select patients without abdominal tenderness, limited extent of perforation or contained free air, and aggressive treatment with antibiotics and drain placement [31].

A unique and complex clinical situation is bowel perforation or fistula formation during treatment with bevacizumab. Bevacizumab is a humanized monoclonal antibody to vascular endothelial growth factor that has been proven efficacious in a number of disease sites, including several phase III randomized trials of patients with metastatic colon cancer [32]. Although generally well tolerated, bevacizumab has been associated with gastrointestinal perforation in 1–2 % of patients. Wound healing complications are increased in patients that undergo surgery during study treatment, and most surgeons exercise caution in performing a gastrointestinal anastomosis in patients with bevacizumab-associated perforation [33].

Anorectal Infections

Anorectal infections and abscesses in noncancer patients are typically straightforward in management consisting of incision and drainage with complex treatment required in only a minority of patients. Anorectal infections in patients with immunosuppression, neutropenia, recent chemotherapy or stem cell transplant, and advanced hematologic disease can be a difficult palliative situation with considerable treatment implications and impact on quality of life. Older reports of anorectal disease in neutropenic patients detailed associated mortality rates of up to 50 %, while more recent reports suggest improvements in survival [34]. Anorectal infections in cancer patients are classified as either an abscess or perianal infectious process (pain or erythema without abscess/fluid). Necrotizing soft tissue infections are rare (~2 %) but associated with significant mortality [34]. Patients often need imaging to evaluate for abscess or fluid formation as physical exam findings can be misleading. Patients with fluid typically undergo an exam under anesthesia with drainage and seton placement or catheter placement via interventional radiology. Patients with a perianal infectious process without documentation of fluid are managed with antibiotics and close monitoring.

Ascites

Malignant ascites can cause considerable discomfort in patients and may require frequent paracentesis to remove fluid. Malignant ascites is associated with limited survival, often on the order of a few months. There are a wide variety of options available including diuretic administration, fluid restriction, systemic chemotherapy, intermittent paracentesis, peritoneal drainage catheters, peritoneovenous shunts, and, more recently, hyperthermic intraperitoneal chemotherapy. Surgeons infre-

quently perform peritoneovenous shunt due to concerns over complications of sepsis, heart failure, disseminated intravascular coagulation, and shunt malfunction/infection.

The PleurX system is a tunneled peritoneal catheter that can be managed outside of the hospital to intermittently remove ascites when needed. The PleurX peritoneal drainage catheter has high reported technical success rates of placement with few complications [35]. The majority of patients with the PleurX catheter report good control of their symptoms, and the need for further interventions to restore catheter function are infrequent [36].

Hyperthermic intraperitoneal chemotherapy (HIPEC) is combined with cytoreductive surgery in the treatment of peritoneal surface malignancy. Cytoreduction with HIPEC has been shown to be efficacious in the treatment of appendiceal mucinous neoplasms and is also being applied to select patients with colorectal cancer carcinomatosis. However, cytoreduction combined with HIPEC is a morbid procedure with an established mortality rate and lengthy postoperative hospitalization that is not generally appropriate for palliative surgical scenarios. Laparoscopic HIPEC, without cytoreduction, has been performed in patients with malignant ascites with excellent results in small series (Fig. 4). The laparoscopic approach appears to alleviate much of the morbidity as seen in a recent multi-institutional analysis of 52 patients undergoing laparoscopic HIPEC that reported a complication rate of only 6 % with no postoperative mortalities [37]. Remarkably, the laparoscopic HIPEC procedure prevented reaccumulation of ascites in all but one patient [37].

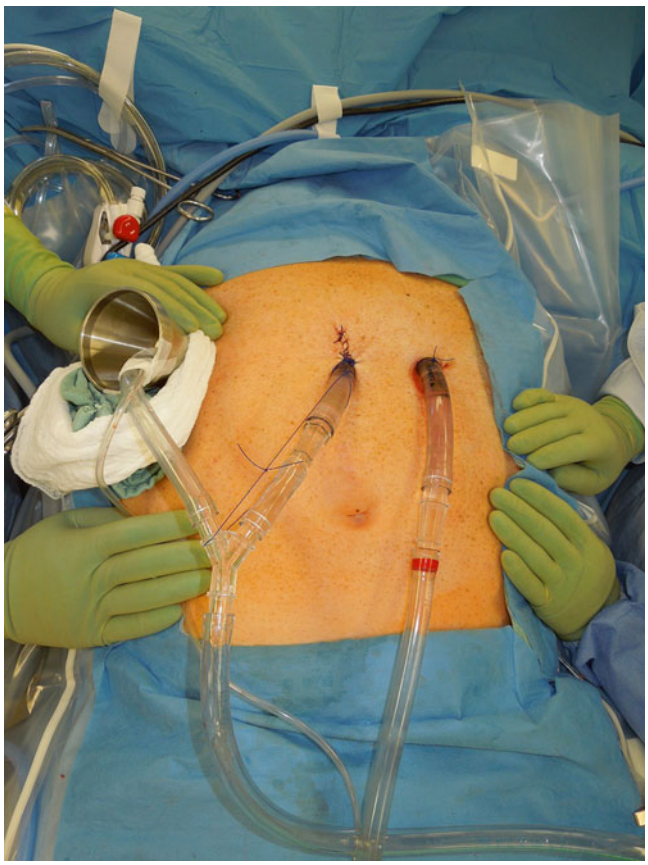

Fig. 4 Intraoperative cannula placement for laparoscopic hyperthermic intraperitoneal chemotherapy administration

Abdominal Pain in Unique Patient Populations

Celiac Plexus Involvement. Tumors with a propensity for perineural invasion, such as pancreatic cancer, can cause debilitating abdominal pain that radiates to the back. Pain in cancer patients, however, is infrequently attributable to a single cause but is more often a multifactorial syndrome of tumor-related causes, treatment-related causes, and chronic preexisting pain unrelated to cancer or its treatment. Opioids are the first line of treatment and often the only treatment that is needed. Palliative radiation is another treatment option for patients with pain secondary to celiac plexus involvement [38]. Celiac plexus neurolysis is a good local treatment option that can be performed through a percutaneous or endoscopic approach. Recent systematic reviews of plexus block procedures demonstrate improvements in pain with side effects usually limited to diarrhea, hypotension, and temporary increased levels of pain [39]. With multiple nonoperative options to alleviate celiac plexus associated pain, surgical chemical blocks are relegated to the intraoperative scenario of finding unresectable disease during attempted pancreaticoduodenectomy. In such a situation, there is evidence from a randomized clinical trial that an intraoperative celiac block can lower pain in patients with preoperative pain and also prevent pain in patients without preoperative pain [40]. In situations where unresectable pancreatic cancer is detected during diagnostic laparoscopy, a laparoscopic celiac block has similarly been proven efficacious in reducing pain scores [41].

Neutropenia. Abdominal pain in neutropenic cancer patients presents a palliative clinical challenge as 90-day mortality rates are approximately 50 %. The differential diagnosis includes causes of abdominal pain common in general surgery consultation such as bowel obstruction, diverticulitis, and appendicitis but also cancer treatment-related causes such as neutropenic enterocolitis and *Clostridium* difficile colitis [42]. Mortality associated with surgical intervention in the presence of neutropenia has been reported as high as 57 % [43]. Surgeons will often deliberately delay treatment to allow for resolution of neutropenia, if possible [42].

Multiple Myeloma. Multiple myeloma is a plasma cell malignancy with systemic overproduction of antibodies resulting in bone pain, anemia, and renal insufficiency with

progressive tumor formation resulting in bone marrow failure. Surgical interventions are primarily palliative for long-bone compression fractures or spinal cord compression. Abdominal pain requiring surgical consultation in myeloma patients is a serious condition with an associated 90-day mortality rate of 43 % [44]. The differential diagnosis in this unique patient population is notable for the frequency of neutropenic enterocolitis (22 %) and bowel perforation (13 %) [44]. Prompt attention should be given to new complaints of abdominal pain in patient with myeloma as surgery may be required, although consideration should be given to the frequent comorbid conditions, severe sepsis, and recent administration of chemotherapy in the setting of a disease with often limited survival.

Outcome Measures

The palliative surgical literature is difficult to interpret due to the lack of commonly accepted outcome measures. In a review of studies from the palliative surgical literature, quality of life measurements were only included in 17 % of studies, while morbidity and mortality were reported in 61 % [45]. Morbidity and mortality, although import outcome measures in the risk analysis of surgery, must be balanced against patient-reported benefits of palliative surgery. Adding to the complexity of palliative surgical studies is the high attrition rate and difficulty in administering burdensome general quality of life instruments [46]. Observational outcome measures may provide some improvement in rates of postoperative symptom evaluation [47]. Future studies of easily administered, quick, patient-reported outcomes will be needed to identify the optimal outcome measure and then identify variables associated with outcome to select patients appropriately for surgery [48].

Conclusion

In summary, palliative surgical care is becoming increasingly recognized as critical in the multidisciplinary treatment of cancer patients. Traditional literature has focused on outcomes of morbidity and mortality with recent efforts to identify optimal patient-reported outcomes. There are few absolute contraindications to surgical intervention, and the decision to proceed with surgery is based on patient, family, and provider discussions based on a risk versus benefit model. Careful consideration is given to prognosis, although difficult and sometimes inaccurate, as well as future oncologic treatment options. As patients undergoing palliative surgical consultation are often dealing with severe symptoms, these discussions should be started as soon as possible, and attempts to anticipate future palliative clinical scenarios are helpful.

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Cardiopulmonary Resuscitation in the Cancer Patient

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Introduction

Cardiopulmonary resuscitation (CPR) can be a lifesaving intervention after cardiac arrest; however, the indiscriminate use of CPR among unselected populations, and particularly among those with cancer, confers only a small proportion of beneficial outcomes, namely, survival to hospital discharge [1–19]. Upon the terminal event of dying in the USA, CPR is provided to the majority of people without their implicit consent. Only when patients give caregivers explicit instructions to withhold CPR is it not performed [1, 20, 21].

In 1960, Kouwenhoven et al. [22, 23] first described closed-chest massage, intending it for administration to otherwise "healthy patients" with reversible conditions who experienced sudden and unexpected cardiorespiratory arrest. Today, despite near universal application of CPR to dying patients unless otherwise specified, in most cases and particularly among cancer patients, CPR merely prolongs the dying process by restoring spontaneous circulation [2–9, 19]. During the last 10 years, researchers have determined that cancer patients have a particularly low rate of return of spontaneous circulation (ROSC) and survival to hospital discharge (SHD) after CPR [1–19]. SHD rates for out-of-hospital CPR and in-hospital CPR in unselected CPR populations are 1–10 % and 15 %, respectively [2–9], but for cancer populations it is <6 % [16, 17]. Cardiopulmonary arrest can be the final pathway for patients with many types of disease, particularly those with end-stage metastatic malignancies [16, 17].

Recently, an increased emphasis on palliative and supportive care for cancer patients has been shown to improve quality of life [24–26]. Palliative services that are incorporated in planning and executing therapeutic interventions hold the promise that CPR might be used more selectively among those with cancer. A more selective approach to initiating CPR, incorporating the patient's goals of care, should lead to higher rates of ROSC and longer-term survival among those who are more likely to benefit.

The emergency physician may be able to mitigate the clinical presentations of those with cancer and prevent incipient cardiac arrest in the acute care setting. This is more likely when emergency care providers recognize and intervene in a timely fashion when confronted by clinical scenarios that commonly precede cardiac arrest among cancer patients.

In this chapter, we will briefly discuss palliative and supportive care resources that can and should be provided as an integral part of the care plan, earlier in the disease evolution, rather than later, we will discuss some adjuncts that the science of CPR has recently incorporated into practice, and we will review the literature with regard to the outcomes of CPR in patients with cancer. We will also examine the issue of family-witnessed resuscitation.

