Textbook of Onco-Anesthesiology

Rakesh Garg
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Preface

The advancement in anesthesiology is occurring in leaps and bounds. This advancement relates to the use of newer drugs, techniques, and equipment. Also, patient-related concerns with regard to special age group and special population with specific disease are also realized. The different subspecialties of perioperative care like pediatric, obstetric, and geriatric anesthesia need consideration with regard to patient profile. Not only the patient profile but perioperative anaesthesia care requires diligence for special types of surgeries. In view of these issues, many subspecialties have emerged in the past like cardiac anesthesiology and neuro-anesthesiology. With the need for more focus, specific understanding, and needs of the patient, other specialties in the field of anesthesiology are emerging. Onco-Anesthesiology is such a recent addition to have emerged as a dedicated separate specialty.

Onco-Anesthesiology is now a well-recognized Sub-Speciality with various teaching and training courses including fellowships and master's courses across the world. The types of onco-surgical interventions are increasing. Also, with increasing patient population diagnosed with cancer, the number of cancer centers is also increasing. Such patients require interdisciplinary involvements like surgical oncologists, medical oncologists, radiation oncologists, and radiologists for perioperative management. These involvements make perioperative anesthesia care for anesthesiologists quite challenging. Presently, there is no formal textbook of Onco-Anesthesiology. The anesthesiologists presently refer to the literature from different sources and at times may not be easily available. The editors of this book are exclusively working in a dedicated Cancer Center and recently started the teaching program in Onco-Anesthesia. During the curriculum setup and preparation of academic schedule, we realized the need of an exclusive book that would be helpful to trainees pursuing their academic course in Onco-Anesthesiology. So there was a definite need for a textbook of Onco-Anesthesiology and we all editors decided to provide an international level textbook that would serve the need of teaching and training material for those who are working in the field of Onco-Anesthesiology. This book may also be useful to other disciplines as perioperative management remains multidisciplinary and understanding each specialty's concerns would improve the overall outcome of the patient. The book would be also useful to general practitioners whenever they encounter the onco-surgical patients for perioperative management.

The book covers all aspects of management of patients undergoing cancer treatment with regard to anesthesiologist's domain. It includes not only the

operating room procedures but also includes periprocedural care outside the operating room requiring anesthesiologists' interventions. It has a special section on palliative care for advanced cancer patient management. We are really thankful to all the esteemed authors who have contributed to chapters in this textbook. All the authors are experts in the field of Onco-Anesthesiology and have notable achievements and contributions in the development of Onco-Anesthesiology. We are really thankful to all these world-renowned authors for providing academic inputs to this important textbook. We understand that contributing a chapter requires a mammoth effort and all the authors have provided updated details of all the chapters.

It was realized that the evidence related to Onco-Anesthesia is emerging. Many new types of interventions for cancer patients are being added. So, it is a fair start and with time would require additions as and when new literature emerges. Many aspects have emerged and evidence is being generated like the impact of perioperative management on cancer recurrence. This would be an interesting and challenging task to formulate cancer protective perioperative techniques. Probably in the near future, evidence would highlight such techniques and interventions as well.

We are sure that the readers would find this textbook useful for increasing their knowledge and thus providing better care of their patients. This would be useful to trainees for various examinations as well.

We would like to acknowledge the efforts of persons who helped us in the book including Ms. Tracy Marton, Mr. Naren Aggarwal, Ms. Jagjeet Kaur Saini, Mr. Ejaz Ahmad and Ms. Hashwini Vytheswaran. Finally, we are thankful to our family who gave their support during this important academic venture of writing the textbook.

New Delhi, India

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Contents

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Rakesh Garg graduated from the University College of Medical Sciences, Delhi University, New Delhi, and completed a specialization degree (MD anesthesiology) from Maulana Azad Medical College, Delhi University, New Delhi. He got his further training from All India Institute of Medical Sciences, New Delhi. He has completed his Fellowship in Palliative Medicine and Post Graduate Certificate Course in Hospital Management. He is a consultant anesthesiologist with a specific interest in Onco-anesthesiology and Palliative Medicine at Dr BRAIRCH, All India Institute of Medical Sciences (AIIMS), New Delhi. Dr Garg is actively involved in teaching and training programs at various levels. He supervises and is involved in teaching and training for DM Onco-anesthesiology and MD Palliative Medicine program at AIIMS. He has more than 250 publications in peer-reviewed national and international journals and has authored more than 30 chapters in various books. He is associate editor of *Indian Journal of Anesthesia*, *Journal of Anesthesiology and Clinical Pharmacology and Indian Journal of Palliative Care. Dr Garg has received various awards at national and international level. He has been awarded Fellowship in Clinical Research Methodology & Evidence Based Medicine (AIIMS, New Delhi), Fellowship of the Indian College of Anaesthesiologists (FICA), Fellowship of International Medical Sciences Academy (FIMSA) and Fellowship of Indian College of Critical Care Medicine (FICCM). Dr Garg is an* editorial board member of various international and national journals. He is actively involved in teaching and training and has delivered over 150 guest lectures at various conferences and workshops. He is an prolific researcher and conducted research in areas of Onco-anaesthesiology, airway, regional anaesthesia and critical care. He is a core committee member for the development of guidelines for airway management, fasting/feeding, and cardiopulmonary resuscitation.

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Part I

Introduction

1 Need for Onco-Anesthesia as Super Specialty

Sushma Bhatnagar

1.1 Introduction

Cancer is not new to humanity and its evidence has been described in the Chinese and Arabic medical writings as well as in Egyptian mummies [1]. Taking a look at the present times, it is clear that the cancer epidemic is engulfing the world including India. The GLOBACON Project by International Agency for Research on Cancer (IARC) had reported in 2012 that the new cases of cancer, cancer deaths, and people living with cancer would be 14.1, 8.2, and 32.6 million, respectively [2]. By 2025, about 19.3 million new cancer cases will be diagnosed every year [3]. The GLOBOCON report 2012 about the commonest cancers in the world suggests that lung cancer, prostate cancer, colorectal cancer among males and breast cancer, colorectal cancer, and lung cancer among females shall be the three commonest cancers worldwide [3].

1.2 The Need

Cancer and its natural course have changed over the last decade. With the increase in the number of cancer patients, early detection and prompt management of the disease are required to reduce morbidity and mortality. With the advancement in diagnostic modalities and surgical techniques needed for the treatment of cancer patients, anesthetic techniques have been modified with the intent to provide holistic perioperative care to these patients. Preoperative evaluation of cancer patients requires specialized knowledge due to the administration of neoadjuvant chemotherapy and radiation therapy. The institution of disease-modifying treatment is associated with distinct considerations due to its toxic effects on all the systems of the body, including the cardiovascular, respiratory, hepatic, renal, and central nervous systems. For example, anthracyclines are most commonly associated with conduction disturbances, arrhythmias, and cardiac failure, whereas bleomycin is implicated as the causative agent of pulmonary fibrosis. Radiation pneumonitis is another pulmonary complication that may occur in up to 20% of irradiated patients. Platinum compounds and alkylating agents have nephrotoxic effects, whereas vinca alkaloids, taxanes, cytarabine, and platinum compounds have neurotoxic effects. Anesthetic care of cancer patients for definitive surgery, different diagnostic, and minimally invasive therapeutic procedures will require special considerations not only due to systemic effects of chemoradiation but also due to factors like altered physiology, immunosuppression, malnutrition, and other psychomimetic factors related to cancer patients and issues related to the unconventional nature of

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oncosurgeries. For example, during the administration of anesthesia for hyperthermic intraperitoneal chemotherapy (HIPEC) surgeries done for pseudomyxoma peritonei arising from the ovary or appendix, the main anesthetic goals are to maintain normovolemia, normothermia, correcting metabolic derangements, perioperative pain management, prevent the development of coagulopathy, and thorough knowledge about the adverse effects of chemotherapeutics used during HIPEC. Furthermore, anesthetic management of pulmonary resections including pneumonectomy necessitates preoperative rehabilitation, one-lung ventilation with the prevention of hypoxemia, physiological changes with lateral decubitus positioning, fluid, and postoperative pain management, and identification and management of postoperative complications. Moreover, anesthetic challenges for head and neck cancer surgeries require skills to manage a difficult airway, maintenance of oxygenation, ventilation, normovolemia, and postoperative surgical complications. Onco-anesthesia also includes administration of general anesthesia to patients posted for head and neck and breast implants and administration of subarachnoid or combination of the subarachnoid and epidural block for patients posted for perineal implants. The reduced postoperative morbidity also influences the ability of these patients to return to their intended oncological treatment, thus improving overall oncological outcomes. Besides, it is increasingly being recognized that different anesthesia techniques can positively influence oncological outcomes and have the potential for disease modification. Pain is another factor in cancer patients that needs particular attention because at times it is more distressing than the primary disease itself. Considering an increasing number of cancer patients with its vast clinical and financial implications, more cancer hospitals need to be established all over the world. At the same time, we also need dedicated professionals with skill, knowledge, and expertise in managing cancer patients not only in the perioperative period but also to take care of cancer pain and related issues in people living with cancer, survivors, and their families.

1.3 Onco-Anesthesiology as a Separate Specialty: Present Scenario

At an international level, centers in the USA, UK, Canada, and Europe are running structured training programs in Onco-Anesthesiology and cancer pain management for the past few years. There is a special interest group of anesthesiologists in this field, which holds annual conferences, to implement strategies to build an effective team in health care and develop quality in perioperative practices. In developing countries like India, the center like Tata Memorial Hospital is providing a 2-year fellowship in Onco-Anesthesia and Pain. However, considering an enormous load of cancer patients and their specialized needs, the subspecialty of Onco-Anesthesiology is the need of the time. Recently a proposal to start Diplomate National Board in onco-anaesthesiology has been sent to National Board of Examinations, India.

1.4 At All India Institute of Medical Sciences (AIIMS)

Dr. BRA IRCH AIIMS, New Delhi, as it is a cancer hospital, this need was felt very early due to the realization of the fact that holistic management of cancer patients is quite different from that of others. Being the leader in the field of academics, research, and patient care and also due to the increasing burden of cancer patients, a super specialty course in "DM Onco-Anaesthesia" was introduced at Dr. BRA IRCH AIIMS with the *goals and objectives* to provide advanced training in the field of anesthesia, pain management, and palliative care for cancer patients of different age groups. Besides these goals, other *objectives* to enumerate are as follows:

1. To provide holistic perioperative care to cancer patients by providing relief from pain and other troublesome physical symptoms in preoperative, intraoperative, and postoperative periods

2. To improve knowledge of contemporary advances and developments in medical sciences in various areas related to the discipline of cancer management
3. To recognize the health needs and accordingly comprehensive management plan to improve the quality of life of cancer patients
4. To acquire skills required for effective communication with cancer patients and their families and the community
5. To learn skills for educating and training medical and paramedical professionals and orient trainee physicians to the principles of research methodology that should be applied in cancer patients
6. To acquire competencies about the specialty and its subareas that are required to practice in the community at all levels to improvise health system

1.5 Future Prospects

Onco-Anesthesiologist will be in high demand in the coming decades as there is a transition in the disease burden worldwide, with a significant number of cancer patients being added. This bunch of trained anesthesiologists in addition to providing anesthesia for oncosurgeries will also provide adequate pain relief in the perioperative period. These specialists will cater to the health care needs of a vast number of cancer patients.

Major cancer centers and teaching institutions in the country are running postgraduate degrees in anesthesiology, but specialized training with specific needs for cancer patients is lacking at many places. Thus, this course will be able to build up a pool of specialists to fill these gaps.

The specialist training will open new avenues for the trainees in the academic posts in medical colleges, institutions with multispecialty facilities, and at cancer centers.

1.6 Summary

The treatment of cancer patients is an amalgam of both curative and palliative modalities. At BRA IRCH AIIMS, New Delhi, the different specialties—Surgical, Medical, Radiation Oncology, and the Department of Onco-Anesthesia, Pain, and Palliative Medicine—work in complete collaboration to provide complete care to the patient.

The Department of Onco-Anesthesia, Pain, and Palliative Medicine integrates Anesthesiology with Pain management and Palliative care and is active in providing world-class services through its excellent infrastructure, hard-working doctors, and good technical support. Being the premier health care and research institute of the South Asian region, it is our responsibility to generate such professionals who could bring up the level of care in cancer patients. Furthermore, no specific, concise book dealing with the subject of Onco-Anesthesia has been written before. This book is a collection of writings from the great stalwarts in this field, which will help budding anesthesiologists to gain knowledge regarding specific issues related to cancer patients and their appropriate management.

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Epidemiology of Cancer

2

S. V. S. Deo, S. Manoj Gowda,
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2.1 Introduction

Cancer is climbing the ladder to become the leading cause of death across the globe. To add to this, the overall incidence is increasing due to the control of communicable diseases, an increase in life expectancy, population explosion, and adoption of lifestyles known to increase cancer risk. Low- and middle-income countries (LMIC) are facing a peculiar problem due to economic transition, cultural shifts, and increased lifestyle risk factors. This increasing cancer burden in LMIC can have profound economic and social consequences.

Epidemiologic principles and methods are applied in cancer studies to do systematic research on these cancer trends. Application of these epidemiological principles in cancer dates back to the eighteenth century, when Bernardino Ramazzini, an Italian doctor, reported a relationship between lifestyle and cancer risk. In his book entitled De MorbisArtificum (1713), he suggested nuns had the absence of cervical cancer and a relatively high incidence of carcinoma breast. He hypothesized that this may be due to the celibate lifestyle followed by nuns. This observation had a breakthrough in understanding the importance of hormones and sexually transmitted infections toward cancer risk [1]. Later in 1775, Percival Pott from London reported that soot collecting in skin folds of the scrotum of chimney sweepers caused scrotal cancer. Pott was the first to attribute a preventable cause of cancer. These two observations laid the foundation for cancer epidemiology [1].

2.2 Definition of Cancer Epidemiology

WHO defines Epidemiology as "The study of the distribution, pattern and determinants of a disease or health-related events in a defined population and application of this study results for the control and prevention of the diseases [2]." "Cancer epidemiology" is a branch of epidemiology that studies the distribution, determinants and frequency of malignant disease in a specific population [1].

The epidemiology branch is different from clinical medicine in various aspects (Table 2.1). Knowing this difference is of paramount importance to do epidemiological studies.

The basic denominators in the field of cancer epidemiology are the concepts of incidence, prevalence, and mortality rates. Incidence and prevalence measure the burden of disease, whereas mortality is an index of the severity and fatality of the disease. The brief description of these terms includes the following:

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Table 2.1 Key differences between clinical medicine and epidemiological study

Parameter	Clinical medicine	Epidemiological study
Unit of concern	Patient only	Population from which the patient has come.
Primary interest	Diagnosis and treatment of the individual patient	Distribution of disease in the population and strategies to decrease the incidence (e.g., screening and immunization)
Primary questions	What is wrong with this patient? What treatment is appropriate?	What is the leading cause of death or disability in a specified population? What can be done to reduce them?

1. Incidence: It is defined as the number of new cases of disease or health conditions that develop in the population at risk during a specific period.
2. Prevalence: Point prevalence is the total number of individuals who have a disease or health condition (both old and new) in a population at a single point in time. It is referred to as point prevalence because it refers to a specific point in time. Prevalence and point prevalence are often used interchangeably.
3. Mortality Rate: Number of cancer deaths observed or expected per year in a population of a specified size.
4. Mortality-to-Incidence Ratio (MIR): MIR is used to measure and compare treatment outcomes or inequalities in cancer outcomes among various countries. Since the incidence and mortality data of most countries are available, we can calculate the MIR by dividing the mortality rate by the incidence rate, for each cancer in a selected population.

2.3 Role of Cancer Epidemiology in Healthcare Improvement

Cancer epidemiology remains an integral part of various health-related policies and programs. The goal of epidemiological studies is as follows:

1. Disease Burden Measurement: By calculating the incidence and prevalence of a disease, epidemiological studies play a major role in identifying the disease burden in a specific population.
2. Global Trends: Cancer registries provide an overview of trends of cancer in various parts of the globe. These studies highlight the difference in incidence, survival rates of cancer, equity, and affordability of cancer treatment between and within the high-income and low-income countries.
3. Policy-Making and Planning in the Health Sector: Epidemiological studies will define the current trends in cancer incidence and mortality. This helps the policy-makers to plan and allocate resources to improve the overall health status of the country.
4. Preventive Strategies: Knowledge provided by epidemiological studies helps in formulating preventive strategies in the community aiming at a healthy population.
5. Research: Epidemiological studies describe and monitor the distribution of cancer in the population by characteristics related to time, place, and person. These factors help to generate hypotheses and initiate research.

2.4 Molecular Epidemiology

Molecular epidemiology (ME) is a branch of epidemiology where we apply molecular biology into epidemiological studies. It involves multidisciplinary research that is based on epidemiology, biostatistics, and cellular basic sciences like biochemistry, cell biology, molecular biology, genetics, analytical chemistry, toxicology, pharmacology, and laboratory medicine. In conventional epidemiology, the focus is on either exposure or outcome, whereas in molecular epidemiology, we study the changes occurring at the molecular level in response to carcinogens or risk factors.

2.5 Sources of Cancer Data

The backbone of any cancer epidemiologic data is a cancer registry. A cancer registry is an organization that collects the data, stores the data for

future use, analyzes, interprets the data, and reports the data from time to time.

The cancer registries are broadly classified as:

1. Hospital-based cancer registry
2. Population-based cancer registry

Hospital-based cancer registries record the information on the cancer patients seen in that particular hospital. They mainly aim at creating an easily accessible database on the cancer patients, their details, their clinical management, and its result. These data are mainly used for the hospital's internal administrative purpose and internal review of the professionals. The main disadvantage of these registries is that they will not allow us to find the exact incidence of cancer in a defined population, as these registries will not have a clearly defined catchment population [3].

Population-based cancer registries record information on cancer incidence in a well-defined population. This population is defined based on a specified geographic area. This registry aims to produce statistics on cancer incidence and its impact on a specified population. These registries emphasize more public health and epidemiology [3].

Various registries are being maintained around the globe. Some of the commonest sources of cancer epidemiology include:

- Cancer Incidence in Five Continents
- GLOBOCAN (2012)
- IARC (CANCER Mondial)
- National Cancer Data Base
- SEER database: United States Cancer Surveillance, Epidemiology, and End Results
- WHO Cancer Mortality Data Bank
- American Cancer Society Facts and Figures
- Cancer Statistics in Japan
- EUROCARE: European Cancer Survival
- SurvCan: Cancer Survival in Africa, Asia, the Caribbean, and Central America
- U.S. Cancer Statistics (CDC).
- NORDCAN: Nordic Cancer Registry Data.
- ICMR NCRP: National Cancer Registry Programme of India.

2.6 Cancer Statistics

1. Overall Cancer Burden: According to GLOBOCAN 2018, the population of the world is 763.28 crores in 2018. Among them, 1.8 crores (18 million) of new cancer cases, 95 lakhs (9.5 million) of cancer-related deaths, and 4.3 crores (43 million) of people living with cancer (within 5 years of diagnosis) are recorded from various registries in 2018 [4]. Figures 2.1 and 2.2 show the estimated inci-

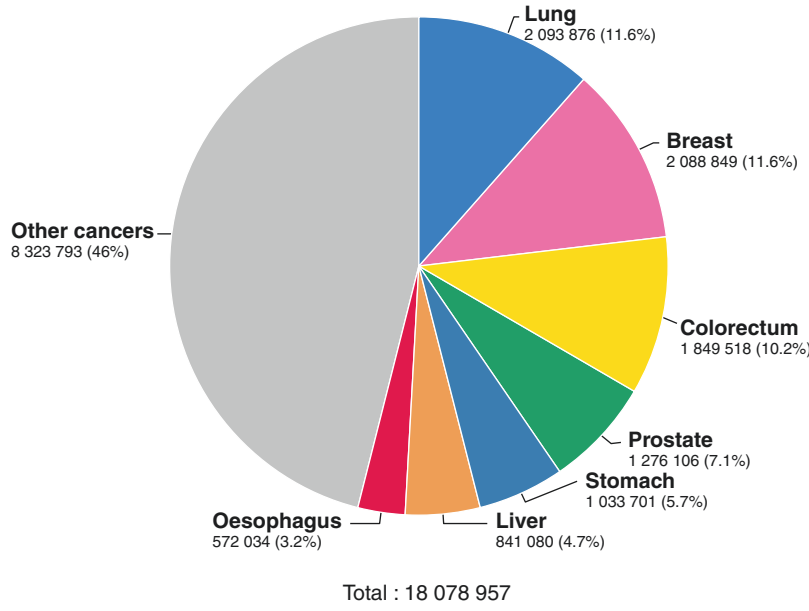

Fig. 2.1 Estimated number of new cancer cases in 2018, worldwide, all cancers, both sex, and all ages

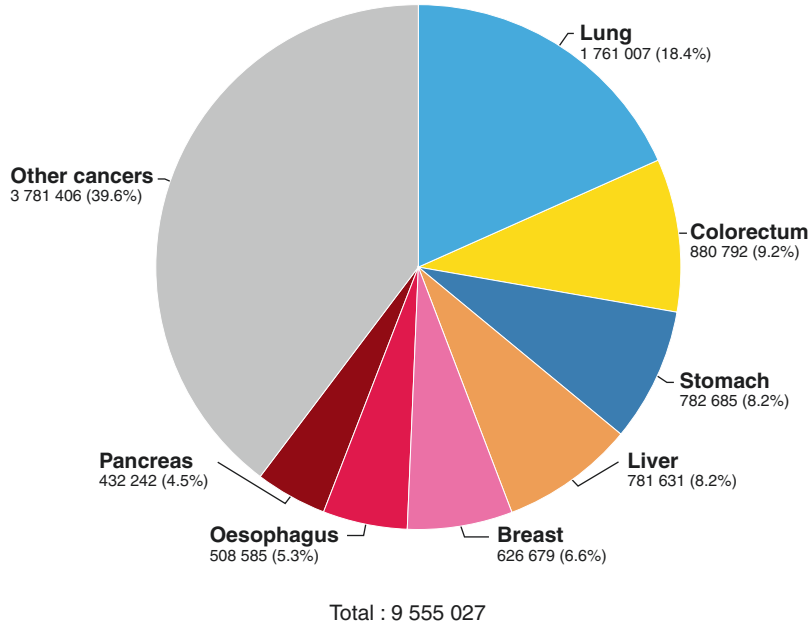

Fig. 2.2 Estimated number of deaths in 2018, worldwide, all cancers, both sex, and all ages

Table 2.2 The summary of incidence, prevalence, and mortality data recorded in 2018 by GLOBOCAN

	Males	Females	Both sex
Population	3,850,719,284	3,782,099,828	7,632,819,272
Number of new cancer cases	9,456,418	8,622,539	18,078,957
Age-standardized incidence rate (World)	218.6	182.6	197.9
Risk of developing cancer before the age of 75 years (%)	22.4	18.3	20.2
Number of cancer deaths	5,385,640	4,169,387	9,555,027
Age-standardized mortality rate (World)	122.7	83.1	101.1
Risk of dying from cancer before the age of 75 years (%)	12.7	8.7	10.6
5-year prevalent cases	21,014,830	22,826,472	43,841,302
Top 5 most frequent cancers excluding nonmelanoma skin cancer	Lung	Breast	Lung
(ranked by cases)	Prostate	Colorectum	Breast
	Colorectum	Lung	Colorectum
	Stomach	Cervix uteri	Prostate
	Liver	Thyroid	Stomach

dence and mortality of different cancers worldwide in 2018. Table 2.2 shows the summary of incidence, prevalence, and mortality data recorded in 2018 by GLOBOCAN.

2. Sex Difference: In 2018, worldwide lung cancer is the most common cancer among men followed by prostate and colorectal cancer, whereas in women, breast cancer followed by colorectal and lung cancer was common. The most common cause of cancer-related mortality was due to lung cancer followed by the liver and stomach in men. Whereas in women, the most common cause of cancer-related mortality is due to breast followed by lung and colorectal cancers [4] (Figs. 2.3 and 2.4).
3. More Developed Versus Less Developed Regions:

   The geographical distribution of cancers varies from region to region. Figure 2.5 shows the epidemiologic trends of cancer in various economic regions. The epidemiologic trend of cancers in low-income countries (LIC) and

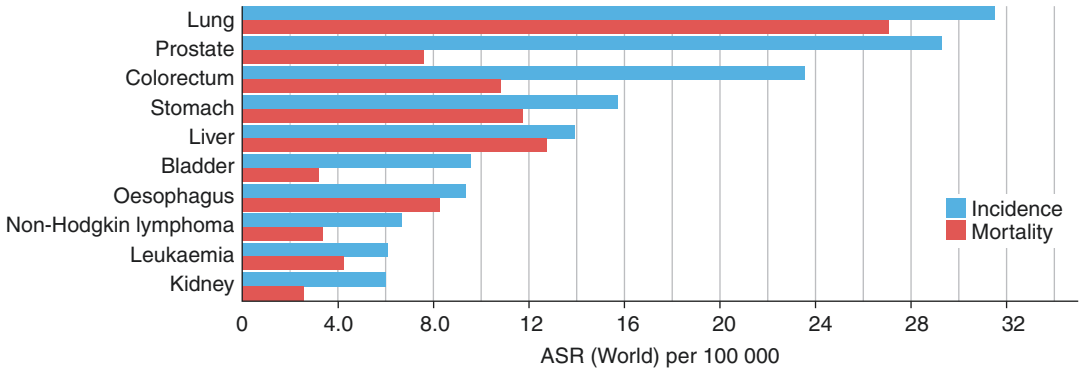

Fig. 2.3 Estimated age-standardized incidence and mortality rates in 2018 among males worldwide

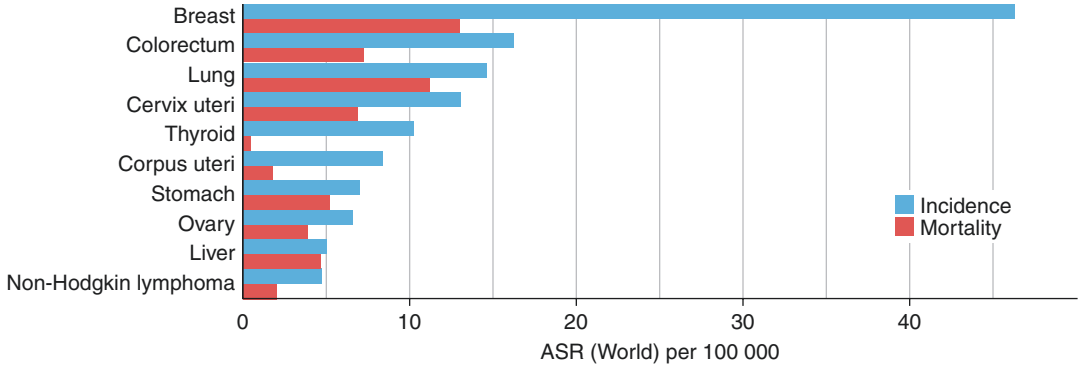

Fig. 2.4 Estimated age-standardized incidence and mortality rates in 2018 among females worldwide

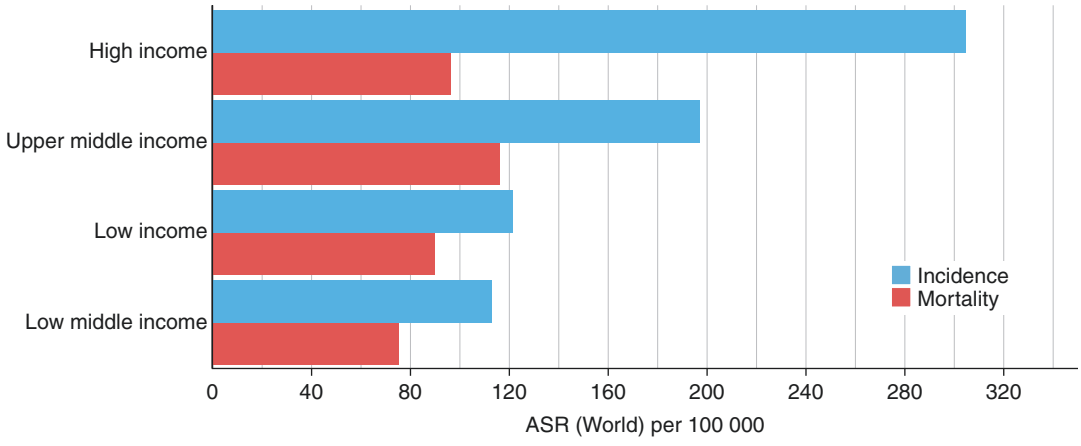

Fig. 2.5 Estimated age-standardized incidence and mortality rates in 2018, all cancers, both sex, and all ages among various income-level countries

low-middle-income countries (LMIC) is of great concern. Despite a lower incidence of cancer in LIC and LMICs compared with high-income countries, total cancer-related mortality is significantly higher in LMIC. This is due to the poor health infrastructure and lack of awareness among the population living in these regions.

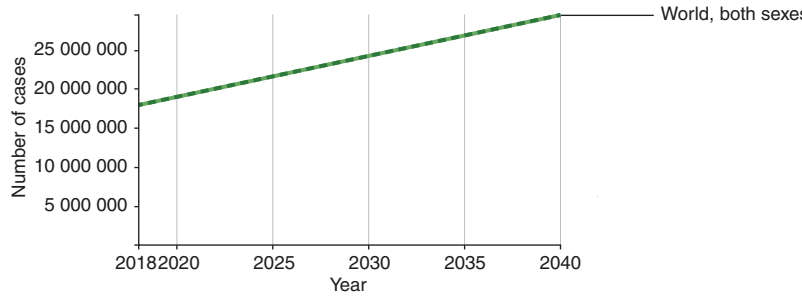

Fig. 2.6 Estimated number of incident cases from 2018 to 2040, all cancers, both sex, and all ages

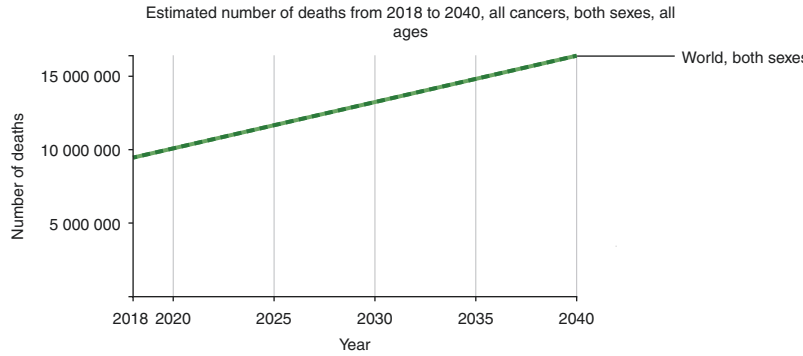

Fig. 2.7 Estimated number of deaths from 2018 to 2040, all cancers, both sex, and all ages

4. Future Predictions:

   By 2040, the incidence of cancer is expected to increase by 63.4%: from 1.8 crores (18 million) in 2018 to 2.9 crores (29 million) in 2040. Similarly, the mortality rate is expected to increase by 71.5%: from 0.9 crores (9 million) in 2018 to 1.6 crores (16 million) by 2040 (Figs. 2.6 and 2.7) [4].

2.7 Conclusion

Epidemiological studies play a crucial role in connecting various points in the timeline of the health status of the whole world. They connect the known past that was already studied epidemiologically with the uncertain present, which we are still studying and plan to make the unknown future better with the available resources. The data provided by these epidemiological studies are crucial for the healthcare setup of various countries to plan for the future treatment and control of cancer.

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Anesthesia and Cancer Recurrence

3

Umesh Goneppanavar and Jasvinder Kaur

3.1 Introduction

Cancer is emerging as one of the major contributors to death worldwide [1–3]. The management of solid tumors is usually surgical resection. The remnant cancer cells following surgical resection may be subjected to chemotherapy and/or radiotherapy. The perioperative period involves preoperative assessment, preparation, counseling followed by surgery under anesthesia, and then a prolonged postoperative period that includes recovery and follow-ups. The perioperative period is influenced by several factors such as the anxiety and stress related to the presence of cancer; need for surgery with or without chemotherapy and/or radiotherapy; pain, medications, blood transfusions, prolonged duration of surgery with possible hypothermia; fluid and blood requirements, anesthesia and related medications, immunomodulatory medicines, etc. This chapter explores the role played by these factors in cancer. These factors may favor cancer cells, either by adversely impacting the host's immune system or by directly enhancing the invasiveness, neovascularization, and proliferative ability of cancer cells. Though abundant literature is available regarding their effect on cancer cells, incisive evidence is lacking in most areas. Often the outcomes observed in animal and in vitro studies are contradicted by human studies, or evidence collected from retrospective or prospective observational studies on humans is contradicted by properly conducted randomized controlled trials (RCTs). This is because most of the retrospective and prospective observational studies on humans and animal studies suffer from too many confounders. Properly conducted RCTs on humans are the need of the hour to establish with clarity the role of each of these factors in cancer progression. Outcomes from animal studies might be more reliable with the use of genetically engineered models. This chapter explores the influence of various perioperative factors on cancer cells and the host's immune responses. Understanding cancer cell biology and the behavior of the host immune system in response to cancer cells is the basic foundation for exploring the role of individual factors starting from surgery to the postoperative period.

3.2 Cancer Biology

Cancer is nothing but the unregulated growth of a specific cell type in the body. The fate of cancer cells in the body at and after surgery is described in three phases: (a) elimination phase where the host's immune system recognizes these cells as nonself and destroys them, (b) equilibrium phase where the host's immune system continues to

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keep a check on active cancer cells, however, some cancer cells may not be detected by the immunosurveillance while continuing to remain in a state of dormancy, and (c) escape phase where these dormant cancer cells proliferate when a favorable environment is created [4]. In the constant struggle between cancer cells and the host immune system, the factors that determine the outcome are the inherent properties of cancer cells (aggressiveness) and the ability of the body to contain them (resilience) [5]. Cancer cell reactivation from dormancy depends upon the ability to neovascularize and escape the host's immunosurveillance, both of which are controlled by the neuroendocrine dynamics of the host's hypothalamo-pituitary-adrenal (HPA) axis [2, 6, 7]. Stress and the resultant elevation in the catecholamine levels alter the neuroendocrine system by their interaction with the β_1- and β_2-adrenergic receptors expressed by the cancer cells. This favors cancer cells by upregulation of the matrix metalloproteinases (MMPs) as well as activation of STAT-3 (signal transducer and activator of transcription 3) which contributes to enhanced survival capacity and proliferation ability of cancer cells [8–10], and increased production of vascular endothelial growth factor (VEGF) with enhanced neovascularization and migration ability [11–13].