CPR Adjuncts

Conventional manual chest compressions may not be as effective as they could be in an actual clinical setting. Here, we describe several examples of technology-driven adjuncts being tested and utilized that have recently demonstrated enhanced short-term survival in unselected cardiopulmonary arrest patients [27]:

1. The active compression-decompression (ACD) device is a hand-held, manually operated suction device applied to the center of the chest wall. In tandem with an impedance threshold (airway) device, active compression-decompression has shown a 65 % improvement in 24-h survival rates (compared with standard cardiopulmonary resuscitation) in a randomized out-of-hospital clinical trial ($n=210$). The mechanism acts by driving blood into the chest during the decompression phase by generating negative intrathoracic pressure and then forcing the blood out of the chest during the compression phase. This ACD device has been used in conjunction with the impedance threshold device (ITD). The ITD is a small, disposable, lightweight plastic device that prevents full passive air movement during chest decompression. This translates into more negative intrathoracic pressure than can be generated by the re-expansion of the chest wall with the ACD device or standard chest compressions alone. The ITC used with an endotracheal tube or facemask improves 24-h survival rates when used in conjunction with ACD-CPR [28, 29].
2. Simultaneous sterno-thoracic cardiopulmonary resuscitation (SST-CPR). This technology has not been studied in humans though the mechanism exploits both the "cardiac pump" and the "thoracic pump" models during CPR. Compared to conventional CPR, SST-CPR results in improved mean aortic and coronary perfusion pressure as well as improved pulmonary artery perfusion and end-tidal CO_2 in mongrel dogs [30].
3. The AutoPulse (AP) CPR. The AP is an automated machine that uses a load-distributing, broad compression band that is applied across the entire anterior chest. An out-of-hospital retrospective case-control study ($n=162$) also revealed improved short-term survival.
4. The LUCAS is a chest compression device that uses a gas-driven mechanism to provide automated active compression-decompression CPR. In the pig model, LUCAS generated significantly higher diastolic and mean arterial pressures than standard CPR in addition to higher end-tidal CO_2 and myocardial and coronary artery perfusion pressures [31].

Palliative and Supportive Care Interventions

Palliative and supportive care services include care given that aims to prevent or treat, as early as possible, the symptoms of the disease, side effects caused by treatment of the disease, and psychological, social, and spiritual problems related to the disease or its treatment. Furthermore, these services focus on the assessment and management of physical and psychosocial distress of patients with advanced cancer and on family support and advance care planning [24, 25]. These services enable patients and families to realize that maximizing both comfort and preparedness along the cancer journey is important. Furthermore, patients make better-informed decisions with less distress when physical and emotional symptoms are controlled [26].

Palliative care is not only provided at the end of life; rather, it can and should be provided early on in the cancer journey. When engaged early, these services improve quantity and quality of life concurrently with the oncology care model [26]. This model enables supportive/palliative care to be integrated into the collaborative model that exists among surgical, radiation, and medical oncologist as the fourth pillar of comprehensive cancer care. This multidisciplinary approach allows many additional caregiving consultants the opportunity to participate in the care plan that should include, but is not limited to, pain specialists; psychiatrists for emotional distress, depression, and anxiety; pulmonologists for relief of bronchial obstruction; and psychosocial interventionists for end-of-life issues to be addressed [16–18, 24–26]. The process of incorporating end-of-life education during the day-to-day management of these patients is essential. These modalities have augmented the time available to introduce and educate the cancer patient to the types of CPR techniques and adjuncts available to the caregiver to revive life when the heart stops.

MD Anderson Experience

We found in our cancer institution that the rates of ROSC after CPR in cancer patients improved by a small amount over the past decade, though these changes were small and statistically insignificant [31] (Fig. 1). Any trend toward improved ROSC outcomes that may exist could result from improvements in CPR quality or use of adjuncts [28, 32]. However, the outcome of SHD had not changed over the two time periods studied (2002–2007 to 2008–2012) [31].

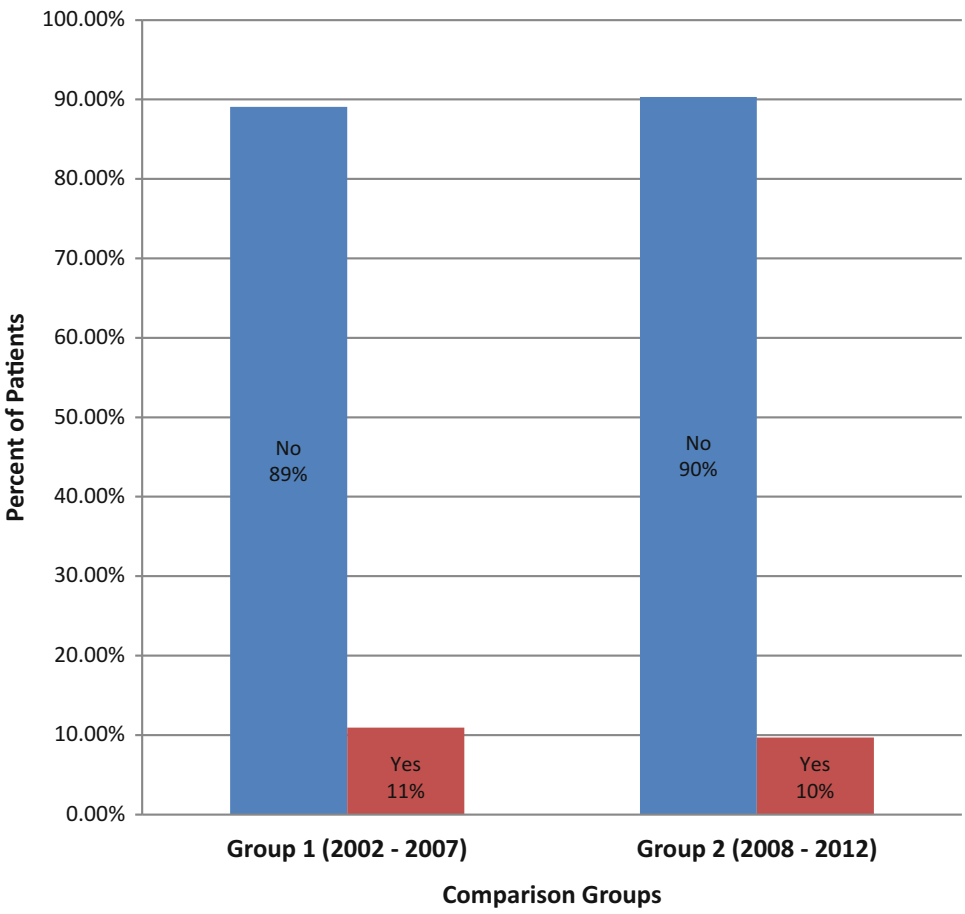

Fig. 1 Survival to discharge among 126 cancer patients undergoing cardiopulmonary resuscitation (CPR) in a comprehensive cancer center comparing group 1 (2002–2007) and group 2 (2008–2012) (Reprinted with permission from SpringerPlus http://www.springerplus.com/content/4/1/106)

Dissimilar to the cancer CPR population, new technologies including the use of automated external defibrillators (AEDs), well-delineated locations of AEDs for improved access, new resuscitation algorithms including cardiac compression rates, ventilation rates and volumes, performance of basic CPR before defibrillation, and therapeutic hypothermia have all been manipulated to maximize resuscitation efforts, demonstrating improvements in neurological recovery and outcomes in the unselected CPR population [18, 33–38]. The lack of improvement in survival to hospital discharge in our study may suggest that CPR in cancer patients continues to be performed on an unselected cancer population, rather than being targeting toward subsets of cancer patients with specific types of malignancies who are more likely to receive benefit. Reisfield et al. [18] reported in 2006 that in 1707 cancer CPR patients with solid tumor, they had a rate of being discharged alive to another facility of 7.1 % compared to only 2 % of those with a hematologic malignancy. And consistent with these data, Hwang et al. [17] reported in 2010 that in 41 patients after out-of-hospital cancer CPR, the discharge alive to another facility in those with solid tumor was 18.0 % compared to 12.5 % in the hematologic malignancies. Ultimately, however, the overall survival to discharge home for these cancers CPR patients was 4.9 %. Perhaps continued efforts to identify the specific type(s) of cancer that would benefit the most in terms of survival to hospital discharge must be further defined, thus, allowing end-of-life and advanced care planning techniques to be more effective. Again, dissimilar to the cancer CPR population, end-of-life and advanced care planning may have already contributed to improved outcomes of CPR in the unselected CPR population by allowing those terminally ill in this general population group to choose an a priori do-not-resuscitate (DNR), effectively decreasing the effect size of those that would have worse outcomes [39]. Therefore, selecting out the least likely to survive before CPR is required, and excluding them from ever entering the sample calculation ultimately improves the total outcome.

Improving communication and/or documentation (living wills and medical powers of attorney) and family education (the meaning of a DNR order) can be exploited to augment the CPR outcome proportions in unselected and selected CPR patients. These interventions will allow the patient and loved ones of the patient to not transport the patient to the hospital and thus not be given CPR when dying occurs if that is the patient's wish [1, 21, 37, 38]. These study results reflect the other two studies referenced [17, 18] pertaining to cancer CPR outcomes whether in or out of the hospital. It is an important topic, as cancer increases in frequency in the USA and the discussion about end-of-life issues becomes more relevant particularly with the economic impact it has [19]. The need to identify the cancer patient that will benefit the most from CPR and end-of-life interventions including DNR is of paramount importance in moving forward.

Though our study [27] had obvious limitations including that it was a retrospective study with selection bias as some potential cases may have been omitted particularly if the documentation did not include the CPT code we queried, CPR was not documented on the medical record, or the CPR designation was missing from the institutional logs and databases. Additionally, some of the Utstein-type data were unavailable for prehospital cases in the databases that we queried including number of resuscitation attempts, bystander witnessed or unwitnessed arrest, bystander CPR or defibrillation, or cardiac vs. noncardiac etiology of arrest. As such, we could not comment on these factors and their effect on survival. Furthermore, the small sample size of this single-center study compared to the other study we referenced [18] makes it difficult to generalize it to other cancer populations, nor does it enable sufficient power to conclude a valid statistical outcome.

Family-Witnessed Resuscitation

As stated earlier in this chapter, survival outcomes measured by improved quality of life are particularly dismal after CPR for cancer patients. Even though the statistics are unfavorable, the decision to resuscitate is often multifactorial. Ideally, end-of-Life (EOL) planning should occur early in the course of treatment so that patient wishes will be clear and based on a comprehensive consideration of alternate treatment plans. Indeed, planning should occur at all stages of disease. An important topic particularly relevant to emergency care is that of family-witnessed resuscitation (FWR). According to Boyd, FWR is "the process of active 'medical' resuscitation in the presence of family members."

The question of whether family members or loved ones choose to be present during resuscitation, or whether the emergency physician should consider offering this choice, is an important policy issue for the emergency department (ED). Planning and establishing procedures for FWR to occur well before the need to make such decisions arise. This chapter will discuss the pros and cons based on perspectives of all parties that may be present during resuscitation and ethical considerations regarding this issue. We suggest conditions under which FWR should be considered based on an examination of existing research.

Background

The concept of having family members present during resuscitative efforts was introduced in the 1980s when Foote Hospital in Michigan began promoting the practice of FWR

[40]. In 1992, Hanson and Strawser presented initial research data on this topic. Twenty years later, in 2000, the American Heart Association published guidelines recommending that family members be allowed to witness CPR. At the time, there was a lack of research to provide quantitative proof that FWR was beneficial. More than a decade later after these guidelines were published, FWR remains the exception in EDs internationally [41].

Perspectives

Family Members

Family members of both pediatric and adult patients play an increasingly larger role in patient care as caregivers given the shift in emphasis of care from the hospital to outpatient setting. Oftentimes, they are the ones to initiate an emergency response in the prehospital setting if their loved one is in distress. Given that family members are now more active in treatment planning and day-to-day care of a cancer patient, it is not uncommon for family members to wish to be present with their loved one during the final moments of life, including resuscitation attempts, when they are pursued.

Multiple studies focusing on the attitudes of family members show that most actually prefer to be present during resuscitation when given the opportunity. One survey assessing bereaved family members living in Michigan in 1982 indicated that 72 % preferred to be present during resuscitation attempts. Other studies confirm the strong desire of family members to be present and that those participating in FWR would recommend the same to other families [42–47].

Given the strong preference of family members to participate in FWR, this practice remains uncommon. Hospital staff have traditionally excluded nonmedical personnel because witnessing the resuscitation was thought to cause emotional distress. Multiple studies counter this belief and indicate that family members do not suffer negative psychological consequences after witnessing resuscitation. In 2013, Jabre et al. performed a 1-year post-resuscitation study of 408 family members measuring symptoms of posttraumatic stress disorder (PTSD), anxiety, depression, and complications of grief. Family members witnessing resuscitation appeared to suffer less PTSD-related symptoms. Piira et al. [46] reviewed 17 studies and concluded that FWR was not associated with family distress. Seven of seventeen studies actually found decreased distress levels, while ten concluded no significant association.

In fact, witnessing resuscitation may provide benefit by facilitating the grieving process. Robinson et al. demonstrated that 3 months after resuscitation, family members participating in FWR had lower grief and PTSD-related symptoms. Goodenough et al. and other studies also reveal that witnessing resuscitation provides emotional benefits helping family members cope with the death of a loved one. A common belief is that participating in FWR allows for a sense of closure after family members witness that everything possible had been done to increase the chance of survival [44, 47, 48].

Healthcare Workers

Despite endorsement by the Resuscitation Council of the UK, Cardiopulmonary Resuscitation and Emergency Cardiac Care, and the American Heart Association, FWR is infrequently performed in the ED. A survey from the British Association for Accident and Emergency Medicine and the Royal College of Nursing revealed that less than 25 % of UK hospitals provide family members the option of witnessing resuscitation [49]. FWR is not universally supported by healthcare workers despite studies suggesting that it is beneficial to family members. A US survey of 132 ED staff members found that 80 % of doctors and 78 % of nurses actually disapproved FWR. Of those surveyed, 32 % of doctors and 24 % of nurses had received requests from relatives to be present during resuscitation within the past 6 months [50].

Attitudes of healthcare workers toward FWR differ by discipline, patient age, and practice environment. Nurses are more open to FWR than doctors, and family members tend to approach a nurse rather than physician asking permission to witness resuscitation of their loved one [51, 52]. Those caring for younger patients and their families are generally more positive toward FWR. One-third of pediatricians surveyed would allow family presence during CPR, and almost 2/3 with FWR experience would allow this to happen again. In a study comparing pediatric vs. adult pulmonologists, pediatric pulmonologists were far more accepting of FWR [53]. The nature of pediatric care may allow staff to be more accepting of FWR as a right for parents who are legal guardians for their children [54].

Practice environment also influences the attitudes of healthcare workers. Staff at urban hospitals are less supportive of FWR than staff at suburban hospitals [55]. Macy suggests that logistics may play a role given that urban hospitals may have inadequate resuscitation space per patient volume. Urban hospitals have smaller staff/patient ratios which may cause staff to feel that family members' presence is a distraction. This study found that patient/personnel ethnicity had no significant effect on overall attitudes toward FWR by medical staff.

In general, healthcare professionals opposing FWR express a common concern that witnessing a loved one undergoing aggressive resuscitation predisposes family members to additional psychological burden [54]. Staff report that witnessing resuscitation may cause family members to suffer flashbacks and other signs of posttraumatic

psychological trauma. The reality of what may occur during resuscitation differs than what is usually depicted in movies or on television, and nonmedical personnel may not be mentally prepared to witness a real resuscitation.

A second concern expressed by many healthcare workers is that FWR negatively impacts staff performance. The presence of family members may cause additional stress to healthcare workers, especially those less experienced with code blue situations. Resuscitation is a stressful event, and coping mechanisms, such as humor or detachment from a patient, may certainly be deemed inappropriate by family members. Unrealistic expectations may also exist as family members are not expected to understand resuscitation procedures and may interfere or interrupt resuscitation efforts. Resuscitation may also be inappropriately extended beyond usual time limits based on family presence. An increase in potential for litigation is also cited as an issue given that relatives in the room may be at risk for needle sticks or being injured by a piece of equipment [56–58].

Given these concerns, most healthcare workers recommend FWR in a controlled setting with protocols in place and specifically trained personnel to accompany family members. Hospital staff would also require additional training which would add to hospital expenses [59, 60]. After receiving education, it is interesting to note that in some studies, staff felt that witnessed resuscitation may indeed lessen the risk of lawsuits and complaints given that family members witnessed firsthand that everything was done for their loved one. Communication about the death of the relative was also found to be easier [50, 54, 61, 62].

Patient

Only 10–15 % of patients receiving CPR following cardiac arrest in the hospital survive to be discharged. Therefore, fewer studies exist which examine FWR from a patient perspective. Albarran performed face-to-face interviews with 21 resuscitation survivors, and although the study was statistically insignificant, it suggests that patients who survive resuscitation favor having family members present. Patients would like the opportunity to be asked to approve FWR and were not as concerned about confidentiality issues. Another pilot study by Robinson et al. consisting of three patients surviving resuscitation reported that their confidentiality and dignity were not compromised by FWR.

Ethical Considerations

Patients are rarely asked about their preference for family-witnessed resuscitation when preparing advanced directives. The lack of documented consent creates medicolegal implications for FWR because of the potential for breaching patient confidentiality. Acceptable guidelines for pediatric patients do not transfer to adults, given that family members have no legal rights to care for their adult relatives. For adults, permission must be granted from the patient before discussing medical care with relatives. Even if a patient is unconscious, these rights are still present; thus, an assumption cannot be made that all patients would give automatic consent for FWR [54]. Consequences must be considered if a patient survives the resuscitation and is not happy with the decision. Hospital staff involved could be at risk for lawsuits alleging neglect of confidentiality [62].

Guidelines

When considering FWR, the interests of patients, family members, and staff must be taken into consideration, and this is difficult during an emergency situation. Optimally, FWR should be discussed with patients prior to potential resuscitations, e.g., during advance directive planning. If a hospital decides to incorporate FWR, it is recommended that an ED-specific protocol be established. Training of specific ancillary staff should occur so that a qualified staff member can accompany the relative at all times during the resuscitation. The role of this staff member will be to debrief the relative prior to entering the resuscitation room, to answer questions during the resuscitation, to escort the relative out of the room if necessary, and to help debrief the relative after resuscitation. Education should also occur for the multidisciplinary resuscitation team on what to expect with FWR so that any fear or apprehension can be addressed. If a protocol for FWR is in place and staff are educated, they will less likely deny family member requests to be with their loved one during resuscitation, and family members can be allowed near or even touch their loved one during the process with less concern interfering with resuscitation procedures [59, 63].

Conclusions

The literature on cardiopulmonary resuscitation (CPR) on the patient with malignancy indicates that the ROSC may have encouraging proportions of success though the survival to hospital discharge continues to remain dismal. This is particularly true in those with metastatic malignancies [16–18].

In this chapter, we have reviewed the literature pertaining to the patient population living with malignancy and the possible improved early care paradigm that includes more teaching and palliative and supportive care to maximize pain control and other services while concurrently treating the malignancy with aggressive radio-, chemo-, and surgical therapies. Though despite well-intentioned resuscitation efforts over the last 40 years, including external manual chest compressions as the foundation of cardiopulmonary resuscitation

and several recent studies confirming the hemodynamic significance of delivering consistent, high-quality, infrequently interrupted chest compressions [5–9, 17, 19, 33–35] and mechanical adjuncts [28–31], the survival outcomes for those with cancer particularly metastatic cancer have not improved [18, 38, 39]. Family-witnessed resuscitation should be considered in the ED; however, the ultimate impact of FWR on family members and loved ones is uncertain.

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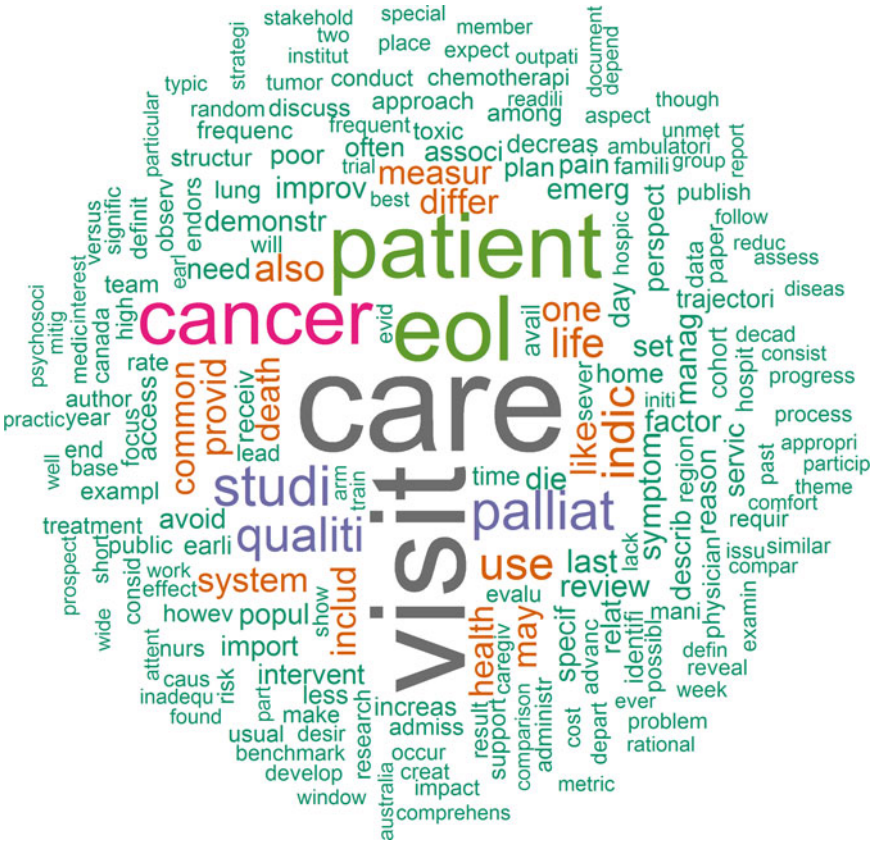
Emergency Department Use at End of Life Among Cancer Patients

Lisa Barbera and Hsien Seow



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There has been increasing interest in describing emergency department (ED) use by cancer patients at the EOL over the past decade. End-of-life (EOL) care specifically refers to the final weeks of a patient's life, when symptoms commonly increase in intensity and death approaches [1]. EOL care is related to palliative care, which is a holistic approach to care, with emphasis on preventing or relieving suffering and improving quality of life [2]. Stakeholders have been advocating for improved EOL care and earlier integration of palliative care into the cancer trajectory for over a decade (Fig. 1, IOM 2001 pal care figure). Without effective EOL or palliative care, many dying cancer patients have unmet clinical needs, uncontrolled symptoms, poor quality of life, and fear, anxiety, and depression, which may cause them to visit the ED [3]. Avoiding unnecessary ED visits may lead to economic benefits (ED visits and the ensuing hospital care are costly), improve patient experience (many patients do not want to be cared for in a hospital or ED at the EOL), and improve quality of care (some causes of ED visits are avoidable with proper planning).

The emergency department (ED) is a setting of care focused on the management of acutely presenting medical problems. It is a fast-paced work environment with a focus on identifying the problem and instituting a solution over a very short interval of time. In contrast, dying cancer patients typically have complex medical histories, multiple symptoms, and difficult psychosocial circumstances. Therefore, EOL optimal care requires a great deal of time to honestly discuss prognostic information, make clear recommendations, facilitate patient-family discussions, affirm patient choices, address holistic and psychosocial aspects of well-being, and plan for unexpected changes in a patient's condition. This is the antithesis of care typically provided in the ED. End-of-life trajectories in the ED have been characterized as being either "spectacular" (e.g., sudden, traumatic death) or "subtacular" (e.g., slow process of dying or a non-emergency death) [4]. ED staff are well trained to deal with "spectacular" deaths but often distance themselves from patients dying "subtacular" deaths. As a result, EOL care in ED is typically far from ideal. Hence, ED visits at the EOL are a widely used indicator of poor quality care [5, 6].