The body's initial response to contain these cells is through cell-mediated immunity (CMI). CMI elicits both innate (nonspecific) and adaptive (antigen-specific) immune mechanisms in response to cancer cells which work in tandem to identify and eliminate the cancer cells from the body. The natural killer cells (NK cells), cytotoxic T cells (CTC)—the CD4+ T helper 1 cytokine (CD4+ Th1), and CD8+ cytotoxic T lymphocytes (CD8+ CTLs), mononuclear and dendritic cells are the most commonly involved cells in CMI responses [1–3]. The NK cells are the most efficient of these and are the most critical defense against invading tumor cells. Their cytotoxic effects are potentiated by the help of cytokines, namely interleukins (IL-) 2, 4, 10, and 12, interferons α, β, and γ, and tumor necrosis factor-α (TNF-α). Only if the tumor cells survive these host responses, they enter a state of dormancy [1–3]. Neovascularization depends upon the release of proinflammatory mediators such as VEGF, transforming growth factor-β (TGF-β), and prostaglandin E_2 (PGE_2) into circulation. When the environment is favorable for neovascularization, the cancer cells enter the last phase, that is, escape phase where they end up causing a recurrence. Newly established vascular channels supply the nutrients essential for cancer cell proliferation with a resultant increase in the tumor size. This contributes to the infiltration of neighboring tissues and subsequent spread of cancer cells to other body parts through the blood vessels and lymphatics of these tissues. The cancer cells repeat the whole cycle at the new host site, thus leading to metastatic spread and development of secondary tumor sites [14–16]. Some host factors too can aid in cancer cell spread such as T helper type 2 (Th2) cells that inhibit NK cell, Th1, and CTL activity, interleukins (IL-1β, -6, and -8), cyclooxygenase (COX), and PGE_2 [17–19]. The cancer cells themselves also play a vital role in recruiting regulatory T cells, myeloid-derived suppressor cells, tumor-associated macrophages that orchestrate cancer lymphangiogenesis and growth, etc. [20]. The host immune responses can be either anticancer or pro-cancer depending upon the influences exerted by various factors. Overall, the Th1:Th2 determines the state of the host immune system. When Th1 is abundant to Th2, the environment is favorable to anticancer effects, while the reversal of this ratio is conducive to cancer [21].

3.3 Effect of Surgery on Cancer

Surgery itself abets in spreading cancer through various means. Firstly, it may adversely alter the immunological responses of the host body [4], inflammatory responses at the surgical site, and neuroendocrine response of the body [22] to aid in the survival and proliferation of cancer cells. These responses suppress the NK cell activity, reduce the T lymphocyte proliferation and cytokine secretion along with decreasing the concentrations of tumor-related antiangiogenic factors such as endostatin and angiostatin which are

responsible for suppressing neovascularization [18, 23–26]. This immunosuppressive effect of the surgery may last for several days in the postoperative period and is directly proportional to the quantity of tissue destruction during surgery [4, 14, 27, 28]. Institution of anti-inflammatory measures has shown promising results in limiting cancer's growth potential (ketorolac and diclofenac in breast cancer and long-term aspirin use in colorectal cancers) [29–31]. Secondly, however extensive and well performed the surgical dissection may be, it cannot clear all the cancer cells. Some cancer cells will be left in the host known as the microscopic minimal residual disease (MRD) [15]. The survival and proliferation of these remnant cells depend largely upon the response of the host's immune system along with factors that promote molecular changes in the cancer cells to alter their behavioral pattern so that they may proliferate again by establishing neovascularization [1–3]. Thirdly, during the process of surgical resection, inadvertently some cancer cells will be released into both blood and lymphatic circulation [3]. Though the CMI should take care of these cells within the next 24 h, suppressed immune responses in the perioperative period might not allow efficient elimination of these cells. The duration between the existence of the MRD and institution of postoperative neoadjuvant chemo-/radiotherapy is crucial in determining the metastatic ability of MRD [14–16]. Finally, MMPs that are responsible for increasing the motility and invasiveness of cancer cells are released in abundance during surgical stimulation and therefore, the surgery itself promotes the invasiveness of the MRD [14].

3.4 Effects of Anesthetic Techniques and Drugs on Cancer

Anesthesia is a necessity for patients subjected to tumor resection surgery. While superficial tumors can be excised with some local anesthetic (LA) infiltration or nerve block, most other tumor resection surgeries require either general anesthesia (GA) or regional anesthesia (RA), or a combination of both. Considering that the effects of surgery on cancer are inevitable, the onus would then be on attempting to control other factors, i.e., limiting or evading the factors promoting cancer growth and instituting measures that help suppress the cancer growth. Therefore, the role of anesthesiologists as perioperative physicians is of paramount importance as he/she will be responsible for maximal patient care during the perioperative period. The anesthesiologist may actively initiate measures to negate the prometastatic effects of various perioperative factors and institute measures to promote anticancer defenses in the host.

3.5 General Factors

COX-2 Inhibitors The inflammatory nature of surgery contributes to the abundant release of cyclooxygenase [19]. Chronic use of morphine results in higher expression of COX-2 in cancer cells which in turn contributes to the pro-cancer environment [32]. Patients with breast, cervical, and lung malignancies having enhanced tumor expression of COX-2 in cancer cells not only had an early recurrence but also reduced survival [33–35]. The tumor-associated macrophages upregulated stromal cyclooxygenases [36]. Cyclooxygenases promote PGE_2 production, resulting in dilatation of lymphatics and consequent cancer spread to adjacent lymph nodes [37]. The use of COX-2 inhibitors has shown reliable suppression of cancer growth and invasiveness in many animal studies [38–40]. PGE_2, which is released abundantly from inflamed tissues, promotes neovascularization, increases the invasiveness of cancer cells, and inhibits protective NK cells and CTC. Therefore, the role of nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors in suppressing cancer metastasis has been widely explored [15, 30, 31]. Cancer pain relief with the short-term and long-term use of NSAIDs for analgesia was associated with tumor regression [41–44]. Both COX-1 inhibitors like the selective cyclooxygenase-1 inhibitor (SC-560) and COX-2 inhibitors like celecoxib decreased cancer cell survival by

inducing G0/G1 phase block in three colon cancer cell lines in an in vivo and in vitro study, though celecoxib was more potent than SC-560. Celecoxib also induced cancer cell apoptosis which was not observed with SC-560 [43]. Intraoperative use of ketorolac, diclofenac, aspirin, and COX-2 inhibitors has shown promising results in breast cancer, malignant melanoma, and colon cancer, though the effects cannot be generalized to all malignancies [30, 31, 44, 45].

β-Adrenergic Blockers and COX-2 Inhibitors In the study on Fischer 344 rats, acute stress was found to stimulate the release of catecholamines from adrenals as well as stimulation of both β_1- and β_2-adrenoceptors with resultant suppression of NK cell activity [46]. The same study also used a MADB106 mammary adenocarcinoma line tumor model. The use of selective β-blocker nadolol attenuated the suppression of NK cell activity while the combined use of both β_1- and β_2-adrenoceptor blockade with atenolol and butoxamine had an additive effect in attenuating the suppressant effects on the NK cell activity exerted by stress [46]. When in vivo bioluminescence imaging of breast cancer was assessed to observe the occurrence of metastasis in an orthotopic mouse model, it was observed that stress-induced neuroendocrine activation led to an almost 30-fold increase in the incidence of metastasis mediated by the activation of β-adrenoceptor signaling. This effect was antagonized effectively by the administration of propranolol. Selective β-blockade is associated with an overall reduction in the metastatic potential of both breast cancer and malignant melanoma [47–49]. The perioperative period is highly stressful, more so for cancer patients, as evidenced by high levels of circulatory catecholamines and cortisol [1–3]. Both catecholamines and prostaglandins have prometastatic effects through a common pathway, i.e., activation of cAMP-PKA (cyclic adenosine 3′,5′-monophosphate-dependent protein kinase) cascade with resultant inhibition of immune cells and similar effects on the HPA axis with the resultant increase in cortisol and adrenaline, both of which suppress CMI. Therefore, combined administration of β-blockers along with COX-2 inhibitors might have a better effect on cancer. The combined administration of propranolol and etodolac during laparotomy in rats reduced lung tumor retention and better preservation of the NK cell function was observed, compared to them being administered alone in similar conditions [50]. Epinephrine and metaproterenol (β-agonist) administration to experimental animal models have shown prometastatic effects such as suppression of CMI by Th2 dominance, reduction in the lymphocyte numbers, and human leukocyte antigen-DR isotype (HLA-DR) antigen expression on both lymphocytes and monocytes [46, 51]. The combined perioperative use of β-blockers and COX-2 inhibitors improved recurrence-free interval and reduced markers of postoperative immunosuppression in animal models [50, 52–59]. Currently, research is ongoing for assessing the effectiveness of preoperative administration of combined treatment with COX-2 inhibitors and β-blockers in patients of breast cancers.

Hypothermia Hypothermia suppresses immunity by stimulating stress response and releasing glucocorticoids. Mild hypothermia contributed to immunosuppression (specifically NK cell activity) in abdominal surgeries in humans. A combination of surgery, GA, and hypothermia contributed to immunosuppression and the prometastatic environment in rats with lung cancer cells [60]. Though animal studies have confirmed that hypothermia (30 °C) results in a prometastatic environment by suppressing the NK cell activity, such association is yet to be established clearly in humans [61].

Blood Transfusion Transfusion-related immunomodulation (TRIM) is suspected to be the main mechanism aiding cancer metastasis. The immunomodulatory effects of blood transfusion (BT) on renal transplants made Gantt suspect and propose that similar downregulatory effects on the host's immune system following BT help cancer growth and recurrence [62]. The mechanisms behind TRIM-mediated pro-cancer effects may be by suppression of the CTL and monocyte activity as well as enhancement of sup-

pressor T-cell activity combined with inhibition of IL-2 production and release of immunosuppressive prostaglandins [63–67]. This was one of the reasons for the controversies surrounding the debate "to or not to use intraoperative cell saver" during cancer surgery. The current evidence does not favor any such association. Initial studies demonstrated that donor leukocyte components promoted cancer growth and that leukocyte depleted allogeneic transfusions do not promote cancer growth [68]. The association between TRIM and cancer recurrence is more reliable with colorectal cancers; however, a similar association with other cancers has not been established [69]. The use of whole blood, blood stored for a prolonged duration, and plasma component transfusions possibly may contribute to the worsening of TRIM and cancer growth. Though initial retrospective and observational studies pointed to the possibility of such an association, a clear-cut causal relation between TRIM and cancer recurrence could not be established through rigorously conducted RCTs [63, 69, 70]. However, intraoperative BT in cancer patients was associated with poorer outcomes, irrespective of the type of blood used (allogeneic, autologous, or leukocyte depleted) [71].

Statins The statins influence cholesterol synthesis through inhibition of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase. Cholesterol is an essential ingredient for cellular proliferation and migration. This enzyme also serves as the rate-limiting step in the mevalonate pathway. Statins' inhibitory effect on HMG CoA reductase results in blocking of the release of downstream products of this pathway as well as the reduction in the cholesterol levels, both of which would contribute to suppression of cancer cell growth and proliferation along with a multitude of cancer-protective effects such as disrupting the cell cycle progression in cancer cells, reduced MMPs, and neovascularization ability, and induction of cancer cell apoptosis [72–75]. Furthermore, statins are also known for their ability to improve the radiosensitization of cancer cells [76, 77]. A large-scale follow-up trial of various cancer patients aged >40 years followed up for 15 years with a median of 2.6 years showed up to 15% reduced cancer-related mortality in patients who used statins regularly until the diagnosis of cancer, compared to those who did not use statins at all [78]. Statins reduced the risk of colorectal cancer by up to 47% in those with long-term use of statins [79]. The use of statins following the diagnosis of colorectal cancer contributed to nearly 29% reduction in cancer-specific mortality [80].

On the contrary, rodent studies demonstrated the carcinogenic effects of statins [81]. The cancer-related mortality was almost three times higher in Japanese with <160 mg/dL cholesterol who received low-dose simvastatin daily for six years when compared to those with normal cholesterol levels or hypercholesterolemia [82]. The incidence of nonmelanoma cancers is on the rise in the USA, despite increased use of low-dose statins for various reasons [83]. Long-term statin use nearly doubled the risk of both ductal and lobular breast cancer [84]. The proponents of the role of statins in promoting cancer believe possible carcinogenic effects of statins and/or adverse impact on host defenses with lowered cholesterol levels to be responsible [85].

Preoperative Immune Optimization Cancer patients are at an increased risk of declining physical activity and effort tolerance during the waiting period for surgery. This may be due to any or combination of the factors such as emotional aspects, chemo-/radiotherapy, comorbidities, organ dysfunction caused by cancer invasion, etc. Identifying and optimizing these aspects in cancer patients may promote effective oxygen and substrate delivery to organs and muscles that can, in turn, have beneficial effects on postoperative recovery and immune function [20].

Exercise A pooled cohort of 12 studies encompassing 1.44 million participants revealed enhanced leisure-time physical activity to be associated with reduced risk of 13 (including lung, kidney, bladder, colon, rectum, breast, myeloma, myeloid leukemia, endometrial, adenocarcinoma of the esophagus, liver, gastric car-

dia, head and neck malignancies) out of 26 different types of cancer patients with a wide variety of cohorts such as obese, overweight, smokers, etc. [86], comparable to past studies [87–90]. With this limited evidence, implementing preoperative exercise regimens may be considered to be beneficial in the overall improvement of the patient and may reduce the risk of cancer or its recurrence in some cases.

Immunonutrition Immunosuppression as a result of stress, surgery, and anesthetic agents is well recognized, though its impact on cancer is not well established. Perioperative immunonutrition can help the host body to improve its defenses against cancer and infection. Antitumor vaccines (immunological checkpoint antagonists and immune agonists) have shown encouraging results where they appear to reestablish the equilibrium between the host's immune status and the cancer cells. Furthering of research and availability of various vaccines for prophylactic as well as therapeutic use against a variety of cancers is an exciting prospect [91–95]. The adoptive cellular therapy concept relies on isolating the lymphocytes from various sources in the host's body, expanding them in vitro, and reinfusing them to the host which may in turn keep the cancer cells under check [96]. The institution of a trimodal preoperative rehabilitation program that involves a combination of preoperative immunonutrition, exercise, and psychological support has shown improved functional recovery in the postoperative period in patients undergoing abdominal, colorectal, and lung cancer surgery [97–99]. A range of psychological interventions has been developed (counseling, role-playing, problem-solving, coping and relaxation techniques, etc.) to alleviate the psychological problems that may arise in the perioperative period [100, 101]. Perioperative immune stimulation with T-cell and dendritic cell boosters such as agonists of toll-like receptor 9 (TLR-9) or toll-like receptor 4 (TLR-4) and their effects on cancer are under investigation, though their effects might be nullified by psychological and surgical stress in the perioperative period [102]. The suggested strategy would be to combine β-blockers and/or COX-2 inhibitors along with immune stimulants. This may have a synergistic effect [1, 103, 104].

The surgical stress suppresses the myeloid-derived suppressor cell production of arginase-1 with resultant depletion of arginine stores which are essential nutrients for the appropriate functioning of the host cell CMI [105]. This altered and impaired CMI response in turn contributes to impaired wound healing and increased risk of infection. Perioperative supplementation with immune-enhancing nutrition, comprising of arginine, omega-3 (ω-3) fatty acids, glutamine, and alanine, has been shown to reverse these effects [106].

Hyperglycemia Infection risk and immunosuppressive effects of hyperglycemia are well established. Hyperglycemia provides energy for cancer cells [107]. This fact is also substantiated by the absence of elevated blood glucose levels in patients entering the cancer remission phase. Chronic hyperglycemia was associated with elevated chronic inflammatory markers (IL-1β, IL-6, and TNF-α); activation of immune response that aids in the progression and development of cancer, and matrix remodeling by working at various regulatory levels such as the messenger RNA (mRNA) and proteins [107]. Type 2 diabetic patients tend to develop cancer more frequently than others [108]. The risk of cancer-related mortality in diabetic patients with cancer of the breast, colorectal and endometrial cancer was 41% higher, compared to normoglycemic [109, 110]. However, a clear causal association has not yet been established between hyperglycemia and risk of metastasis.

3.6 Specific Agents and Techniques Used in Anesthesia and Their Influence on Cancer

The huge variety of malignancies along with a wide range of anesthetic medications has resulted in significant confusion about the effects of anesthetics on malignancy. If one has to establish a

clear association between these two factors, the following elements have to be stringently considered: (a) RCTs of the highest standard having a specific cohort of patients with minimal confounding factors, (b) standardized anesthetic regimen, and (c) long-term follow-up of the patients.

Volatile Anesthetic (VA) Agents The VAs may alter the host's immune system to favor cancer growth by mechanisms such as suppression of CMI (reversible, dose- and time-dependent suppression of NK cell activity), inhibitory effect on interferon-mediated stimulation of NK cell activity, withholding the production of reactive oxygen species thereby suppressing the neutrophil-mediated bactericidal activity, by deranging the T-cell interaction with target cells, inhibition of both recruitment of and phagocytosis by macrophage cells, disrupting the cytotoxic lymphocyte function by promoting mitochondrial membrane disruption and by suppressing the functioning as well as the proliferation of CTLs [1, 3, 4, 20, 21, 42, 111–116]. When neuronal cell line SH-SY5Y and breast cell line MCF-7 cells were subjected to enflurane, isoflurane, desflurane, halothane, sevoflurane, or nitrous oxide in an in vivo study, it was observed that these agents modulated gene expression in these cell lines in a time-dependent and unique manner [117]. Also, VAs directly promote neovascularization of cancer cells by their positive influence on the upregulation of hypoxia-inducible factor-1 (HIF-1) within the cancer cells [114]. Indirect disadvantage of VAs is their inability to suppress the neurohumoral stress response to surgery (this is controlled better with propofol-based anesthesia and very effectively with RA) [111, 118, 119].

(a) Halothane:

Pro-cancer studies—Both halothane and ketamine significantly suppressed the NK cell activity during excision of the Lewis lung carcinoma (3LL) tumor and accelerated the tumor metastasis in mice [120]. Both halothane and isoflurane inhibited interferon-mediated stimulation of NK cytotoxicity in unstimulated NK cells of the splenic mononuclear cell pool [121]. Studies on mice inoculated with tumor cells have shown that a combined effect of the surgery, halothane-based anesthesia, and immunosuppression contributed to increased pulmonary metastasis [122]. Combination of halothane and nitrous oxide accelerated lung tumor progression in mice [123]. Halothane and isoflurane both enhanced melanoma tumor progression in mice [124].

Neutral studies—The effects of halothane, enflurane, and nitrous oxide in clinically relevant concentrations were studied in an in vitro model of erythroleukemia cell line K562. Dose-dependent suppression of NK cell cytotoxicity was observed with each of these agents, though it could not be completely suppressed even at 12 MAC h dosage. The study results demonstrate that at clinically relevant concentrations, none of these agents contribute to reliable pro-cancer effects [125]. Exposure to clinically relevant concentrations of halothane and nitrous oxide did not affect the NK cell activity significantly in patients undergoing benign or malignant breast cancer surgery [126].

Anticancer effects—In an in vitro study, when human colon cancer cell line HT-29 was exposed to various concentrations of halothane for 8–72 h, halothane potentiated the antitumor activity of interferon-γ (IFN-γ) [127]. Significantly greater low molecular weight proteinase inhibitor activity was observed in the lungs of female mice bearing B16-F10 melanoma cells when exposed to halothane in oxygen, which was responsible for the inhibition of tumor cell proliferation [128]. Possible antitumor effects of various anesthetic agents (like halothane, isoflurane, and sevoflurane) in their routine anesthetic doses have been studied in certain cancer models including colon (Caco-2), larynx (HEp-2), pancreas (MIA PaCa-2), poorly differentiated cells from lymph node metastasis of colon carcinoma (SW-620), and normal fibroblasts. Though all three VAs demonstrated cytotoxic effects on tumor cells in a time and cell line dependent

manner, halothane had superior effects compared to isoflurane [129]. Halothane reversibly suppressed the HIF-1 in the human hepatoma derived cell line, Hep3B, and also downstream target gene expressions as a response to hypoxia [130]. In a follow-up study on breast cancer resection patients, population receiving halothane-based anesthesia had higher survival rates compared to ether-based anesthesia [131].

(b) Isoflurane: Isoflurane activated the endoplasmic reticulum membrane inositol 1,4,5-trisphosphate (IP3) receptor by triggering apoptosis and the production of excessive calcium release in chicken B lymphocytes [132]. Perturbation of lymphocyte function-associated antigen-1 activation by isoflurane in clinically relevant concentrations with resultant inhibition of T-cell interactions with target cells and ligand-triggered intracellular signaling may be the mechanism behind the immunomodulatory properties of isoflurane [133]. Exposure to isoflurane for three hours in seven dogs suppressed the cytotoxic activity of peripheral lymphocytes for almost 120 hours [134]. Both halothane and isoflurane inhibited interferon-mediated NK cell induction in mice models [121]. In clinically relevant concentrations, isoflurane promoted the growth and migration of glioblastoma cells when an appropriate incubation period was allowed [135]. When ovarian cancer cells (SK-OV3) were exposed to isoflurane for 2 hours in vitro, isoflurane contributed to a significant increase in insulin-like growth factor-1 (IGF-1) and its receptor IGF-1R expression along with increased cell cycle progression and proliferation in those cancer cells [136]. Isoflurane also contributed to the upregulation of hypoxia-inducible factor-1 α and -2α (HIF-1α and -2α), and intensified the expression of vascular endothelial growth factor A (VEGF-A) when renal cancer cells were exposed to isoflurane for 2 h [137]. Apoptosis was induced in a dose-dependent manner in an in vitro study by both isoflurane and sevoflurane in human T cell lymphocytes [138]. On the contrary, when the effects of isoflurane on apoptosis and its regulation by caveolin-1 were evaluated on human colon cancer cell lines, a brief exposure to isoflurane at 1.2% concentration lead to the development of resistance against apoptosis via caveolin-1 dependent mechanisms [139]. The Th1/Th2 ratio was reversed with isoflurane-based anesthesia with resultant significant suppression of CMI [140]. The serum levels of interleukins-6 and -10 and TNF-α were significantly increased in patients undergoing open cholecystectomy, while total intravenous anesthesia (TIVA) based on propofol and remifentanil demonstrated much lower levels of these markers of inflammation [141].

(c) Sevoflurane: Sevoflurane appears to attenuate the hypoxia-induced elevation in the VEGF levels in tongue squamous carcinoma cells through its DNA methylation effects [142]. Also, sevoflurane appears to have an inhibitory role in the migration and matrix metalloproteinase-2 (MMP-2) activity in glioma cells [143]. Similarly, sevoflurane inhibited glioma cell migration and invasion by promoting the upregulation of microRNA 637 (MIR637) with resultant suppression of Akt1 activity and expression [144]. Sevoflurane also suppressed in vitro platelet activity, thus indirectly suppressing the platelet-induced invasiveness of lung cancer cells [145]. Contrary to this, the following studies demonstrated its harmful effects. Both cell division control protein 42 homolog (Cdc42) and A579 are essential for the clinical benefit of cancer therapy, which was negated by combined therapy with sevoflurane and 6 MV photon (ionizing radiation), as they contributed to the downregulation of Cdc42 overexpression and decrease in the migration speed of A549 cells [146]. At the clinically relevant concentration of 1%, sevoflurane exposure for 6 h contributed to enhanced proliferation of human colon cancer cells via adenosine triphosphate-sensitive potassium [k(ATP)] channels in tumor cells [147]. Desflurane (1,2,2,2-tetrafluoroethyl difluoromethyl ether) appeared to provide a

longer disease-free interval and lowered the overall recurrence rate of ovarian cancer, compared to sevoflurane [148]. In women undergoing laparoscopic pelvic surgery for benign ovarian cyst excision, sevoflurane-based anesthesia improved the neuroendocrine stress response to surgery, compared to isoflurane-based anesthesia [149]. Preconditioning with 2.2% sevoflurane or 6% desflurane of isolated human neutrophils resulted in the downregulation of matrix metalloproteinase 9 (MMP-9) and subsequent migration of cancer cells in vitro, when these were subjected to stimulation with interleukin-8, phorbol myristate acetate (PMA), or chemokine CXC-ligand 1 (CXCL1) [150]. In a study that showed the differential effects of sevoflurane on cancer cells, sevoflurane induced apoptosis in colon cancer cells but failed to do the same with laryngeal cancer cells [151].

(d) Desflurane: There is not much literature on the effects of this agent on cancer cells or cancer surgery.

(e) Nitrous Oxide: It is known to suppress neutrophil chemotaxis and decrease mononuclear cell production [152]. Acceleration in the development of lung and liver metastasis in mice was influenced by nitrous oxide [123]. Coadministration of nitrous oxide (N_2O) for its anticobalamin activity along with antifolates in leukemia patients appears to be emerging as a promising chemotherapeutic regimen [153]. It contributed to significant changes in amino acid metabolism in cancer-bearing patients and the study advocates avoiding N_2O in cancer surgery patients [154]. However, limited data on humans do not attribute any prometastatic effects to N_2O [155].

All the available evidence, though not completely convincing, points to a weak possibility of VAs abetting cancer spread. Intravenous based anesthesia, especially a propofol-based anesthetic regimen, may therefore be used, instead of VA-based anesthesia where possible.

3.7 Intravenous Anesthetic Agents

(a) Thiopentone: 51Cr-labeled YAAC-1 tumor cells from the peritoneal cavities of syngeneic A/JAX white mice were incubated along with immune leukocytes from the peritoneal cavities of allogeneic C57/black mice. In this model, the effects of thiopentone in clinically relevant concentrations were studied and it was observed that the thiopentone inhibited tumor-cell killing in a dose-related manner [156]. The suppressor-cell activity was suspected as one of the mechanisms by which thiopentone may promote tumor growth [157]. Thiopentone contributed to an increase in pulmonary metastasis by suppressing the CMI responses in a murine fibrosarcoma system [158]. Thiopentone also inhibited the proliferation of T lymphocytes [159]. At clinically relevant concentrations, thiopentone, etomidate, and methohexitone, but not propfol, suppressed T-lymphocyte proliferation in an in vitro study on blood samples retrieved from healthy donors [159]. Thiopentone decreased the interferon-γ and interleukin-4 levels without affecting the interleukin-2 levels, which were not observed with propofol. This shows the possible reversal effect of thiopentone on the Th1/Th2 ratio and its adverse immune effects in promoting cancer [160].

(b) Propofol: Propofol exerts anticancer effects by the following mechanisms: suppressive effects on neurohumoral stress response to surgery, inhibition of COX-2, thus decreasing the PGE_2 release (anti-inflammatory effects), negligible β-adrenergic receptor binding, direct suppressant effects on the cancer cells, inhibition of HIF-1, absence of adverse impact on the CMI (positive influence on activation and differentiation of peripheral T-helper cells, and reduced concentration of cytokines such as IL-1, IL-6, and TNF-α), increase in the nitric oxide levels by stimulation of circulating neutrophils,

etc. [1–3, 5, 114, 141, 161–164]. Specifically, propofol is known to improve the host immune responses to fight against cancer by the following mechanisms: (a) promotes CD4+ cells to differentiate into Th1 cells [160, 165], (b) propofol not only enhances the NK cell's antitumor activity in vitro but also improves NK cell's cytotoxic potential [166–168], (c) induces macrophage-mediated apoptosis, stimulates miR-142-3p overexpression in macrophage, and induces differentiation to tumor-associated macrophages [168–170], (d) suppresses both production and activity of MMPs [171, 172], and (e) propofol's organoprotective effects in clinical concentrations are thought to be due to its effects on the heme oxygenase-1 (HO-1), which is also known to play a role in cancers [173]. HO-1 is the rate-limiting enzyme for catalyzing the oxidative degradation of cellular heme. However, the enzyme also has antioxidative and anti-inflammatory functions. Many cancers show increased expression of HO-1, which supports the idea that HO-1 may favor carcinogenesis and proliferation of cancer cells [173]. At clinically relevant concentrations, propofol suppressed the invasiveness of human cancer cells due to its effects on ras homolog gene family member A (RhoA) or extracellular signal-regulated protein kinases 1 and 2 (ERK1 and ERK2) [168, 174].

Propofol has anticancer effects in breast cancer resection patients by inhibiting cellular migration and adhesion through its conjugates (propofol-docosahexaenoate and propofol-eicosapentaenoate) and their effects on inducing apoptosis in malignant cells [162]. Propofol-based TIVA improved the 5-year survival of breast cancer patients post modified radical mastectomy surgery in a retrospective study [175]. Propofol reversibly inhibited the HIF-1α activity and the gene expression mediated by this, which has anticancer effects [176]. Propofol inhibited micro RNA (miR-21) and reduced slug expression with resultant dose- and time-dependent inhibition of growth and invasion of PANC-1 pancreatic cancer cells while also inducing apoptosis of these cells [177]. Propofol induced apoptosis in cultured human promyelocytic leukemia HL-60 cells also [170]. Propofol suppressed the pulmonary metastasis of intravenously injected tumor cells in a dose-dependent way by downregulating the metastasis-associated protein 1 (MTA1) and Wnt Family Member 1 (Wnt1) expressions in injected tumor cells in rats [178]. Propofol suppressed the invasiveness of hepatocellular carcinoma cells in tumor-bearing mice through microvesicle (MV)-mediated in vivo transfer of miR-142-3p from macrophages to cancer cells. It improved the CTL activity and suppressed the tumor cell growth in mice [164]. When the in vitro effects of intravenous (IV) anesthetics such as propofol, etomidate, and dexmedetomidine were compared on colorectal cancer cell migration, propofol inhibited the migration of these cells while etomidate favored progression of these cells and dexmedetomidine did not have much influence [179]. TIVA based on propofol and remifentanil combination did not contribute to increases in the TNF-α or interleukin-6 and -10 levels in patients undergoing open cholecystectomy, due to its anti-inflammatory effects [141].

Contradictory results were obtained in a few studies. Propofol induced proliferation as well as promoted invasion of human gall bladder cancer cells by activating the NF-E2-related factor 2 (Nrf2), which is abundantly expressed in cancer cells, while at similar concentrations propofol contributed to increased migration of breast cancer cells via activation of gamma-aminobutyric acid (GABA) [180]. Similarly, propofol reversibly activated gamma-aminobutyric acid type A (GABA-A) receptors in MDA-MB-468 breast carcinoma cells, resulting in a sustained elevation in the intracellular calcium levels and facilitation of migration in the studied breast carcinoma cells. These effects were reversed with the administration of the

calcium channel blocker verapamil and the GABA-A antagonist bicuculline [181].

A large-scale retrospective study conducted on more than 7000 participants undergoing various cancer resection surgeries showed >50% 3-year mortality with sevoflurane- or isoflurane-based anesthesia technique compared to the propofol-based TIVA technique, irrespective of the influence of other factors [182]. Serum from patients undergoing propofol-based anesthesia for breast adenocarcinoma surgery showed the suppression of proliferation of negative estrogen receptor compared to VA-based anesthesia [183]. Propofol-based anesthesia seems to protect circulating lymphocytes better than sevoflurane-based anesthesia in patients undergoing laparoscopic radical hysterectomy for cervical cancer [184].

When various cancer surgery outcomes were analyzed in a retrospective study, propofol-based anesthesia had longer overall survival rates compared to sevoflurane-based anesthesia, though this difference was negated after adjustment was made for confounders and effect modifiers [185]. Not much difference was observed about immune status in the perioperative period when they were compared in patients undergoing laparoscopic radical colorectal cancer resection. Propofol had superior inhibitory effects on interleukin-8 secretion and improving the interleukin-10 secretion compared to enflurane or isoflurane [186].

Overall, the present literature is in favor of the anticancer effects of propofol. Where applicable, the use of propofol-based anesthesia can be considered as a safer option for patients undergoing cancer surgery.

(c) Etomidate: There is very limited literature on the possible effects of etomidate on cancer cells. In vivo suppression of macrophage viability in a dose-dependent manner was observed in rats [187]. In patients undergoing lung cancer surgery, etomidate-based TIVA had fewer immune side effects compared to propofol-based intravenous anesthesia [188]. Etomidate is an agonist at peripheral-type benzodiazepine receptors (PBRs) and the GABA receptors. The expression of these receptors is increased in breast cancers. When the MDA-MB-468 cells were incubated with clinically relevant concentrations of propofol, etomidate, and lidocaine, the velocity and migration of these cells were found to increase with both propofol and lidocaine, while etomidate did not have any influence on cancer cell progression [189].

(d) α_2-Agonists: These agonists may promote cancer cell proliferation and limit their apoptosis [190]. Dexmedetomidine had negligible effects on in vitro migration of colorectal cancer cells compared to propofol or etomidate [179]. Dexmedetomidine activated α_2B-adrenoceptor/ERK signaling pathway in a dose-dependent manner contributing to proliferation, migration, and invasion of breast cancer cells in an in vitro study [191]. Activation of α_2-adrenoceptors contributed to breast cancer progression in the absence of direct sympathetic input to the cells [192]. In an in vivo breast cancer model, both α_2-agonists clonidine and dexmedetomidine produced prometastatic effects while the introduction of α_2-blocker rauwolscine reversed these effects reliably, though similar effects were lacking with yohimbine, another α_2-blocker [190].

(e) Ketamine: Ketamine's positive effects on β-receptors are prometastatic and in high doses are known to suppress CMI, and thus may indirectly contribute to prometastatic effects. The NK cell activity was suppressed and the tumor activity was enhanced in rat models with thiopentone, ketamine, and halothane but not with propofol. Ketamine had the maximum effects on tumor retention and metastasis which were almost 2.5 times more than other agents [166]. When rats were exposed to ketamine 10 mg/kg for one hour before surgery, significant suppression of NK cell activity was observed [193]. Ketamine reversibly suppressed the NK cell activity during the excision of Lewis lung carcinoma (3LL) tumor in mice [120]. The opioid-sparing ability and opioid's analgesic poten-

tiating ability of ketamine probably resulted in minimal NK cell suppression in women receiving 0.5 mg/kg ketamine IV for postoperative analgesia after oromaxillofacial surgery [194]. Beneficial effects of ketamine on cancer were observed due to its suppressive in vitro effects on the production of lipopolysaccharide-induced TNF-α, interleukins- 6 and -8, and recombinant human TNF-induced IL-6 and IL-8 production in human whole blood [195], suppression of endotoxin-induced TNF-α production [196], and suppression of lipopolysaccharide-induced TNF-α production in glial cells [197]. In clinically relevant concentrations, ketamine suppressed the inflammatory responses of lipopolysaccharide-treated astrocytes and microglial cells by inhibiting the PGE_2 production mediated by lipopolysaccharides in astrocytes and lipopolysaccharide-stimulated production of TNF-α in astrocytes, microglia, and glial cells [197–200]. Subnarcotic doses of ketamine decreased the water content of tumor cells in vitro (beneficial effects on tumor cells) [201, 202].

Neuromuscular Blockers The nicotinic acetylcholine receptors and acetylcholine, their physiologic agonist, are now demonstrated to be expressed not just in the nervous system but in all mammalian cells and cancer cells also. These receptors are involved in the regulation of the synthesis and release of factors regulating cancer growth and angiogenesis [203]. Atracurium induced astroglial differentiation of glioblastoma stem cells and irreversibly inhibited the clonogenic ability of different glioblastoma stem cell lines. Vecuronium induced astrocytic differentiation. The survival of mice xenotransplanted with glioblastoma stem cells was found to increase considerably when they were pretreated with atracurium ex vivo [203]. Both atracurium and cis-atracurium suppressed the proliferation of two different types of human cells in vitro (hepatoma HepG2 cells and human umbilical vein endothelial cells (HUVECs)), even at very low plasma concentrations [204]. When both normal and cancerous breast cells were treated with increasing doses of different neuromuscular blockers, the number of MCF-10A and MCF-7 cells decreased without affecting the MDA-MB-231 cells with increasing doses of both rocuronium and suxamethonium. However, no changes were observed when the cells were exposed to different concentrations of vecuronium [205].

Unpublished Observations Atracurium but not mivacurium in clinically relevant concentrations suppressed the in vitro human cell proliferation in a concentration-dependent manner, possibly due to the oxidative stress from reactive metabolites [206]. A study sponsored by a Korean University that compares the oncological benefits of deep neuromuscular blockade in obese gastric cancer patients is underway [207].

Opioids and Cancer Recurrence Nearly all patients undergoing extensive surgery for tumor removal require opioids intraoperatively and at least for the first few days postoperatively while many may require opioids on a long-term basis for relief of chronic pain caused by cancer. The stepladder approach for an analgesic prescription for pain relief developed by the World Health Organization in 1986 has legitimized the use of oral and systemic opioids for chronic cancer pain relief. Opioids relieve pain by their antinociceptive mechanisms by acting on the classical G-protein coupled receptors [mu (μ), delta (δ), and kappa (κ)] in the nervous system and endorphin, encephalin, dynorphin, and endomorphin peptides are the endogenous ligands at these receptors [208]. Most of the analgesic effects of opioids in cancer pain relief are mediated by the μ receptors. The role of opioids in the host immune system of the cancer patient and cancer cells is quite controversial. In a wide range of both human and animal cancers arising from all embryological layers (ectoderm, endoderm, and mesoderm), endogenous opioids and their receptors were found to be expressed in considerably high numbers, as detected during radioimmunoassay studies [209]. This evoked considerable interest in identifying the role of opioids in cancer progression. Several epidemiological, animal,

and in vitro studies in a variety of malignancies added fuel to this possibility by concluding the possible role of opioids in cancer progression. Also, reports that avoiding or minimizing opioids by the use of RA reduces the risk of malignancy and spread of cancer cells [210–212] and that opioid antagonists (naloxone and naltrexone) inhibit the growth of chemically stimulated mammary tumors in vivo in animal models [213, 214] have furthered the interest and belief that opioids may play a serious role in cancer metastasis.

Opioids and the Immune System Both forms of immunity, that is, the CMI and the humoral immunity, are suppressed to a variable extent by different opioid types [18, 215]. These effects are mediated by the action of opioids on the classical as well as the nonclassical (the effects of opioids on these receptors are not antagonized by the administration of opioid antagonists) opioid receptors [216].

(a) Morphine: The effect of morphine on immune responses and cancer cellls has been extensively studied. While there is modest evidence on the role of morphine and many other opioids on the suppression of the host's immune system, their role in abetting cancer proliferation is controversial. Animal experiments and in vitro studies have established a possible role of morphine in the progression of cancer cells. Morphine suppresses immunity by inhibiting PGE_2 production mediated by the cyclooxygenase enzyme, by stimulating the nitric oxide (NO) synthesis via mitogen-activated protein kinase stimulation; it inhibits both immature and mature forms of CD4+ and CD8+ type of CTLs; increases TGF-β by chronic morphine use, and causes μ opioid receptor-mediated chemokine-induced suppression of IL-2 and IFN-γ levels, suppression of mast cells and NK cell activity when administered in low doses, stimulation of proinflammatory cytokines along with suppression of the anti-inflammatory cytokines [1, 216, 217]. Morphine also contributes to cancer cell survival and growth by the following mechanisms: neovascularization mediated by the upregulation of VEGF mediated by μ receptor [1, 216], increased expression of neuroepithelial cell transforming gene 1 (NET1) promoting cancer cell migration [218], phosphorylation of epidermal growth factor receptor (EGFR) expression on cancer cells with resultant increased cancer cell proliferation and invasiveness [219], increasing the metastatic potential of cancer cells by triggering the toll-like receptor-4 (TLR4) and activation of Nuclear Factor Kappa B (NF-kB) protein complex in the cells, which is responsible for controlling the transcription of DNA, cytokine production as well as cell survival [1, 216, 220], mast cell activation resulting in cancer cell progression and reduced peritoneal innate immunity by inhibiting mast cell TNF-α release [221, 222].

Contrary to this, morphine activated the CD8+ cell function and promoted anticancer activity in vitro [223] and activation of the cytolytic activity of NK cells in porcine models [224], nonclassical opioid receptor-mediated suppression of pro-inflammatory activity [225], opioid receptor-mediated suppression of hypoxia-inducible factor-1α and angiogenesis in clinically relevant concentrations [226], opioid receptor-mediated inhibition of adhesiveness and invasiveness of colon cancer cells [227], cancer cell inhibition through antagonism of peripheral μ opioid receptors [228], anticancer effects through nonopioid receptor-mediated inhibition of extracellular matrix degradation [216, 229] and protecting the host by suppressing the glucocorticoid-mediated immunosuppressive effect [216, 230, 231].

(b) Other Opioids: Fentanyl depressed NK cell activity in both operated and nonoperated rats much more than clonidine or ketamine [193]; codeine and methadone too suppressed NK cell activity [232]. Buprenorphine has been found to have a neutral effect, stimulatory effects, and inhibitory effects on the cytotoxic effects of NK cells in different studies [232]. Remifentanil appears to have a negligible influence on the immune system

and cancer cells [232]. Alfentanyl, oxycodone, and hydromorphone also appear to have little effects on the immune system. Moreover, there is very scant literature available about their effects [1, 233]. Tramadol, on the other hand, appears to stimulate the NK cell cytolytic effects as well as inhibiting the metastatic potential of lung cancer cells [1, 232, 234].

Limited data from randomized controlled trials make it difficult to rely on the existing evidence. Considering the variety of cancers with varying stages, different opioids administered mostly in combination with multimodal analgesia and other agents either for pain relief or for surgery and several other coexisting factors in the management of patients with cancer render establishing isolated effects of individual opioids on cancer extremely difficult.

3.8 Regional Anesthesia

Reduction in surgical stress response as a means to reduce postoperative tumor recurrence has been a popular area of research. The possibility that LA and RA may reduce surgical stress and postoperative tumor spread was explored and a study demonstrated that spinal anesthesia, when administered with halothane to rats undergoing laparotomy, showed better preservation of the immune response [235]. Spinal anesthesia added to sevoflurane anesthesia in rat laparotomy models resulted in fewer hepatic metastases from inoculated tumor cells as greater preservation of hepatic mononuclear cell activity and attenuation of Th1/Th2 imbalance occurred [119]. Research comparing RA and GA in cancer surgery was spurred when a retrospective study demonstrated that paravertebral block improved 3-year disease-free survival in breast cancer surgery compared to GA alone (94% vs. 77%) [211]. Reduction in the postoperative mortality rate with RA and analgesia was described in a retrospective study of patients with ovarian serous adenocarcinoma who received intraoperative epidural anesthesia (EA) with epidural analgesia postoperatively, as compared to GA with intravenous opioid postoperatively [235]. Similar conclusions regarding improved long-term outcomes when RA or LA was employed were reported in retrospective studies involving malignant melanoma [210], prostate carcinoma [236–238], esophageal cancer patients, and in those undergoing surgery for laryngeal or hypopharyngeal cancer [238, 239].

Not all studies have obtained equally encouraging, or unequivocal results. Given the heterogeneity of the disease itself, it is hardly surprising that very variable results have been obtained across patient cohorts suffering from identical cancers. A retrospective analysis found that although EA appeared to be associated with improved survival, it did not affect the rates of cancer recurrence [240]. On the other hand, improved recurrence-free survival without any influence on "overall" survival was reported in patients undergoing resection of colorectal liver metastases [241]. EA may have context-specific effects dependent on the tumor phenotype, as no relation was found between EA and tumor recurrence in patients younger than 64 years, but, a beneficial effect was observed in older patients [242]. Similarly, the context-specific effect of RA related to the time of provision and location of cancer has been suggested [243, 244]. In a retrospective analysis of patients with colon cancer, EA was shown to convey a survival benefit only in the early postoperative period (1.46 years) in patients without metastases but did not affect the survival of those with metastases [212]. Similarly, the benefit of LA during melanoma excision was evident only in those patients who had intermediate local advancement [245]. It needs to be noted that almost an equal amount of literature evidence refutes any beneficial effect of RA on survival and cancer recurrence following surgery for cancer of the breast [246, 247], cervix [248], esophagus [249], ovaries [250, 251], bladder [252], prostate [253–259], and the gastrointestinal system [242, 260–263]. RA was associated with reduced survival in patients of hepatocellular cancer who underwent radiofrequency ablation [264].

Most studies demonstrating a beneficial effect of RA and LA are limited, in that they are either

retrospective in nature or involve subgroup analyses from previous RCTs, and hence pose difficulty in obtaining clinically meaningful conclusions [18]. Meta-analyses [265–269] and systemic reviews [5, 270–272] based on clinical trials have been equivocal and do not support an association between RA and cancer recurrence, though association with improved survival has been indicated. Improvement in both recurrence-free survival and overall survival was suggested with neuraxial anesthesia, especially in colorectal cancer surgery [273]. A narrative review opined that even though regional anesthetics have not emerged as universally beneficial in cancer surgery, they are good perioperative techniques that should be considered where applicable (based on patient characteristics and the planned surgery), rather than to reduce cancer recurrence [1].

Results of RCTs comparing RA with GA (NIH clinical trial NCT00418457, NCT01588847, NCT01318161) are currently underway (recruiting at the time of writing) [273, 274]. While the results of RCTs are likely to improve our understanding of this issue, the comparability between trial participants and nonparticipants and hence the universal applicability of cancer clinical trial results can be called into question, considering that cancer is an immensely heterogeneous disease [1, 15, 275]. Moreover, it is yet to be unequivocally proven whether the effects on cancer progression associated with regional anesthetics are due to direct antiproliferative effects of LA [276], or due to the reduction of surgical stress response secondary to neural blockade [113, 277, 278] and improved analgesia as compared to opioids, since pain can be a mediator of carcinogenesis, as evidenced in animal experiments [279, 280]. It is equally possible that the beneficial effect attributed to RA is in part secondary to the reduction or complete elimination of VAs [281] and opioids from the anesthetic since factors beyond the selection of anesthetic techniques are also likely to play a role [282].

Intraoperative EA has been shown to attenuate neurohumoral stress response, while only minimally affecting cytokine and immune cell response [278, 283, 284]. Addition of EA to GA for ovarian cancer surgery has been found to preserve NK cell cytotoxicity and Th1 cytokine responses. It has also been shown to decrease reduction in IFNγ levels while preventing an increase in IL-1β and IL-8 [285]. Paravertebral block used with propofol showed reduced serum pro-inflammatory cytokines and MMPs, as compared to sevoflurane and opioid in breast cancer surgery [286]. Systemic administration of lignocaine has also been shown to have a beneficial effect by limiting inflammation [287, 288]and reduction of early apoptosis of lymphocytes, resulting in better preservation of CMI [289]. The neuroendocrine stress response secondary to surgery has been demonstrated to be reduced by EA and this effect is associated with an increase in antitumorigenic cytokines IL-2 and IL-10; preserved NK cell activity, reduced C-reactive protein levels, and fewer circulating regulatory T-cells and Th2 cells [290, 291].

Several other studies have determined that LA has antiproliferative, pro-apoptotic, and anti-inflammatory effects, and also reduces migration and invasiveness of tumor cells [292–294]. The cytotoxic property of LA appears to be related to concentration and lipid solubility [295, 296]. In vitro studies have attempted to explain the possible molecular basis of interaction between LA and cancer cell lines.

Voltage-gated sodium channels (VGSCs) located on neuronal membranes are the targets for LA. These same VGSCs are present on several varieties of tumor cells and appear to be involved in invasion and metastasis. Blockade of tumor VGSCs by LA may be a possible mechanism of their antiproliferative effect [297–302], but nonlocal anesthetic VGSC-blockers have been shown to significantly increase mortality in patients with breast, bowel, and prostate cancer [303]. Demethylation of DNA displayed by lignocaine in breast cancer cells [304] and by procaine in several malignant cell lines [305–307] is also a possible mechanism of antiproliferative activity. Lignocaine has been shown to reduce the activation of EGFR, by inhibiting tyrosine kinase activity in the receptor [308–310]. Both lignocaine and ropivacaine have been shown to induce apoptosis and activate mitogen-activated protein

kinase pathways in nonsmall cell lung carcinoma cells, thus limiting their growth and invasiveness [311]. Work on nonsmall cell lung carcinoma cells [311], lung adenocarcinoma cells [312], breast cancer cells [313], and thyroid cancer cells [314] proposes that activation of the mitogen-activated protein kinase pathway, caspases, and mitochondrial apoptosis pathway can be induced by LA [315]. Demethylation of breast cancer cell DNA in vitro by lignocaine has been noted as a possible route of antitumor activity [304]. Definitive anticancer effect of lignocaine on a hepatocellular carcinoma xenograft model was demonstrated in a study that showed induction of caspase-3, as well as an imbalance between pro-apoptotic (Bax) and antiapoptotic (Bcl 2) proteins to be a likely molecular mechanism [316]. The exact molecular pathway by which a LA may exert its antitumor effect is not yet determined, but in vitro studies have displayed that lignocaine can improve therapeutic effects of anticancer medications like cisplatin [317] and also help some instances of cancer drug resistance [318].

Many in vitro studies have utilized LA concentrations higher than advocated for routine clinical use, but a study described the apoptosis of breast cancer cells at clinically relevant concentrations of lignocaine and bupivacaine [313]. Clinically relevant concentrations of bupivacaine were also shown to reduce cell viability, proliferation, and migration in ovarian and prostate cancer cells [293]. Due to the high concentrations required to display antitumor activity in vitro, it is possible that such an effect attributed to RA in clinical studies is not related to the direct effect of LA on cells [319].

Several cellular messengers and pathways involved in cellular growth and apoptosis are tempting targets for LA action. VEGF stimulates signaling pathways that lead to proliferation and migration of endothelial cells, resulting in angiogenesis. Increase in vascular permeability and recruitment of regulatory T cells can also be induced by VEGF secreted by tumors [320]. However, a prospective randomized study on women undergoing mastectomy for breast cancer showed that despite inhibition of stress response by paravertebral anesthesia and analgesia as compared to GA, there was no effect on the levels of VEGF and PGE_2 [321]. A subsequent study on women receiving propofol with paravertebral anesthesia however, showed reduced levels of VEGF and TGF-β (transforming growth factor), as compared to those receiving GA and opioid [310]. Similar reductions in VEGF, TGF-β, and IL-6 with elevation of IL-10 with the use of propofol-epidural anesthesia was demonstrated during colon surgery [322]. MMPs are endopeptidases that can induce and inhibit apoptosis, promote angiogenesis by degrading extracellular matrix, and release chemokines that attract inflammatory cells [286, 323]. TNF-α, which regulates immune cells, other cytokines, and MMPs, in turn plays a role in angiogenesis [320]. Transforming growth factor β (TGF-β), is a cytokine that can stimulate angiogenesis and in normal cells ends proliferation and induces apoptosis. Its signaling pathway has been found to malfunction in several varieties of cancer, resulting in uncontrolled proliferation of cells [320, 324]. EGFR mutations have been observed in varieties of tumors. They are normally involved in epithelial cell proliferation. Phosphorylation of EGFR by EGFR-binding ligands secreted by tumor cells results in autoactivation with increased cell invasion. Lignocaine has been shown to have an inhibitory effect on these receptors in vitro [325]. Other targets for LA action include Src tyrosine-protein kinase (Src) which is involved in the metastasis of tumors; causes a reduction in cell adhesion, and also has a role in epithelial-to-mesenchymal transformation [312]. Intercellular adhesion molecule-1 (ICAM-1), a cell surface receptor normally involved in leukocyte adhesion, has been implicated in tumor growth and metastasis [312]. Activation of Src and increases in the activity of ICAM-1 are induced by TNF-α as well as inflammation [312]. PGE_2 normally limits the activation of cytotoxic cells and has an important role in phagocyte-mediated immunity. It promotes cancer progression by aiding the inhibition of apoptosis, stimulation of angiogenesis, and invasion [326]. Another pathway of tumor progression is DNA hypermethylation, which results in transcriptional "silencing" of tumor suppressor genes [260, 327]. Most of these factors are concomi-

tantly activated by surgical stress and result in reduced cell-mediated immunity and increased tumor progression noted in the postoperative period [328].

It can be expected that advances in research may simplify and rationalize the choice of the anesthetic technique, the agents employed, and even their dosages to target improved outcomes for specific cancers in the future. The goal, now and always, centers on providing optimal surgical conditions while ensuring safety and comfort of the patient perioperatively.

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Part II

Basics of Onco-Anaesthesiology

4 Anaesthetic Implications of Chemotherapy and Radiotherapy

Seema Mishra

4.1 Introduction

The cancer burden is increasing across the globe and is expected to rise further. It is estimated that the world will need about 45 million cancer surgeries annually by the year 2030 [1, 2]. The cancer management is primarily multidisciplinary and various teams like medical oncologists, radiation oncologists, and surgical oncologists remain an integral part. Surgical intervention is required for both curative and palliative intent. Therefore, the burden of surgical interventions for cancer is also poised to increase significantly in the coming years. Upfront surgical resection is performed soon after diagnosis and offers the best loco-regional control and potential for cure. However in certain patients, based on tumour type, site, and its extent, upfront surgery is not feasible. These cancer patients receive either alone or combination of treatment modalities including systemic chemotherapy, radiation therapy to reduce the tumour bulk before surgery. Disease recurrence after initial therapy may also lead to surgical intervention. Alongside curative surgery, many patients also undergo palliative surgeries for various cancers. Thus, a large proportion of patients who undergo surgery for cancer could have possibly received chemo-radiation before they end up on the operating table.

Levels of cancer care worldwide have significant variations. In the developed world, most of the surgical burden of cancer is upon comprehensive cancer centres and tertiary level hospitals. It is therefore vital for anaesthesiologists working in comprehensive cancer centres and otherwise to have insight into the basics of chemotherapy and radiotherapy, their perioperative implications and management.

4.2 Concerns in the Preoperative Period Due to Cancer Therapy

The preoperative cancer treatment including radiation therapy and/or chemotherapy has an impact on various body system physiology and mandates not only its assessment but also perioperative care accordingly. Various chemotherapeutic regimens are administered based on tumour type, site, and response. These combinations of chemotherapeutic agents induce cell apoptosis by the various mechanism of drug–receptor interaction. However, the toxicity of such chemotherapeutic agents may involve all organ systems. Newer anticancer agents provide targeted therapy and differentially affect the tumour cells. Despite its preferential target on fast-growing cancer cells, still, these agents have

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a toxic effect on various body cells and functions. Radiotherapy is frequently used along with chemotherapy or alone to achieve tumour response. It causes tissue damage and death by the formation of oxygen-free radicals and causes a multitude of changes which have widespread implications on the perioperative course of the patient. The most significant among them are cardiopulmonary toxicity of chemo-radiation and airway changes induced by radiation that can directly influence the delivery of and response to anaesthesia. With the gradual adoption of hyperthermic intraperitoneal chemotherapy (HIPEC) for management of peritoneal surface disease, a new paradigm of chemotherapy and its perioperative effects has emerged that is significant to the anaesthesiologist.

4.3 Basic Principles of Chemotherapy

Cytotoxic chemotherapy targets the various functionality of nucleic acids, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA) leading to the destruction of cells. Most of the contemporary chemotherapy regimens comprise a combination of various cytotoxic drugs in an attempt to increase the 'fractional cell kill'. Combination therapy is designed in a way so that each drug has a different mechanism of activity and works in different parts of the cell cycle. Drugs with similar resistance mechanisms and toxicity profiles are usually not grouped.

The timing of administration of chemotherapeutic agents varies and its usefulness can be achieved at various time points of the cancer trajectory. Based on the course of multidisciplinary treatment, the chemotherapy regime is labelled as:

- Neoadjuvant therapy: The therapy is administered before upfront definitive surgical intervention for the primary tumour, local or distant metastasis, or both. The intent for neoadjuvant therapy is to decrease the tumour bulk at the primary site or metastatic site for feasibility for attempting complete tumour resection. It also aims to prevent extensive or less mutilating surgical intervention like lumpectomy vs mastectomy for breast cancers.
- Adjuvant therapy: The therapy is administered after the surgical removal of the tumour mass and is aimed at managing any micrometastasis and thus preventing cancer recurrence.
- Palliative therapy: The therapy is primarily aimed at improving the quality of life and possible survival and does not assure curability of cancer.

4.4 Chemotherapeutic Agents

The medical management of cancer uses various chemotherapeutic agents and in various combinations. These agents have a different mechanism of action and thus are combined for multipronged action. However, each of these has associated side effects as well.

4.4.1 Anti-tumour Antibiotics

These chemotherapeutic agents, also known as anti-neoplastic antibiotics, are one of the commoners used drugs for cancer management. These interfere with DNA and RNA synthesis for its cytotoxic action and are usually cell-cycle non-specific. These are derived from microbial fermentation. These include anthracyclines, mitoxantrone, actinomycin D, and mitomycin C.

4.4.1.1 Anthracyclines

The anthracyclines group of antitumor antibiotics includes doxorubicin and daunorubicin. These are used for management of solid tumours and haematological malignancies. Newer analogues (epirubicin, the analogue of doxorubicin; idarubicin, the analogue of daunorubicin) of these drugs have improved toxic profile and better antitumour efficacy.

Pharmacology Although these drugs are structurally similar with a similar mechanism of action

and resistance, the drugs have differing clinical activity and toxicity. These drugs have multiple modes of action:

1. Inhibit DNA and RNA synthesis in tumour cells by intercalating in its base pairs and thus stops tumour cell replication.
2. Blocks DNA transcription and replication by inhibiting topoisomerase enzyme that causes relaxation of supercoiled DNA.
3. Damage of DNA, proteins, and cell membranes of tumour cells by iron-mediated free oxygen radicals.
4. DNA damage response, epigenome, and transcriptome are deregulated by induction of histone eviction from chromatin.

Pharmacokinetics and Metabolism These drugs are redistributed to body tissues leading to a rapid fall in plasma concentration after its intravenous administration. It is principally metabolised by reduction and undergoes hepatic elimination. So, dose reduction of these agents is desirable in patients with liver dysfunction.

Uses These are one of the most common chemotherapeutic agents used in clinical practice and usually used as combination therapy with other agents. Doxorubicin and epirubicin are effective for cancer of the lung (small cell), breast, and soft tissue sarcomas. These are also effective in certain haematological cancers and paediatric solid tumours. These drugs may be administered intravenously as bolus or infusion and usually repeated every three weeks. The route of administration for idarubicin is oral. Daunorubicin and idarubicin are effective for acute lymphoblastic or myeloblastic leukaemia and multiple myeloma, non-Hodgkin's lymphomas, breast cancer, respectively.

Toxicity

Cardiotoxicity

Cumulative cardiotoxicity is specific to the anthracycline group of drugs and remains one of the important concerns for perioperative management. These drugs lead to toxic oxygen-free radicals (ROS) formation which in turn damages myocytes [3, 4]. The drug-induced oxidative stress causes cellular membrane lipid peroxidation which subsequently damages cells by vacuolisation. The damaged myocytes are replaced with fibrous tissue. Doxorubicin has been found to bind topoisomerase II and DNA to form a complex, which triggers cell death [5].

The overall reported incidence of anthracycline related cardiotoxicity is 9% [6–8].

Risk factors:

Anthracycline-induced cardiotoxicity is seen in certain clinical scenarios. These include:

- Age > 65 years or < 4 years old,
- Female gender,
- Preexisting cardiovascular disorders (e.g. left ventricular ejection fraction [LVEF] ≤50%),
- Hypertension, smoking, hyperlipidaemia, obesity, diabetes,
- High cumulative anthracycline exposure,
- Radiation therapy involving the chest, and
- Use of trastuzumab.

Clinical manifestations:

The anthracycline related cardiotoxicity includes cardiac failure, left ventricular dysfunction, reduced left ventricular ejection fraction (LVEF), etc. [6]. In elucidating symptoms, it should be kept in mind that anthracycline-induced cardiac injury may be present with maintained left ventricular ejection fraction [7]. So sole criteria of a normal LVEF should not be considered as the absence of cardiotoxicity during preoperative assessment. Other limitations of LVEF are that it is affected by transient conditions such as preload, afterload, and adrenergic state and is subject to variation. Other earlier and more sensitive markers may be helpful for detection of cardiotoxicity beyond LVEF include serum biomarker levels, myocardial strain using echocardiography, and detection of myocardial fibrosis using cardiac magnetic resonance.

In a large study of 2625 patients [8], cardiotoxicity was defined as either absolute drop of LVEF below 50% or reduction of >10% from the baseline. The onset time was 3.5 months from the end of chemotherapy and 98% cases were

detected within a year. The time course of anthracycline-induced cardiotoxicity is traditionally and arbitrarily defined as:

- Early or acute: Less than 1% incidence. Manifests largely as the acute reversible decline in contractility immediately after infusion.
- Early progressive or subacute: Features manifest within a year of exposure.
- Late progressive or chronic: Features manifest years after exposure.

The other manifestations include electrocardiographic abnormalities, arrhythmias (supraventricular or ventricular), atrioventricular block, and a pericarditis-myocarditis syndrome. Late features include cardiac failure-related symptoms like dyspnoea, fatigue, oedema, and orthopnoea. Depressed LVEF and/or dilated ventricles may be detected with or without heart failure.

Baseline Assessment, Monitoring, and Diagnosis

- A detailed clinical history, cardiac examination, an electrocardiogram are performed in all individuals before initiating anthracycline-based chemotherapy. A repeat clinical history and examination is done at least every three months by a clinician during the treatment course.
- Baseline cardiac imaging (usually by echocardiogram) to assess LVEF is performed before the initiation of anthracycline therapy. This baseline assessment is to identify preexisting cardiac abnormalities and thus to plan an alternative drug.
- 2D echocardiography is the recommended initial test, with 3D echocardiography preferred if available.
- The other options of assessing LVEF like radionuclide ventriculography (RVG, also known as multiple gated cardiac blood pool imaging [MUGA]) may also be considered, if available. Advantages include a high degree of reproducibility, although the test entails radiation exposure.
- A cardiac magnetic resonance scan with quantification of LVEF is suggested in cases of inadequate echocardiographic results.
- Cardiac troponins have shown some utility in the diagnosis of anthracycline-induced cardiomyopathy but are not routinely used.
- Brain natriuretic peptide has failed to show any benefit in the diagnosis of the same.

Management: A stepwise approach is desirable along with assessment for anthracycline-induced cardiotoxicity (Fig. 4.1).

Other toxicities of anthracycline chemotherapy include mucositis, myelosuppression, hair loss, etc.

4.4.1.2 Bleomycin

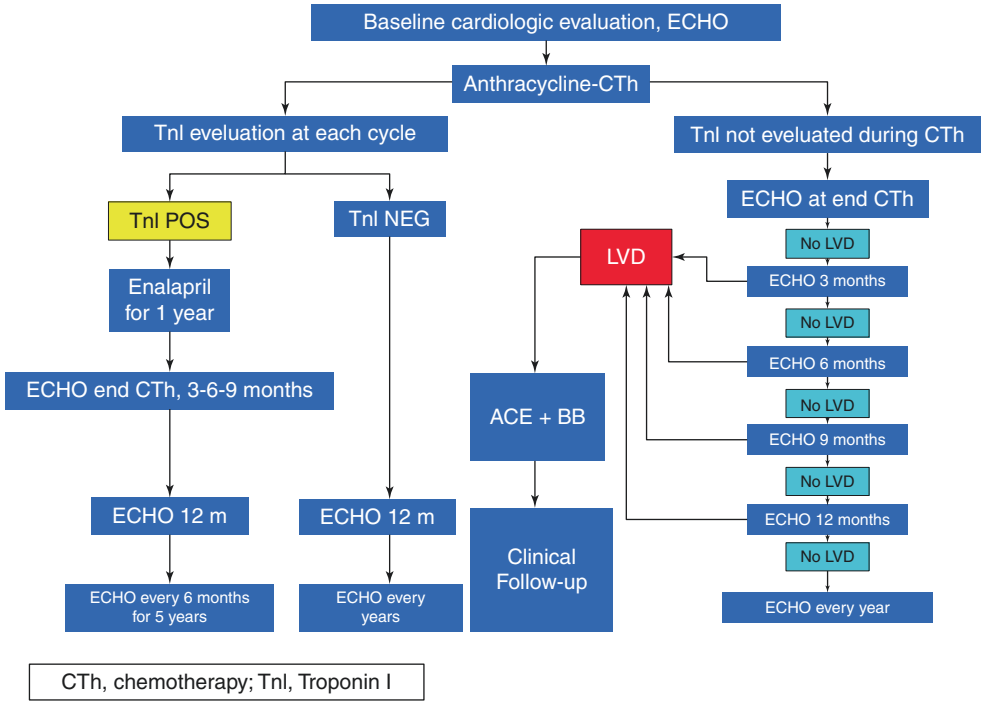
It is a non-ribosomal molecule used for cancer therapy. It has two binding regions: one for DNA and other for the iron molecule. So, this structure leads to chelation of metal ions (primarily iron) leading to pseudoenzyme formation that in turn produces oxygen-free radicals (superoxide, hydroxide free radicals) on its reaction to oxygen. These subsequently lead to cleavage of DNA strands leading to cellular death.

Bleomycin is primarily used in head and neck cancers, germ cell tumours, lymphoma, and squamous cell carcinomas of the skin, cervix, and vulva. It is also one of the sclerosing agents for the management of malignant pleural effusion.

Pharmacokinetics and Pharmacodynamics:

The oral bioavailability of bleomycin is poor. Peak plasma levels are obtained after 60 minutes of IM administration, but it reaches only one-third of an IV dose. After IV administration, plasma levels fall in a biphasic pattern as it is redistributed into tissues. It is metabolised in the liver and kidney by enzyme hydrolase and around 50–70% unchanged form is excreted via the kidney. So, drug toxicity can occur in patients with renal dysfunction.

Toxicity:



From: Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines †
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Fig. 4.1 Algorithm for the management of cardiotoxicity in patients treated with anthracyclines. Reproduced from Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol. 2012 Oct 1;23(suppl_7):vii155–vii166 with permission from Oxford University Press

The bleomycin-induced pulmonary toxicity is an important concern for perioperative management of the patient.

Pathogenesis: The exact mechanism of pulmonary toxicity by bleomycin is not well elucidated. One of the proposed mechanisms includes oxidative pulmonary injury [9]. This mechanism is considered as use of anti-oxidants and chelating agent-induced iron depletion has been found to reduce pulmonary toxicity of bleomycin [10, 11]. The predilection of the lung may be due to the absence of bleomycin hydrolase which degrades bleomycin in the lung [12].

Rates of any grades of pulmonary toxicity range from 5 to 16% and rates of fatal pulmonary toxicity are between 0 and 3% [13]. The occurrence of bleomycin-induced pulmonary toxicity is higher in adults receiving ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) for Hodgkin lymphoma and ranges from 10 to 53%, and rates of fatal pulmonary toxicity are 4 to 5% [14]. Long-term functional respiratory impairment has been observed in 15–18% of the population receiving bleomycin [15].

Risk factors:

- Age: more common in old age.
- Dose-toxicity increasing with an increase in cumulative dose of bleomycin administration. The occurrence of high-grade bleomycin lung toxicity in a patient receiving cumulative bleomycin dose of <270 IU vs >360 IU is 0–2% vs 6–18%, respectively.

- Concomitant therapy affecting lung-drugs like cisplatin, gemcitabine, and radiation therapy when administered along with bleomycin exaggerates lung toxicity.
- Administration of high fraction of inspired oxygen in critical care setup or perioperative management has been reported to exacerbate lung dysfunction in patients who have received bleomycin.
- Cigarette smoking

Screening: The baseline lung function tests including pulmonary function tests (PFTs) and diffusing capacity for carbon monoxide (DLCO) should be done inpatient planned for bleomycin-based chemotherapy regime. Patients with poor PFTs and DLCO may be more likely to develop life-threatening pulmonary toxicity and bleomycin be discontinued if DLCO falls more than 30–35% of pre-treatment values.

Clinical presentation:

- Early or acute: May range from asymptomatic reduction in PFT or DLCO values to acute onset dyspnoea, cough, chest pain, and crackles on auscultation. Chest radiographs may show opacities. These usually develop within days to weeks of bleomycin exposure and before 6 months most patients. Acute chest pain syndrome is seen at the time of bleomycin infusion in 1% of the patients.
- Chronic progressive lung fibrosis may be diagnosed several years after exposure to bleomycin. Postoperative respiratory impairment may be the first evidence of such toxicity in some patients.
- The rapid progression of clinical symptoms is seen in patients who manifest bleomycin-induced hypersensitivity pneumonitis and diffuse alveolar damage.
- Fibrotic bleomycin toxicity presents with the indolent onset of dyspnoea on exertion which is manifested after several months of bleomycin administration.

Evaluation: Apart from the clinical evaluation on the background of cancer and bleomycin administration, certain other assessment tools are required for evaluation.

- Imaging: The pulmonary fibrosis is imaged as lung volume loss and bibasilar subpleural reticular opacification in the early stages. Fine nodular opacities and costophrenic angle blunting are also seen. Subsequently, these findings may evolve to progressive lung consolidation and honeycomb appearance. The high-resolution computed tomography (HRCT) chest reveals ground-glass opacities in dependent locations, extensive reticular markings at the periphery. Organising pneumonia may present as subpleural nodules which may mimic metastases.
- PFTs typically demonstrate a restrictive pattern with decreases in forced vital capacity (FVC), total lung capacity (TLC), and functional residual capacity (FRC). The DLCO is usually decreased.
- Broncho-alveolar lavage, per se does not provide a clue for pulmonary toxicity but rules out infection or malignancy as the differential diagnosis for symptoms.
- Lung biopsy is rarely needed for diagnosis. Lung biopsies reveal lung injury and fibrosis primarily with the subpleural distribution.

Treatment:

The definite treatment for bleomycin-induced lung injury is not known. The cessation of bleomycin therapy for all patients with signs and symptoms or asymptomatic fall in DLCO should be considered. For symptomatic patients, treatment with glucocorticoids may offer some benefits. Usually, patients who manifest hypersensitivity pneumonitis, organising pneumonia, diffuse alveolar damage, interstitial pneumonia respond to the administration of steroids [16, 17].

Other bleomycin related toxicities:

- Skin reactions: it is manifested in most cases with erythema, hyperpigmentation, striae, and vesiculation. Other manifestations include skin thickening, hyperkeratosis, and ulceration.
- Patients may manifest fever chills primarily as hypersensitivity response. It is seen in almost one-fourth of patients receiving bleomycin.

- Rare manifestation includes myocardial infarction, stroke, and Reynaud's phenomenon.
- Vascular events including myocardial infarction, stroke, the phenomenon are rarely reported.
- Patients may feature suggestive of mild myelosuppression.