The field of ED visits at the EOL is still developing. A recent review of care at the EOL in the ED was conducted [7]. The focus of this review was to evaluate evidence for managing dying patients in the ED and to identify areas for improvement. The authors observed that of the 160 papers included in the overview, most were cited infrequently when compared to other articles published in the same journal, and only 28 % of articles had more than ten citations each. This suggests that EOL research has received less attention among researchers and practitioners relative to other topics published in the same journal. Of note, ED visits at the EOL were not included in Dartmouth's EOL Atlas [8] or as a Quality Oncology Practice Initiative (QOPI) measure [9]. Nonetheless, the growing numbers of older adults, the increased pressures of access to high-quality care in a timely manner, and the escalating costs of healthcare delivery are bringing more attention to appropriate use of ED services, especially for cancer patients at the EOL with well-documented symptom needs.

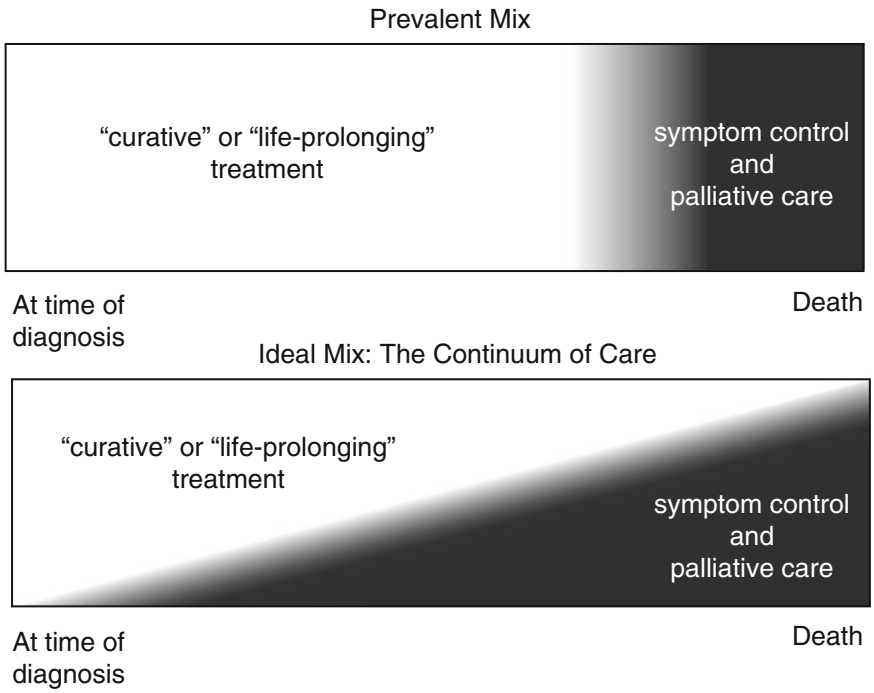

Fig. 1 Relationship of "curative" or "life-prolonging" treatment to symptom control and palliative care for cancer (Reprinted with permission from the National Academies Press, Copyright 2001, National Academy of Sciences)

This chapter will review the topic of ED use at the EOL with a specific focus on:

- The rationale for scrutinizing ED use at EOL
- The frequency with which ED visits occur
- Common reasons for ED visits at the EOL
- Factors associated with ED visits at the EOL
- Evidence of strategies to mitigate ED use at the EOL

Rationale for Scrutinizing ED Use at EOL

Indicator of Poor Quality Care

In 2003, Earle et al. published a landmark paper describing quality indicators of EOL cancer care that could be measured with administrative healthcare data [5]. The impact of this publication was significant because (1) stakeholders began to discuss the merits of the quality indicators, selected through literature review, focus groups with patients and family members, and an expert panel and (2) researchers began measuring them using readily available administrative healthcare data. One of the key indicators of poor quality care identified was frequent ED visits near the EOL. It became operationalized as more than one ED visit in the last 30 days of life [6]. The rationale for this indicator is because high rates of unplanned medical encounters at EOL, exemplified by ED visits, may indicate overuse of aggressive care, inattention to symptom issues, poor planning by providers to anticipate patient needs, insufficient support or education for the caregivers, lack of advance directives, or inadequate availability of palliative care resources, such as hospice services; when these elements are provided or addressed, they can help avoid unnecessary ED visits at EOL. Examples of other poor quality care measures that emerged from this publication include a short interval of time between chemotherapy and death, ICU admissions near EOL, and short time between hospice enrollment and death.

Patients and Families' Perspective on ED Visits at EOL

When cancer patients experience difficulties requiring medical assessment, most would prefer management by their usual provider or someone from the cancer center where they usually receive care. Most reports indicate that patients prefer to be at home at the EOL [10, 11]. Earle et al.'s original indicator [5] was developed by including perspectives from 12 patients with incurable cancer and 4 family members: they associated ED visits primarily with toxicity management of aggressive chemotherapy. Early in the trajectory, this was expected and described as a necessary part of receiving therapy. Later in the trajectory of care, patients' willingness to tolerate toxicity for non-curative therapy diminished. In turn, the willingness to endure ED visits or accept them as a necessary component of care also diminished. Interestingly, in a study of Japanese bereaved family members, only 14 % endorsed the appropriateness of frequency of ED visits an indicator of poor quality care. This suggests that this particular measure may be perceived differently in different cultures where the perspective on a "good death" is different [12].

In a study of stakeholder perspective of quality indicators for EOL care, 16 women with metastatic breast cancer and 8 bereaved family caregivers participated in focus groups to provide their perspective on quality indicators at EOL [13]. The dominant themes that emerged were support for, access to, and early enrollment for palliative care services, continuity of care, and multidisciplinary care. The authors do not describe a dominant theme related to ED visits, though ED visits clearly disrupt continuity of care in the ambulatory setting and lack of adequate access to palliative care may lead to ED visits.

Healthcare Provider Perspective on ED Visits at EOL

Healthcare providers strongly endorsed ED visits as a quality indicator. In a Delphi process conducted in Canada with healthcare professionals evaluating the acceptability of frequency of ED visits near the EOL, more than 80 % of participants agreed the indicator was meaningful and important [13]. An American qualitative study of perspectives of care providers in the ED, including physicians, nurses, and other providers, revealed several emerging themes. These include conflict among providers about the feasibility and desirability of providing palliative care in the ED, not seeing a difference between palliative care and EOL care, poor communication between providers in the in-patient and outpatient setting, conflicts about withholding life-prolonging treatment, and inadequate training for pain management. A similar study from Germany describes ED physicians as having difficulty dealing with palliative patients because of uncertainty regarding aspects of psychosocial care and EOL decision-making [14]. Related, a survey from Australia indicates that ED physicians feel that the care they provide to EOL cancer patients is futile [15]. These sentiments conceptually endorse the notion that, from a provider perspective, the ED may not be the best place to care for this patient population.

System Perspective on ED Visits at the EOL

In some jurisdictions, ED use at EOL is being measured at a population level and has even become a system-wide metric in some countries. A study in Australia examined the ED use in the last year of life among cancer and non-cancer patients revealing that 70 % had at least one ED visit [16]. Similarly in the UK, the National EOL care Intelligence Network, now a part of Public Health England, measured ED use for urological cancer patients in the last year of life: they found that emergency admissions tended to be significantly longer and more costly than planned admissions to hospital. As well, emergency admissions were far more common than planned admissions to hospital in the three largest urological cancer groups [17]. As a system-wide quality indicator metric, the US National Quality Forum has led a large initiative for several years to develop a performance measurement strategy for hospice and palliative care and identify and endorse quality indicators. The proportion of the population with more than one ED visits in the last days of life was reviewed by the initiative as a quality indicator; however, the measure was categorized as requiring further development beyond the cancer population before full endorsement by the NQF committee [18]. In contrast, in Ontario, Canada, Cancer Care Ontario, the provincial cancer agency, has created "The Cancer System Quality Index" which includes ED visits in the last 14 days of life as a quality indicator since the index's inception in 2005 (www.csqi.on.ca). The index, published annually on the Internet, is unique in North America and includes a plethora of quality indicators for cancer across the care trajectory.

How Often ED Visits Occur at EOL

The frequency of emergency department visits depends on several definitional and contextual factors. Table 1 lists a review of publications describing the frequency of ED visits at the EOL. The studies were conducted in Canada, the USA, Australia, Korea, and Taiwan, ranging in cohort sizes from 46 to 242,530, where years of study spanned 1991 to 2010. The prevalence of ED visits ranged from 1.7 % having more than one ED visit in the last 30 days of life [19] to 65.3 % having an ED visit in the last year of life [20]. The duration of the observation window from death varies from 2 weeks to 12 months, with 30 days being most common. The patients in the numerator may be counted with any ED visits, but in several papers, more than one visit is required. Many studies are population based, but some are institutional. Some include all cancer types, where others include only specific cancers. These differences in study design, definitions, and inclusion/exclusion criteria need to be considered when making comparisons.

The majority of studies used an observation window looking backwards from the date of death to create a decedent cohort, i.e., people who have died, rather than a prospective cohort that followed patients until they all died. This approach has been criticized since people who have died may not be the same people one would identify as actively dying [21]. However, when used with administrative data, this approach allows for easy identification of relevant cohorts, efficient study of all patients who died (rather than a nonrandom subset), and timely evaluations for quality improvement [22].

Contextual factors must also be considered. Specifically, what are the palliative care supports available for study participants, and more generally, how is care structured? For example, in Warren et al., ED use was compared in Ontario, Canada, and the SEER regions in the USA. The methods of the study explicitly harmonized all the definitions in both jurisdictions to ensure a fair comparison. ED rates differed by about 10 % which is likely a reflection of differences in structures and process of care in the two settings [23].

Despite these differences, most authors conclude that ED use in cancer patients at EOL is too high and that this population-based metric should be driven down as low as possible. Only one paper has attempted to define what rate is right: in 2005, Earle et al. described the regional variation in ED visits rates at the EOL and found almost threefold variation among different healthcare service areas [24]. They defined an empiric benchmark as the top decile of performers to derive a benchmark of <4 % with more than one ED visit in the last 30 days. This benchmark was achieved in only one other study in a community setting [25]. In fact, the majority of the studies with a similar definition exceed this proposed benchmark. While negative publication bias may partially explain this, the existing data support the impression that improvements in care are required. It is important to remember that this measure is meant to be considered at a population level. It would be impossible to have a system where the value of this measure is zero. ED care may be entirely appropriate for a particular individual. But when population values are in excess of 30 %, one ought to further examine the systems of care.

Reasons for ED Visits at the EOL

There have been several publications examining why cancer patients go to the ED though most do not restrict their evaluation to the EOL period [26, 27]. A systematic review of reasons for ED use by all cancer patients [28] revealed that many visits are likely chemotherapy-related toxicity as demonstrated by frequent visits for fever, neutropenia, and gastrointestinal complaints. Beyond treatment, in a Korean study [27] of a cancer-specific ED, 55 % of visits were related in some way to disease progression. This disease progression often leads to worsening

Table 1 Frequency of ED visits at end of life

First author	Year Published	Country	Jurisdiction	Year of study	Cancer type	Cohort size	Method	% Patients with ED
At least one visit in the last 2 weeks of life								
Barbera	2010	Canada	Province of Ontario	2003–2004	Died of ovary, endometrium, cervix cancer	2040	Population-based, retrospective, admin data	34 %
Barbera	2006	Canada	Province of Ontario	2001	Died of any cancer	21,323	Population-based, retrospective, admin data	27.60 %
Barbera	2008	Canada	Province of Ontario	2002	Died of lung cancer	5855	Population-based, retrospective, admin data, supplemented with chart review	32.20 %
POWER	2009	Canada	Province of Ontario	2003–2004	Died of CRC	NR	Population-based, retrospective, admin data	31 % women/36 % men
POWER	2009	Canada	Province of Ontario	2003–2004	Died of lung cancer	NR	Population-based, retrospective, admin data	42 % women/49 % men
POWER	2009	Canada	Province of Ontario	2003–2004	Died of breast cancer	NR	Population-based, retrospective, admin data	44 % under 65/36 % 65–79/28 % 80+
At least one visit in the last 30 days of life								
Tang	2009	Taiwan	Taiwan	2000–2006	Died of any cancer	242,530	Population-based, retrospective, admin data	16–21 %
Temel	2008	USA	Single institution		Prospective collection of 46 LA NSCLC	46	Prospective, feasibility of introducing early pal care	48 %
Warren	2011	US/Canada	SEER regions/ province of Ontario	1999–2003	Died of NSCLC	13,533 US/8100 ONT	Population-based, retrospective, admin data	37 % US/49 % ON
Maddison	2012	NS	Province of Nova Scotia	2001–2008	Died of CRC	1201	Population-based, retrospective, admin data	23.20 %
Setoguchi	2010	USA	State of Pennsylvania	1997–2004	Pts who died of lung, breast, CRC, prostate cancer (or heart failure)	7565	Population-based, retrospective, admin data	38.90 %
Hui	2014	USA	Single institution	2009–2010	Hematologic ca decedents/solid tumors	816	Retrospective single institution	53 % in heme; 43 % in solid tumors
More than one visit in the last 30 days of life								
Cowall	2012	USA	Single county registry	2004–2008	Random sample of cancer deaths	390	Retrospective review	2 %
Earle	2004	USA	SEER regions	1993–1996	Died of lung, breast, CRC, other GI	28,777	Population-based, retrospective admin data	7.2–9.2 %
Ho	2011	Canada	Province of Ontario	1993–2004	All cancer deaths	227,161	Population-based, retrospective admin data	8.6–10.53 %