4.4.1.3 Mitomycin C

This is an anti-neoplastic antibiotic isolated from streptomyces caespitosus and used for various solid tumours. This agent is valuable as radio-sensitiser in patients receiving combined chemotherapy and radiation therapy. Its mechanism of action is via inhibition of synthesis and function of DNA by its action of alkylation to cross-link DNAs. It also targets DNA dependent RNA polymerase and thus inhibits transcription leading to inhibition of DNA synthesis. It has a hepatic metabolism using cytochrome P450. It metabolites have active and inactive forms.

Uses: This chemotherapeutic agent is used for upper gastrointestinal cancers like oesophagal, stomach, breast cancer, as bladder instillation for superficial bladder cancer, cervical cancer, non-small cell cancer, and head and neck cancer (in combination with radiation therapy).

Toxicity: The mitomycin manifests various adverse effects and is primarily dose-related. These include myelosuppression (most important and usually delayed onset), nausea, vomiting, anorexia, fatigue, pulmonary toxicity (interstitial pneumonia, pulmonary oedema), and haemolytic uraemic syndrome (microangiopathic haemolytic anaemia, thrombocytopenia, and renal failure).

4.4.2 Alkylating Agents

These are one of the oldest groups of anti-neoplastic agents. They bind covalently to guanine within the DNA via the alkyl groups and lead to apoptosis by causing arrest in the G1-S transition.

Major Groups of Alkylating Agents

1. Oxazaphosphorines: Cyclophosphamide, ifosfamide

These drugs are converted to their active form in the liver by cytochrome P450 system. The cytotoxic metabolites are phosphoramide mustard and acrolein. The antitumor mechanism is DNA synthesis inhibition by forming cross-linkages between DNA. These agents are non-specific to the cell cycle. It has hepatic metabolism and exclusive renal excretion.

Uses: These chemotherapeutic agents are used extensively in the treatment of various solid tumours and haematological malignancies. These are used for breast cancer, ovarian cancer, neuroblastoma, Wilms' tumour, sarcomas (bone and soft tissue), rhabdomyosarcoma, chronic lymphocytic leukaemia, and non-Hodgkin's lymphoma.

Toxicity: These agents' toxicity to various body functions:

- Myelosuppression is severe and dose-limiting. The nadir leukopenia is observed between 7 and 14 days and starts recovering by day 21. High dose of these agents leads to decrease platelets as well.
- Urinary bladder toxicity is seen in 5–10% of patients, occurs usually within 24 hours of drugs administration but may be delayed to some weeks in some patients. The manifestations are related to haemorrhagic cystitis, dysuria, and increased urinary frequency. The optimal hydration and use of mesna are uro-protective and may be sued in patients requiring high dose therapy.
- Cardiotoxicity is observed in patients receiving high dose therapy [18–20]. Patients who have received anthracyclines as well may present with subclinical myocardial toxicity [20]. The cardiac manifestations include left ventricular dysfunction, myocarditis, pericarditis, pericardial effusions, and QT prolongation [18, 19].
- Nausea vomiting, alopecia, hypersensitivity reactions.

2. Nitrogen mustards: Melphalan, chlorambucil.

These drugs are classic alkylating agents that inhibit DNA synthesis and function by forming inter- and intra-strand cross-links with DNA. The action of these agents remains cell cycle non-specific and acts at all cell cycle stages. Melphalan is used for cancers like breast cancer, ovarian cancer, multiple myeloma, polycythemia vera, etc. Chlorambucil is used for leukaemias, especially chronic lymphocytic leukaemia (CLL), non-Hodgkin's lymphoma, Hodgkin's lymphoma, Waldenstrom macroglobulinemia.

Toxicities include myelosuppression, nausea vomiting, hypersensitivity, alopecia, skin lesions. Chlorambucil may cause pulmonary fibrosis and seizures.

4.4.3 Anti-metabolites

These chemotherapeutic agents are weakly acidic molecules and include various agents like methotrexate, fluorouracil, cytarabine, mercaptopurine, etc.

4.4.3.1 Methotrexate

It is an anti-folate analogue, cell cycle-specific, and acts at the S-phase of the cell cycle. The folates levels are reduced by inhibition of the dihydrofolate reductase (DHFR). This action causes a reduction in the synthesis of thymidylate and purine synthesis and subsequent inhibition of the synthesis and function of DNA.

Methotrexate is well absorbed orally but is usually administered IV. It is extensively distributed into body tissues and third space in case of fluid collections. Hepatic metabolism occurs for 10% of the drug and the rest of the drugs is excreted unchanged in the urine.

Uses: Methotrexate is used in various cancers including breast, head and neck, osteogenic sarcoma, urinary bladder, etc. It is also useful in the management of acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, primary CNS lymphoma, meningeal leukaemia, carcinomatous meningitis, and gestational trophoblastic cancer.

Toxicity: The adverse effect profile of the methotrexate is dose-dependent. It causes myelosuppression, mucositis, pneumonitis, etc. The drug and its metabolite can precipitate in the renal tubules leading to acute renal failure and azotemia. Liver toxicity may manifest as the elevation of liver enzymes and bilirubin.

4.4.3.2 5-Fluorouracil

It is a pro-drug which is activated into several metabolites. The drug has various mechanisms and the major mechanism appears to be the inhibition of thymidylate synthase resulting in depletion of thymidine triphosphate (TTP) essential in the in vivo synthesis of DNA. It also inhibits RNA synthesis and processing. It is widely used in a variety of different malignancies like that of the breast, stomach, pancreas, oesophagus, head and neck, and ovaries.

Toxicity:

1. Common toxicities include nausea, vomiting, mucositis, headache, alopecia. Diarrhoea may be severe and may be dose-limiting.
2. Cardiotoxicity is fairly common and is usually limited to mild angina like symptoms associated with coronary artery spasm, but in about 1% develop life-threatening cardiotoxicity in the form of arrhythmias, ventricular tachycardia, and cardiac arrest, secondary to transmural ischemia may occur.
3. Neurotoxicity in the form of demyelinating degenerative changes within the CNS may be seen. Acute cerebral syndrome following injection of the drug that may persist for variable periods after cessation has also been described. Symptoms include ataxia, nystagmus, gait abnormalities.

4.4.4 Cisplatin and Analogues

Cisplatin is one of the most common chemotherapeutic agents with wide spectrum anti-neoplastic activity. The mechanism of action of cisplatin is via its covalent binding to DNA, leading to cross-linkage and thus affecting DNA functioning. Cytotoxicity is cell cycle independent. Significant

synergy is observed with concurrent administration of anti-metabolites. After IV administration, plasma concentrations decay rapidly due to redistribution. It has renal excretion with 10–40% excreted within 24 h and up to 50% excretion within 5 days.

Various cisplatin analogues have been introduced and used in cancer management. Carboplatin is one of the promising agents and has been used for many of the chemotherapeutic regimes except that of germ cell tumours where cisplatin is still preferred. Carboplatin is especially suitable for high-dose regimens in haematological malignancies owing to its low degree of non-haematological toxicity.

Uses: Cisplatin is used along with other chemotherapeutic agents for the management of ovarian cancers, malignant pleural mesothelioma, gastric cancer, colon cancer, lung cancers (small cell, non-small cell), head neck cancers, germ cell tumours, and pancreatic cancer cell lines.

Toxicity: These chemotherapeutic agents have various systemic toxicity. Renal toxicity is seen in 35–40% of patient receiving these chemotherapeutic agents and dose limited. The nephrotoxicity usually manifests after 10–20 days of drugs administration as electrolyte abnormalities (hypokalemia, hypomagnesaemia, hypocalcaemia), acute renal failure and may progress to chronic renal insufficiency. These effects are usually reversible. The adverse effect on the central nervous system is usually dose and duration dependent. It manifests as peripheral sensory neuropathy with primary clinical presentation as a classic glove and stocking pattern of paresthesias and numbness. Some patients also manifest motor neuropathy, focal encephalopathy, and even seizures. Ototoxicity is more common in children and manifests as tinnitus and high-frequency hearing loss. Ocular effects may manifest as optic neuritis, papilledema, and cerebral blindness. Vascular adverse events like myocardial infarction, cerebrovascular accidents, thrombotic microangiopathy, and vasculitis may be seen. Reynaud's phenomenon has also been reported. Myelosuppression is seen in 25–30% of patients. Nausea vomiting, headache, fatigue are all common. Renal, neurological, vascular toxicities are all relatively less with carboplatin as compared to cisplatin.

4.4.5 Anti-microtubule Agents

These are a class of anti-neoplastic agents which act by inhibiting microtubule formation, which remains one of the core structural units for cells and its activities. These drugs bind on specific sites on tubulin and inhibit their polymerisation.

4.4.5.1 Vinca Alkaloids: Vincristine, Vinblastine

These are not absorbed orally and only administered IV. Vinca alkaloids are metabolised by cytochrome P450 in the liver and excreted in bile. Only a small amount is excreted in the urine.

Uses: These chemotherapeutic agents are primarily used for haematological malignancies including ALL, multiple myelomas, and lymphomas. Other indications include neuroblastoma, Wilms' tumour, rhabdomyosarcoma, Ewing's sarcoma, and thyroid cancer.

Toxicity: Neurotoxicity is one of the dose-limiting toxicity. It manifests at various levels including peripheral neuropathy, cranial nerve palsies, autonomic dysfunction, and various CNS related manifestations. CNS toxicity may even lead to seizures and coma. The toxicity may affect bowel function as well as leading to pain abdomen, constipation, and ileus. So, patients receiving vinca alkaloids are administered laxatives prophylactically. Myelosuppression is generally mild. Alopecia, skin rash, and hypersensitivity reactions may be seen. Vinblastine also has several cardio-respiratory effects like hypertension, vascular events like stroke or myocardial infarction, acute pulmonary oedema, bronchospasm, dyspnoea, and interstitial infiltrates.

4.4.5.2 Taxanes: Paclitaxel, Docetaxel

The development of taxanes in the 1990s was the most encouraging development in oncology at the time. Paclitaxel offered significant prolongation of survival for patients with ovarian cancer.

Docetaxel has shown to improve survival in patients with metastatic cancer. These are poorly absorbed orally. After intravenous administration, these agents are redistributed in various body spaces and have extensive hepatic metabolism by the cytochrome p450 system. The major excretion is via the faecal route (70–80%) and some amount is cleared in urine (<10%).

Uses: The taxanes are primarily used in malignancies of breast, ovary, lung (non-small cell and small cell), oesophagus, urinary bladder, and prostate.

Toxicity:

1. Taxanes cause dose-limiting myelosuppression. The impact is maximum at 8th–10th day with maximum fall in leukocyte counts and starts recovering by day 15–21.
2. Hypersensitivity reactions occur in up to 20–40% of patients. The taxane induced hypersensitivity is manifested by cutaneous symptoms (rash, flushing, erythema), respiratory (bronchospasm, dyspnoea), and hypotension.
3. Sensory neuropathy in the form of numbness and paraesthesia is common.
4. Cardiotoxicity in the form of arrhythmias ranging from transient asymptomatic bradycardia to all degrees of heart block as well as ventricular arrhythmias.
5. Mucositis, diarrhoea, and transient elevation in bilirubin and liver enzymes may be seen.

4.4.6 Topoisomerase II Inhibitors: Etoposide, Teniposide

Topoisomerase enzymes are nuclear proteins which regulate the topology of the DNA helix. Two subtypes, i.e. topoisomerase I and II have been recognised. Etoposide initially found to have anti-neoplastic activity in the 1960s is a topoisomerase II inhibitor and its action by stabilisation of the topoisomerase II-DNA complex. Teniposide is structurally like etoposide but is more potent. These drugs are widely used in adult as well as paediatric malignancies. These agents are effective for lung cancer (small cell), germ cell tumours, ALL, neuroblastoma, rhabdomyosarcoma as well as preoperative regimens for bone marrow transplantation.

Myelosuppression is dose-limiting in most instances. Other toxicities include nausea, vomiting, anorexia, alopecia, and hypersensitivity reactions.

4.5 Systems Wise Approach to Pre-anaesthetic Assessment and Management

The chemotherapeutic agents have a short- and long-term effect on various systemic physiology. So patients scheduled for surgical interventions require a thorough assessment to identify these systemic effects and attempt to optimise should be done.

4.5.1 Cardiovascular System

Cardiovascular effects of prior treatment chemotherapeutic drugs are a frequently encountered challenge in the perioperative period. Careful evaluation, risk stratification, planning, and management are essential for optimum outcomes. Several chemotherapeutic agents have cardiac effects that may complicate the perioperative course. These drugs and their effects are summarised in Table 4.1 [18, 21].

4.5.1.1 Preoperative Assessment

Active screening and identification of patients who have received chemotherapeutic drugs for cardiovascular risk are desirable. These high-risk individuals (cumulative dose, female gender, electrolyte disturbances, other cardiotoxic agents, preexisting heart disease) need to be further assessed by elaborate history, clinical examination and required investigations need to be done. The assessment needs to consider the timing of drugs administration, its doses and impact on the cardiovascular system (before and after cardiovascular system assessment findings). Patient-reported effort tolerance and estimation of

Table 4.1 Various chemotherapy drugs causing cardiotoxicity and their manifestations

Drug category	Drug name	Manifestation of cardiotoxicity
Anthracycline	Doxorubicin, epirubicin, daunorubicin	Acute and chronic forms. Usually in the form of decline in LVEF, heart failure, arrhythmias
Alkylating agents	Cyclophosphamide, ifosfamide	Left ventricular dysfunction, pericarditis and pericardial effusions, heart failure, acute QT prolongation
Anti-microtubule agents	Taxanes: paclitaxel, docetaxel	Arrhythmias: sinus bradycardia, Mobitz type I and II and complete heart blocks, ventricular ectopics. Low incidence of heart failure
Anti-microtubule agents	Vincristine, vinblastine	Hypertension, acute vascular events like stroke or MI, acute pulmonary oedema
Monoclonal antibodies	Trastuzumab, bevacizumab	Dyspnoea, peripheral oedema, and left ventricular dysfunction. Increased risk when used with anthracyclines. Reversible in most instances Arterial and venous thromboembolic events: stroke, angina, MI, deep vein thrombosis; hypertension
Tyrosine kinase inhibitors	Imatinib, sorafenib, sunitinib, lapatinib	Fluid retention, ankle oedema. Asymptomatic drop in LVEF, QT prolongation
Selective oestrogen–receptor modulator	Tamoxifen	QT prolongation, fluid retention. Thrombotic events like DVT, pulmonary embolism

maximum metabolic equivalent achieved is a powerful tool in risk assessment.

Apart from the routine preoperative investigations, a 2D echocardiogram and 12 lead electrocardiogram (ECG) provide a multitude of information. Many patients have at least one or serial echocardiogram performed during treatment with cardiotoxic agents. A repeat scan can be requested in patients deemed at high risk. Specific information to be looked for includes details of cardiac contractility, left ventricular ejection fraction, pericardial fluid collection. Patients with borderline reported effort tolerance or those with reduced left ventricular function benefit from a formal cardiopulmonary exercise test (CPET) and assessment of maximal oxygen consumption (VO_2 max) and anaerobic threshold (AT). Exercise-induced ST-segment changes and arrhythmias also indicate a high risk for perioperative events. Most patients who receive neoadjuvant chemotherapy have significant reductions in their CPET derived values after the completion of chemotherapy [22, 23]. This may be because of a variety of reasons including cardiorespiratory complications of chemotherapy, muscle deconditioning, or anaemia. Numerous studies have demonstrated thresholds for VO_2max and AT for perioperative morbidity [24–27]. Generally, the risk of perioperative complications begins to rise with a VO_2 max < 15 mL/kg/min or AT <11 mL/kg/min. The assessment using the revised cardiac risk index (RCRI) combined with echocardiogram and CPET should be sufficient for risk assessment in most patients. Biomarkers for cardiac injury like levels of B-type natriuretic peptide (BNP) (a hormone produced by heart), and N-terminal-pro hormone BNP (NTproBNP), cardiac troponins can provide the clue for any associated cardiac insult due to chemotherapeutic agents [28, 29]. NTproBNP is a useful marker for identifying heart failure patients. The patients who have cardiac symptoms or remains at high risk should get a cardiologist's consultation for further assessment and optimisation, if possible. Certain drugs like angiotensin-converting enzyme inhibitors are beneficial for these patients. The cardiac interventions should be weighed against the delaying of cancer surgery as it may lead to cancer progression.

4.5.1.2 Perioperative Management

Perioperative management requires planning based on individual assessment (Fig. 4.1). Patients who have been chemotherapy-induced cardiac toxicity have increased chances of perioperative cardiac events. These patients should be monitored accordingly to identify any such

events and timely management. The intraoperative monitoring depends on the underlying cardiac conditions and usually invasive arterial pressure and cardiac output monitoring are useful. The hypothermia is associated with increased cardiac events, so core temperature monitoring is useful. This should also be continued during the initial postoperative period and all measures to maintain normothermia should be followed.

The myocardial depressant effects of anaesthetic agents are amplified in patients treated with cardiotoxic chemotherapeutic agents. Treatment with chemotherapeutic agents like anthracyclines exacerbates the cardiac depressant effects of the anaesthetic agents even if the preoperative patient is not manifesting cardiac symptoms [30]. The prolongation of QTc with isoflurane is seen in patients who received isoflurane based anaesthesia. Significant cardiac depression and decompensation may occur with induction boluses of myocardial depressant drugs like propofol and with neuraxial anaesthesia [31]. There is some recent evidence that shows that neoadjuvant chemotherapy reduces subsequent requirements of volatile anaesthetics [32, 33].

Several drugs used in anaesthesia and the perioperative period may cause prolongation of QT interval and exacerbate a chemotherapy-related long QT syndrome (LQTS). These include antiarrhythmics like sotalol, quinidine, amiodarone, procainamide, flecainide, antibiotics like clarithromycin, quinolones, anti-depressants, antifungals like voriconazole, fluconazole, itraconazole, antiemetics (granisetron, dolasetron, ondansetron), and bronchodilators like salmeterol, terbutaline [34]. These drugs should be avoided. However, beta-blockers should be continued. Premedication with drugs like droperidol [35], atropine [36], ondansetron should be cautious and possibly avoided. Benzodiazepines appear to be safe [37]. Drugs like ketamine, etomidate, isoflurane, sevoflurane, and desflurane can all possibly cause QT prolongation [38]. Opioids like fentanyl, remifentanil, and alfentanil are considered safe [39, 40]. Non-depolarising muscle relaxants are preferred as succinylcholine can significantly prolong QT interval [41]. Local anaesthetics in their toxic dose cause prolongation of QT interval by inhibiting cardiac sodium channels. The techniques that cause sympatholysis like thoracic epidural anaesthesia may reduce QT interval.

A plan for postoperative care should be in place preoperatively. Elective admissions to PACU/ICU/HDU are associated with better outcomes as compared to emergency admissions [42]. Continuous cardiac monitoring should include continuous ECG with automated QT interval analysis. Invasive cardiac output monitoring has become essential in guiding fluid and vasopressor/inotrope therapy. Temperature monitoring and maintaining normothermia are vital in the postoperative period. Adequate and though pain management cannot be emphasised enough. Multimodal analgesia with NSAIDs, opioids, and regional techniques should be employed. Figure 4.2 provides an algorithm for the perioperative care of patients who have received potentially cardiotoxic chemotherapy.

4.5.2 Respiratory System

Respiratory signs and symptoms after chemotherapy treatment present both a diagnostic challenge as well as for management of anaesthesia. Several chemotherapy drugs have implications on the respiratory system (Table 4.2).

4.5.2.1 Preoperative Evaluation

Pulmonary signs and symptoms in patients who have received chemotherapy are a diagnostic dilemma as well as a challenge for anaesthesia management. Pulmonary signs and symptoms in cancer patients may arise due to many mechanisms: infection, metastasis, mass effects of the tumour, pleural effusion, pulmonary embolism, and drug-induced toxicity.

The patient's presentation due to pulmonary complications of chemotherapy ranging from an asymptomatic decline in PFTs and DLCO to mild cough and dyspnoea to life-threatening lung fibrosis results in the severe restriction on PFT and respiratory failure. So, a high index of suspicion is warranted especially for asymptomatic patients as underlying pulmonary limitations may be manifested during the stressful perioperative phase. Several patterns of pulmonary com-

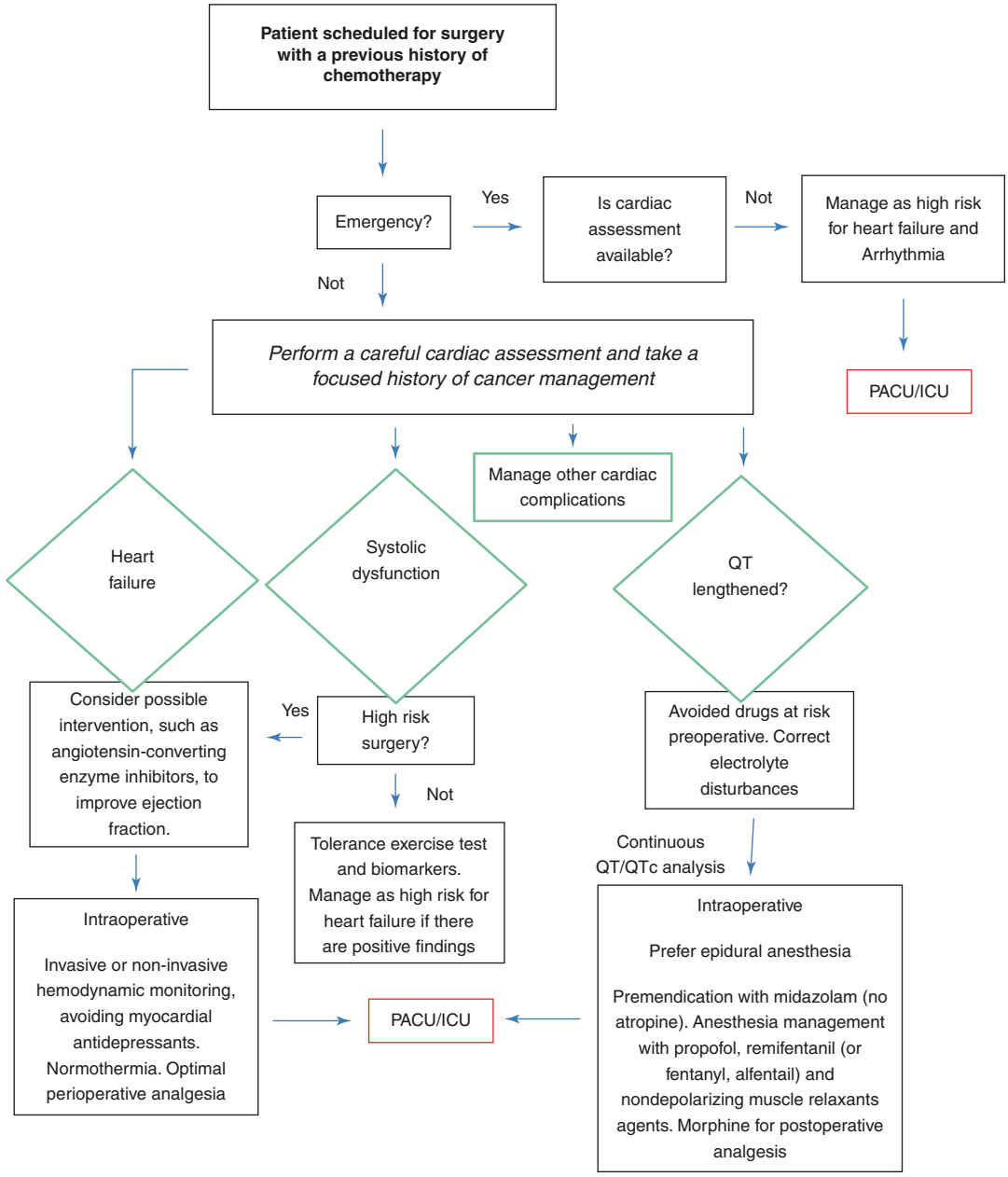

Fig. 4.2 Algorithm for perioperative management of patients who have received chemotherapy. Reproduced with permission from Cascella M. Preoperative cardiac evaluation and anaesthetic considerations for cancer patients who underwent chemotherapy. Trends Anaesth Crit Care. 2017;14:9–18

plications are seen and may be common among the various chemotherapeutic agents. Patients may present with interstitial pneumonitis or hypersensitivity pneumonitis. At times, these conditions may progress to fibrosis. This complication is dose-dependent. The patient may also manifest as bronchitis obliterans with organising pneumonia. Pleural effusions, chest pain syndrome, pulmonary venoocclusive disease are the other manifestations.

A meticulous history should include details of oncologic therapy, drugs and their dosages, and the time elapsed since the last cycle of chemotherapy. A chronological relation between che-

Table 4.2 Various chemotherapy drugs with pulmonary toxicities and their manifestations

Drug category	Drug name	Manifestation of pulmonary complications
Anti-tumour antibiotics	Bleomycin	Acute—Asymptomatic deterioration of PFT and DLCO to features like cough, dyspnoea, chest pain, crackles. Chronic progressive interstitial fibrosis, hypersensitivity pneumonitis, diffuse alveolar damage
Anti-metabolites	Methotrexate	Hypersensitivity pneumonitis, organising pneumonia, acute interstitial pneumonia, lung fibrosis, pleural effusion, pleuritis
Taxanes	Paclitaxel, docetaxel	Acute/subacute diffuse interstitial pneumonitis, lung fibrosis Docetaxel induced capillary leakage—peripheral oedema, pulmonary oedema, pleural effusions
Alkylating agents	Cyclophosphamide	Early onset (<6 months of therapy)—cough and dyspnoea, fever, fatigue. Ground-glass opacities on CT Late onset (> 6 months of therapy)—progressive lung fibrosis with cough, inspiratory crackles, reticular, or nodular opacities
Anti-tumour antibiotics	Mitomycin C	Acute bronchospasm (4–6%) Acute lung injury due to diffuse alveolar damage (6–8%)—high FiO_2 contributes to the risk Interstitial pneumonitis (<5%) Thrombotic microangiopathy and acute respiratory failure

motherapy and pulmonary symptoms is often revealed by the patient and is a vital clue for possible pulmonary toxicity. The severity of the condition can be assessed by patient-reported changes in effort tolerance and grading of the dyspnoea experienced by the patient at rest or during exercise. Presence of fever and productive cough may indicate an infective aetiology. Cancer-related to mass effects and metastasis can be ruled out by reviewing the oncologist's notes and radiologic findings. As systemic glucocorticoid therapy has shown to be of some benefit in chemotherapy-related pneumonitis/toxicity, symptomatic patients may be referred to a pulmonologist for evaluation and initiation of therapy. The systemic examination should include signs of breathing difficulties like respiratory rate, use of accessory muscles, and nasal flaring. Chest auscultation is often unremarkable; crackles may be present in some instances. A quick surrogate pulmonary function test like breath-holding time > 25 sec may be used in the outpatient department or at the bedside to screen and identify patients at risk.

Patients receiving bleomycin often will have a baseline PFT and/or DLCO done before the initiation of treatment. Few patients also undergo serial PFTs and DLCO monitoring during treatment. A review of these is immensely helpful to ascertain or rule out the possibility of chemotherapy mediated lung toxicity. Repeat testing is indicated if there is significant worsening or new onset of symptoms. The role of PFT values like FEV1, FVC, and peak expiratory flow in predicting complications in lung resection surgeries is well recognised. The FEV1 and DLCO <30% have been predicted as the risk of increased perioperative complications for lung resections [43, 44]. However no such consensus exists for non-cardiothoracic surgeries. However, dynamic testing with CPET has shown to be predictive of outcomes after non-cardio-thoracic surgeries. Chest X-rays in such patients reveal basal reticular opacification and blunted costophrenic angles. At times these patients also present with fine nodular densities on imaging which may progress to consolidation and honeycombing. On an HRCT of the chest, it may be evident as ground-glass opacities in dependent locations, extensive reticular markings at the periphery. Organising pneumonia may present as subpleural nodules which may mimic metastases.

Perioperative management:

Although no direct evidence exists, supervised pulmonary prehabilitation is likely to benefit patients with pulmonary toxicity of chemotherapy especially in those undergoing thoracic or upper abdominal surgeries. This may include steam inhalation, respiratory muscle training, deep breathing exercises, incentive spirometry, smoking cessation. CPET guided prehabilitation programmes have shown to

improve postoperative recovery [45, 46] but it must be weighed against the risk of cancer progression.

Exacerbation and worsening of bleomycin lung toxicity due to perioperative oxygen supplementation or hyperoxia has been a significant cause of concern and debate. It all began in 1979 when Goldliner et al. reported 5 patients at a single institution who received bleomycin and were administered $FiO_2 > 39\%$ intraoperatively, developed ARDS and died [47]. Subsequently, a perioperative protocol was developed with perioperative oxygen restriction and judicious fluid administration. Thirteen patients who then underwent surgery did not have any pulmonary complications [48]. Subsequently, La Mantia et al. presented a different story and reported a series of 16 patients who received FiO_2 above 40% and had an uneventful perioperative course [49]. The patients who had received bleomycin and underwent resection surgery developed minor pulmonary complications only when $FiO_2 > 40\%$ [50, 51]. In these reports the occurrence of severe pulmonary compromise was seen in only very few patients and no meaningful concern of increase oxygen supplementation was reported. The threshold of FiO_2 beyond which the risk of exacerbation of bleomycin toxicity increases or the interval after bleomycin treatment when the patient is at high risk is still unknown.

The guiding principles of oxygen therapy in the perioperative care of patients who had received bleomycin need to be individualised. The most sensitive indicator of subclinical pulmonary toxicity of bleomycin is single breath DLCO. The decrease in DLCO by 10–15% is clinically significant. Patients without any major risk factors may be administered oxygen as per need. However, patients with the presence of risk factors should be administered lowest possible FiO_2 and SpO_2 of 88–92% is acceptable. The use of steroids may have some benefit and thus may be considered wherein oxygen supplementation is required.

Other measures to be followed in the patient who received bleomycin which has shown to reduce pulmonary complications after surgery [52] should also be employed to reduce the further lung damage. These include:

(a) Lung protective ventilation: The strategies need to be followed with tidal volumes of 6 mL/kg and airway pressures to <30 cmH_2O. The judicious use of PEEP has also been shown to reduce lung injury.
(b) Avoidance of hypervolemia: Overzealous fluid administration especially in thoracic procedures is a risk factor for ARDS. Optimal fluid administration may be guided by cardiac output and arterial waveform monitoring.
(c) Analgesia: The multimodal optimal analgesia maintains the lung function as such and should be ensured.
(d) Postoperative lung expansion: The strategies like pulmonary physiotherapy including deep breathing exercises, incentive spirometry, etc. need to be started preoperatively and continued in the postoperative period. In patients, who are either unable to perform these activities or have lung compromise, application of non-invasive respiratory support is useful.

4.5.3 Gastrointestinal System

Gastrointestinal toxicity is a common complication of chemotherapy with most anti-neoplastic agents. The common manifestations include nausea, vomiting, diarrhoea, and mucositis. These toxicities including mucositis not only cause patient discomfort but also compromise the nutritional status of the patient. Thus, owing to these complications, systemic chemotherapy combined with other factors like chronic inflammation, biochemical, and mass effects of cancer leads to the development of nutritional deficits in cancer patients. The spectrum may range from minor weight loss to severe cachexia. This is discussed in detail elsewhere in the text.

It is not surprising then that dehydration may be present in patients who have undergone chemotherapy. Fluid and electrolyte correction may be needed preoperatively. Rapid sequence induc-

tion may be considered in patients who are prone to vomiting. Oro-pharyngeal trauma during laryngoscopy in the presence of mucositis can cause severe bleeding and result in a catastrophic airway situation.

Abnormal liver function tests are common in patients who have undergone chemotherapy. Most of such instances will be inconsequential increases in liver enzymes or bilirubin. Occasionally a patient presenting for surgery may have markedly altered liver function directly attributable to the toxic effects of chemotherapy (methotrexate—liver fibrosis, cirrhosis; cyclophosphamide—diffuse hepatocellular damage). The various anaesthetic drugs and their dosages need to be modified as per the severity of hepatic dysfunction.

4.5.4 Renal System

The various chemotherapeutic agents like platinum-based agents cause renal toxicity (both acute and chronic). Carboplatin and oxaliplatin are less nephrotoxic compared to cisplatin with equal anti-neoplastic activity in most cases. The pathogenesis is multifactorial, including the increased renal concentration of the drug, renal vasoconstriction and inflammation [53]. This was before the use of intensive hydration regimens. Currently, the incidence is around 30% [54]. Both the incidence and severity of renal failure increase with subsequent courses and may become irreversible. Cisplatin is usually discontinued progressive renal impairment. Most patients typically develop non-oliguric acute kidney injury. Few will have a progressive renal failure, while others will show resolution over weeks. Hypomagnesemia may occur due to urine magnesium wasting in many patients with cisplatin nephrotoxicity. Concomitant hypocalcaemia or hypokalemia may also be present. Hypomagnesemia produces neuro-muscular signs like tremors, spasms, and seizures. On ECG QT prolongation may be noted which may progress to torsades de pointes and ventricular arrhythmias. Limiting the dose of cisplatin appears to be the foremost factor in preventing cisplatin-induced renal toxicity. Hydration regimens with intravenous saline, often with potassium or magnesium supplementation are also often employed. Amifostine is an organic thiophosphate that has renal protective action by donation of a thiol group. It is used as a prophylactic agent to prevent renal toxicity due to cisplatin. Other agents like sodium thiosulphate, N-acetylcysteine, theophylline, and glycine have all been used to prevent renal injury [55].

Other drugs which cause renal damage include methotrexate (intratubular precipitation related renal damage), mitomycin C (microangiopathic haemolytic anaemia, renal failure), ifosfamide (proximal tubular abnormality), and cyclophosphamide (haemorrhagic cystitis).

4.5.4.1 Perioperative Implications

- Previously undetected subclinical renal injury may get unmasked in the perioperative period due to the effects of acute blood loss and hypoperfusion. Careful assessment of renal function and employment of renal protective strategies in the perioperative period mitigate the risk to a significant extent.
- Blood urea nitrogen, creatinine, and serum electrolytes should be done routinely. Assessment and correction of dehydration and electrolyte abnormalities preoperatively are vital.
- For patients with established acute or chronic renal injury, standard anaesthetic precautions must be taken. Dose modifications of anaesthetic drugs will be needed.
- Maintenance of normovolemia along with avoidance of nephrotoxic drugs in the perioperative period (e.g. NSAIDs, antibiotics) helps to mitigate the risk for AKI.

4.5.5 Nervous System

Chemotherapy can also have toxic effects on the human nervous system, complicating anaesthesia and perioperative management. The vincristine and cisplatin remain the most common chemotherapeutic agents that cause neurotoxicity.

The vinca alkaloid vincristine can cause severe and debilitating neuropathy. It is probably the only agent with neurotoxicity as the dose-limiting toxicity. The mechanism of neuropathy is the disruption of axonal microtubules and involves both sensory and motor fibres [56]. Initial symptoms are in the form of paresthesias in the fingertips and feet and muscle cramps. Pain and mild distal weakness may or may not be seen. Loss of deep tendon reflexes especially knee jerk and ankle jerk may be present at this stage. Symptoms generally develop after weeks of treatment, however, it may also be seen after the first dose or even develop after discontinuation of the drug. Symptoms may progress with or without additional exposure and may result in proximal parenthesis, gait and motor abnormalities, and seizures. Occasionally severe motor weakness with foot and wrist drop or profound sensory loss may also be seen. Mononeuropathies may develop and could involve cranial nerves. Usually, the oculomotor nerve gets involved but others such as the recurrent laryngeal, facial, auditory, or the optic nerve may also get involved.