(continued)

Table 1 (continued)

First author	Year Published	Country	Jurisdiction	Year of study	Cancer type	Cohort size	Method	% Patients with ED
Keam	2008	Korea	Single institution	2002	Met cancer receiving pal chemo and died	298	Retrospective single institution	33.60 %
Keating	2010	USA	Veterans Health Administration matched with SEER	Dx in 2001/2002	Died of lung or CRC before 2006	2913 in each group	PS match those from VA and those in Medicare	13.1 % in VA 14.7 % in SEER
Lopez-Acevedo	2013	USA	Single institution	1999–2008	Women who died of ovarian cancer	220	Retrospective chart review	1.70 %
Miesfeldt	2012	USA	Medicare	2003–2007	Poor prognosis cancer decedents	235,821	Retrospective cohort, admin data, Medicare	10 %
Saito	2011	USA	SEER regions	1991–1999	Died of NSCLC	7879	Population-based, retrospective, admin data	23.20 %
Smith	2009	USA	SEER regions	1992–1999	Died of lung, CRC, breast, prostate	40,960	Population-based, retrospective, admin data	5–10 %
Hui	2014	USA	Single institution	2009–2010	Died of hematologic ca or solid tumors	816	Retrospective single institution	15 % in heme; 12 % in solid tumors
At least one visit in the last 12 months of life								
Bergman	2010	USA	Enrolled in IMPACT study	2010	Low income, ninsured on public asst who died, men with prostate ca	60	Retrospective review of IMPACT data (public funding mechanism)	62 %
Rosenwax	2011	Australia	State of Western Australia	2005–2006	Death from cancer or one of nine other conditions amenable to palliative care	1071	Population-based, retrospective admin data	70 %
McNamara	2013	Australia	State of Western Australia	2005–2006	Died of cancer	746	Population-based, retrospective admin data	65 %
Other measures								
Lawson	2008	Canada	Province of Nova Scotia	1999–2005	Patients on palliative care service who died	4444	Population-based, retrospective admin data	26.6 % at least one visit, variable follow-up time
Burge	2003	Canada	Province of Nova Scotia	1992–1997	Died of cancer	8702	Population-based, retrospective admin data	Mean number visits 1.33 between diagnosis and death
Earle	2004	USA	SEER regions	1993–1996	Died of lung, breast, CRC, other GI	28,777	Population-based, retrospective admin data	Mean # visits in last 30 days: 0.4–0.46
Warren	2011	US/Canada	Province of Ontario, SEER regions	1999–2003	Died of NSCLC	13,533 US/8100 ONT	Population-based, retrospective admin data	Mean # visits in last 30 days 1.34 US/1.30 ON
Bergman	2011	USA	SEER regions	1992–2005	Died of prostate cancer	13,804	Population-based, retrospective admin data, SEER	Mean # visits in the last 6 months 1.53

symptoms. Indeed, one study showed that physical symptom burden in the ambulatory cancer setting was strongly associated with the likelihood of an ED visit [29].

Specific reasons for visits to ED were described for the last 2 weeks and last 6 months of life in one Canadian study [30]. These reasons are listed in Table 2 (reproduced from CMAJ). Pain was responsible for about 5 % of visits. As well, dyspnea, pneumonia, and pleural effusion were also very common. This study used administrative sources of data and was limited by the coding system for the diagnoses associated with each visit. As such, lung cancer was the most common "reason," although this does not actually reveal the cause of the visit. This likely reflects the impact of progression of disease in a common cancer type and is consistent with other works specific to lung cancer [31]. In a US study of cancer patients who died in the ED, over one third of those deaths had a cause of death due to lung cancer. Across all cancer deaths, the most common chief complaints were respiratory, gastrointestinal, and neurological [32].

Pain management warrants specific attention because it is commonly experienced by ambulatory cancer patients at the EOL [1] and often leads cancer patients to visit the ED [26, 27, 29, 30]. Two recent studies indicate about a third of cancer patients have inadequately managed cancer pain [33, 34]. This observation is essentially unchanged over the past two decades [35]. Meanwhile ED physicians have indicated they are not comfortable managing pain in this population [36]. Furthermore, overcrowding, which is a common ED problem, is associated with worse pain management [37]. Cancer patients deserve meticulous management of their pain by those best trained to do so.

When considering why patients visit the ED, a natural follow-up question is whether the visit was possibly avoidable or was the ED the best and only place for the patient to

Table 2 Reasons for ED visits at during the last 2 weeks of life (Reproduced with permission from [30])

Rank	Reasons	Frequency ($n = 36{,}600$)	%	(95 % CI)
1	Lung cancer	3242	8.86	(8.57–9.15)
2	Dyspnea	1844	5.04	(4.81–5.26)
3	Pneumonia	1832	5.01	(4.78–5.23)
4	Abdominal pain	1126	3.08	(2.90–3.25)
5	Malaise and fatigue	1084	2.96	(2.79–3.14)
6	Palliative care	1042	2.85	(2.68–3.02)
7	Dehydration	944	2.58	(2.42–2.74)
8	Pleural effusion	717	1.96	(1.82–2.10)
9	Altered consciousness	689	1.88	(1.74–2.02)
10	Pancreatic cancer	585	1.60	(1.47–1.73)
11	Colon cancer	580	1.58	(1.46–1.73)
12	Congestive heart failure	521	1.42	(1.30–1.54)
13	Intestinal obstruction	484	1.32	(1.21–1.44)
14	Breast cancer	474	1.30	(1.18–1.41)
15	Gastrointestinal hemorrhage	468	1.28	(1.16–1.39)
16	Cardiac arrest	466	1.27	(1.16–1.39)
17	Nausea or vomiting	460	1.26	(1.14–.37)
18	COPD	448	1.22	(1.11–1.34)
19	Anemia	446	1.22	(1.11–1.33)
20	Malignant neoplasm[a]	434	1.19	(1.07–1.30)
21	Lung metastasis	403	1.10	(0.99–1.21)
22	Non-Hodgkins lymphoma[a]	381	1.04	(0.94–1.14)
23	Renal failure	379	1.04	(0.93–1.14)
24	Chest pain	376	1.03	(0.92–1.13)
25	Septicemia	368	1.01	(0.90–1.11)
26	Prostate cancer	358	0.98	(0.88–1.08)
27	Urinary tract infection	328	0.90	(0.80–0.99)
28	Ascites	305	0.83	(0.74–0.93)
29	Fever	292	0.80	(0.71–0.89)
30	Neutropenia	281	0.77	(0.68–0.86)
	Other	15,242	41.64	(41.14–42.15)

COPD chronic obstructive pulmonary disease
[a]Type unspecified

receive care? In a Canadian study, potentially avoidable visits was defined as ED visits being related to a technical issue, such as catheter issues or prescription refills, and occurred about 1 % of the time in the last 2 weeks of life. 8.4 % of visits were for reasons such as malaise, fatigue, or need for palliative care, which likely represent some version of the patient "not coping" at home [30]. Arguably, these visits are also avoidable. In one small Irish study that prospectively documented reasons for ED visits in cancer patients who were under the care of a specialist palliative care program, about half of the visits were felt to be avoidable [38]. To a certain extent, the concept of avoidable ED visits is highly dependent on the alternative places available for care. In the absence of readily available access to care elsewhere, ED visits may not be avoidable at all.

In summary, cancer patients at the EOL visit the ED because of symptoms related to their malignancy. Pain and respiratory issues are common, as are difficulties coping at home. Chemotherapy toxicity is a problem for all patients, regardless of their trajectory, and contributes significantly to ED visits.

Factors Associated with Increased Risk of ED Visits

ED visits at EOL have been shown to be associated with several different patient, tumor, treatment, and health system factors. However, the differences in definitions and populations studied lead to inconsistent results in the literature.

Among patient factors, sex has been most consistently demonstrated as an important factor with men more likely to visit the ED than women [6, 39–46]. Age is also important with older patients less likely to make visits [6, 40–42, 44–50]. Those with more significant comorbidity are also more likely to visit the ED [6, 39, 40, 42, 51]. With one exception [50], those living in rural regions are also more likely to visit the ED [39–43, 47, 52]. ED visits are also more likely for patients who live in lower-income neighborhoods [39, 41, 43], with some exceptions [40].

Some tumor factors have been examined. Hematologic patients are more likely to make ED visits than patients with solid tumors [42, 49]. Among solid tumors, lung is at the highest risk [39, 43, 46]. Patients with higher symptoms are more likely to visit the ED [29].

Treatment factors are also important. Patients with metastatic cancer receiving chemotherapy are more likely to visit the ED [53]. As will be reviewed in the next section, palliative care interventions may decrease the likelihood of ED visits.

The influence of healthcare system factors has also been demonstrated. For example, as previously mentioned, harmonized comparisons between countries give some insight into the possible effects of different systems, such as the US hospice system versus more generalized access to palliative care [23]. Similarly, within the USA, those within the Veteran's Affairs (VA) system were less likely to have ED visits than those in Medicare [54].

Possible Strategies to Mitigate Risk of ED Visits at the EOL

It is unrealistic to expect that no patient will ever visit the ED at the EOL. Regardless, an ED visit can be a very taxing ordeal for patients at this point in their cancer journey, and most agree it happens more often than is desirable. This section will review the evidence for interventions to mitigate the risk of ED visits.

Temel et al.'s study in a comprehensive cancer care, where patients with advanced non-small cell lung cancer were randomized to early palliative care versus usual care, showed how early referral could reduce ED visits. In their paper, those randomized to the intervention arm experienced fewer ED visits in the last 30 days of life (22 % versus 30 %) [55]. Possible mechanisms of this decrease would include improved symptom control, decreased chemotherapy use, and improved knowledge of expectations. Indeed their study showed that the intervention arm had better quality of life and less depression and anxiety. Evidence also exists for community-based palliative care interventions to reduce ED visits. A randomized controlled trial of home-based palliative care versus usual care also demonstrated a decrease in ED visits for those in the intervention arm, from 33 % to 20 % [56]. In addition, a pooled matched analysis of a retrospective cohort that was exposed to a specialized palliative home care team or usual home care demonstrated that the risk of having an ED visit at the EOL was 32 % less for those who received care from the specialized palliative care teams [57]. Common features of these specialized palliative care teams included interdisciplinary care, education and symptom management support, home-based services, and services available 24/7. The impact of early palliative care referral has also been demonstrated in observational datasets. For example, in an Australian cohort of 746 patients, 32 % of those with early palliative care visited the ED at the EOL compared with 52 % of those without [20].

Not all studies have been positive though [58–60]. Some studies have been positive for other outcomes, such as satisfaction, cost, or hospitalization but not for ED visits [10, 58, 61]. For example, Bakitas et al. published a palliative care randomized trial using a nursing-led, multicomponent, psychoeducational intervention in a comprehensive cancer center [58]. This trial showed improvements to quality of life and mood, but did not reduce ED visits at the end of life. The

nature of the interventions may be one reason for the differing results.

Intensity of care is also important. In a study of patients receiving palliative home nursing, Seow et al. demonstrated a dose-response such that patients receiving more nursing hours of care at home were less likely to visit the ED [40]. Studies conducted in two different provinces in Canada have demonstrated that increase continuity of physician care in the outpatient setting also decreased ED visits [41, 43].

Structural aspects, for example, of a palliative care team, the health system, or the care setting itself, are also important. A case series of four regions with either high or low ED visit rates demonstrated that regions with lower ED rates have specific features of their palliative care systems that were absent in the other regions. These included overall palliative care needs planning, a common chart, standardized patient assessments, 24/7 palliative care team access, advance practice nursing expertise available, and designated roles for the provision of palliative care services [62]. Related to the physical structure of care settings, some jurisdictions have restructured the ED to create cancer-specific ED programs as an alternative place for assessment [27]. This particular structural change would facilitate easier access with short waits for cancer patients. It would also potentially hone the expertise of the ED staff working there and improve communication with the ambulatory team. Such an approach, however, seems to result from failure to optimize care upstream in the trajectory.

Clear documentation of advanced care plans has also been associated with fewer ED visits. A prospective cohort study of 1231 patients with stage IV lung or colorectal cancer was conducted as part of the Cancer Care Outcomes Research and Surveillance Consortium (CCORS). The authors demonstrated that patients who had and EOL discussion more than 30 days prior to their death were much less likely to use acute care services (ED and hospitalization) in the last 30 days [63]. A single institution retrospective chart review of 220 women who died of ovarian cancer found that when an EOL discussion occurred more than 30 days prior to death, visits to ED decreased [19]. However, ED physicians commonly report the lack of documentation regarding discussions of advance care planning or goal setting in the outpatient setting.

There has been little to no research done evaluating the impact of psychoeducational interventions for informal caregivers on ED visits at EOL. A systematic review of informal caregivers' needs identified a lack of practical support for nursing skills [64]. The clinical approach taken for patients at EOL may be quite different [65], and these skills are important to be prepared. A systematic review of qualitative and quantitative studies of unmet needs for patients and carers identified that the most frequently unmet need was effective communication with healthcare professionals [66].

Conclusion

Most practitioners are familiar with the aphorism, "To cure sometimes, to relieve often, to comfort always." The field of medicine has excelled in technical aspects of providing care, and we cure much more often than we ever did in the past. As a result, the importance of offering relief and comfort are sometimes forgotten. Population-based measures of ED visits in cancer patients at the EOL are a meaningful indicator of quality of care. With administrative healthcare data, this measure is easy to follow. Currently, ED visits are happening more often than is desirable. Increase efforts are needed to minimize the use of toxic therapies at the EOL and to create effective palliative care structures and processes which are readily accessible.

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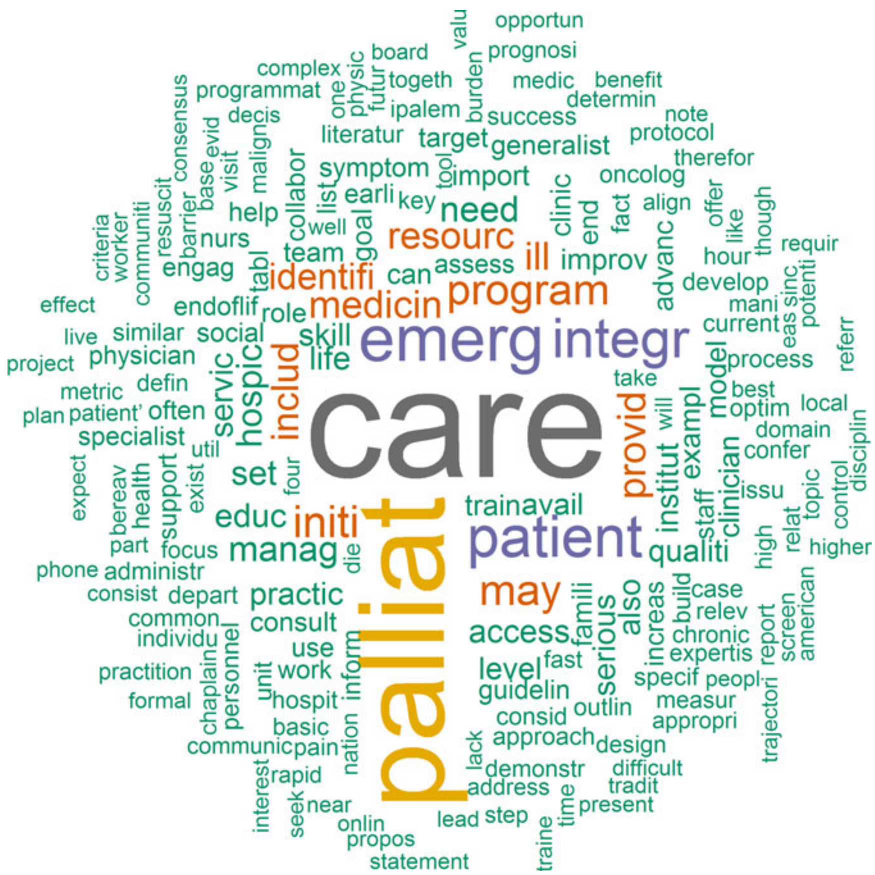
Capacity Building: Integration of Palliative Care in Emergency Medicine

Sangeeta Lamba



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Integrating Emergency Palliative Care for Patients with Advanced Cancer

Seriously ill patients (with malignant and nonmalignant chronic illnesses) who suffer from a high disease and symptom burden often visit the emergency department (ED) for acute crisis events related to their illness [1–13]. Though the ED is primarily designed to resuscitate and stabilize the acutely ill and injured, increasingly those with chronic serious underlying disease processes such as malignancy seek care in this setting [1–5, 7, 10–18]. Malignancy-related symptoms and oncologic emergencies therefore often lead to ED visits, and these visits tend to increase as the patient's clinical status deteriorates and as they approach the end of life [1, 3, 4, 11]. Most hospitalizations in patients with underlying malignancy are initiated from the ED, and these early hours of care often include life-sustaining decisions such as ventilator support, and establishes, for better or for worse, the trajectory of future in-hospital care [15–20]. When a patient with a life-threatening oncologic emergency presents to the ED, these rapid decisions often occur in the context of uncertain prognosis, especially if the event was unexpected [17–20]. Determining goals of care rapidly so that initial treatment pathways align with patient values (thus avoiding future conflict) is challenging in most circumstances but perhaps even more so in the uncertain nature of the ED setting [17–20]. Sometimes the ED providers may need to change gears and shift their focus to the comfort and quality of life for the patient (palliative care) as opposed to the traditional focus on cure and prolongation of life. Some strategies to provide optimal care to the seriously ill include (1) use of best practice-based clinical decision-making models [21, 22] and (2) incorporation of patients' values and goals in the plans of care [15–19].

The World Health Organization defines palliative care as an approach that "improves the quality of life of patients and their families when facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification, impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [23]. Palliative care applies to *all phases* of a life-limiting condition and is not just for dying patients (Fig. 1) [11, 16, 17, 23–25]. In fact, maximal benefit from this approach is likely when there is early integration of palliative care into management plans as opposed to only sequentially considering such care as a last resort measure when "no more can be done" for the patient [1, 7, 16, 17, 23–31]. The use of this simultaneous care model with early integration of palliative care is associated with a higher quality of life, including better understanding and communication, access to home care, emotional and spiritual support, well-being and dignity, care at time of death, and lighter symptom burden. Some evidence suggests that, on average, palliative care and hospice patients may live longer than similarly ill patients who do not receive such care [6, 17, 32]. Palliative care also has the ability to simultaneously improve quality and control the cost of care for the most seriously ill patients [25, 28, 30–38].

The Institute of Medicine (IOM) report "Dying in America: Improving Quality and Honoring Individual Preferences Near the End of Life" highlights the current disconnect between how most Americans wish to be cared for at the end of their lives and the care that is actually provided to them [32]. The report lists a similar disconnect between the services that seriously ill patients and families need and the services they currently receive [32]. People nearing the end of life often experience multiple transitions between healthcare settings (the emergency department being a major setting for end of life crises) and high rates of apparently preventable hospitalizations—which can further fragment the delivery of care and create burdens for patients and families [32].

The IOM report makes a recommendation that "All people with advanced serious illness should have access to skilled palliative care or, when appropriate, hospice care in all settings where they receive care (including health care facilities, the home, and the community)" [32]. This report also proposes that comprehensive care for individuals with advanced serious illness who are nearing the end of life should:

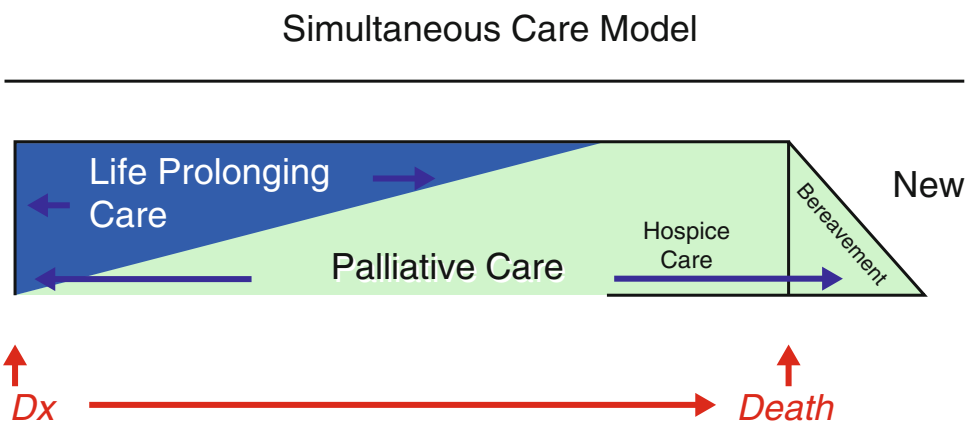

Fig. 1 Simultaneous care model of palliative care

Table 1 Principles and elements of palliative care[a]

Patient- and family-centered care Care plan is aligned with preferences and determined by goals of patient and family Support system to help family cope with the patient's illness and with bereavement
Timing Support starts early in course of illness and may exist along with therapies that are intended to prolong life (such as chemotherapy) Support continues until disease cure or patient death
Interdisciplinary team approach to care A team meets the needs of patients and families (may include nurses, social workers, clergy, nursing assistants, pharmacists, and volunteers)
Comprehensive care Multidimensional assessment to treat physical, psychological, social, and spiritual distress
Relief of suffering Prevent and relieve suffering from pain and other distressing symptoms
Skills in the care of the dying and bereaved Prognostication Offers a support system to help patients live as actively as possible until death
Quality of life Focus on enhanced quality of life (may also positively influence the course of illness) Regards dying as a normal process while affirms life
Continuity of care Ensure communication and coordination of care in transitions across settings Prevent crises and unnecessary transfers are important outcomes
Quality assessment and performance improvement[b] Address safety and incorporate the systems of care that reduce error Use validated instruments for data to measure outcomes, when feasible

[a]Patient population: patients of all ages experiencing a serious chronic or life-threatening illness or injury
[b]Crucial emergency department (ED) and hospital metrics may include ED visits, ED length of stay, time of arrival to time of disposition, hospital and intensive care unit (ICU) length of stay, hospital readmissions, ICU admissions, documenting advance directives, and pain/symptom control
Adapted from the National Consensus Project for Quality Palliative Care—Clinical Practice Guidelines for Quality Palliative Care and the World Health Organization palliative care Definition [23, 26, 32]

- Be seamless, integrated, patient-centered, family-oriented, and consistently accessible.
- Consider the physical, emotional, social, and spiritual needs of individuals and family.
- Include coordinated, efficient information transfer across all providers and all settings.
- Be consistent with individuals' values, goals, and informed preferences [32].

These proposed goals are consistent with palliative care principles and are integral components of both palliative care and hospice care (Table 1) [23, 26, 32]. However, it is important to note that hospice care services are primarily based on prognosis (as reimbursed by Medicare). Hospice services are therefore considered when a patient has a terminal prognosis with 6 months or less of predicted survival [16, 17, 20].