Cisplatin has a neurotoxic effect as well along with nephrotoxic effect. The usual manifestation includes peripheral neurotoxicity (primarily large myelinated sensory affecting dorsal root ganglia), ototoxicity, and encephalopathy. Symmetrical sensory neuropathy with subacute development of numbness, paresthesias (abnormal sensations), and pain sometimes which ascends proximally and decreased. Decreased vibratory sensitivity in the toes and loss of ankle jerks may be the earliest signs.

Methotrexate can also cause acute, subacute, and chronic neurotoxicities. This may be manifested as aseptic meningitis, transverse myelopathy, and acute and subacute encephalopathy. Intrathecal methotrexate is often administered to treat leptomeningeal metastases and as prophylaxis in haematological malignancies. It is associated with aseptic meningitis, seizures, and focal neurological deficits.

Paclitaxel, and to a lesser extent docetaxel are associated with a predominantly sensory peripheral neuropathy. It presents as burning paresthesias in distal limbs with loss of tendon reflexes. Other features include perioral numbness, autonomic neuropathies, and seizures. Cytarabine administration in high doses may lead to the acute cerebellar syndrome that begins with somnolence and encephalopathy within days of administration. Ifosfamide and 5 fluorouracil can also cause cerebellar dysfunction, encephalopathies, and extrapyramidal abnormalities.

Perioperative considerations:

(a) Patients who have received neurotoxic chemotherapeutic agents need a detailed assessment including history and clinical examination. Many perioperative factors may lead to the worsening of neurological condition and hence baseline documentation is an absolute must. Signs and symptoms of autonomic neuropathy if present should be recognised. Various physiological tests directed at heart rate and blood pressure variations during standing up from sitting position, Valsalva manoeuvre, deep breathing, and sustained handgrip may be used to ascertain the diagnosis.
(b) Regional anaesthesia is a relative contraindication in the presence of neurological deficits. It may cause worsening of a subclinical unrecognised neuropathy or flaring of existing neuropathy. In case a regional block is desirable, the documentation of neurological status needs to be done and follow-up should be comprehensive.
(c) Several anaesthetic drugs have adverse effects related to the nervous system. Succinylcholine administration in patients with motor neuropathy and related muscle wasting may lead to rhabdomyolysis and life-threatening hyperkalemia. Judicious use of benzodiazepines and thiopentone is helpful in patients with seizures and drugs like tramadol and atracurium should be avoided as they may induce seizures in susceptible individuals.
(d) Perioperative hypotension and hypoxia can both lead to worsening of neurological status and should be carefully managed.

(e) Patients with autonomic neuropathy are prone to extreme haemodynamic response to laryngoscopy and intubation, surgical stress, and blood loss. These patients also often have autonomic gastroparesis and are at increased risk of aspiration. Adequate fasting times and prokinetic premedication along with rapid sequence intubation may be employed.

4.5.6 Haematopoetic System

Adverse effects on the bone marrow and peripheral blood cells are caused by most chemotherapy agents. Myelosuppression may affect any or all cell lines. Anaemia is a common occurrence in cancer patients. The reduced oxygen-carrying capacity of blood could cause several complications in the perioperative period. Blood transfusion itself is associated with numerous adverse effects. Of special concern in the oncologic population is transfusion-related immune-modulation which may contribute to cancer recurrence. Thus a balanced approach with restrictive transfusion thresholds, nutritional prehabilitation, and use of haematinics for prehabilitation, blood salvage techniques, and transfusion of leuko-depleted PRBCs should be adopted.

Leukopenia and neutropenia are fairly common in the initial weeks after chemotherapy. Although usually elective surgeries are usually not performed during this period, occasionally emergent or urgent procedures may be performed in a neutropenic patient. Severe and often refractory infections may occur leading to sepsis, multiorgan failure, and eventually death. Careful attention to aseptic precautions is necessary. Prophylactic antibiotics are usually administered in the perioperative period.

Thrombocytopenia is also frequently encountered in the pre-anaesthetic assessment. Guidelines often refer to thresholds of 50,000/mm^3 for general surgeries and 1,00,000/mm^3 for surgeries of closed cavities like ophthalmic and neurosurgeries. A count of 80,000/mm^3 is considered 'safe' for neuraxial anaesthesia but this is largely anecdotal.

4.6 Anaesthetic Effects of Radiation Therapy

4.6.1 Basic Principles of Radiation Therapy (RT)

The utility of radiotherapy to treat cancer was first described over a century ago. Since then the technology and its understanding and implications in oncology have grown leaps and bounds. Increasingly, RT has been used before or after surgery and other systemic therapies in a combined fashion for a wide range of malignancies to maximise tumour control and quality of life while minimising toxicity and preserving the organs.

RT primarily works by inflicting damage to the DNA of cancer cells by delivery of ionising radiation which results in broken atomic and molecular bonds. The therapeutic basis lies in the fact that normal cells have intact mechanisms to identify and repair DNA damage which many cancer cells do not, thus resulting in cell death.

Various techniques of radiotherapy are used clinically:

1. External beam radiation therapy (EBRT): It is the most common approach and includes delivery of radiation from a source outside the patient. Radiation may be produced by the decay of radioactive substances like cobalt or by the electronic acceleration of charged particles like electrons or protons. Linear accelerators have replaced cobalt and have become the most used modality in recent times. Anatomical determination of the radiation field along with the dose as the schedule of treatment is 'planned' before the actual treatment. Using high definition imaging studies like CT or MRI for planning, 3-dimensional conformed radiation beams are delivered to minimise tissue toxicity.
2. Brachytherapy provides radiation therapy using the catheter to deliver the dose to the desired area. This technique allows the delivery of dose to the dedicated tumour lesion only and surrounding normal tissues are

spared. It is mostly used in cancers of the prostate, cervix, vagina, and breast.

3. Stereotactic radiotherapy refers to the administration of the full dose of radiation in a very limited number of fractions using high-resolution imaging to delineate the tumour and its surroundings.

4.6.1.1 Adverse Effects of Radiation [57, 58]

RT can lead to various treatment-related side effects which depend on the anatomic area, cumulative dose, dose per fraction, and tissue sensitivity. These adverse effects have been classically described as acute and late effects. The acute effects of RT are related to the cellular response to radiation exposure and it may be dose-limiting. Acute effects are predominantly caused due to loss of reproductive capacity of cells, thus interfering with the cellular turnover. Thus it primarily involves tissues with a rapid cell turnover like mucosa, skin, and bone marrow. Oral and pharyngeal mucosa is affected early. Erythema is often seen after 1 week of treatment. This may progress in following weeks through various stages of mucositis—from small patches to confluent or ulcerated areas. Salivary glands are also affected and the volume and composition of saliva are altered. Decreased volume and pH lead to altered mucosal flora and predispose to dental caries. Skin reactions like desquamation and altered colour may be seen. Gastrointestinal mucositis associated with diarrhoea is also commonly seen in the weeks following RT of abdominal or pelvic cancers.

Late effects of RT may be caused by tissue fibrosis, damaged microvasculature, obstructed lymphatics, or stem cell depletion. Fibrosis of the subcutaneous tissues of head and neck areas and masticatory muscles are of particular importance to the anaesthetist. The tissues may develop a woody texture with limited movement along with trismus. Xerostomia may develop and may be irreversible at a higher dosage. Irradiation of the spinal cord may result in transverse myelitis like syndrome, usually with sensory symptoms. The condition may progress and also show motor symptoms. Thyroid dysfunction may be seen due to direct effects or secondary effects on the hypothalamic-pituitary axis. Radiation-induced changes on various organ systems are summarised in Table 4.3.

Table 4.3 Toxicity of radiation therapy on various organ systems

Organ	Effects
Skin	Early effects: Erythema followed by_ desquamation and ulceration *Late effects include*: Atrophy, contraction, radiation fibrosis, and telangiectasia
GIT	Acute mucositis often causes diarrhoea and gastritis; if occurs Late effects: Mucosal ulceration, atrophy, fibrosis, necrosis
Nervous system	Risk if higher in doses more than 50 Gy Early reaction (6 months): Demyelination in the CNS. Brain (somnolence); spinal cord (Lhermitte's syndrome) Later reaction (1–2 years): Radiation-induced CNS necrosis, initially in white matter; telangiectasias, focal haemorrhage
Lung	Radiation pneumonitis: 2–6 moths Lung fibrosis: Late (6 months to years)
Kidneys	Radiation nephropathy: Proteinuria, hypertension, usually develops late
CVS	Pericarditis (6 months–2 years); settles spontaneously Cardiomyopathy: Decreased ventricular ejection; conduction blocks (10–20 years)

4.6.1.2 Airway Changes Due to Radiation [59, 60]

RT produces a gamut of changes involving the airway. Patients with head and neck cancers frequently present for surgery post radiation therapy. During the acute phase, radiation-induced oedema and mucositis may lead to a difficult airway situation even in patients with otherwise normal airways. Mucosal injuries and bleeding may be severe due to the presence of inflammation. Oedema of the oropharynx, vocal cords, and other peri-glottic structures make visualisation difficult. Oedema of the tongue may also lead to difficult laryngoscopy and also result in airway obstruction. The Mallampati classification may also be falsely obscured.

Longer-term changes of the airway and associated structures are responsible for most of the difficult airway situations encountered due to effects of radiation. Many different structures

may be involved including the mucosa, temporomandibular joint, muscles of mastication, tongue, dentition, the floor of the mouth, body structures, pharyngeal and laryngeal areas, and the trachea. Thus due to varying involvement of the different structures, each patients' airway is unique and has its own set of challenges. Difficult mask ventilation may result from ulcerations and fistulae in the face and buccal mucosa, loss of dentition, osteonecrosis of the mandible. Osteonecrosis of the mandible is a relatively rare complication caused due to disruption of intraosseous blood supply resulting in the non-vital bone. This leads to trophic changes in the bone and demise of osteocytes and destruction of the bone matrix. Secondary infection of the necrosed area may be severe and protracted. This ultimately results in a reduction of mandibular space, difficult mask ventilation, and laryngoscopy. Long-term fibrosis of various structures poses various kinds of threat. Fibrosis of the TMJ and facial muscles may lead to reduced mouth opening. Glossomegaly and fibrosis of floor of mouth result in limited tongue mobility and can cause difficult visualisation of the glottis. Fibrosis and oedema of the suprahyoid region lead to thickening and stiffness of neck tissue and limited mobility. The mobility of the larynx is also compromised rendering external manipulation to optimise the view almost impossible. Video laryngoscopes are an essential aid for limited mouth opening and reduced working space in the airway. The CMAC D blade is very useful in cases with an anterior and fixed larynx.

4.6.1.3 Pulmonary Effects of Radiation [61, 62]

Radiation-induced lung injury (RILI) was first described over a century ago soon after the development of X-rays. Today a vast body of literature exists about the development of RILI, risk factors, pathological mechanisms, clinical presentation, diagnosis, and treatment.

RILI results from the combination of direct cytotoxic effects and radiation-induced fibrosis. Several biochemical pathways have been described including proinflammatory cytokines, interleukins, platelet-derived growth factor, and interferon-gamma.

Two separate entities, namely radiation-induced pneumonitis and radiation-induced fibrosis are recognised. The immediate phase begins within hours to days following radiation exposure characterised by hyperaemic and congested mucosa, leukocyte infiltration, increased capillary permeability, and oedema. Tracheobronchial secretions increase and degenerative changes are seen in the alveolar epithelium. This is followed by the accumulation of thick secretions due to ciliary dysfunction. After weeks of exposure, radiation pneumonitis ensues. It consists of sloughing of endothelial and epithelial cells. Narrowing of capillaries and thrombosis can also be present. A fibrin rich exudate leaks into the alveoli and results in hyaline membrane formation. Following this, there may be a resolution of pneumonitis or migration of fibroblasts and collagen deposition and thickening of the interstitium. Within months a final phase of fibrosis ensues and may progress for years. Anatomic narrowing of alveolar spaces results in reduced lung volumes, traction bronchiectasis, and chronic infections. Symptoms include cough, dyspnoea, fever, chest pain. Auscultation may be normal or crackles may be heard over the affected area. Chest X-ray may show perivascular haziness progressing to patchy densities. CT is considered superior to conventional X-rays. Scans may reveal ground-glass opacities followed by patchy areas of consolidation. Fibrotic phase shows linear opacities or dense consolidations. On PFTs a restrictive pattern is seen. DLCO and resting SpO_2 may be reduced.

4.6.1.4 Cardiac Effects of Radiotherapy [63, 64]

Toxic cardiac effects of radiotherapy may occur in patients with radiation for thoracic malignancies, especially Hodgkin's lymphoma. The toxicity is related to radiation dose, its volume, dose per fraction, and combined use of cardiotoxic chemotherapy. The myocardium is affected leading to its fibrosis and manifesting as restrictive cardiomyopathy. Conduction abnormalities may

also occur due to fibrosis and manifests as various conduction abnormalities and arrhythmias. An echocardiogram may detect diastolic dysfunction even in asymptomatic survivors. A myocardial infarction may be seen in these patients. Heart failure usually develops after years of exposure, especially in the setting of anthracycline-based chemotherapy. Coronary artery disease is a long-term complication seen in many survivors who have undergone thoracic radiation, especially in left-sided breast cancer. Valvular heart disease is relatively common in survivors who have received mediastinal RT. It may involve aortic, mitral, or tricuspid valves. Administration of antibiotics for endocarditis prophylaxis is required in the perioperative period.

4.7 Summary

- The global burden of cancer surgery is huge and is rising. Lack of an adequate number of comprehensive cancer centres results in the majority of cases being treated in general hospitals often in smaller towns and cities. Surgery for cancer may be required in various stages of the disease and many patients receive chemotherapy and/or radiotherapy before presenting for surgery.
- Systemic chemotherapy has widespread effects on all major organ systems which may complicate the perioperative course and are vital for the anaesthesiologist to be well versed with the same.
- Anthracyclines cause cumulative cardiotoxicity by the production of oxygen-free radicals. Classically it is defined as a symptomatic or asymptomatic drop in LVEF, but other features may include ECG abnormalities, arrhythmias, varying degrees of heart blocks, and pericarditis-myocarditis syndrome. All patients who have received anthracycline-based chemotherapy are considered high risk for perioperative adverse cardiac events.
- Bleomycin-induced lung injury is likely caused by reactive oxygen species. Tissue iron stores are also implicated in the pathogenesis. Early manifestations in the form of a symptomatic or asymptomatic reduction in PFT or DLCO values may progress to chronic lung fibrosis. These patients are at risk of exacerbation of lung injury due to perioperative hyperoxia. In the absence of any consensus, it may be prudent to limit oxygen supplementation until necessary.
- Direct or indirect gastrointestinal effects of chemotherapy include mucositis, diarrhoea, malnutrition, cachexia, and dehydration. Transient derangement of liver function is also fairly common. Methotrexate can cause hepatic fibrosis and cirrhosis. Cyclophosphamide can also cause diffuse hepatocellular damage.
- Cisplatin and to a lesser extent carboplatin frequently cause adverse effects in the kidneys. Most commonly a non-oliguric acute kidney injury is seen which may progress to chronic renal failure along with electrolyte abnormalities. Subclinical renal dysfunction may get exacerbated in the perioperative period. Proper hydration and avoidance of nephrotoxic agents help mitigate the risk.
- Vinca alkaloids cause sensory and motor neuropathies. Cisplatin typically involves large myelinated sensory fibres resulting in numbness and paresthesias in the hands and feet. Methotrexate, taxanes, cytarabine, and ifosphamide are all known to cause CNS dysfunction. Thorough documentation of neurological status preoperatively is a must. Regional anaesthesia is a relative contraindication in the presence of neurological deficits. Autonomic neuropathy should also be looked for and adequate precautions must be in place.
- Haematological toxicity is caused by almost all chemotherapy drugs and may affect any or all cell lines. Generally, elective surgery is performed after 6 weeks of chemotherapy which allows for recovery of blood counts. Emergent procedures may have to be carried out which warrants extra caution. Guidelines for blood and blood product transfusion, blood salvage techniques should be employed.
- Radiation therapy affects normal tissues as it does the malignant ones. Acute effects are

caused due to loss of the ability of rapid turnover in tissues like skin, mucous membranes, and bone marrow. Late effects are caused due to tissue fibrosis, damaged microvasculature, and lymphatics. Resulting changes in the airway, respiratory, and cardiac systems pose a considerable challenge in the perioperative period.

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5 Preoperative Assessment and Optimization of the Cancer Patient for Onco-Surgery

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5.1 Introduction

The National Cancer Institute projects the worldwide number of patients with cancer to increase by 50% from 14 million in 2012 to 21 million by 2030. The number of cancer-related deaths is projected to jump 60% from 8 million in 2012 to 13 million in 2030 [1] (Cancer Statistics National Cancer Institute, 2017).

This unprecedented growth in cancer patients necessitates that the onco-anesthesiologist be acquainted with the impact of cancer and its therapies on the patient. This allows for an appropriate preoperative assessment and the need for any further investigations. This also allows the need for optimization of these patients before onco-surgery. Risk stratification and prognostication are crucial matters to consider in preparation of the patient for anesthesia and onco-surgery. Multiple strategies may be undertaken in these cancer patients scheduled for surgical interventions for perioperative optimization which include assessing the degree of deconditioning and prehabilitation.

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5.2 Global Assessment of the Cancer Patient

The preoperative anesthesia-related assessment for patients undergoing cancer surgeries begins with a complete medical history, including the associated comorbidities and history of present cancer illness along with its treatment including chemotherapy or radiotherapy. These therapies may affect the patient's functional status and thus needs to be assessed holistically. The associated comorbidities should be elicited and its impact on various body systems like cardiorespiratory, renal, hepatic, and neurological needs to be assessed. Any previous history of cardiovascular disease, diabetes, pulmonary disorders, renal impairment, or neurological deficits can be further impacted by cancer therapy and major surgical interventions. The past medical and surgical history along with anesthesia management and related concerns needs to be elicited as these may have an impact on perioperative management plan and outcome. The laboratory values, radiological findings, cardiac or pulmonary studies, and a focused physical examination need to be performed. The detailed assessment of the signs and symptoms related to their cancer diagnosis is a crucial first step to determine their preparation for surgery. The patient's "cancer story," which details their path to diagnosis or recognition of the presence of cancer, as well as any neoadjuvant therapies

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they have received are significant to understanding the pathophysiology of their current disease process. This helps the anesthesiologist appreciate the nature of their symptoms and the inherent issues placing the patient at risk during anesthesia and surgery. A critical assessment of a patient's level of pain, nausea or vomiting, respiratory status, cardiovascular stability, and neurological function will guide the anesthesiologist for the overall current status of the patient. A thorough, focused systemic examination is important and includes the patient's airway, heart, lungs, as well as any systems that are implicated in the patient's comorbidities and oncologic history. It is imperative to keep in mind that while many oncological surgeries are not necessarily emergent, they are often considered urgent. Time is of the essence when evaluating, optimizing, and preparing a patient for onco-surgery and consideration must be given to the risk for disease dissemination with delays in surgery [2].

A cancer patient's prior history of chemotherapy and radiation therapy is an important aspect of their perioperative assessment and risk stratification. These neoadjuvant treatments have acute and chronic side effects which must be assessed before surgery [3]. There are numerous chemotherapeutic agents which may profoundly affect major organ systems. These are listed by the class of drugs and common perioperative concerns (Table 5.1).

Table 5.1 Representative chemotherapy agents and perioperative concern

Class	Agent	Common perioperative concerns
Alkylating agent		
Nitrosourea	Carmustine	Pulmonary fibrosis
	Lomustine	
Methylating agent	Procarbazine	Edema, tachycardia
	Dacarbazine	Hepatic necrosis and occlusion
		Hepatic vein thrombosis
	Temozolomide	Seizure and gait abnormality
		Peripheral edema
Platinum	Cisplatin	Acute renal tubular necrosis
	Carboplatin	Magnesium wasting
	Oxaliplatin	Peripheral sensory neuropathy
		Paresthesia
		Ototoxicity
Nitrogen mustard	Cyclophosphamide	Pericarditis
	Ifosfamide	Pericardial effusions
		Pulmonary fibrosis
		Hemorrhagic cystitis
		Water retention
		Anemia
	Melphalan	SIADH
	Chlorambucil	SIADH
		Seizures
Antimetabolite		
Anthracycline/anthraquinolone	Doxorubicin	Cardiomyopathy
	Daunorubicin	Electrocardiogram changes
	Epirubicin	
	Idarubicin	
	Mitoxantrone	
	Valrubicin	
Antitumor antibiotic: natural product	Bleomycin	Pulmonary fibrosis

Table 5.1 (continued)

Class	Agent	Common perioperative concerns
	Mitomycin C	Pneumonitis
		Pulmonary hypertension
Antimetabolite: pyrimidine analogue	Capecitabine	Myocardial ischemia/infarction
	Cytarabine (Ara-C)	Coronary vasospasm
	5-Fluorouracil	
	Gemcitabine	Edema
		Proteinuria
Antimetabolite: purine analogue	Thioguanine	Hepatotoxicity
	Pentostatin	Pulmonary toxicity
		Deep vein thrombophlebitis
		Chest pain
		Edema
		Atrioventricular block
		Arrhythmia
		Hypotension or hypertension
	Cladribine	Thrombosis
		Tachycardia
		Acute renal failure
		Tumor lysis syndrome
	Fludarabine	Cerebrovascular accident/transient ischemic attack
		Angina
		Thrombosis
		Arrhythmia
		Congestive heart failure
		Acute renal failure
		Tumor lysis syndrome
	Mercaptopurine	Intrahepatic cholestasis and focal centrilobular necrosis
Antimetabolite: folate antagonist	Methotrexate	Elevated liver enzyme levels
		Pulmonary edema
		Pleural effusions
		Encephalopathy
		Meningismus
		Myelosuppression
Substituted urea	Hydroxyurea	Seizure
		Edema
Microtubule assembly inhibitor		
Taxane	Paclitaxel	Peripheral neuropathy
	Docetaxel	Bradycardia
		Autonomic dysfunction
Alkaloid	Vinblastine	Hypertension
		Angina
		Cerebrovascular accident
		Coronary ischemia
		Electrocardiographic abnormalities
		Raynaud phenomenon
		SIADH
		Gastrointestinal bleeding

(continued)

Table 5.1 (continued)

Class	Agent	Common perioperative concerns
	Vincristine	Paresthesia
		Recurrent laryngeal nerve palsy
		Autonomic dysfunction
		Orthostasis
		Hypotension and hypertension
		SIADH
Biologic agent		
Monoclonal antibody	Alemtuzumab	Dysrhythmia/tachycardia/supraventricular tachycardia
		Hypotension or hypertension
	Bevacizumab	Pulmonary bleeding
		Hypertension
		Thromboembolic events
	Cetuximab	Cardiopulmonary arrest
	Rituximab	Tumor lysis syndrome
		Electrolyte abnormality
	Trastuzumab	Cardiomyopathy
		Thrombus formation
		Pulmonary toxicity
		Tachycardia
		Hypertension
	Daclizumab	Chest pain
		Hypertension and hypotension
		Thrombosis
	Ibritumomab	Peripheral edema
	Palivizumab	Arrhythmia
	Muromonab-CD3	Tachycardia
		Hypertension and hypotension
Biologic response modulator		
Interleukin	Aldesleukin	Capillary leak syndrome
		Peripheral edema
	Denileukin diftitox	Hypotension
		Electrocardiographic changes
Interferon	Interferon alfa-2b	Arrhythmia
	Interferon alfacon-1	Chest pain
		Pulmonary pneumonitis
		Ischemic disorders
		Hyperthyroidism
		Hypothyroidism
	Peginterferon alfa-2a	Pulmonary infiltrates
		Ischemic disorders
	Peginterferon alfa-2b	Hyperthyroidism
		Hypothyroidism
Vascular endothelial growth factor inhibitor		
Tyrosine kinase inhibitor	Imatinib	Edema
		Left ventricular dysfunction
	Sorafenib	Cardiac ischemia and infarction
		Hypertension
		Thromboembolism

Table 5.1 (continued)

Class	Agent	Common perioperative concerns
	Sunitinib	Cardiac ischemia and infarction
		Thromboembolism
		Adrenal insufficiency
		Pulmonary hemorrhage
		Hypertension
		Hypotension
		Cardiomyopathy
		QT prolongation
		Torsades de pointes
	Dasatinib	Fluid retention
		Cardiomyopathy
		QT prolongation
		Pulmonary hemorrhage
		Platelet dysfunction
	Nilotinib	QT prolongation
		Hypertension
		Peripheral edema
Epidermal growth factor receptor inhibitor		
	Erlotinib	Deep vein thrombosis
		Arrhythmia
		Pulmonary toxicity
		Cerebrovascular accidents
		Myocardial ischemia
		Syncope
		Edema
	Lapatinib	Cardiomyopathy
		Pulmonary toxicity
		QT prolongation
	Panitumumab	Pulmonary fibrosis
		Peripheral edema
Angiogenesis inhibitor		
Immunomodulator	Thalidomide	Thromboembolism
	Lenalidomide	Edema
		Bradycardia
Enzyme		
	Asparaginase	Thrombosis
		Glucose intolerance
		Coagulopathy
Miscellaneous		
Topoisomerase I inhibitor	Irinotecan	Neutropenia
	Topotecan	Diarrhea
	Rubitecan	Cholinergic syndrome
Topoisomerase II inhibitor	Etoposide	Neutropenia
		Steven-Johnson Syndrome
		Toxic epidermal necrolysis
		Myocardial infarction
		Congestive heart failure

From Sahai [3], adapted with permission from Elsevier SIADH, syndrome of inappropriate antidiuretic hormone

5.2.1 Cardiovascular Assessment

Cardiovascular assessment of the cancer patient begins with not only a review of a patient's cardiovascular comorbidities but importantly the impact of chemotherapy or radiation therapy on the cancer patient. The symptoms like chest pain, fatigue, respiratory compromise, restricted functional status may be due to associated comorbidities or systemic adverse effects of cancer therapy and need to be ascertained. The American College of Cardiology/American Heart Association (ACC/AHA) 2014 guidelines on perioperative cardiovascular evaluation and management of patients undergoing non-cardiac surgery [4] is the recommended tool for evaluation and risk assessment of patients undergoing cancer surgeries [2]. Chemotherapeutic agents may affect various body systems leading to arrhythmias and cardiac conduction abnormalities, alterations in blood pressure, coronary vasospasm, coronary artery disease (CAD), and congestive heart failure (CHF) [3, 5]. Radiation to the chest is a known cause of accelerated CAD and myocardial infarction unrelated to coronary vasospasm [5]. The risk factors for cardiac toxicity stemming from neoadjuvant therapies include cumulative chemotherapy dosage, pre-existing heart disease, hypertension, and thoracic radiation [5]. Radiation to the head and neck remains an important etiology for the occurrence of carotid vascular disease and stroke [6].

5.2.2 Pulmonary Assessment

Pulmonary assessment must include evaluation of the past medical history of pulmonary disease, questioning the patient for symptoms of shortness of breath, coughing, smoking history, and any neoadjuvant chemotherapy or radiation of the chest. Some chemotherapeutic agents may cause pulmonary fibrosis, toxicity, pleural effusion, pneumonitis, or hemorrhage. Bleomycin and radiation administered to the chest are both known causes of pulmonary fibrosis.

5.2.3 Neurological Assessment

A thorough understanding of a patient's history of carotid artery disease, seizure, stroke, neurological deficits, and neuromuscular function helps the anesthesiologist determine which medications may be harmful to the oncology patient, their risk for perioperative ischemia or stroke, and postoperative evaluation of mental status and neurological function. Radiation to the neck increases the risk of ischemic stroke.

5.2.4 Renal Assessment

Assessment of renal function includes evaluation of any nephrotoxicity associated with chemotherapy as well as a determination of any renal insufficiency or failure. Cisplatin is known to cause acute renal tubular necrosis.

5.2.5 Airway Assessment

The assessment of the oncology patient's airway is of utmost importance to the Onco-Anesthesiologist. Tumors may invade the airway making ventilation and/or intubation challenging and perhaps impossible. Mediastinal masses are present with some liquid tumors and lung cancers and are a tremendous risk for the induction and maintenance of anesthesia. Prior radiation to the head and neck, as well as past airway and neck surgeries, increase the risk of difficult ventilation and/or intubation.

5.3 Risk Stratification and Prognostication

Risk assessment in anesthesia is performed when the physician, after examining a patient's clinical predictors, functional capacity, and inherent surgical risks, determines their potential for perioperative morbidity and mortality. A patient's functional capacity has been defined as "the dif-

ference between basal and maximal function" [7] and is an estimation of the oncology patient's fitness. The determination of preoperative functional capacity is important that one may not only appreciate the risks for complications of major non-cardiac surgery but also that appropriate prehabilitation measures may be undertaken if possible. Asking a patient about their daily activity level and exercise tolerance helps determine their metabolic equivalent (MET) level, which is a method of establishing the functional capacity and cardiopulmonary reserve of a patient. One MET is the oxygen uptake of 3.5 ml/kg/min. Metabolic levels span from 1 to 10, on a scale corresponding to increasing activity levels. When a patient can care for one's self, eat, dress, and use the toilet they are at 1 MET. The ability to climb stairs, walk uphill, or participate in mild sports equates to 4 METs, while strenuous activities correspond to a level of 8–10 METs. When a patient is unable to reach 4 METs they are considered to be at an elevated level of perioperative risk. This subjective determination of functional capacity may limit our ability to accurately predict future complications and optimize the patient for surgery. Objective measurement of the onco-patient's functional capacity could give a more accurate prediction of morbidity and mortality.

The most common, subjective measurement of perioperative risk is the American Society of Anesthesiologists (ASA) physical status classification. The ASA classification (Table 5.2) of a patient ranges from I to VI and corresponds to increasing perioperative morbidity and mortality [8]. The surgical risk of a procedure is dependent on factors such as urgency, surgical site, and duration, extent, the potential for blood loss and fluid shifts, body temperature variation, and anesthetic technique. Risk stratification involves categorizing patients into a level of risk and has been defined as "a process of medical decision making within which a collection of activities (e.g. laboratory and clinical testing), is used to determine a person's risk for suffering a particular condition, and need, or lack thereof, for preventive interventions" [7]. The American College of Surgeons (ACS) has developed the ACS NSQIP (National Surgical Quality Improvement Program) Surgical Risk Calculator which combines 20 patient characteristics to stratify the individual's postoperative risk for the first 30 days after surgery [9].

Table 5.2 American society of anesthesiologists classification

ASA Class	Definition
I	Normal, healthy patient
II	Patient with mild systemic disease
III	Patient with severe systemic disease
IV	Patient with severe systemic disease that is a constant threat to life
V	Moribund patient, unlikely to survive without the operation
VI	Brain-dead patient who is to be an organ donor
"E"	Denotes an Emergency procedure

Prognostication in medicine is the ability to predict a patient's outcome based on one's clinical judgment. The Measurement of Exercise Tolerance before Surgery (METS) study aims to determine the prognostic accuracy of Cardiopulmonary Exercise Testing (CPET), the Duke Activity Status Index (DASI), and the measurement of serum concentration of N-terminal pro-B type natriuretic peptide (NT pro-BNP) as objective measures of functional capacity, in comparison to subjective measurements by the physician [10]. CPET has emerged as a gold standard technique for evaluation of the patients' functional capacity objectively. DASI is a questionnaire about daily activities that have shown promise as an indication of functional capacity. NT pro-BNP is a biomarker that may indicate cardiac failure or ischemia, thus providing an indirect determination of functional capacity. Assessment of the oncology patient's frailty (age-related physiological changes leading to intolerance to stressors) and degree of sarcopenia (loss of muscle mass and strength) can precisely predict an oncology patient's risk of poor outcomes following complex gastrointestinal surgical procedures [11]. Frailty is a clinically recognizable state of increased vulnerability to

physiological stressors from the age-associated decline in reserve and function across multiple physiological systems [12]. Sarcopenia is an acceptable quantitative measure of frailty. Measurement of an oncology patient's sarcopenia may aid in prognostication and guide prehabilitation.

5.3.1 Prehabilitation

The role of prehabilitation for cancer patients is emerging with its benefits and improving the overall perioperative outcome [13]. Cancer prehabilitation can be described as "a process on the cancer continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment, includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides interventions that promote a patient's health to reduce the incidence and the severity of future impairments" [14]. This targets various modifiable risk factors for optimization and thus affecting treatment outcomes [13]. Suboptimal functional capacity in the preoperative period affects adversely the postoperative outcome [15]. Traditionally, patients undergo rehabilitation during the post-surgical period. But with the emerging evidence, this may not be very beneficial as patients may not be able to accept and perform various prehabilitative strategies in the immediate postoperative period due to pain, fatigue, and lack of appetite. So, the prehabilitation needs to be started from the first contact in preoperative period itself. The pre-surgical period provides a window of opportunity during which to prepare for the stress of oncological surgeries. Many cancer patients are older, have multiple comorbidities, and aged-related changes such as frailty, deconditioning, decreased muscle mass, and aerobic capacity. The goals of prehabilitation are to increase functional capacity, improve cardiorespiratory reserves and thus to improve tolerability to perioperative stress response [13]. The various strategies of prehabilitations should be based on underlying cancer, proposed surgical intervention, associated comorbidities, and patients baseline functional status. In conjunction with perioperative enhanced recovery protocols, prehabilitation may reduce postoperative morbidities and length of hospital stay. Although promising, the current evidence is limited, and further studies are needed [16].

Prehabilitation programs use either a unimodal or multimodal approach addressing physical fitness, nutrition, anemia correction, alcohol/smoking cessation, and stress reduction.

5.3.1.1 Physical Activity

Several studies have shown significant improvements in functional quality of life (QOL), fatigue, and aerobic capacity following exercise training during the pre-treatment, treatment, and post-treatment periods in patients undergoing cancer surgeries [17, 18].

5.3.1.2 Nutrition

Cancer patients are often malnourished due to chemotherapy-induced gastrointestinal symptoms such as anorexia, malabsorption, diarrhea, nausea, and vomiting. Tumor related catabolism and insulin resistance also contribute to malnutrition [18]. The prehabilitation nutritional goals are to increase protein intake to attain anabolism and to enhance immunity [19].

5.3.1.3 Anemia Correction

The European Cancer Anaemia Survey, a prospective, epidemiological survey involving 24 European countries, found that anemia is prevalent in 39.3% of patients with cancer. The survey defines anemia as a hemoglobin <12 g/dL, regardless of gender [20, 21].

The World Health Organization (WHO) advocates preoperative measures to normalize hemoglobin levels. Allogeneic blood transfusion is associated with worse prognosis, especially in colorectal cancer patients [22]. Oral or intravenous iron and erythropoiesis-stimulating agents are therapeutic options. Intravenous iron infusion to treat iron deficiency anemia is better tolerated than the oral form. Although safe, the intravenous form is infrequently prescribed due to misinformation. The use of erythropoiesis-stimulating agents for improving the anemia status reduces the need for blood transfusion

perioperatively but it has been found to increase the occurrence of various adverse events like thromboembolism and death [23].

5.3.1.4 Smoking/Alcohol Cessation

Smoking is one of the risk factors for adverse events in the postoperative period for the patient undergoing cancer surgeries. The prior and current smokers are at increased risk of postoperative complications, including surgical site infection, pneumonia, respiratory failure, and mortality as compared to non-smokers [24]. Studies have found that smoking cessation for 6–8 weeks before surgery significantly lowers postoperative complications, including wound infection, myocardial infarction, and congestive heart failure [25, 26]. For patients undergoing esophagectomy, it has been reported that smoking cessation for more than 90 days before surgery is ideal to decrease postoperative morbidities, including surgical site infection, anastomotic leakage, cardiovascular and pulmonary complications [27]. The same group of researchers also found smoking cessation of at least 31 days significantly decreases postoperative morbidities in minimally invasive esophagectomies [28].

5.3.1.5 Stress Management

Anxiety and high catecholamine levels adversely affect immune function. Interventions such as music, yoga, deep breathing exercises have been used. Reduced anxiety and lower analgesia requirements have been achieved with music therapy [29].

5.3.2 Cardiopulmonary Exercise Testing (CPET)

With the increasing life expectancy, more elderly patients with multiple comorbidities will need oncological surgical procedures. These patients may have compromised cardiorespiratory reserves. At times, such compromise may be subclinical as well. Cardiopulmonary exercise testing (CPET) has emerged as an important modality to assess the patients' functional capacity holistically. It is a non-invasive assessment tool and can detect clinically occult heart disease, risk-stratify patients for surgery, and to predict postoperative outcome [30]. It can also be used to guide prehabilitation and rehabilitation. According to the Joint Statement of the American Thoracic Society (ATS) and the American College of Chest Physicians (ACCP), CPET "provides a global assessment of the integrative exercise responses involving the pulmonary, cardiovascular, hematopoietic, neuropsychological and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function" [31].

Various conventional tests like 6-min walk and the incremental shuttle walk also evaluate exercise tolerance, however, CPET is considered the gold standard. CPET is considered safe, with a reported mortality risk of 2–5 per 100,000 tests in the cardiovascular disease patient population [31]. Class I indications listed by the American College of Cardiology and the American Heart Association for CPET testing are to evaluate the exercise capacity preoperatively, to evaluate patients with cardiovascular disease and heart transplantation candidates, and to help differentiate the cardiac versus pulmonary causes of impaired exercise capacity. The CPET should be avoided in patients of acute myocardial infarction, unstable angina, uncontrolled heart failure, uncontrolled asthma, severe aortic stenosis, and acute pulmonary embolism [31]. The test is terminated if the patient develops sustained tachyarrhythmias, ischemic EKG changes, second or third-degree heart block, severe hypertension, or severe desaturation [32].

Using a cycle ergometry or treadmill as modes of exercise, a test protocol typically involves measurements during 3 min of rest, 3 min of cycling or treadmill exercise without resistance, followed by increasing work rate until exhaustion. Blood pressure, heart rate, electrocardiogram, oxygen saturation, and spirometry are continuously monitored. The various parameters like minute ventilation (VE), oxygen uptake (VO_2), and carbon dioxide output (VCO_2) are analyzed by the machine. Peak oxygen consumption (VO_2 peak), anaerobic threshold (AT), and VE/VCO_2 are the most important derived CPET measurements for perioperative use. "VO_2 peak is defined as the highest oxygen uptake recorded

during an incremental exercise test at the point of symptom limitation", and reflects a person's maximal ability to uptake, transport, and utilize oxygen, and therefore their cardiopulmonary fitness (Table 5.1). During the initial phase of testing, lactic acid production by the muscles is minimal. Anaerobic metabolism occurs when the oxygen supply becomes inadequate to maintain the metabolic demands of the exercising muscles, and lactic acid levels increase. The AT, also known as the lactic acidosis threshold, "characterizes the upper limit of exercise intensities that can be accomplished wholly aerobically" [33].

It has been reported widely that CPET to be used for risk assessment in high risk and to predict postoperative complications for a wide range of procedures, including intra-abdominal, colorectal, and liver transplant surgeries [33–35].

The optimal CPET derived variable, however, appears to differ between surgical procedures. An AT of less than 11 mL/kg/min correlates with an increased postoperative risk after major intra-abdominal surgery. For AAA repair surgery, VE/$VCO_2 \geq 42$ is a better indicator of increased mortality [34].

CPET provides preoperative risk stratification and helps guide clinical decisions (Table 5.3). Patients deemed high risk for adverse outcomes may undergo a palliative procedure rather than the full planned procedure. Also, CPET helps with postoperative disposition decisions (ward versus intensive care) [35, 36]. Many of those studies are single-centered, observational, unblinded studies with a small sample size and thus there is an utter need for future research for CPET derived cut-off values for specific surgeries before this expensive test is more widely implemented.

Table 5.3 Cardiopulmonary exercise test variables with important predictive utility in published perioperative case cohorts

Variable	Definition	Interpretation
Anaerobic or lactate threshold (AT)	The oxygen uptake above which lactate begins to increase and a metabolic acidosis occurs. This is identified by the associated changes in gas exchange.	An index of submaximal or sustainable exercise capacity. Associated with postoperative morbidity and mortality in the majority of published case series.
VO_2 peak	Highest oxygen uptake value achieved during an exercise test.	An index of maximal aerobic exercise capacity. Associated with postoperative morbidity and mortality in most published case series.
VE/VCO_2	Ventilatory equivalent for CO_2 is the ratio of minute ventilation to pulmonary CO_2 production.	An index of efficiency of gas exchange reflecting ventilation-perfusion matching. If elevated, gas exchange efficiency is reduced reflecting increased dead space. It is associated with postoperative morbidity and mortality in some but not all published case series.

From Richardson [36], adapted with permission from BJA

5.4 Summary

To conclude, a holistic thorough preoperative assessment is of utmost importance to improve the overall perioperative outcome. Such assessment helps in risk stratification and optimization of the patient preoperatively to reduce the occurrence of various adverse events. Also, the prehabilitative strategies need to be implemented to improve the patient's physiology and thus allows them to tolerate the perioperative stressors.

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6 Prehabilitation for Onco-Anesthesiology

Chun Hin Angus Lee and Bernhard Riedel

6.1 Introduction

Prehabilitation is defined as multimodal interventions to improve preoperative functional capacity with aims to enhance resilience in perioperative physiological stressors of patients undergoing major surgery [1]. Prehabilitation was first proposed in the early 2000s by Dimitryer and Topp for patients undergoing orthopedic surgery and before Intensive Care Unit (ICU) admission [2, 3]. The body of evidence has grown since numerous reports have demonstrated the feasibility of the prehabilitation program in various surgical subspecialty including, cardiac, orthopedics, vascular, and gastrointestinal (GI) surgery, but the evidence of improved patient's outcome is not conclusive [4–6]. This is in parts due to the heterogeneous study population with different surgical approaches (open vs. minimal invasive surgery) and this is further confounded by variable outcome measure reported including hospital length of stay (LOS), complication rate (severity), mortality, return to baseline function, and quality of life (QOL).

The Enhanced Recovery After Surgery (ERAS) program has epitomized the recent advances in perioperative medicine. ERAS initiative has been proven to be cost-effective for reducing complications and LOS in several large population studies and Cochrane review [7]. In line with the goal of the ERAS program, each component in the prehabilitation program should complement each other in reducing complications and promoting the earlier return to baseline function after major surgery. As a significant proportion of patients would not be able to receive adjuvant therapy due to postoperative complications, reducing complication rate, using optimizing patients before surgery, should facilitate the use of adjuvant therapy for cancer patients [8]. Ideally, clinicians should identify patients in need of prehabilitation at the time of cancer diagnosis and optimization and preconditioning should take place as soon as possible to maximize benefit [1].

Patients with GI cancer are particularly vulnerable due to several known risk factors predisposing adverse outcomes after surgery (Fig. 6.1). Both malnutrition and iron deficiency anemia are prevalent in GI cancer [9–13]. Accordingly, the three key elements of prehabilitation: (1) structured preoperative exercise, (2) nutritional support, and (3) hematinic management target

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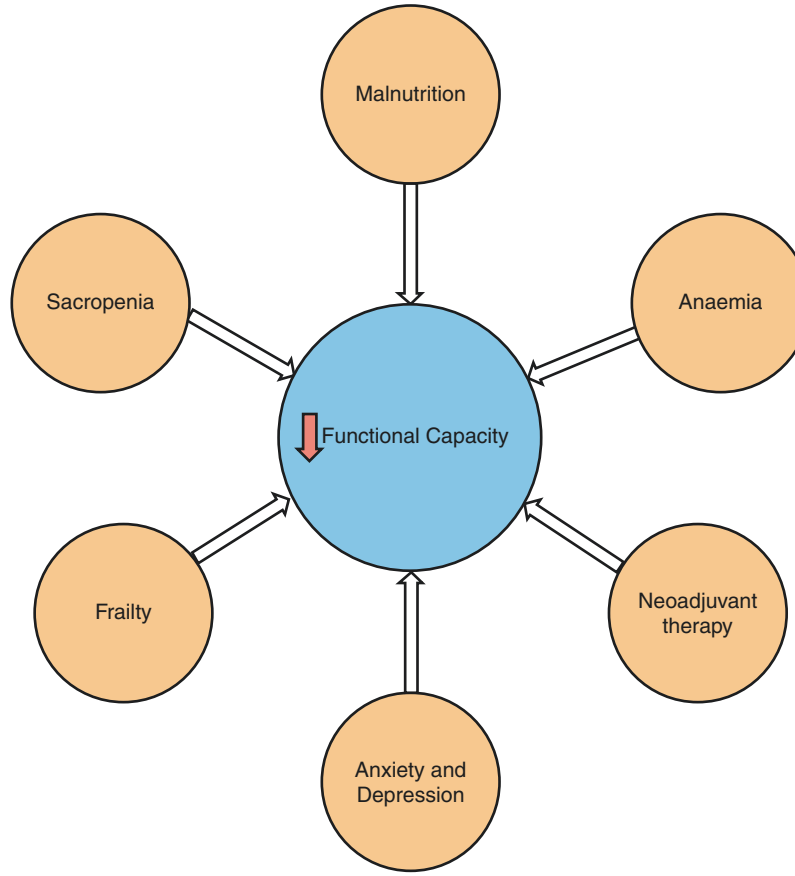

Fig. 6.1 Factors contributing to a decline in functional capacity in patients with cancer

these specific issues to improve patient's resilience to surgical stress (Fig. 6.2). This chapter will focus on discussing the three key elements of prehabilitation based on current evidence.

Although psychological support and counseling are not the focuses in this chapter, they need to be taken into consideration when implementing a prehabilitation program as anxiety and depression are common features in newly diagnosed cancer patients which can interfere with cancer treatment [14, 15].

6.2 Preoperative Exercise Program

6.2.1 Rationale

The decline of preoperative physiological reserve and functional capacity in the elderly group undergoing major GI cancer surgery poses significant challenges during the perioperative period. Poor functional capacity is associated with worse postoperative outcomes and cancer survivorship [16, 17]. Also, functional capacity declines abruptly after major surgery and may not regain baseline function for at least 3–6 months [18].

6.2.2 Method of Assessing Functional Capacity/Fitness

Simple tools such as the American Society of Anesthesiologists (ASA) physical status score, metabolic equivalents (METS), and Duke Activity Status Index (DASI) can be used in the clinic as part of preoperative assessment. More objective measurement of functional capacity such as a 6-min walk test (6MWT) can also be utilized in an outpatient setting.

Cardiopulmonary exercise testing (CPET) has been used extensively in assessing fitness in elite

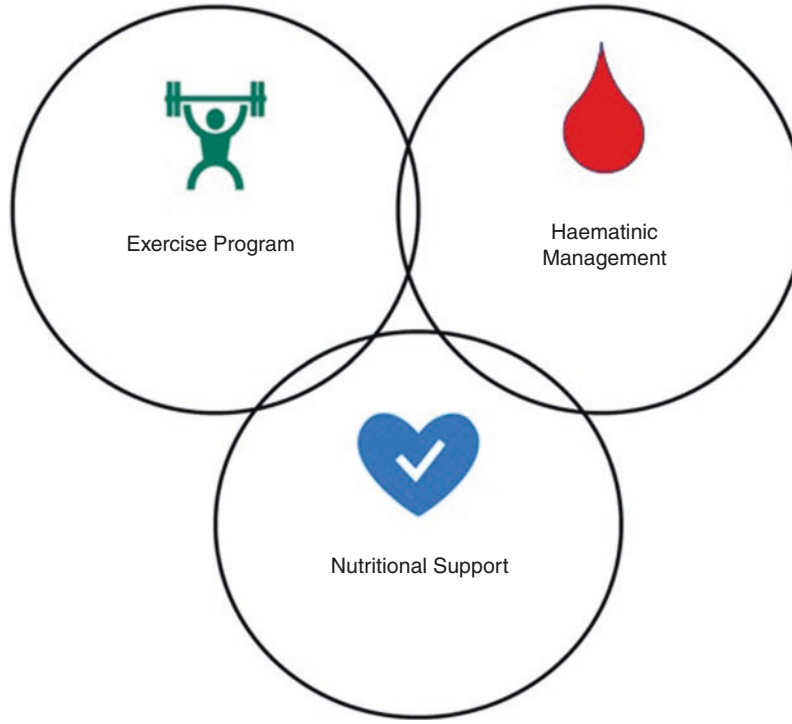

Fig. 6.2 Three pillars for prehabilitation program

athletes and in recent years it has become more commonly utilized in a clinical setting. Pertinent information such as maximum oxygen consumption (VO_2 peak) and anerobic threshold (AT) can be obtained from analyzing the patient's expired gas while the patient is performing exercise on a cycle ergometer or treadmill. In a cohort of 547 patients who underwent major abdominal surgery, patients without a history of ischemic heart disease who had AT ≤10.9 ml/kg/min had higher all-cause hospital and 90-day mortality (relative risk 10.0) [19]. The predictive value of preoperative VO_2 peak and AT in correlation to postoperative complication and mortality has also been evaluated in several retrospective studies involving patients undergoing upper gastrointestinal, hepatobiliary pancreatic, and colorectal surgery. In a cohort of 204 patients who underwent hepatic resection, Junejo and researchers reported that AT less than 9.9 ml/kg/min is predictive of inpatient mortality (sensitivity 100% and specificity 76%) [20]. Moyes and co-investigators reported patients with postoperative cardiopulmonary complications after oesophagogastric cancer surgery had lower AT compared to those who did not have cardiopulmonary complications (9.9 ml/kg/min vs. 11.2 ml/kg/min, $p = 0.05$) [21]. For patients with pancreatic cancer requiring pancreatectomy, the risk of developing pancreatic fistula and major intraabdominal sepsis increases significantly if AT is less than 10 ml/kg/min [22]. Similarly, in a multicenter analysis of patients who underwent major colorectal surgery ($n = 703$), West and co-investigator identified a cutoff of AT and VO2 peak (11.1 ml/kg/min and 18.2 ml/kg/min, respectively) which correlated with postoperative complications [23].

6.2.3 Exercise Strategies

In conjunction with the ERAS program, preoperative strategies to improve functional capacity have been explored in view to improve postoperative outcomes. Carli and co-investigators from Montreal conducted a randomized controlled trial to examine the impact of a preoperative exercise program in patients scheduled for colorectal surgery ($n = 112$). Patients were randomized into two groups: structured bike and strengthening exercise (intervention) versus walking and breathing exercise (control) [24].

Functional capacity was assessed by 6MWT before and after exercise prehabilitation and after surgery. Overall adherence to exercise regimen in the intervention group is low. There was no significant difference in 6MWT throughout the study period when comparing the two groups. However, subsequent reanalyzing of the data indicated that a subset of patients (33%) who responded to exercise prehabilitation with increased walking distance in 6MWT were more likely to recover to baseline walking distance after surgery compared to the non-responders [25]. Comparing to rehabilitation, prehabilitation over 1 month period results in more patients return to baseline walking distance 8 weeks after colorectal cancer resection [26]. Trimodal prehabilitation (median 33 days) incorporating nutritional support and psychological counseling in addition to structured preoperative exercise was shown to improve walking distance after colorectal cancer resection with 81% return to baseline walking distance compared to 40% in those without prehabilitation ($p < 0.01$) [27]. Overall improvement in fitness is measurable and reproducible after prehabilitation using CPET. In a small cohort of 39 patients with rectal cancer requiring neoadjuvant chemoradiation (NACRT), AT was reduced by 1.9 ml/kg/min after NACRT. Patients who did not have exercise prehabilitation continued to have a decline in functional capacity 6 weeks after NACRT. In contrast, AT of patients who had exercise prehabilitation increased by 2.1 ml/kg/min at 6 weeks after NACRT [28].

Although improvement in functional capacity after structured preoperative exercise is measurable objectively, the evidence supporting the notion of translation to better surgical outcomes is lacking. Of note, there is only one study that demonstrated a reduction of complication rate after the preoperative exercise program [29]. While most of the other studies did not demonstrate any statistically significant reduction in various outcome parameters specifically LOS and associated complication rate (Table 6.1) [24, 26–28, 30–35]. Results from a recently published Spanish randomized controlled trial ($n = 144$; 75% gastrointestinal cancer surgery) showed that the complication rate was halved in the exercise prehabilitation group ($p = 0.001$) [29]. In contrast to other studies, this RCT is the only study that included high-risk patients only (ASA score of 3 and above).

At present, the evidence is limited due to the small sample size in each study. Larger prospective trials are currently underway to examine the impact of prehabilitation in postoperative complications for high-risk patients undergoing gastrointestinal cancer surgery [36, 37]. Results derived from these larger studies may provide more meaningful results with sufficient statistical power in the future and guide us in identifying the high-risk individuals who will benefit the most from exercise prehabilitation.

6.3 Nutritional Support

The prevalence of malnutrition is estimated to be 30–50% in patients with gastrointestinal cancer [9, 38]. Patients with GI cancer are particularly at risk of malnutrition due to various factors including tumor pathology, host response, and treatment side effects. Dysphagia in oesophageal cancer can limit oral food intake, whereas locally advanced colorectal cancer can cause bowel obstruction. Chemotherapy-induced nausea and vomiting can also limit the patient's oral intake. The systemic inflammatory response (SIR) mediated by various pro-inflammatory cytokines is implicated in driving cancer cachexia and involuntary muscle wasting which can lead to significant functional impairment [13].

Malnutrition is an important adverse prognostic indicator for the response to surgical treatment of cancer and survival [39, 40]. As such, clinicians should be vigilant in screening for and identifying at-risk individuals at the time of cancer diagnosis. Assessment of the severity of malnutrition will guide the appropriate level of nutritional support.

Table 6.1 Impact of preoperative exercise program on postoperative outcome after gastrointestinal cancer surgery

Study (number of patients in the intervention group)	Supervised component	Home component	Duration	Other intervention	LOS (ICU/hospital)	Complication rate (compared to control)
Barberan-Garcia et al. [29] ($n = 62$)	Progressive high-intensity endurance training (cycle ergometer) Up to 80% of age-predicted max HR 1–3 sessions week	Daily steps monitored by pedometer ± sit-stand exercise, stair climbing, elastic bands	6 weeks	Nutritional counseling; smoking cessation and alcohol reduction; Iron infusion for iron def psychology	Mean ICU LOS 3 vs. 12 days ($p = 0.046$) Mean hospital LOS 8 vs. 13 days ($p = 0.078$)	Overall 31 vs. 62% ($p = 0.001$) Clavien–Dindo classification Medical: Cardiovascular 2 vs. 13% $p = 0.033$ Infection (uncertain source) 0 vs. 11% = 0.013 Surgical: Paralytic ileus 0 vs. 16% $p = 0.001$
Chen et al. [30] ($n = 57$)	Mixed aerobic and resistant exercise (40 mins) 50% of age-predicted max HR 3 sessions per week	–	4 weeks	Nutrition Psychology (anxiety reduction and relaxation technique)	–	–
Minella et al. [31] ($n = 113$)	Mixed aerobic and resistant exercise (20–30 min) Moderate intensity (Borg scale)		4 weeks preop and 2 months postop	Nutrition Psychology (anxiety reduction and relaxation technique	Median hospital LOS 4 vs. 3 days (0.806)	No difference (Clavien–Dindo 0–5, $p = 0.752$)
Dunne et al. [32] ($n = 20$)	30 min of interval training on a cycle ergometer (alternating moderate up to 60% VO_2 peak to high intensity up to 90% VO_2 peak) 12 sessions over 4 weeks	–	4 weeks	–	No statistical difference (no p-value) Median ICU stay 1 vs. 1.5 days Median hospital LOS 5 vs. 5 days	No statistical difference Overall: 42.1 vs. 46.7% Grade 3 and 4 Clavien–Dindo 15.8 vs. 6.7%
Cho et al. [33] ($n = 18$)	Unclear whether the program is hospital or home-based Mixed aerobic 3–7 times/week (treadmill, cycle ergometer, swimming, jogging or dancing), resistance 1–2 times/week Stretching pre and post-exercise		4 weeks	–	Median hospital LOS 9 vs. 10 days ($p = 0.038$)	No statistical difference in each complication including respiratory, wound infection, intraabdominal abscess, anastomotic leak, pancreatic fistula, and bleeding
West et al. [28] ($n = 22$)	40 min interval training on the cycle ergometer (alternating moderate to severe intensity) 3 sessions/week Commence immediately after completion of NACRT	–	6 weeks	–	–	–

(continued)

Table 6.1 (continued)

Study (number of patients in the intervention group)	Supervised component	Home component	Duration	Other intervention	LOS (ICU/hospital)	Complication rate (compared to control)
Gillis et al. [26] ($n = 38$)	–	Mixed aerobic and resistance exercise 50 min aerobic exercise (walking, jogging, swimming, or cycling); at least 3 times a week; intensity tailored by max HR and Borg Scale	25 days	Nutritional counseling (whey protein supplement) and anxiety reduction strategy	No difference 4 vs. 4 days ($p = 0.812$)	No difference in overall complication 32 vs. 44% $p = 0.277$
Li et al. [27] ($n = 42$)	–	Moderate aerobic exercise at 50% of target maximal HR (30 min 3 times/week) and Resistance exercise	3–6 weeks	Nutritional counseling (whey protein supplement) and anxiety reduction strategy	No difference 4 vs. 4 ($p = 0.71$)	Overall complication rate 36 vs. 44% (NS) No difference in each Clavien–Dindo I–III ($p = 0.67$)
Kaibori et al. [34] ($n = 25$)	Unclear whether program is hospital or home-based 60 min aerobic exercise (walking) 3 times a week 20 min of stretching exercise		1 month (continued for 6 months postop)	–	Not significant 13.7 vs. 17.5 days $p = 0.1200$	Not significant 4.3% (2/23) vs. 1.3% (3/23) $p = 0.6710$
Carli et al. [24] ($n = 58$)	–	Bike/strengthening exercise (50% of max HR initially then increased by 10% each week) Weight training 3 times a week Total of 20–45 min of exercise per day	52 days	–	Not significant 11.9 vs. 6.6 days (p-value not provided)	Not significant No complication: 61 vs. 67% Clavien–Dindo Grade 1: 16 vs. 7% Grade 2: 13 vs. 20% Grade 3 or more: 11 vs. 6% (p-value not provided)
Dronkers et al. [35] ($n = 22$)	Mixed aerobic (55–75% of maximal HR) and resistant exercise + inspiratory muscle training	Minimum of 30 min of walking or cycling a day	2–4 weeks	–	16.2 vs. 21.6 days $p = 0.31$	Overall complication 45 vs. 38%, $p = 0.65$ Pneumonia 5 vs. 15%, $p = 0.27$

6.3.1 Nutritional Assessment

Several nutrition screening tools are available; however, there is no consensus on which method of assessing nutritional status is the most useful in the surgical cohort [41]. Albumin is a protein synthesized in the liver exclusively (half-life 17–19 days) and can be used as a surrogate marker for nutrition status. However, its reliability is subjected to many conditions such as posture and various inflammatory states. Similar to albumin, transferrin and prealbumin are negative acute phase reactants produced by the liver. Their serum level falls in the presence of infection, surgical stress, and trauma regardless of nutritional status, therefore limiting their specificity [42]. Nonetheless, in recent years, the Glasglow Prognostic Score (GPS) which incorporates both albumin and C-reactive protein (CRP) has been shown to correlate to nutritional status in surgical patients [43, 44].

Nutrition focus history taking and physical examination should be the focus of objective nutritional assessment rather than relying on laboratory markers. History of weight loss over 5% in 4 weeks [45] and poor oral intake should prompt formal dietetic consultation.

Measuring body mass index (BMI) alone can be unreliable as patients can have significant muscle mass loss without any loss in total body fat content, a term called sarcopenic obesity [46]. Many validated nutritional assessment tools can be used to assess the severity of malnutrition. Subjective Global Assessment (SGA) is one of the commonly used assessment tools in both research and clinical settings and its validity and inter-rater reliability have been demonstrated in surgical patients [47, 48].

6.3.2 Nutrition Goal

The goal of nutrition support is to restore lean body mass and maintain energy level and functional capacity. The recommended target energy intake is 25–30 kcal/kg/day with 1.2–1.5 g of protein/kg/day with a higher requirement in severe malnutrition [49]. The oral/enteral route is the preferred route with fewer complications compared to the parenteral route; also, enteral nutrition minimizes mucosal atrophy in the gastrointestinal tract. The parenteral route is necessary in case of intestinal obstruction and refeeding syndrome can be minimized by slowly titrating infusion rate along with fluid and electrolytes replacement [50].

Immunonutrition aims to work with enteral feeding synergistically to maintain gastrointestinal tract integrity and restore dysregulated immune response. Early trials in patients (both malnourished and well-nourished) undergoing upper gastrointestinal and colorectal cancer surgery have shown the use of immunonutrition such as arginine and glutamine reduces complication rate and length of hospital stay [51, 52]. Body of evidence has grown since and multiple systematic reviews and meta-analyses are demonstrating the potential benefit of immunonutrition both in the preoperative and postoperative periods in GI surgery [53–57].

However, it remains unclear regarding which type of immunonutrition should be used, the timing of administration (preoperative only, postoperative only, or both), and duration, owing to the heterogeneity of the study population and immunonutrition formula in each study.

As part of the ERAS program, fasting before surgery is minimized, allowing fluid up to two hours and solid up to 6 h before induction of anesthesia. Preoperative carbohydrate loading is recommended in several international guidelines [58, 59]. A 12.5% carbohydrate-rich drink containing 100 g of maltodextrin is recommended to be administered the night before and 50 g two to three hours before induction. It has been theorized to reduce insulin resistance and enhance perioperative glycemic control [60, 61].

6.4 Anemia

Anemia is defined as hemoglobin <13 g/dL in men and <12 g/dL in non-pregnant females [62]. Overall, 60% of patients with gastrointestinal cancer have underlying anemia [63] whereas colorectal cancer has the highest prevalence

amongst all the GI cancer (30–70%) [64]. Furthermore, anemia can be exacerbated by anemia of chronic disease and chemotherapy-induced anemia. Hepcidin is an iron regulatory hormone that is primarily synthesized by hepatic cells. This hormone blocks the ferroportin-mediated release of iron from enterocytes, macrophages, and hepatocytes. In anemia of chronic disease, functional anemia can occur as a result of increased production of hepcidin [65].

Although anemia may not be apparent, up to 60% of patients with colorectal cancer have iron deficiency due to occult blood loss [66]. The diagnosis of iron deficiency can be made when serum ferritin is <30 g/l. However, in the presence of inflammation, serum ferritin <100 μg/l and transferrin saturation less than 20% are diagnostic [67].

Management of anemia in the perioperative is crucial as hemoglobin plays an important role in oxygen transportation to tissues. Anemia is one of the independent predictors for an impact on a patient's functional capacity and quality of life (QoL) [68, 69]. Although blood transfusion can correct hemoglobin levels quickly during the perioperative period, there are concerns in regard to its association with adverse perioperative outcomes and poorer cancer-specific long term survival [70–72]. A more restrictive blood transfusion practice is adopted in most countries with a transfusion threshold of 7–8 g/dl.

For patients who have iron deficiency anemia (IDA), iron supplementation is recommended to replenish iron storage [67]. Although a Cochrane systematic review failed to demonstrate any significant advantage of the use of iron supplements due to the paucity of large sample studies, results obtained from recently published randomized controlled trials can shed some light into this area [73].

In a randomized controlled trial included 72 patients with IDA (50 patients with colorectal cancer), the use of IV iron is associated with a 60% reduction in allogenic blood transfusion compared to the control group (no iron). Although a modest increase in hemoglobin in the IV iron group was observed, there was no difference in morbidity and QOL after surgery between the two groups [74]. The use of IV iron in anemic patients with colorectal cancer was compared to oral iron supplement in another randomized controlled trial (n = 116). No difference in blood transfusion rate and transfusion volume was found between the two groups [75].

Based on current evidence, IV iron is more effective in replenishing total body iron storage compared to oral iron. However, it is still debatable whether the use of IV iron translates to improved postoperative outcomes.

6.5 Conclusion

The multimodal approach in prehabilitation works synergistically with the ERAS program. There is a growing body of evidence supporting the use of prehabilitation in gastrointestinal cancer surgery. Rather than using a "one size fits all" approach, the clinician should tailor the prehabilitation program to the patient's needs.

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7 Airway Management in Cancer Patients

Rakesh Kumar and Akhilesh Gupta

7.1 Introduction

Anesthesiologists are called upon for airway management of cancer patients in a variety of situations, be it their surgery, imaging, treatment, or any airway emergency. Airway management may be difficult in many of these patients. The reasons for these difficulties are quite obvious for cancers in and around the airway (Fig. 7.1). However, airway management issues may be present for patients having cancers at other locations as well. Airway management in these patients must take all this into account as discussed below.

7.2 Reasons for Difficult Airway in Cancer Patients

The various reasons for difficult airway in cancer patients include:

- The disease process itself
  - Directly because of the location: facial deformities, intraoral growths, growth over the head, neck, or back. Friable growth in and around the upper airway may make airway management both difficult and messy.
  - Indirectly because of cancer-induced generalized changes (malnutrition, poor or missing dentition, anemia, edema, etc.) [1]
- The factors that caused cancer
  - Tobacco chewing [2]: sub-mucosal fibrosis, poor oral hygiene, loose/missing teeth
  - Smoking: poor lung compliance, high carboxy-hemoglobin induced reduced duration of apnea without desaturation (DAWD) [3]
  - Exposure to carcinogens (e.g., aniline dyes) [4]: methemoglobinemia induced hypoxia and reduced DAWD
- Surgery related
  - Previous mandibular/maxillary resection, hemi-glossectomy, laryngectomy, etc. can lead to disfigurement and altered anatomy, making airway management difficult
  - Post-surgical dressings may also result in disfigurement, edema, bleeding, inter-dental wiring, free flaps over the airway, fixed and abnormal head and neck position to reduce tension on the free flap.
- Secondaries in and around the airway
  - Secondaries in the neck may cause deformities and restricted neck movement

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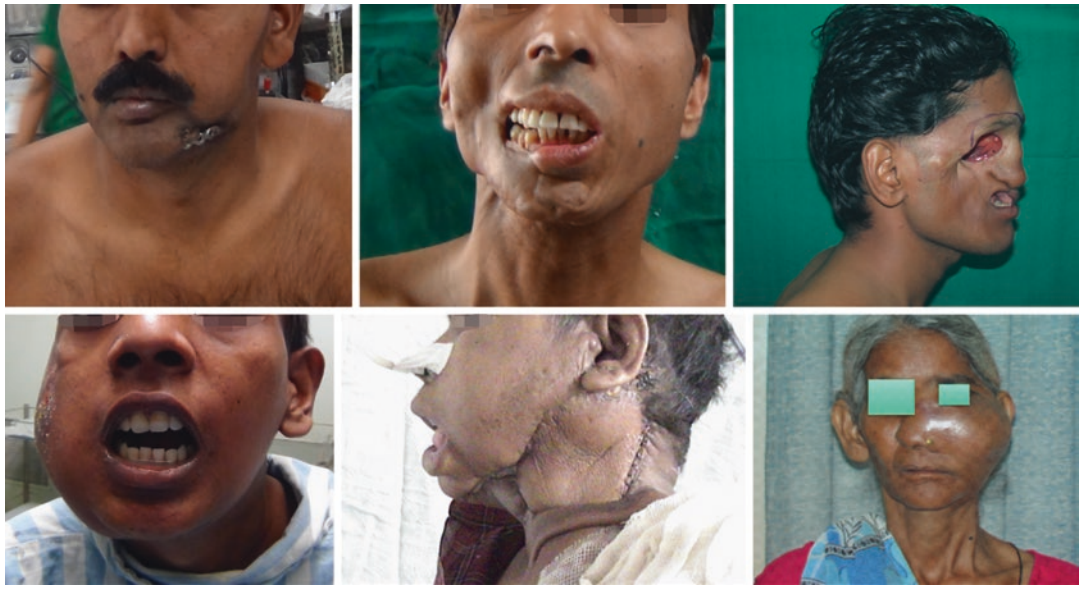

Fig. 7.1 Airway concerns in cancer patients

  - Secondaries in the cervical vertebrae can make neck movements risky
- Chemotherapy related changes [5–7]
  - There may be sequelae of chemotherapy for cancer such as restricted jaw mobility or rigid cervical spine.
  - There can be features of mucositis secondary to chemotherapeutic drug overdosage which may lead to bleeding during intubation.
- Radiotherapy related changes [8]
  - Can induce an acute inflammatory reaction in terms of epidermitis in and around the airway
  - Osteoradionecrosis of the bones [9]
- Age-related: although cancer happens to patients of all age groups, it is still a disease of the old.

7.3 Types of Airway Difficulties in Cancer Patients

As detailed in the American Society of Anesthesiologists (ASA) difficult airway management guidelines [10], airway management can become difficult because of problems with ventilation (through the mask or supraglottic airway devices (SADs)), intubation (because of issues with laryngoscopy or the introduction of the endotracheal tube (ETT) through a visualized glottic opening or both) and access into the airway through the front of the neck. Another dimension is added if the patient does not consent for or is not cooperative during airway management in an awake state. The patient's airway management is not complete until the airway is exited safely [10, 11]. Thus extubation difficulties have also to be anticipated, prevented, and managed.