Palliative care is "whole person care," and as such it encompasses access to an interdisciplinary team, including board-certified hospice and palliative medicine physicians, nurses, social workers, and chaplains, together with other healthcare professionals as needed [16, 17, 20]. Depending on local resources, access to this team may be on site, via virtual (phone) consultation or by transfer to a setting with these resources and this expertise level, such as an in-hospital palliative care unit [16, 17, 20]. Although most now recognize the importance of the ED setting in caring for the seriously ill, many barriers and competing priorities for both ED and palliative care providers jeopardize a more widespread integration of the disciplines [16, 17, 39]. The term "integration" is used to indicate the incorporation of palliative care principles (outlined in Table 1) [23, 26, 32] into daily ED practice with or without the involvement of a dedicated hospital palliative care team or inpatient palliative care unit.

Generalist Versus Specialist Emergency Palliative Care [17, 40, 41]

Similar to other disciplines that integrate with emergency medicine, some routine skills such as basic management of pain and other symptoms as well as aligning management with a patient's goals are expected to be delivered by any emergency practitioner at a so-called generalist level [7, 17, 22, 40, 41]. However, more complex skills such as negotiating a difficult family meeting and managing advanced or refractory symptoms may require added training to gain a "specialist level" of expertise [7, 17, 22, 40, 41]. Though it may be ideal to have a specialist manage all elements of palliative care, the reality of the current workforce is such that there are not enough specialists to do so. As people live lon-

Table 2 Generalist versus specialist levels of palliative care [40, 41]

Generalist level palliative care Provided by healthcare professionals who manage seriously ill patients, but palliative care is not the main focus of their daily work Includes care in settings not specialized in palliative care such as the emergency department	*Examples of tasks* • Basic management of pain and other distressing symptoms • Basic discussions about prognosis, goals of treatment, and advance directives
Specialist level palliative care Provided by healthcare professionals where main activity is the provision of palliative care Includes care in settings specialized in palliative care such as inpatient palliative care unit or hospice	• Management of refractory pain or other difficult-to-treat complex symptoms • Conflict resolution regarding goals of care (between family members and between family and healthcare team) • Futility of care conversations

ger with a higher burden of chronic illness, the demand for both generalist and specialist palliative care will rise [40]. Palliative care training programs have expanded nationwide, but the current levels of new trainees in palliative medicine will not meet the needs for all patients that may benefit from such "specialist" care [40, 42]. An optimal care model would therefore be such that the generalist emergency palliative care (skills that all emergency clinicians should have) coexist and support patients with specialist emergency palliative care (skills for managing more complex cases) (Table 2) [17, 40, 41]. The Education in Palliative and End-of-life Care (EPEC), EPEC-EM, and End-of-Life Nursing Education Consortium courses are examples of courses that seek to build the generalist level of skills for emergency practitioners [44, 45]. Workshops and guides available from multiple resources also target further specific skill development for interested practitioners [46, 47]. Due to this workforce gap, there is a growing call to address development of generalist level palliative care skills for emergency medicine resident training and also to provide continuing medical education to practicing clinicians [17, 40]. Some state licensing boards require completion of palliative care education credits as part of ongoing licensure [48]. Performance and quality measure metrics can be used to reinforce the ongoing emphasis on generalist emergency palliative care as part of overall high-quality patient care [27, 43].

Integrated Emergency Medicine-Palliative Care Initiatives

The Improving Palliative Care in EM (IPAL-EM) project is a resource development and dissemination initiative that begun in 2010 by the Center to Advance Palliative Care (CAPC) with funding provided by the Olive Branch Foundation [7, 49, 50]. The goal of this initiative was to help accelerate the integration of palliative care services into ED settings. It brought together an advisory panel of nationally recognized leaders in the disciplines of emergency medicine and palliative care [7, 22, 49, 50]. IPAL-EM offers an online portal for sharing essential expertise and available best evidence, tools, and practical resources to assist emergency clinicians and ED administrators in the successful integration of palliative care and EM [22, 49]. Currently, an institutional subscription to CAPC can provide access to all the resources gathered as part of the IPAL-EM initiative including clinical practice guidelines, needs assessment tools, and sample quality metrics specific to ED palliative care along with a relevant library of peer-reviewed literature and consensus/policy statements [49].

Demonstration Models of Integrated Emergency Palliative Care

In the last decade, several programs have established ED palliative care initiatives to identify patients that may benefit from early palliative care interventions [22]. The IPAL-EM initiative collected information on existing models or demonstrations of ED and palliative care service integration. Eleven US hospital-based clinical integration programs were interviewed after they were identified from a review of literature, national presentations, and feedback from peer emergency palliative care experts [22]. These programs had different levels of collaboration between their institutional palliative care program and the ED. Four themes emerged regarding ED palliative care programmatic development to include (1) traditional consultation, (2) basic integration, (3) advanced integration, and (4) ED-focused advanced integration models (Fig. 2) [22].

Traditional consultation programs: Similar to other consultation services that interact with the ED, a palliative care expert or consultant is contacted by the ED provider to help answer questions or issues in patient care and to help manage difficult-to-control symptoms [24, 40]. In this model there are no common programmatic goals or process steps to improve overall care delivery [22].

Basic integration programs: In these models there exists a somewhat more formal relationship between the palliative care program and the ED such that they may work together to achieve some common programmatic goals and objectives. For example, there may be defined protocols for improved patient workflow such as expedited admission to a palliative care unit or targeted generalist level palliative care education for the ED staff. Demonstration programs include Virginia Commonwealth University, Richmond, Virginia [22].

Advanced integration programs: These programs build on the basic integration models to set up common program-

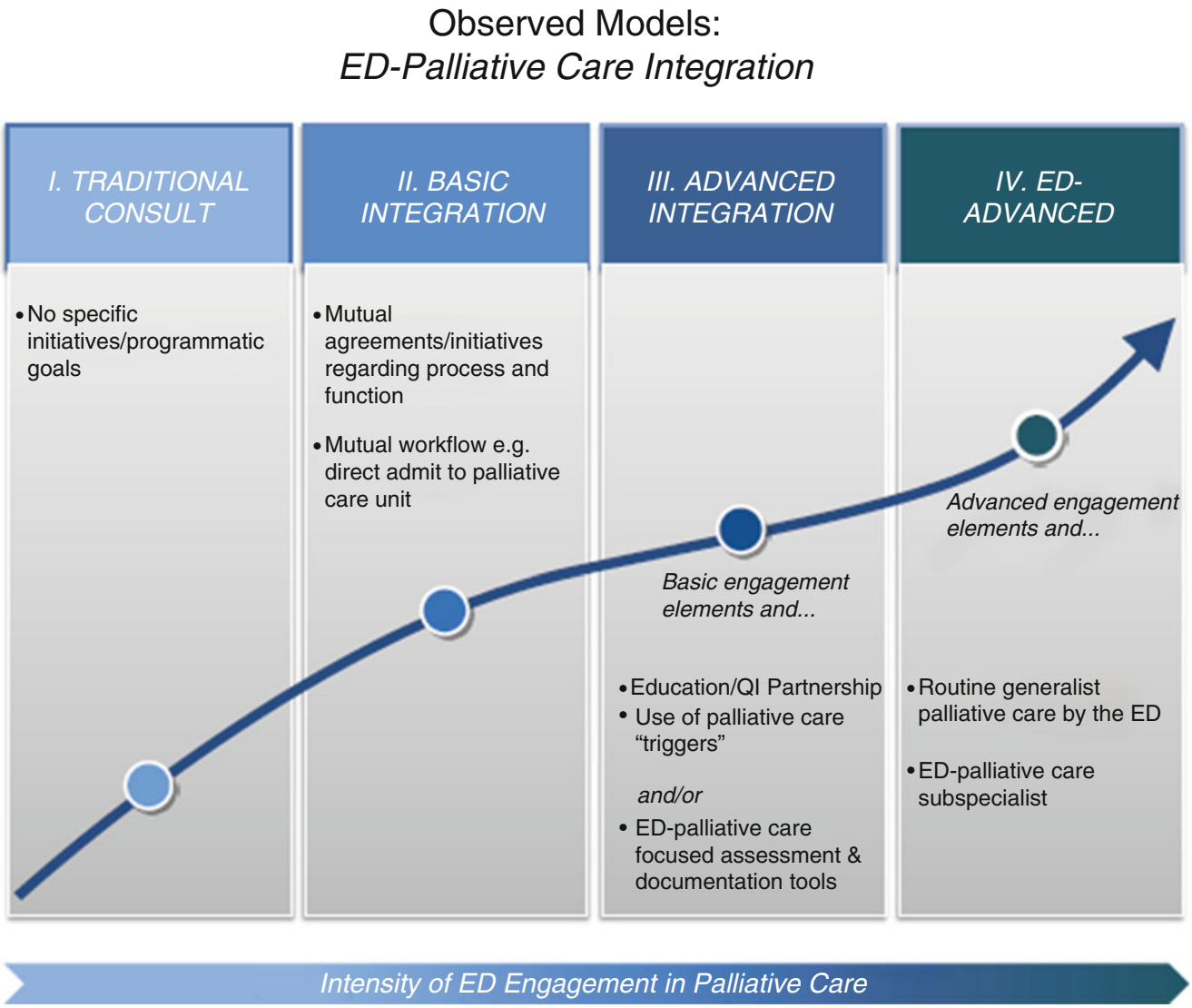

Fig. 2 Observed models of emergency department and palliative care integration [22]

matic processes and protocols with the ED increasingly taking on a more active role while an enhanced level of ED generalist level palliative care is provided. Demonstration programs include Baylor, Texas [22, 51].

ED-focused advanced integration programs: In these programs the ED is very engaged and focused on palliative care-related processes. In some cases the ED may lead the integration and the palliative care services in the institution. Common themes in these programs include case management for high-risk palliative care patients and existence of dual EM and palliative medicine-certified physicians who are passionate about the integration initiatives. Additionally, these programs often have increased numbers of personnel for palliative care such as ED social workers or bereavement supporters for families. They may also implement reorganization and structural changes to improve patient care at end of life, such as a designated private room or space for imminently dying patients and their families. Demonstration programs include Emory in Atlanta and the Life Sustaining Management and Alternatives or LMSA program at St. Joseph's Medical Center in Patterson, New Jersey [22, 52].

Jump-Starting an ED Palliative Care Integration Initiative

Literature has identified some important barriers to emergency medicine and palliative care integration. Surveys of physicians, nurses, and administrators list barriers such as (1) the ED culture of life-prolonging care and resuscitation that places a lower emphasis on nontechnical skills, (2) palliative care staffing and availability for the 24 h needs of the ED, (3) logistical issues including lack of access to patient medical records, and (4) medicolegal concerns particularly if life-prolonging therapy is not offered [10, 15, 39, 53]. One manuscript describes the ED as being "caught in the middle" when caring

for such patients. It lists the challenging physical environment (privacy, noise, lack of information and delay, and lack of defined pathways), with limited resources (overcrowding, time pressures, competition with other emergencies) and variable roles and expectations of the staff providing care (comfort with dying, views of dying in the ED, expertise and comfort in caring for those with serious and advanced illnesses) [10]. On the other hand, the emergency medicine resident and attending physician surveys report that they believe that PC skills are important for EM practice but that they are not yet adequately educated and trained in providing PC [15, 54]. Domains of particular interest that were identified for training for emergency physicians include management of patients under hospice care, withdrawal of life-prolonging measures, prognostication, and pain management [15, 17, 54].

It is important to begin an ED-PC initiative with identified ED "champions" who can effectively build upon lessons learned from other prior successes and failures so that the initiative is tailored to fit the unique ED setting [7, 50]. The design of the initiative should take into account the preexisting hospital and community resources, availability and hours of access to palliative care consultation services to the ED, and key institutional deficiencies in ED palliative care [7, 50]. Some common examples of initial targets for integration may include:

- Setting up an ED bereavement program
- Defining screening criteria to identify high-risk patients for early palliative care team interventions
- Educating ED staff on pain and palliative care protocols
- Embedding palliative care staff in ED rounds
- Improving throughput to inpatient palliative care unit, when available

These initiatives have a higher chance of success if aligned with the key metrics important to the institution such as ED length of stay, hospital readmission rates, and utilization metrics related to observation and intensive care units [7, 17, 43, 50]. Described below are four steps that may help jump-start such an integration initiative [7, 50].