With this background, the airway difficulties to expect in cancer patients are:

- *Mask ventilation*: This can be due to:
  - Facial deformities
  - Missing teeth
  - Reduced neck movement
  - Increasing age (age > 55 years)
- *Supraglottic airway device (SAD) use*:
  - Reduced mouth opening
  - Friable oral mass occupying almost whole of the oral cavity
- *Laryngoscopy*:
  - Missing teeth
  - Reduced mouth opening
  - Deformity or growth in the mouth entrance itself
  - Reduced subluxation of the lower jaw
  - Distorted oral cavity

  - Non-compliant or altered submandibular area
  - Altered neck condition(shape, mobility, frailty, etc.)
- *Intubation* (*after* a good laryngoscopic view):
  - Growth in and around the glottic opening
  - Mucositis leading to bleeding during intubation
  - Gross distortion or infiltration of larynx/trachea
- *Front-of-neck access*:
  - Growth, scar, dressing
  - Acute inflammation (epidermitis)
  - Grossly reduced neck extension
- *Extubation*:
  - Post-surgical disfigurement, dressings, edema, bleeding, free flaps
  - Inter-dental wiring during surgery
  - Abnormal head and neck position to reduce tension on the free flap
  - Untreated initial cause (unresectable growth)

7.4 Planning Airway Management in Cancer Patients

Planning remains the most important aspect of airway management especially in the difficult airway of cancer patients. This consists of the following steps:

1. Airway assessment
2. Optimization of "difficulties"
3. Reviewing surgical requirements
4. Arranging means to ensure good oxygenation throughout airway management
5. Making main and subsidiary airway management plans

7.4.1 Airway Assessment of Cancer Patients

Any good planning is based on good anticipation of possible difficulties and arrangements made to prevent it or to mitigate its ill effects. A thorough airway assessment helps identify or anticipate the possible difficulties [10]. Building on the suggestions of ASA guidelines [10], the airway management foundation (AMF) uses the following 3-step approach [12]:

1. Focused history
2. Focused general physical examination
3. Focused airway examination following the AMF "line of sight" approach

This 3-step airway assessment aims to identify those airway access routes that are *impossible* to access and those that are *difficult* to access. This then leads the operator to the next step of planning, optimization of the "difficult" areas.

7.4.1.1 Focused History

In addition to the usual history of symptoms/signs and diseases with airway implications (e.g., inability to lie straight, snoring, diabetes, rheumatoid arthritis, etc.), the *focused history* in these patients should elaborate on airway events or their absence during previous attempts of airway management (review old records whenever available). The events during and after the previous intervention(s) that have the potential to affect the airway (surgery, irradiation, chemotherapy, tobacco chewing) are equally important for the reasons mentioned above.

7.4.1.2 Focused General Physical Examination

This should elicit characteristics unique to these patients that can have bearing on airway management such as poor nutritional status and breath holding, breathlessness, altered vocal quality, chemotherapy and radiotherapy induced changes etc.

7.4.1.3 AMF "Line of sight" Airway Examination

Finally the airway manager should conduct the airway specific examination. The ASA 'Line of Sight' (LOS) approach is very laryngoscopy-oral intubation-centric [10]. On the other hand, many of the cancer patients are managed by other than oral intubation based approaches such as nasotracheal intubation, elective tracheostomy and even SADs, especially for non-airway cancers.

Table 7.1 Airway Management Foundation (AMF) suggested plan of "line of sight" airway examination [12]

LOS Parameter	Variation that points to airway management problem
Nose	Deformed, narrow nares/nasal passage
Malar region	Deformed, masses, sunken cheeks
Mouth	Deformed, microstomia, poor access
Teeth	Edentulous, missing, buck, irregular, overbite
Inter-incisor gap (IIG)	<3 cm for laryngoscopy; <2 cm for VL and SAD
Subluxation of lower jaw	<1 cm
Oral cavity	MMP > 2, space occupying masses
Palate	High arched; cleft
Lower jaw	Receding, prognathic, too narrow/too wide, injury, mass
Submandibular space	*Dimensions*: TMD < 6 cm *Compliance*: poor compliance, scarring, growth
Neck length	SMD < 12 cm
Neck circumference	>40 cm in females, >42 cm in males
Head-neck ROM	<90°
Neck landmarks	Poorly palpable landmarks, e.g., cricothyroid membrane

LOS Line of site, *VL* Videolaryngoscopy, *SAD* Supraglottic airway devices, *MMP* Modified Mallampati class, *TMD* Thyro-mental distance, *SMD* Sterno-mental distance, *ROM* Range of motion

We, therefore, use the '*Line of Sight'* approach suggested by AMF [12] for airway examination because it is more elaborate and inclusive to address nearly all-possible areas of likely difficulty during airway management of these cancer patients (Table 7.1). These difficult airway areas should next be managed using optimization tools.

7.4.2 Optimization of Areas Deemed "Difficult" During Airway Assessment in Cancer Patients

A simple way to represent almost all the optimization techniques available is the one described with the vortex approach [13] (Fig. 7.2). This allows the operator to assess beforehand whether and which of these optimization options are possible in his patient. Out of these, *manipulations of head-neck/larynx/device*, *change of type/size of the device*, and *use of suction/O_2* are universally applicable to all airway management events. The use of oxygen is discussed in greater detail below.

Conversely, *muscle tone* can be altered by either deepening/lightening anesthetic depth or administering muscle relaxant/reversing the neuromuscular block. What will work for a particular patient needs to be decided on a case-to-case basis. As a generalization for the cancer patients, those undergoing cancer surgeries in and around the airway, deepening of anesthesia, or administration of neuromuscular blocker when facing problems with airway management may not be prudent. For those having cancers at other locations, the deepening of anesthesia or administration of neuromuscular blockers may help tide over many airway crises.

Adjuncts and maneuvers usually applicable for optimization in cancer patients are:

- *For mask ventilation*: two-person mask holding, nasopharyngeal airway, and oropharyngeal airway (may not be possible in oral cancers). Also blowing out the cheeks of a malnourished, edentulous patient may be of great help.
- *For SADs*: lateral approach may be needed to bypass a growth and lateral or upside down introduction [14] may succeed in cases where there is a mass over the anterior neck.
- *For laryngoscopy*:
  - Video laryngoscopes, especially the more curved ones like C-Mac (D-blade) allow visualization of the laryngeal inlet with minimal pressure on the airway structures
  - Flexible video-endoscopes (fiberscopes) do the same and also provide nasal access needed quite often in airway cancers. These are better tolerated by awake patients under topical anesthesia
  - Methods to protect friable denture/gums/growth may be needed. A teeth guard or gauze pack may come in very handy for missing teeth.

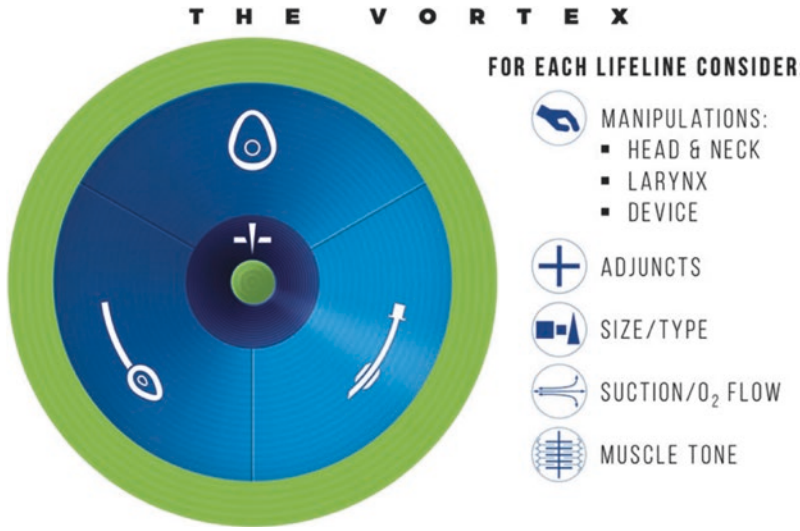

Fig. 7.2 The top view of the three-dimensional Vortex [13]. The three "non-surgical airway management lifelines" (face mask, SAD and endotracheal tube) and the front-of-neck surgical access represent the life-saving ways out of the depth of the whirlpool. The increasing depth and shade of blue represent increasing hypoxia. The optimization techniques mentioned on the right are common to all lifelines, although the adjuncts, understandably, are different for different lifelines

- *For intubation*
  - *Nasal*: cuff inflation technique to guide the ETT into larynx under laryngoscopic/video laryngoscopic vision is quite useful as it avoids the entry of other equipment (Magill forceps) into the airway that may have growth or some friable tissue [15].
  - *Oral*: adjuncts such as stylet and ETT introducer (bougie)and maneuvers like cuff inflation are often used to facilitate oral intubation in difficult cases.
- *For the front-of-neck access*: removal of the bulky dressing and leaving just a thin layer of the dressing over the neck wound just *before* starting airway management is a useful maneuver. It may be advisable to identify and even mark the cricothyroid membrane beforehand in doubtful situations.

7.4.3 Review of Surgical Requirements

In addition to reviewing all the above points as relevant to the particular patient being managed, the main and subsidiary plans will be guided by the surgical requirements as well. In general, the surgical requirements for cancer patient about airway management will be:

- No procedure during or after surgery that can undo the surgical repair
- Airway device directed away from the surgical field
- Extra care to prevent soiling of larynx and trachea
- Oral cavity free of airway device in case of oral surgery
- Awareness about the effects of surgery and dressings on the airway

Although not a surgical requirement per se, it is very important for the airway manager to understand that in cancer surgeries where there is large blood loss, loss of functional lung tissue, impact on ventilation or perfusion, etc., it is vital that the extubation is considered "at-risk" until these otherwise non-airway related factors are allowed to stabilize.

7.4.4 Means of Maintaining Good Oxygenation

With the advent of the latest guidelines of Difficult Airway Society (DAS) in 2015 [16] and the inclusion of the work of many investigators in it [17–20], the stress on pre-oxygenation in every airway management has been substantiated and the concept of oxygenation *during* airway management (called *paraoxygenation* by our airway team [12, 21] and *NODESAT (nasal oxygenation during efforts of securing a tube)* by Levitan [19]) has been highlighted noticeably. Extrapolating these to airway management for cancer patients, all patients for cancer surgeries should be preoxygenated until the FeO_2 (expired fraction of oxygen) is >0.9. Thereafter, oxygen should be provided through nasal prongs while trying to secure the airway whether the patient is breathing spontaneously or is apneic. In the small subset of patients for cancer surgery who have a reduced diffusion capacity of lungs (chemotherapeutic agent-induced reduction in diffusion capacity of lungs for carbon monoxide (DLCO) and thus reduced duration of apnea without desaturation (DAWD)), these maneuvers become vital in avoiding desaturation during airway management. The maximum flow available through the auxiliary oxygen port should be used for this. *THRIVE (transnasal humidified rapid insufflation ventilatory exchange)* [16] has been shown to increase the apnea time by maintaining oxygenation, this much prolongation of apnea is unlikely to happen during airway management for cancer surgeries.

7.4.5 Making Main and Subsidiary Plans

Having elaborated on all the airway issues in cancer patients, their likely effects, and the ways to minimize their impact, let us discuss the decision-making principles that we would suggest for airway management of cancer patients. The basic principles of *any* airway management, like optimum positioning of the patient, operator, and the operation table, etc., should be strictly adhered to while managing the airway in a cancer patient as well so that focus remains sharply on the difficult areas.

1. *The initial method of airway access—surgical or non-surgical*: Unless mask ventilation and SAD use appear impossible or extremely difficult, the choice of airway access should be non-surgical [22].
2. *Airway access after general anesthesia (GA)?* If mask ventilation or SAD placement or both appear normal or only slightly difficult (manageable with devices that can be used in the patient being managed), the airway can be secured under GA or awake as per the choice of the airway manager. However, if both mask ventilation and SAD placement are deemed impossible or very difficult, a rarity even in oral cancer surgery, it will be better to secure the airway before the patient is anesthetized, after the only topicalization of the airway. If it is decided to secure the airway before anesthetizing the patient, a safe level of sedation-amnesia (that does not compromise the respiration or airway patency), achieved by using small, graded doses of sedative-amnesic agent(s) is helpful.
3. *Airway access after neuromuscular block?* If the airway access has been planned and started after administering GA, the airway manager needs to decide whether or not neuromuscular blocking agent can be used to facilitate the introduction of definitive airway device. If mask ventilation is satisfactory after induction of GA, one may consider administering neuromuscular blocking agent to facilitate airway access. It will however be advisable to have the facility to ensure good oxygenation during the period of apnea in place before paralyzing the patient.
4. *Choice of airway access device*: In case the surgery is for cancers other than those in and around the airway, a SAD or ETT may be chosen for securing the airway. However, for cancers in and around the airway, the endotracheal tube is the device of choice. The pharyngeal pack is very commonly placed after tracheal intubation in cancer patients undergoing sur-

geries that are likely to cause trickling of blood, pus, etc. around the laryngeal inlet.

Nasal intubation is often chosen as it allows both the anesthesia and surgery teams better control of "their" part of the airway. The special cuffed ETT recommended to be used with intubating laryngeal mask airway (ILMA-ETT) is the least traumatic ETT when introduced nasally [15]. The reinforced ETT is the second-best choice. Using cuff inflation rather than Magill forceps to facilitate its passage from the oropharynx into the glottic inlet is preferred as it reduces the interventions through the mouth in the presence of friable tissues [15].

5. *Choice of the device for laryngoscopy and intubation*: Video laryngoscope is better than the usual laryngoscope as the first choice to guide the ETT (both oral as well as nasal), to ensure intubation with less traction on the oral and pharyngeal structures. Rigid fiberscope (e.g., Bonfils retromolar scope, meant for oral intubation) allows working in a relatively small passage alongside friable midline oral growths. It also makes it simpler to slide and fix the ETT in the retromolar space, so that the surgeon gets adequate space if the surgery is intraoral. Flexible video endoscope (fiberscope) guided intubation (oral or nasal, as required) is performed by many airway managers as the first choice and by others when video laryngoscopy/laryngoscopy is not possible for any reason. It is even better than a video laryngoscope in protecting the friable tissues in the oral/pharyngeal region. The basic principles of fiberscopy remain the same as in all patients except for certain specific considerations for cancer patients:
   (a) It may be difficult to perform various nerve blocks using intraoral and external approach in some of these patients due to distorted anatomy or neck mass. Topicalization in these patients can be performed by nebulization, atomization, SAYGO (Spray-As-You-Go technique), or a combination of some of these.
   (b) Ensure paraoxygenation at all times through the drug port as well as through the nasal prongs, especially in cancer patients with poor cardio-respiratory reserves.

   Whatever be the method chosen for intubation, the ETT should be secured with great precision as intraoperative displacements/dislodgements are common and access to ETT may be difficult during surgery (especially in case of surgeries in and around the airway).
6. *Planning extubation*: Tracheal extubation in cancer patients is best performed following all the principles of extubation mentioned in the DAS extubation guidelines [11], depending upon the location of cancer, the surgery performed, and the patient's general condition. In cancer patients who fall into the category of "at-risk" extubation (for airway or non-airway reasons), extubation should be performed in a fully equipped operating room (OR) or intensive care unit (ICU) environment (if not performed immediately post-operatively) with extra help around. It must be ensured that the pharyngeal pack if put has been removed and documented before extubating the trachea. The options available for extubation are:
   (a) If the surgery is away from the airway and the airway is "normal," extubate like any other "low risk" extubation.
   (b) If the intubation was difficult and remains difficult at the end of anesthesia, extubate when the patient is fully awake and then too over airway exchange catheter (AEC).
   (c) If there is airway edema, put off extubation till the airway edema subsides substantially and then to extubate over an airway exchange catheter (AEC).

   Whenever extubation is performed over AEC, keep the AEC in place until the patient can maintain his airway and expected level of oxygenation even during sleep.
   (d) If the patient is likely to remain intubated for longer than acceptable period for an ETT to be kept *in situ* for any reason (condition of the airway, condition of the patient, e.g., GCS < 8, etc.), it is best to perform a planned tracheostomy and then decannulate at the appropriate time [23].

Following the above-mentioned principles, the airway manager should create the main and subsidiary plan(s) for airway management of the cancer patient that is being managed. These plans should be made keeping the available resources (equipment, expertise, and manpower) in mind. Once the plans are made, the required resources should be aligned *before* embarking on the airway management to get the best outcome [12].

7.5 Summary

Airway management in cancer patients can be confounded by several factors. These include the location of cancer in and around the airway, the effects of cancer-causing agents, chemotherapy, or radiotherapy, and previous or impending surgery on the airway and oxygenation. Thorough knowledge of these effects on the airway allows the airway manager to anticipate and document these before embarking on the airway management in these patients.

Once documented, the planning for their optimization and management becomes streamlined, keeping the available resources in mind. It is important to realize that in cancer patients (including those with cancers involving the airway) one does NOT always need to secure the airway using flexible fiberscope with the patient awake; and surgical access is rarely needed to access the airway or even post-operatively.

However, exiting the airway may be as or even more tricky than airway access in many of these cancer patients and should thus be seen and managed with due respect. It is important that the airway is reevaluated frequently during cancer surgery and surely before planning the extubation.

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Drugs, Fluids and Cancer

8

S. Bala Bhaskar and M. Manjuladevi

8.1 Introduction

The emerging growth of the subspeciality of onco-anesthesia has made it imperative for the anesthesiologist, as "perioperative physician" to understand the perioperative immunosuppression and cancer biology. In the past decade, the clinical practice has focused on evidence-based factors to improve overall outcomes with various strategies to decrease the risk of cancer recurrence or its dissemination [1]. Evidence is emerging also on how anesthetics and analgesics could impact cancer biology in the perioperative period [2].

Surgery, chemotherapy, radiotherapy, pharmacotherapy, immunotherapy, or a combination of these modalities are the options involved in treating cancer, cancer pain, metastasis, and recurrence [3]. The advances in diagnostic and therapeutic modalities have allowed for early surgical management of many types of cancers.

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8.2 Effects of Surgery

Major cancer surgeries affect the physiological systems including the neuroendocrine system. The body response due to surgical stress is an interplay of many factors including neuroendocrine, inflammatory, immune, and metabolic components. The net result of this interplay is immunosuppression [4]. The cell-mediated immunity (involving NK cells, cytotoxic cells, mononuclear cells, and dendritic cells) is the primary defense mechanism against tumor cells dissemination [5]. Adjuvant oncological therapy in the perioperative period in the form of immunomodulation therapy (e.g. recombinant NK T cells) provides anti-tumor effects and has shown therapeutic benefit and survival potential [6]. Overall, the body responses and the various interactions create a milieu for increased risk of dissemination of cancer with suppression of humoral and cell mediated responses [7].

Anesthetic techniques, drugs and perioperative factors have an impact on immune mechanisms and thus may affect the cancer outcomes [7, 8]. Data on the role of the stress of surgery and anesthesia on cancer metastasis and recurrence has been derived from in vitro and in vivo retrospective, underpowered and inconclusive studies. Surgery as part of cancer management is performed for diagnostic, preventive, debulking, staging, supportive, and palliative purposes. Various mechanisms are involved in

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the increased risk of immunosuppression and risk of cancer metastasis [5, 9, 10]:

(a) Inadvertent dispersion of tumor cells into circulation during surgical manipulation and tumor handling.
(b) Suppression of cellular immune system and loss of tumor surveillance protection, proportionate to surgical insult.
(c) Tumor spread is related to angiogenesis, which is regulated by a balance between pro- and anti-angiogenic factors. The proangiogenic factors include vascular endothelial growth factors (VEGF), fibroblast growth factor, and transforming growth factor (TGF)β. The antiangiogenic factors include angiostatin and endostatin. This balance is affected by surgical stress leading to exaggerated angiogenesis and decreased circulation of antiangiogenic factors that are noted post-surgery [11]. The primary tumor has an inhibitory response on angiogenesis but by its removal during surgery, this inhibitory action is lost promoting recurrence of cancer.
(d) Matrix metalloproteinases interact with host cells and enhance metastatic process [12].

8.3 Anesthetic Agents

Anesthetic and analgesic agents can affect tumor progression and metastasis by different mechanisms (Table 8.1). Major surgery per se has an immune suppressive effect and hence to isolate these anesthetic and analgesic agents as primarily responsible for cellular immunity suppression is a challenge. Researchers measured immune suppression caused by these agents by noting altered immune responses and fluctuations in specific cytokines—interleukins (IL-2, IL-10, IL-12) and interferon-gamma (INF γ). Studies to identify the impact of anesthesia (in vitro, animal model, and human studies) have been able to detect indirect effects on neuroendocrine and immune function, as well as direct effects on tumor cell signaling pathways [13].

The anesthetics exert a direct (non-immune) effect on the cellular biology of cancer cells by their interaction with specific cell signaling especially the hypoxic inducible factors (HIFs) [13]. Inhalational anesthesia upregulates HIFs, inhibits NK cell function, and mediates angiogenesis [7]. Volatile anesthetic agents such as isoflurane, desflurane, and xenon upregulate HIFs. The phenomenon of tumorigenesis and metastasis is primarily regulated by HIF 1α and HIF 2α. The expression of HIF 1α is accumulated in the cellular cytoplasm and then it translocates to the nuclear pole of the nucleus and binds to HIF β. This heterodimeric complex further binds to target genes that are related to hypoxic elements. This leads to gene transcription resulting in the formation of mRNA which in turn promotes angiogenesis, metabolic shift, pH regulation, tumor cell proliferation, migration, and its invasion leading to the possibility of metastasis. On the other hand, propofol, thiopentone, thiamylal, and halothane downregulate HIFs. The effect on HIF expression by different anesthetics varies and is affected by tumor pathology and tissue of origin. Nitrous oxide has immunomodulatory effects as shown in experimental and clinical studies. Nitrous oxide affects the synthesis of DNA, purine, and thymidylate and inhibits hematopoiesis and neutrophil function leading to tumor dissemination [14]. Thus, understanding the impact of anesthetic agents on cells and optimal selection and usage of these agents can have a favorable impact on the outcomes.

The effect of ketamine, thiopentone, halothane, or propofol on NK cell activity and resistance to experimental metastasis was studied in an animal model of mammary adenocarcinoma for pulmonary metastasis. The authors demonstrated that ketamine anesthesia was associated with a 5.5 fold increase and thiopentone with a 2-fold increase in the number of lung tumor cells when compared to controls [15]. The NK cell activity was suppressed by all agents except propofol. The NK cell number was significantly reduced by thiopentone, ketamine, and propofol; not much suppression was observed with halothane [15]. However, a recent study on a pancreatic cell model reported that ketamine, s-ketamine, and MK 801 inhibited cancer cell proliferation and cell death [16]. Ketamine, because of immune

Table 8.1 Effects of anaesthetic, analgesic, sedative agents and other drugs on cancer

Anesthetic agents	Probable mechanisms
Intravenous agents	
(a) Propofol	Inhibits matrix Metalloproteinases(MMP) and prevents tumor spread Reduces NK cell number in animal models
(b) Thiopental	Decreases number of circulating NK cells in animal models and promotes tumor metastasis
(c) Ketamine	Reduction of both NK cell activity and NK number in animal models
(d) Benzodiazepines	
Diazepam	No significant effect
Midazolam	Affect signaling pathways leading to cancer cell death, manifest as necrosis and apoptosis
Inhalational agents	
(a) Volatile agents	Promote apoptosis of NK cells and human T lymphocytes and promote tumor metastasis Reduction of NK cell number in humans, inhibition of interferon stimulation of NK cell cytotoxicity in animal models
(b) Nitrous oxide	Interferes with DNA, purine and thymidylate synthesis and inhibits neutrophil function, inhibits formation of hematopoietic cells, promotes tumor metastasis
Muscle relaxants	
Rocuronium	Promotes breast cancer cell growth, migration and invasion
Vecuronium, Cisatracurium, succinylcholine	Safe (?)
Analgesics	
Opioids	Promote angiogenesis and immunosuppression
Morphine	Inhibits cellular immunity including NK cell activity in animal models and humans
Fentanyl	Inhibits NK cell activity in humans
Non-steroidal anti-inflammatory drugs (NSAID)	Antiangiogenesis effect and inhibit tumor spread
COX-2 inhibitors	Antiangiogenesis and anti-tumor effects in animal models Useful with Beta-adrenergic blockers (?)
Tramadol	Stimulation of NK cell activity
Local anesthetic agents	Inhibition of epidermal growth factor receptor Voltage gated sodium channel mediated anti metastatic effect Impairment of Src signaling Impairment of kinesin motor machinery of neoplastic cells
Others	
Beta-adrenergic blockers	Antimetastasis; useful with COX-2 inhibitors (?)

suppression effect probably has a pro-tumor effect but direct effects on cancer cells is not established. The cellular adhesion, migration and apoptosis in mammary cells have been observed to be inhibited by propofol conjugates (propofol docosahexaenoate and propofol eicosapentaenoate) [17]. Etomidate at higher doses has been shown to reduce the viability of rat macrophages in an in vitro study [18]. Alpha 2 adrenoceptors have been identified in human breast cell lines. The drugs like dexmedetomidine and clonidine, by agonistic action on alpha 2 adrenoceptors were reported to have a pro-tumor effect in animal models [19]. Diazepam does not appear to have a significant effect on cancer cell viability [15]. Midazolam may affect signaling pathways leading to cancer cell death, manifest as necrosis and apoptosis [20]. Cell cycle progression could also be inhibited by midazolam.

8.4 Analgesics

Inadequate postoperative analgesia is related to the suppression of NK cells and increased metastasis in animal studies [5]. In vitro and in vivo studies have produced conflicting results with opioids, to inhibit or promote cancer growth [2].

Administration of opioids like morphine for both acute and chronic pain has also been reported to suppress cell-mediated immunity and humoral immunity [9, 10]. Opioid receptors exist on tumor cells originating from various organs and tissues like neurons, pancreas, thyroid, endometrium, colon, breast, lung, pancreas, thyroid, endocrines and others [21]. The mu (μ) opioid receptor (MOR) is expressed in significant amounts and opioids exert their effect directly on proliferation and invasion of tumor cells and indirectly with immunosuppression, pro-inflammation, and pro-angiogenesis effects and induced apoptosis in cancer cells [21–23]. The opioid type, the dose and the route of administration can influence the effect on cancer cells [7]. The dose-dependent suppression of the NK cell cytotoxicity has been seen with morphine. When morphine is administered in high doses as a continuous intravenous infusion, it inhibits tumor growth and metastasis in rodents, unlike intermittent injections which stimulate the HPA axis and facilitate cancer progression and metastasis [24]. Fentanyl inhibits NK cell activity postoperatively. Sufentanil and alfentanil affect leucocyte function and also have an inhibitory action on NK cells [25]. Buprenorphine is devoid of intrinsic immunosuppressive activity and therefore has a favorable immune profile [26]. Enhanced endogenous opioids (β endorphins) production which is released in response to physiological stress response leads to increased NK cell cytotoxicity, increased anti-inflammatory cytokines, and decreased pro-inflammatory cytokines. This antineoplastic benefit of β endorphin has been suggested to be exploited for possible therapeutic cancer management modality [5]. Prostaglandins have immunomodulatory effects by inhibitory action on cytotoxic and dendritic cells. They downregulate TNF α, β, and upregulate IL10, IL4, and IL6, which are immunosuppressive cytokines [5]. The non-steroidal anti-inflammatory agents (NSAIDs) affect the cyclooxygenase-2 (COX-2) receptors present on cancer cells and also antagonize prostaglandin production by NK cells [27]. The cancer cells of epithelial origin like breast, urinary bladder, cervix, colon, and rectum have overexpression of COX-2 and prostaglandin E-2 (PGE-2) [28]. Given this phenomenon, COX inhibitors decrease the risk of breast, colon, lung, and prostate cancers. COX 2 inhibitor drugs like celecoxib have been part of certain chemotherapeutic regimens as they inhibit cancer cell growth and its dissemination [29]. Tramadol has serotonergic, adrenergic, and opioid receptor-based action, stimulates NK cell activity and this action has been shown to block both surgery-induced NK cell suppression and surgery-induced lung metastasis in rats [30]. Beta-adrenergic stimulation can be a basis for metastasis associated with the use of ketamine. This was confirmed in another rat study where beta-adrenergic blockade with nadolol attenuated the effect of ketamine [15]. Combining nadolol with an immunostimulator (poly I-C) resulted in the complete neutralization of ketamine effects. Various tumors secrete prostaglandins (PGs) to counter the host's cell-mediated immunity and also, many tumor lines express beta 1 and beta 2 adrenoceptors. We may surmise that the perioperative use of COX-2 inhibitors and beta-adrenergic blockers may have beneficial cancer outcomes [31].

8.5 Local Anesthetic Agents And Neuro-muscular Blocking Agents

Local anesthetics (LAs) exhibit anti-tumor effects by anti-inflammatory actions and by inhibitory actions on cancer cell proliferation and its migration. Lignocaine (lidocaine) has direct inhibitory effects on epidermal growth factor receptors. This inhibitory effect prevents the proliferation of tumor cells, especially of epithelial origin [32]. Lignocaine and to a lesser extent, bupivacaine and ropivacaine prevent tumor progression by DNA demethylating effects in breast tumors. They also activate tumor suppressor genes, thereby lessening the tumor progression [33]. Kinesin motor machinery of neoplastic cells may be affected by lignocaine and tetracaine, impairing microtubular protrusions and thereby prevent metastasis. The amide local anesthetics are potent inhibitors of voltage-activated sodium channels and inhibit metastatic

invasion [34]. Some of the anti-tumor effects of LAs are mediated via potassium or calcium channels [25]. Lignocaine and ropivacaine have an inhibitory effect on proto-oncogene Src but chloroprocaine has no effect [35]. Overexpression of this gene in certain solid tumors may lead to cancer progression, invasion, and dissemination. Lignocaine augments NK cell cytotoxicity by increased expression of genes leading to augmentation of the NKG2D receptor. This is useful for solid malignancies and thus has a beneficial effect on its use in the perioperative period [36]. Lignocaine infusion in radical hysterectomy has been found to prevent lymphocyte apoptosis, maintain INFγ to IL-4 ratio, thereby conferring protective effect on cell-mediated immunity, with potential benefit in inhibiting recurrence of the tumor [37].

Neuromuscular blocking agents used in anesthesia practice have also been studied in vitro for their effect on breast cancer cells and gastric cancer cells [38, 39]. Rocuronium has been reported to be associated with tumor cell growth, migration and invasion in patients of breast cancer but vecuronium and succinylcholine were almost inert in these respects. Similar effects of rocuronium were observed in gastric cancer cells but vecuronium and cisatracurium hardly affected the malignant phenotype.

8.6 Effect of Other Perioperative Factors

8.6.1 Hypothermia

Cool ambient theater temperature, surgical factors, and blunted thermoregulation under anesthesia result in perioperative hypothermia. Hypothermia influences function at the cellular level and negatively impacts adaptive immunity [9]. Immunosuppressive effect of hypothermia occurs by its influence on NK cell activity. Rat studies have also revealed that hypothermia can increase metastasis four fold [40, 41]. Significant reduction in overall survival (34 months compared to 45 months) was noticed in the presence of hypothermia in a study of advanced ovarian cancer debulking surgeries [42]. Hypothermia per se can increase bleeding and need for allogeneic blood transfusion, which has implications on cancer dynamics, discussed in the next section [5].

8.6.2 Blood Transfusion

The perioperative transfusion of blood has been found to have an immunomodulatory effect and reported to be associated with increased risk of cancer recurrence, infections, and mortality [43]. A recent meta-analysis strengthens the evidence of blood transfusion-related decreases in cancer-free survival in lung cancer patients even though results of almost half of the trials were either negative or equivocal [44]. Whether there is a true association of transfusion with cancer (as an independent risk factor) or the outcomes represent a cause-effect role for anemia for which blood transfusion was indicated is not known.

It has been reported that the immunosuppressive effect with allogenic blood transfusion (transfusion-related immunomodulation-TRIM) was more pronounced when compared to autologous blood transfusion in patients of stomach cancer [45]. However both types of blood transfusion were associated with reduction in T-helper cell and NK cell count. Also, cytokine production (IL-2 and INF γ) and T-helper/cytotoxic T cell ratio were reduced. The leucocyte related adverse transfusion reactions can be reduced by the use of leucocyte depleted red cell transfusion but the impact on disease-free rates and overall survival rates is not much when compared to those not receiving any transfusion [46]. Thus, the leucocyte induced immune modulation may not be the only mechanism but some unknown mechanisms may be involved in the poor outcomes [46].

8.6.3 Other Perioperative Factors

Acute postoperative pain suppresses NK cell activity. An animal study reports that the stress-

related reduction in host resistance against metastasis is decreased by different pain management techniques, with varying effects on host immunity including anti-tumor defense mechanisms [47].

Anxiety, depression, and psychological stress associated with cancer patients in the perioperative period stimulate HPA and sympathetic nervous system which has a significant impact on the tumor microenvironment. It has been reported that chronic stress in breast cancer patients is a significant predictor of immunosuppression [48]. Immunotherapy has modest success in humans, but its use in the critical perioperative period may be beneficial for overall outcomes. Administration of IFNα and IFNβ before surgery may offset the inhibitory effect of NK cell cytotoxicity due to perioperative surgical stress [49].

8.7 Anesthetic Technique

The perioperative anesthetic management has an impact on immune cells, inflammatory markers, and other serum factors that have an association with cancer recurrence and dissemination. Many preclinical and retrospective studies show that both immunological and non-immunological mechanisms are responsible for cancer recurrence, metastasis due to various types of anesthetic management.

8.7.1 Role of Regional Anesthesia or Analgesia

Multiple retrospective studies have evaluated cancer recurrence and metastasis with the use of regional anesthesia (RA) alone or when combined with peripheral nerve blocks (paravertebral blocks) or neuraxial (spinal/cervical, thoracic, and lumbar epidural) blocks along with general anesthesia (GA) [24, 50, 51]. A meta-analysis of the role of regional anesthesia or analgesia on overall survival, disease-free survival, and recurrence-free survival in many onco-surgeries such as on breast, lung, esophagus, abdomen (colorectal, gastric), bladder, prostate and ovary has shown conflicting results [52]. Some potential benefits that can be attributed to the use of RA include minimal effect on the immune system and possibly reduced risk of cancer recurrence [9, 10]. The mechanisms could be:

- RA induced attenuation of the intrinsic (neuroendocrine response) immunosuppression from surgery.
- Reduction in the amount of general anesthetic requirement (opioids, volatile agents) when GA is combined with RA [52, 53].
- Excellent analgesia with the subsequent reduction in perioperative opioid requirement during surgery (e.g. paravertebral block in breast surgeries) [51].

8.7.2 Propofol Versus Inhalational Anesthesia

A retrospective study on long term survival with the use of volatile or intravenous anesthesia in a large group of cancer patients undergoing surgery (n = 7030) demonstrated that intravenous anesthesia with the use of drugs such as propofol was associated with lesser cancer recurrence than inhalational agents [54]. Propofol by its anti-inflammatory and antioxidant properties, unlike sevoflurane which is pro-inflammatory, has the potential to be beneficial in cancer patients. Positive benefit (50% reduction of mortality) was noted with propofol when compared with inhalational agents like sevoflurane. Propofol anesthesia has also been associated with better survival in patients undergoing colorectal and breast cancer surgeries [55, 56].

Pending publication of more evidences by the ongoing, prospective studies on onco-surgeries and anesthetic technique, an approach to avoid immunosuppressive agents, minimal use of volatile anesthetics and opioids need to be considered in the clinical practice of cancer management [57].