1. *Put together a Team: Palliative Care "Champions" in the Emergency Department*

It is important to recruit work group or team members who are interested and committed to the integration of palliative care in the ED. For example, identifying those individuals who have previously expressed concern, frustration, or sensitivity to a patient's palliative care needs in the ED. The interdisciplinary collaborative nature of palliative care allows for engagement of varied professional disciplines based in the ED such as social workers and case managers, as well as other providers throughout the institution who interact with the ED, such as chaplains. Since the integration initiative has the potential to impact other hospital services and processes, a wider range of administrative and clinical personnel should also be considered for inclusion. Table 3 lists some of the members to consider when setting up an initial work group. Though the type of members engaged in such an initiative will likely vary from one ED to another, it is vital to include key ED administrators such as the ED medical director and nurse manager(s) in the work group. They not only know their own ED's needs but can also provide valuable perspective taking into account resources (staffing, training needs) that may be critical for designing and implementing feasible integration efforts [7, 50]. The ED administrators may also be best equipped to engage support among both the ED colleagues and at a broader institutional level.

2. *Explore the Resources Available: Existing Literature and Resources*

The available literature in emergency palliative care is increasing rapidly. Consensus statements on the role of palliative care and ED such as the policy statements and the Choosing Wisely campaign from the American College of Emergency Physicians and Emergency Nurses Association on roles of the ED and ethical issues at end of life are important to note [55–57]. The Choosing Wisely campaign guides emergency clinicians to, "Don't delay engaging available

Table 3 Suggested members for the emergency department (ED) palliative care integration initiative [7]

• ED medical director
• ED physician(s)
• ED nurse manager and ED nurse(s)
• Director or designee of the palliative care program
• Nursing educator
• Social workers
• Case managers
• Chaplain
• Representatives of key hospital services (e.g., hospitalists, ICU, surgery, oncology) that may be affected by this initiative in the ED
• Hospital leadership: administration and finance
• Others relevant to the success of a specific part of the initiative (e.g., ethics consultant, mental health professional, pharmacist)

palliative and hospice care services in the emergency department for patients likely to benefit" [55]. While there is no identified optimal model of ED integration of palliative care, there are a growing number of examples in the literature of specific strategies and programs that have proven to be successful as outlined above [21, 22, 30, 31, 58]. Other topics relevant to emergency palliative care include:

- Palliative and end-of-life care in the ED [1, 2, 4, 5, 7, 16–20]
- Communication [5, 15]
- Family experience and surrogate decision-making [5]
- Palliative care specialists in the ED [19, 40]
- Ethical issues [5, 15]
- Quality improvement/practice change [43]
- Protocols and screening criteria [30, 31, 58]
- Family presence during resuscitation [17]
- Bereavement care [17, 25]
- Education and training [54, 59]

An open access educational online resource, *Fast Facts and Concepts*, is worth noting since it provides concise, practical, peer-reviewed, and evidence-based summaries on key topics important to clinicians and trainees caring for patients facing life-limiting illnesses [60]. *Fast Facts* are free, easily accessible, and clinically relevant monographs on palliative care topics. They are intended to be quick teaching tools for bedside rounds, as well as self-study material for trainees and clinicians who work with patients with life-limiting illnesses. For example, Fast fact # 033 presents steps for a ventilator withdrawal protocol, Fast fact # 036 for calculating opioid dose conversions, and Fast fact # 247 for initiating a hospice referral from the emergency department [60, 61]. There are several formal educational opportunities in palliative care targeted to ED clinicians. Some programs address overall palliative care skills for many types of providers, and others target profession-specific skill development, for example, those for social work and chaplains. Sponsoring some or all of the identified "champions" at such a conference may help build an institutional pool of qualified candidates who can not only train others but could then be targeted for future career development. Some opportunities include:

(a) EPEC-EM (Education in Palliative and End-of-life Care for Emergency Medicine): Education in Palliative and End-of-life Care for Emergency Medicine is a 2-day conference designed to teach clinical competencies in palliative care to healthcare professionals working in the ED in a train-the-trainer format. The conference covers topics specific to ED practice including rapid palliative assessment, disease trajectories and prognosis, care of the hospice patient, chronic and malignant pain management, family-witnessed resuscitation, communication, and more. There is also a focus on techniques for teaching the curriculum to other emergency practitioners [44].
(b) ELNEC (End-of-Life Nursing Education Consortium): Offers a modular train-the-trainer end-of-life training program for nurses [45].
(c) Communication skills building workshops [46, 47].
(d) Hospice and Palliative Medicine Fellowship.

The American Board of Emergency Medicine is one of the ten sponsoring boards for the Hospice and Palliative Medicine subspecialty. The ACGME provides a program listing and additional information about the individual programs that can be accessed online [62].

3. *Identify and Ease Access to Local Hospice and Palliative Care Resources*

Identify palliative care resources (both personnel and services) that are available in the (1) ED such as case managers; (2) institution such as a chaplain, social worker, or bereavement counselor; and (3) community such as collaborative arrangements with a hospice [30, 31]. Though these resources may exist often, they are not known to the ED staff and even if known are not easily identifiable by ED staff at the time of critical need. Collating information and making it easy to access would therefore be valuable, and other steps to ease access to palliative resources may include (a) identifying and listing various hospital and community resources (Table 4); (b) cataloguing their roles, responsibilities, and contact numbers; (c) posting call schedules for personnel in a visible, high traffic area of the ED for ease of access; and (d) identifying clearly the hours of availability of sup-

Table 4 Potential list of institutional and community resources [7, 50]

• Palliative care team call schedules
• Palliative care team hours of in-person availability
• Outpatient palliative care clinic availability and practice hours
• Community hospice: home and residential hospice
• Chaplaincy support and availability
• Social work support and availability
• Bereavement support and availability
• Ethics consultant
• Child life specialist support and availability (for pediatric patients or children of adult patients)

Table 5 Screening criteria for a palliative care assessment at the time of admission [58]

A potentially life-limiting or life-threatening condition (such as malignancy)[a] and…
Primary criteria:
Global indicators that represent the minimum that hospitals should use to screen patients at risk for unmet palliative care needs
• The "surprise question": Would you be surprised if the patient died during this admission?
• Frequent admissions (admissions for same condition within several months)
• Difficult-to-control (moderate-severe) physical or psychological symptoms
• Complex care requirements (functional dependency; home support for ventilator or tube feedings)
• Decline in function or overall failure to thrive
Secondary criteria:
Specific indicators that may suggest a high likelihood of unmet palliative care needs
• Admission from a long-term care facility
• Metastatic or locally advanced incurable cancer
• Chronic home oxygen use
• Out-of-hospital cardiac arrest
• Current or past hospice program enrollee
• Limited social support (family stress, chronic mental illness, etc.)
• No history of completing an advance care planning discussion/document

[a]Life-limiting or life-threatening condition is defined as any disease known to be life-limiting (e.g., chronic obstructive pulmonary disease, metastatic cancer) or that has a high chance of leading to death (e.g., multi-organ failure, sepsis). Serious medical conditions for which recovery to baseline function is routine (e.g., community-acquired pneumonia in a healthy adult) are not included in definition

port personnel and whether they are available in person or by phone. Consider listing roles and responsibilities of personnel, for example, social work and case managers may be essential partners when navigating disposition issues and maximizing community resource utilization [7].

If the institution has availability of a specialty-level palliative care team, it may be important to collaborate and with them to create screening criteria that assist ED staff in identifying appropriate reasons for consultation (Table 5) [7, 58]. Since many such palliative care consultation teams offer in-person services during regular working weekday hours and phone support during off-hours and weekends, it may be useful to create collaborative guidelines to determine what will constitute a nonurgent or urgent/emergent level of consultation [7, 40, 58]. Similarly, if the institution offers a specialized inpatient palliative care unit, it may be useful to not only establish formal guidelines and processes for admissions from the ED but also educate ED staff on the scope and capabilities of care in this setting. This collaboration with the palliative team and ED may be able to prevent some unwanted ED visits, for example, by referrals to an outpatient palliative care clinic. Similarly, appropriate referrals to hospice from the ED are feasible and may facilitate early dispositions [20, 61]. Since these decisions are based on patient determined goals of care with engagement of loved ones, they have the potential to increase patient and family satisfaction with ED care [20]. Fostering collaborative relationships with local hospice agencies and engaging them in a timely manner for appropriate patients may help ED clinicians initiate hospice referrals directly from the ED [20]. These relationships also have the potential to improve dialogue when managing patients under hospice care who arrive to the ED with a crisis event related to control of distressing symptoms [20].

4. *Complete a Needs Assessment and ED Palliative Care*

An assessment of needs helps identify opportunities for improvement in ED palliative care. This may help with targeting of areas where simple interventions can lead to early success that in turn provides momentum to the integration initiative. The needs assessment can outline barriers to the integration initiative, the institutional strengths and weaknesses, and finally identify adherence gaps between best practice guidelines and local practice. This information would determine where to focus initial attention and where to assign resources [7].

Core guidelines for effective palliative care are outlined by the National Consensus Project for Quality Palliative Care (NCP) and address eight palliative care domains, for example, physical aspects of care and social aspects of care [26]. These guidelines represent goals and ideal practices that enable programs to define their own palliative program organization, resource requirements, and performance measures. These guidelines have been adapted to set ED-specific clinical practice guidelines that have also been translated into a "needs assessment tool" that programs may also find useful to identify areas for improvement (Table 6) [63].

Table 6 Sample section of the needs assessment tool [26, 63]

Domain 2: Physical aspects of care				
Guideline 2.1: ED clinicians use a multidisciplinary approach to pain and symptom control				
Indicator		*Present*	*Absent*	*Comment*
2.1	ED clinicians collaborate with specialists from different disciplines to create a comprehensive pain/symptom control plan of care	☐	☐	
Guideline 2.2: ED clinicians assess symptoms using validated assessment tools appropriate for patients across the life span				
Indicator		*Present*	*Absent*	*Comment*
2.2.1	Standardized pain assessment tools are used	☐	☐	
2.2.2	Standardized symptom distress assessment tools are used	☐	☐	
Guideline 2.3: Emergency nurses use nurse-initiated protocols to relieve the symptom burden of patients				
Indicator		*Present*	*Absent*	*Comment*
2.3	The ED uses nurse-initiated analgesic protocols	☐	☐	

Table 7 Potential measurable quality metrics and outcomes for an emergency department (ED) palliative care integration initiative

Operational
Mean/median ED length of stay (hours)
Discharge disposition status
ED arrival to time of disposition (to palliative care unit)
% With repeat ED visits within 30 days (within 60, 90 days)
% With repeat hospital admits within 30 days (within 60, 90 days)
Number of hospice referrals from the ED
Number of palliative care referrals from the ED (if available)
Clinical
% Charts with documentation of the healthcare decision-maker/advance care directives
% Of patients prescribed opioids with bowel regimen on discharge
% Of patients with documented pain assessment on presentation and % reassessed
% Of families with documented offer of spiritual support after ED death
% Of patients in target populations who have a documented palliative care assessment
% Of caregivers in target patient populations screened for caregiver strain
Patient satisfaction
% Of ED patients who report being adequately informed about their condition or treatment plans and options
% Of families who report excellent overall end-of-life care after patient's ED death
% Of patients reporting satisfaction with communication regarding discharge instructions

Monitoring Integrated Palliative Care Initiatives

The Agency for Healthcare Research and Quality (AHRQ)/American College of Emergency Physicians conference on "Improving the Quality and Efficiency of Emergency Care Across the Continuum: A Systems Approach" identified four key topics or questions that should be addressed further in emergency medicine and palliative care: (1) which patients are in greatest need of palliative care services in the ED (identifying the target population in need), (2) what is the optimal role of emergency clinicians in caring for patients along a chronic trajectory of illness (what skills are necessary), (3) what is the effect on healthcare utilization after the integration and initiation of palliative care training and services in the ED setting, and (4) what are the educational priorities for emergency clinical providers in the domain of palliative care? The conference proposed that future emergency palliative care research would be expected to target gathering of evidence in these domains using six categories of inquiry: descriptive, attitudinal, screening, outcomes, resource allocation, and education of clinicians [43, 64]. Examples of some relevant quality indicators to measure outcomes and success of ED palliative care integration initiative are listed in Table 7.

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