8.8 Fluids and Cancer

8.8.1 General Principles

As per Starling's principle, the transvascular fluid filtration occurs due to pressure gradients related to hydrostatic and oncotic pressures acting in opposite directions. The perioperative fluid management is primarily influenced by the role of endothelial glycocalyx (EGC) and bound plasma constituents (mainly albumin) [58]. The EGC is physiologically active with a functional thickness of 1 μm and its main constituents are membrane-bound proteoglycans and glycoproteins mainly syndecan and glypican [59] with negatively charged side chains (heparan sulfate, dermatan sulfate, and chondroitin sulfate). The EGC system can retain 700–1000 ml of plasma at the endothelial surface and is involved in many physiological processes such as inflammatory and hemostatic modulation; prevention of firm adhesion of leukocytes and platelets and in the transmission of shear stress. Surgery, trauma, inflammation/sepsis, ischemia/reperfusion and volume overload may damage the EGC layer [60]. The integrity of this layer plays a vital role in vascular permeability, intravenous infusions and fluid shifting [58].

Another concept that has been updated is the "*Third Space*." It is a functional compartment and accommodates fluid and remains a major concern for fluid management in the perioperative period [61]. It is classified as an anatomical part and non-anatomical part. Anatomical loss or the functional extracellular volume is the pathological fluid accumulation within the intravascular space and interstitial space, which has an intact vascular barrier, and the excess of it is managed by the lymphatic system. An overload on the lymphatic system (hypervolemia) is resolved through redistribution and urine output. Non-anatomical loss or non-functional extracellular volume is that which is functionally and anatomically lost permanently by surgery and trauma and not available for transcellular exchange [62].

The Starling principle has been updated with the consideration of the EGC concept. The EGC by virtue of its constituents exerts oncotic pressure on the luminal side and remains an important primary molecular filter. The hydrostatic pressure in the vascular lumen exceeds the interstitial pressure forcing the fluid outwards. The oncotic pressure just beneath the EGC is low. This pressure gradient leads to the inward movement of the fluid. The protein molecules below the glycocalyx layer are cleared to the interstitium. The phenomenon of the fluid shift to the interstitial side is a normal environment that includes a protein-free shift of fluid and electrolytes across an intact vascular barrier. This is labeled as physiological type I shift. Pathological type 2 shift relates to protein-rich fluid shift related to the altered morphological vascular barrier [58, 62, 63]. Various factors can disrupt the glycocalyx and this may lead to increased permeability across the endothelium, platelet aggregation, and leukocyte adhesion [62, 63].

Cancer patients carry a high risk for hemorrhage and thromboembolism and pose a unique challenge in the perioperative period. The hemostatic dysfunction is multifactorial and is related to the impact of cancer and its treatment on body biology. The manifestations for such an event may range from macrovascular to thrombotic microangiopathic complications with variable morbidity and mortality [60]. The illness of a cancer patient and the adjuvant therapies involved may result in organ level, cell level and genetic level changes [57].

8.8.2 Perioperative Management of Fluids in Cancer Surgeries

The basic principles of fluid management of "when, what and how much" to administer depends on the underlying disease, its pathological impact, and the fluid status [64]. The target for the adequacy of fluid resuscitation depends on its impact and optimization of macro and microcirculatory parameters [65]. The timely fluid management strategies are important to maintain perfusion of all vital organs and thus to limit any cellular damage by maintaining optimal perfusion and oxygenation in onco-surgeries.

Perioperative stress has an impact on the neuroendocrine system. The activation of the Renin-Angiotensin aldosterone system (RAAS) leads to variations in fluid and electrolyte physiology. This mandates an optimal supplementation of various electrolytes like sodium, potassium and fluids to meet the daily maintenance requirement. The additional requirement is given only with ongoing losses such as vomiting or diarrhea or gastric drainage. Balanced salt solution (Ringer lactate/acetate or Hartmann's) is preferred for replacement unless there is vomiting or gastric drainage causing hypochloremia when 0.9% saline is used. The use of dextrose based fluids can lead to hyponatremia as such solutions are sources of free water. The composition of crystalloids and colloids used in clinical practice is shown in Tables 8.2 and 8.3.

8.8.2.1 Preoperative Fluids

Non-particulate oral fluids are allowed 2 h before elective surgery in patients without disorder of gastric emptying. The current concept is to continue oral clear fluids until 2 h of surgery and initiate fluid intake at the earliest in the postoperative period. The Enhanced Recovery After Surgery (ERAS) concept in the perioperative period is being used for various onco-surgeries including mainly colorectal surgeries and aims to reduce preoperative fasting and increase per os (PO) fluid intake. The use of preoperative carbohydrate loading 2 h before surgery has been reported to be beneficial without any additional risk of aspiration [66, 67]. The beneficial effect of such a strategy is related to the prevention of catabolic state with fasting for long periods where complex lipids, proteins, carbohydrates are broken down to maintain energy source. It also allays anxiety, hunger, thirst, postoperative nausea and vomiting. It improves overall patient satisfaction with better maintenance of volume status. Physiologically, it maintains glucose homeostasis and prevents episodes of perioperative hyperglycemia, which is associated with concerns of infections [68]. This strategy is an integral part of the enhanced recovery pathways [69, 70].

The use of mechanical bowel preparation leads to various fluid and electrolyte imbalances and thus is not being used regularly in present scenarios. In the case of specific clinical conditions, wherein bowel preparation is desirable, monitoring is required and appropriate supplementation of fluid and electrolytes are desirable. Recent evidence recommends iso-osmotic mechanical bowel preparation [71].

Table 8.2 Composition of crystalloids

Contents	Plasma	0.9% NaCl	5% Dextrose	DNS	RL	Isolyte P®	Plasmalyte®	Sterofundin®
Sodium (mmol/l)	140	154	0	154	131	140	140	140
Potassium (mmol/l)	5	0	0	0	5	5	5	5
Chloride (mmol/l)	100	154	0	154	111		98	127
Calcium (mmol/l)	2.2	0	0	0	2	0	0	2.5
Magnesium (mmol/l)	1	0	0	0	1	3	1.5	1
Bicarbonate (mmol/l)	24	0	0	0	0	0	0	0
Lactate (mmol/l)	1	0	0	0	29	0	0	0
Acetate (mmol/l)	0	0	0	0	0	27	27	24
Gluconate (mmol/l)	0	0	0	0	0	23	23	0
Maleate (mmol/l)	0	0	0	0	0	0	0	5
Glucose (g/dl)	<126 mg/dl	0	5	5	0	0	0	0
Osmolarity (mOsm/l)	295	308	252	585	273	295	294	309
pH	7.35–7.45	6.0	4.5	4.0	6.5	6.6	6.6	5.9

Nacl sodium chloride, *DNS* dextrose normal saline, *RL* Ringer's Lactate

Table 8.3 Composition of colloids

Contents	Albumin 4%	Plasmion Geloplasma®	Gelofusine®	HES 6%, 130/0.4[a]	HES 6%, 130/0.4[b]	HES 6%, 670/0.75	HES 6%, 130/0.42[x]	HES 6%, 130/0.42[y]
Sodium (mmol/l)	140	150	154	154	137	143	154	140
Potassium (mmol/l)	0	5	0	0	4	3	0	4
Chloride (mmol/l)	128	100	125	154	110	124	154	118
Calcium (mmol/l)		0	0	0	0	2.5		2.5
Magnesium (mmol/l)		1.5	0	0	1.5	0.5		1.0
Additional components	Octanoate—6.4 mmol/l	Lactate—30 mmol/l		0	Acetate—34 mmol/l	Lactate—28 mmol/l		Acetate—24 mmol/l Maleate—5 mmol/l

HES Hydroxyethyl starch
[a]Waxy maize hydroxy ethyl starch in normal saline
[b]Waxy maize hydroxy ethyl starch in balanced salt solution
[x]Potato based HES in normal saline
[y]Potato based HES in balanced salt solution

Enhanced Recovery After Surgery

Early recovery of physiological functions, reduction of morbidity, and shorter hospital stays are targeted in cancer surgeries. The Enhanced Recovery After Surgery (ERAS) strategies have been found useful in colorectal surgeries. These have reduced the duration of hospital stay without any adverse events [66, 72, 73]. The modified protocols in obstructive colorectal cancer which can be beneficially applied are intensive preoperative counseling by the surgeons and the anesthesiologists with a multidisciplinary team approach. The strategies include goal-directed fluid management, maintenance of normothermia, minimizing fasting preoperatively, resuming oral feeding postoperatively, faster ambulation and early removal of tubes and catheters [73].

Excess fluid can cause pulmonary edema, venous congestion and anastomotic leak, whereas less fluid might result in suboptimal perfusion of the anastomosis and cause a leak [74]. A study on perioperative fluid management of colorectal cancers compared two groups, 96 patients receiving restricted regimen and 89 receiving standard regimen [75]. The regime used in the restricted group included no preloading, 7 ml/kg lactated Ringer's solution (RL) in the first hour followed by 5 ml/kg/h. intraoperatively, and 1000–1500 ml crystalloid on the following postoperative days. The standard fluid regime included preloading 500 ml 6% HAES, 12 ml/kg/h of RL intraoperatively, and 2000–2500 ml crystalloid postoperatively. The restrictive fluid therapy in the perioperative period was found to be beneficial with regard to better preservation of cellular immunity and reduced complications. The fluid overloading is related to tissue edema, delayed bowel function and wound healing.

8.8.2.2 Intraoperative Fluids

The intraoperative period is influenced by many factors such as vasodilatory effects of anesthesia, hormonal response to surgery, ongoing blood and insensible losses, increased capillary permeability and albumin escape rate. Maintaining adequate tissue perfusion remains the basic principle in fluid management. The choice of fluids includes crystalloid, colloids, and blood products. Blood products should be used for optimizing cardiac output and oxygen delivery. But blood transfusion has an immunomodulatory effect and should be used cautiously.

Fixed volume strategies have been practiced in the past whereby estimated volume fluid regimen is commenced and then modified based on conventional hemodynamic monitoring to the preoperative and ongoing losses. Whether to use a liberal or restricted fluid regimen as a baseline approach has been a debate. Monitoring response by clinical parameters and use of arterial waveform analysis based monitors are the suggested options for fluid management [65, 76]. These strategies improve hemodynamics and significantly reduce postoperative complications.

The "liberal" fluid administration can lead to negative consequences on the cardiorespiratory, abdominal, and renal systems. More blood loss leads to a higher tendency for use of blood transfusion due to decreased blood viscosity and dilution of coagulation factors [77]. Malnourished patients such as those with esophageal cancer are hypoalbuminemic and thus intravascular fluid retention is compromised leading to hemodynamic fluctuations [78–80]. The improved perioperative outcomes of restrictive fluid practices have been observed in colorectal and pancreatic surgery. The beneficial effect includes less patient-related complications, preserved cellular immunity, lesser surgical site infections, improved wound healing and maintained cardiopulmonary function [79, 80].

The intraoperative fluid infusion covers the basic principles of maintenance and volume replacement. The balanced crystalloid solutions continue as the main stay maintenance fluids to maintain homeostasis. Volume therapy primarily targets tissue perfusion and oxygen delivery. The fluid requirement varies with patients and depends on many patient and surgery-related factors. This requires individualized fluid therapy using a goal-directed approach [66].

8.8.2.3 Postoperative Fluids

The pre and postoperative details on volume status (fluid losses, insensible loss), volume, and

type of fluids used during surgery need to be scrutinized in the recorded documents. On arrival to the ward, the patient has to be reassessed for hemodynamic status. The fluid shift after surgery usually peaks after 5 h of surgical trauma and persists variably up to 72 h depending on the extent of surgery, site and duration [62]. Increase in body water by 10% has been reported in almost 40% of the surgical patients [62]. The increase in perioperative weight has been related to increase in the postoperative mortality; weight gain of less than 10%, 10–20% and more than 20% being associated with mortality rates of 10%, 32% and 100% respectively. These evidences indicate for cautious use of perioperative fluids not only to maintain perfusion but also prevent fluid overloading. Once achieved, the volume and content of the fluids should match the daily maintenance requirement and replacement is only for any additional ongoing losses.

Monitoring for the fluid status should follow the basic protocol of clinical assessment and vital parameter monitoring and laboratory inputs. The clinical signs like change in pulse rate, urine output, capillary refill, etc. are good indicators for fluid status, either over or underhydration. Minimally invasive techniques that assess stroke volume and cardiac output measurements such as transthoracic echocardiogram, transesophageal Doppler, or pulse contour analysis are available. Microcirculatory parameters like serum lactate levels, central venous oxygen saturation, and the difference between partial pressure of arterial and central venous carbon dioxide are also useful to identify any deficit in tissue perfusion [65, 76]. Patients who can return to oral intake and are euvolemic should resume oral intake as soon as possible.

8.9 Summary

The perioperative goal-directed therapy should aim at avoiding harmful effects of hypovolemia (organ hypoperfusion, sepsis, multiorgan failure) or fluid overload (edema, postoperative ileus, postoperative nausea and vomiting, cardio-pulmonary complications) and aim at a balanced fluid strategy to enable an early postoperative recovery.

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Part III

Specialty Anaesthesiology for Cancers

Anesthesia for Oral Cancer Surgery

9

Sheila Nainan Myatra and Sushan Gupta

9.1 Introduction

The cancers of the lip and oral cavity comprise around 2% of all malignancies and 1.9% of all cancer deaths with the cumulative age-specific rate being 5.8% in males and 2.3% in females. Cancers of the lip and oral cavity are more common in Southern Asia [1]. Tobacco use is the commonest etiological factor for head and neck cancers (HNC) [2].

Anesthetic management, including perioperative airway management, is challenging in head and neck cancer patients. Primary lesions of the airway structures not only tend to obstruct the airway but are also associated with a risk of bleeding during manipulation. Also, several other factors make airway management challenging during oral cancer surgery. These include sharing the airway with the surgical team for surgical intervention, the prolonged nature of the surgery, the presence of trismus, and decreased submental compliance due to prior radiation therapy. The airway may be further compromised intraoperatively due to surgical handling leading to laryngopharyngeal edema and bulky flaps encroaching into the oral cavity and reducing the airway caliber, both of which may make re-securing the airway after extubation of the trachea extremely difficult. Thus, airway management in oral cancer surgeries poses unique challenges for the anesthesiologist not only during the surgery but also in the post-operative period. Moreover, cancer therapies like radiation therapy and chemotherapy, cancer itself, poor nutrition, and associated comorbidities may also have an adverse effect on the patient's general condition and should be taken into account while assessing the patient.

Also, with Enhanced Recovery After Surgery (ERAS) protocols [3] being available for head and neck surgeries, there is growing evidence that outcomes in these patients can be improved significantly by standardizing perioperative treatment protocols. The emphasis is on goal-directed therapies, nutrition, post-operative analgesia, and perioperative rehabilitation of these patients and the anesthesiologist is expected to play a significant role in achieving these goals. A future goal is to extend the adoption of ERAS to head and neck cancer surgeries [4].

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9.2 Applied Anatomy of the Oral Airway

Cancer surgeries differ from other routine surgeries mainly because complete resection and achieving clear margins take priority over the extent of resection and hence these surgeries are generally extensive. It is essential, therefore, to understand the effect of various intra-oral structures in maintaining the airway. The tongue, mandible, and maxilla form the external anatomical boundary of the oral airway. The genial tubercle present posteriorly, at the center of the mandible provides for attachment of two important muscles that maintain patency of the airway, the genioglossus, and the geniohyoid. The geniohyoid muscle is not only responsible for dilation of the upper airway during respiration, but also during the act of deglutition, when the hyoid bone and tongue are pushed upward and forward by geniohyoid muscle along with the digastric and the mylohyoid muscle, thereby pushing food into the oropharynx [5, 6]. Also, the genioglossus muscle contracts and maintains patency of the upper airway and at the same time prevents uprolling of the tongue. Loss of function of these muscles may lead to loss of airway patency and obstruction of the airway. Similarities may be drawn with REM sleep, where the functional loss of these muscles leads to obstruction of the upper airway and snoring [5].

9.3 Oral Cancer Surgery

Oral cancer surgeries are carried out with the intent of removal of cancerous tissue while ensuring margins of normal tissue around the primary cancerous growth to prevent recurrence of growth, these surgeries are usually accompanied by a neck dissection for nodal clearance [7]. These resections may sometime be minor requiring closure by simple approximation of leftover tissue called as primary closure or else sometimes may involve placement of flap to fill the void left after extensive removal of tissue. Plastic reconstructions not only help to retain anatomic appearance, but also improve the functions of chewing and swallowing. These reconstructions may be done using a pedicled flap, where the original blood supply of tissue is retained or in some cases, flaps are extracted from distant sites called free flaps, wherein microscopic vascular anastomosis is achieved at the primary cancer site. The different types of oral surgeries are based on the site of the tumor.

9.4 Glossectomy

The term "glossectomy" is used to signify the excision of part or whole of the tongue. By nomenclature, the base of the tongue is considered as part of the oropharynx whereas the rest of the tongue is considered as part of the oral cavity. Types of glossectomies may be partial or hemiglossectomies which do not cross the midline during excision. Near-total glossectomy involves 3/4th of the tongue or total glossectomy wherein more than 3/4th of the tongue is removed.

9.5 Mandibulectomy

There are three main types of mandibulectomies: (1) marginal mandibulectomy, wherein only a rim of mandible bone is removed. Since continuity of jaw bone is maintained, in most cases primary closure may suffice, as enough bone is maintained to ensure structural support while eating, (2) segmental mandibulectomy, in these surgeries, one entire segment of the mandible is removed. This creates extensive anatomical distortion, which requires a reconstructive procedure to ensure normal external appearance and at the same time restore chewing and swallowing functions, (3) extended mandibulectomy, where the resection crosses the midline. This essentially means loss of genial tubercle over the mandible and its attachment. Genial tubercle provides attachment to the genioglossus and the geniohyoid muscle. Loss of genial tubercle leads to loss of anatomical support to these muscles and hence leads to the uprolling of tongue and obstruction of the airway. This is an extensive procedure that usually needs reconstruction along with a flap cover and tracheostomy for ensuring airway patency.

9.6 Maxillectomy

These may be medial maxillectomies wherein part of the maxilla that is close to the nose is removed, while the eye and the hard palate are preserved. Or it may be an infrastructural maxillectomies, wherein part of the hard palate and lower maxilla is removed leaving orbital floor intact or it may be suprastructural maxillectomies wherein the orbital floor along with upper part of maxilla is removed and rest of hard palate is left intact. Sometimes, if the disease is extensive, to ensure normal tissue margins, total maxillectomy or total palatectomy is performed which involves excision of the hard palate, orbital floor, and maxilla of one side or both sides, respectively. These surgeries require reconstruction along with a flap, to prevent the eyeball from sinking and ensure chewing and swallowing function and normal anatomic appearance.

9.7 Floor of Mouth (FOM) Excision

The boundaries of the FOM are formed posteriorly by the lingular surface of the lower gingiva and anteriorly by the alveolar ridge of the mandible. The FOM is surrounded laterally by the insertion of the tonsillar pillar and medially by the free inferior surface of the tongue. Small FOM lesions may be excised with primary closure, however, most lesions extend into adjacent tissues requiring extensive excision.

9.8 Bite Composite Resections

At times, the tumor extent in the head and neck may involve various adjacent tissues for tumor resection with safe margins, and composted resection of multiple structures is required. Such composite resection requires tissue plane dissection differently for different tissues like tongue, maxilla, mandible, etc., and remains challenging for surgeons. Such airways are challenging not only at beginning of airway management but also extubation remains challenging because of the risk of bleeding and edema.

9.9 Concerns for Anesthesia

9.9.1 Airway

The airway is challenging in oral cancer surgery patients due to multiple factors like trismus, oral fibrous bands, ankyloglossia, pre-existing comorbidities, pre-operative radiation, and most importantly the size and site of tumors that may itself obstruct the airway [8, 9]. One must be judicious during instrumentation of the airway, as manipulation of the tumor may cause bleeding that can further compromise the airway. Also, these patients may be edentulous secondary to age, tobacco consumption, radiation therapy, etc. The airway anatomy may also be altered by tumor mass itself. These factors can lead to difficulty, mask ventilation, and difficult conventional direct laryngoscopy as well [8]. Airway management may be further challenging intra-operatively due to the shared airway with surgeons, risk of loss of airway, and the decision to either perform tracheostomy or keep patient intubated with a plan of extubation either on the table or on the next day These conditions make both securing and maintaining the airway challenge. Thus, a careful advanced airway management plan with the entire team is essential to avoid airway loss and subsequent complications.

9.9.2 Nutrition and Anemia

In addition to cancer-related cachexia, patients with oral cancer may have poor nutrition due to decreased oral intake, which may be due to painful intra-oral lesions, decreased mouth opening, oral ulcers, etc. Hence, they are at risk of infection, electrolyte abnormalities, anemia, etc. Another reason for anemia apart from poor nutrition is chronic bleeding from the tumor site, which the patient usually swallows and thus is most often missed.

9.9.3 Effects of Previous Chemotherapy

Myelosuppression and complications related to previous chemotherapy (detailed below) may complicate the surgery and need to be considered pre-operatively.

9.9.4 Comorbidities

The most common cause of oral cancer is the use of tobacco. The use of tobacco either in oral chewable form or smoking may have adverse effects on multiple organ systems, especially the cardiovascular and the respiratory system. These patients are prone to coronary artery disease, hypertension, stroke, chronic obstructive respiratory syndrome, asthma, etc. Age-related comorbidities may also be present.

9.9.5 Intra-operative Blood Loss

Oral cancer surgeries can be extensive and may be associated with acute major blood loss. Surgeries more commonly associated with blood loss are maxillectomy and glossectomy procedures [10]. Hence, adequate crossmatch of blood and blood products should be done in advance, depending on the site and extent of surgery planned.

9.9.6 Hypothermia

Complications related to hypothermia may occur during long-duration surgery, especially in those involving major microvascular reconstruction.

9.10 Pre-operative Assessment and Optimization

A careful history and examination related to the following is essential for proper planning of the anesthetic technique and perioperative management of the surgery

9.10.1 Airway Assessment

One of the most important aspects of anesthesia for oral surgeries is a thorough assessment of the airway pre-operatively. Careful history taking for pain, bleeding, difficulty in swallowing or breathing, especially in different positions is useful while evaluating patients with intra-oral lesions. Unlike other patients for cancer surgery, certain airway problems are exclusive to head and neck cancer patients. In addition to routine airway assessment like Mallampati, thyromental, hyomental distances, assessment of neck movements, etc., the following should be assessed in head and neck cancer patients.

9.10.1.1 Facial Defects

The presence of any facial defects related to the invasion of the skin by the tumor or previous surgery, scars, radiation, presence of a beard, or an edentulous patient may make face mask ventilation difficult and sometimes even impossible, due to improper fit or seal with the face mask

9.10.1.2 Evaluation of Trismus

The mandible moves across the temporomandibular joint (TM) joint, capable of upward and downward movements, with limited forward and backward movement. Unlike the mandible, the maxilla is fixed. Kazanjian [11] classified ankylosis of TM joint into true ankyloses in which there is the pathology of TM joint itself and false ankyloses wherein the restrictions of movement are secondary to extra-articular factors.

False ankylosis is clinically classified as trismus. Mostly associated with submucous fibrosis due to tobacco chewing, radiation-induced, or the disease itself is common in head and neck cancer patients. It may also develop secondary to the presence of fibrotic bands or if the disease involves the retromolar trigone (Fig. 9.1). It is by far the most important factor to be considered while making a plan for securing the airway preoperatively. Postextubation, the presence of preexisting trismus might make re-securing the airway extremely difficult.

Painful trismus due to inflammation and infection associated with the tumor may resolve after

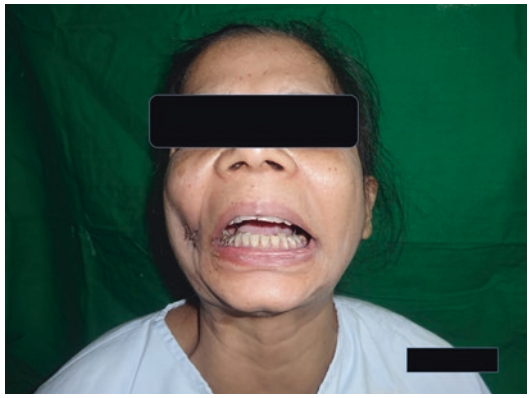

Fig. 9.1 Trismus in a patient with carcinoma buccal mucosa

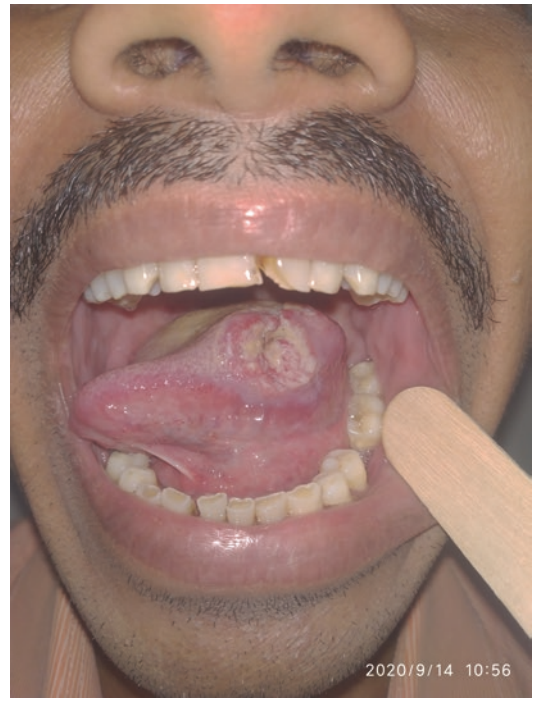

Fig. 9.2 Cancer of the lateral border of the tongue

induction of anesthesia. However, painless trismus and trismus due to submucous fibrosis, radiation-induced fibrosis of the TM joint, and infiltration of tumor into the infra-temporal fossa and pterygoid muscles may not get relieved post-induction of anesthesia and hence in these subsets of patients, it might be prudent for the anesthetist to secure the airway awake.

The functional staging of trismus [12] is classified between M1 and M4. An interincisal mouth opening up to or greater than 35 mm (M1), between 25 and 35 mm (M2), between 15 and 25 mm (M3), and opening less than 15 mm (M4).

Roughly the mouth opening should permit more than two fingers when inserted sideways. For practical purposes and ease of assessment, trismus is generally taken as mouth opening less than 2.5 cm [13].

Viewing the CT scan image before surgery can help assess the extent of disease and whether the trismus is likely to improve after giving anesthesia.

9.10.1.3 Oral Cavity Examination

Size, Site, and Extent of Tumor

Proliferative tumors arising from the tongue especially the right side of the tongue or oropharynx may hamper laryngoscope insertion and the laryngoscopic view, due to obstruction of the glottis. Previous imaging like CT scan, MRI, or previous ENT examination may provide reasonable information regarding the extent of the tumor (see below). These tumors may also bleed during laryngoscopic manipulation making it difficult to secure the airway [8] (Fig. 9.2).

Ankyloglossia

This is usually seen in cancers involving the tongue secondary to deep infiltration of cancer into the root of the tongue. This prevents protrusion of the tongue. As the movement of the tongue is restricted, the anesthetist may not be able to move the tongue to one side during laryngoscopy, making the glottic view sub-optimal [8].

Kotlow classified ankyloglossia into four classes—"Class I: Mild ankyloglossia: 12–16 mm, Class II: Moderate ankyloglossia: 8–11 mm, Class III: Severe ankyloglossia: 3–7 mm, and Class IV: Complete ankyloglossia: Less than 3 mm" [14].

The Base of Tongue Involvement

The risk of bleeding is higher in tumors of the base of the tongue and the vallecular during

laryngoscopy creating difficulty in mask ventilation and subsequent attempts at intubation and may sometimes result in complete airway loss. The presence of these lesions may sometimes not allow the Macintosh blade to enter the vallecula [15].

Proper evaluation of tongue lesions for size, extent, the involvement of the base tongue, disease crossing midline will help determine whether an awake fiber-optic intubation may be a safer option to secure the airway in these patients

Dentition and Oral Hygiene

Tobacco can lead to the destruction of teeth enamel and eventually cavitation. Most of these patients have loose teeth or may even be edentulous due to age. Oral hygiene in these patients may also be poor. Also, radiation of the head and neck region may lead to dental decay and loss of teeth [8]. These factors may make laryngoscopy more difficult, with the risk of dislodging loose teeth.

9.10.1.4 Intra-nasal Examination

Patency of airway needs to be checked pre-operatively in these patients, as most of these patients would undergo nasotracheal intubations only. Nasal airway patency may be evaluated by careful history taken from the patient regarding his or her ease of breathing from either nare when the other nare is occluded. It can be further corroborated by the findings of clinical examination and/or CT scan evaluation. Clinical Examination [16]—By feeling the strength of the blast of air or via patient's assessment for ease of inhalation while asking the patient to breathe normally while closing each nostril one after another after administration of nasal vasoconstrictors. This examination should be coupled with findings from imaging (see below).

9.10.1.5 Previous Radiation Therapy

Radiation can affect almost all parts of the airway and make airway management very difficult [17]. So, it is prudent to elicit the history of radiation therapy in pre-operative evaluation. The radiation therapy can lead to edema in the acute phase which subsequently can lead to tissue fibrosis.

Table 9.1 Airway complications due to radiation therapy

Site	Tissues involved	Complications
Upper airway	Oral cavity	Oral thrush Necrosis and ulceration Oro-cutaneous fistula Pain
	Tongue	Oral thrush Edema Glossitis
	TM Joint	Fibrosis Trismus
	Teeth	Caries Increased mobility
	Mandible	Osteoradionecrosis
Lower airway	Glottis	Edema Fibrosis
	Trachea	Perichondritis / chondronecrosis Fibrosis Stricture/Stenosis

Also, osteomyelitis or tissue necrosis can occur in the exposed region [18]. This may include both upper and lower airway. Also, radiation-induced decrease in submental compliance and its effect on airway structures could further alter airway anatomy and make both intubation and mask ventilation difficult [17]. Airway complications secondary to radiation have been described in Table 9.1.

Kheterpal et al. [19] in their study examining more than 50,000 attempts at mask ventilation found that changes due to radiation of the neck were the most significant clinical predictor of difficult mask ventilation. Radiation can also make oropharyngeal tissues extremely rigid and less compliant, thereby making intra-oral manipulation during laryngoscopy and achieving a good laryngoscopic view extremely difficult (Fig. 9.3). Extensive laryngeal edema may even force anesthesiologist to use smaller size ETT to secure the airway. Although now with recent advances and development of image-guided radiation therapy (IMRT), edema of normal adjoining tissue has significantly reduced. However, one should be aware that sometimes the effect of radiation may be obscured and not be visible externally and in such cases, careful history regarding radiation and its associated complications may be useful in identifying a potentially difficult airway.

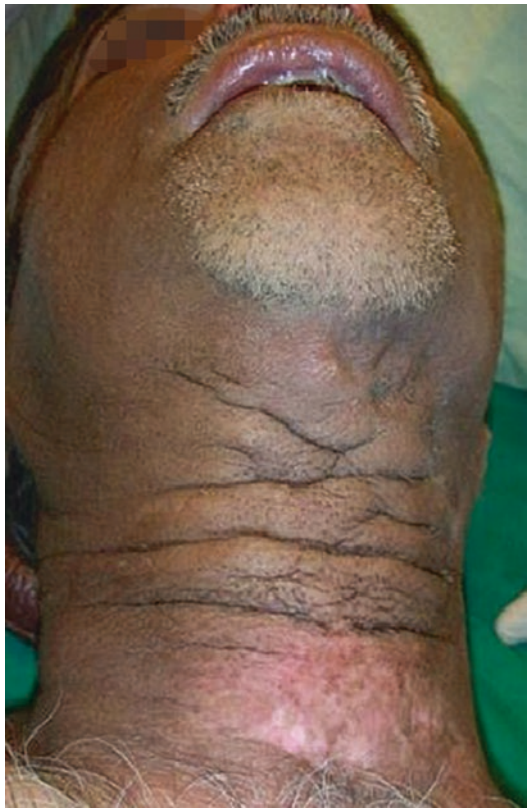

Fig. 9.3 Reduced submental compliance post-radiation in a patient with oral cancer

9.10.1.6 Role of Imaging and Previous Airway Examination Findings

Airway imaging can be very useful in making an airway plan in oral cancer surgery. This is especially useful during short procedures like examination under anesthesia (EUA), and Direct Laryngoscopy (DL) Examination. These might not be surgically morbid procedures; however, loss of airway or airway compromise during the procedure under anesthesia could lead to significant morbidity. In such procedures, previous imaging could help us assess the extent of disease and nature of airway compromise. The CT scan is done by the surgeon to assess the extent of the tumor and its respectability. Although imaging is not mandatory for anesthetic management, considering that most of these patients would have a prior scan, it would be worthwhile to look at them before surgery to plan the airway management and anesthetic technique [20]. Also bedside ultrasonography of the neck anatomy, before induction of anesthesia especially in an anticipated difficult airway case, to identify cricothyroid membrane, any aberrant vessels, and altered anatomy may be helpful if the need arises to perform an emergency cricothyroidotomy.

It would be wise to examine the CT scan for patency of nostrils [20]. In case of equal patency, the nostril to be used for intubation should be decided based on the side and site of surgery. In the case of maxillectomies, the opposite nostrils should be chosen especially if the hard palate is going to be excised. If both nares are found to be equally patent, the right nostril is preferred as the bevel of the endotracheal tube will then face the flat nasal septum which may reduce the damage to the turbinates [21]. CT scans should be used to look for prominent intra-nasal spurs [20]. These spurs can cause a rupture of the cuff of the endotracheal tube because resulting in volume loss during ventilation and requiring a tube change.

9.10.1.7 Virtual Endoscopy

The basic principle of managing a difficult airway is to identify the difficult airway. Accurate prediction should reduce the risk of potential complications. Many studies have demonstrated that there is no one predictor or scoring system that best identifies difficult airway [22, 23].

A newer technique in the identification of difficult airway is virtual endoscopy [24]. It is a radiologically simulated accurate anatomical demonstration of the airway from the oropharynx to the carina. In this approach, patients' previous diagnostic CT images are reconstructed into a 3D "fly-though" video of airway anatomy, thereby improving the interpretation of the existing 2D CT images and better identification of a difficult airway. This is an upcoming technique with a definite advantage in airway management of head and neck cancer patients and can help in planning to secure the airway awake or asleep depending on the level of difficulty anticipated.

9.10.1.8 Previous Awake Airway Assessment Findings

These patients usually undergo awake Fiber-Optic Laryngoscopy (FOL) or Indirect Laryngoscopy (IDL) for disease mapping before surgery. This might be present in a video format, a diagrammatic representation, or described in the case notes, either of which should be evaluated before formulating an airway plan.

It is also essential to consider the date of last imaging or examination performed, as cancers tend to progress rapidly and the extent of the disease might have changed significantly since the last evaluation. All previous radiological and examination findings should be corroborated with clinical findings.

9.10.2 Nutrition and Anemia

Oral cancer patients may have a poor general condition secondary to cancer itself, but also due to poor oral intake due to extensive radiation-induced mucositis [18]. Hence, baseline complete blood count to look for anemia and serum electrolytes should be done. Anemia may further get aggravated by chronic tumor site bleed. Whenever possible, nutritional status should be optimized before surgery for a smooth recovery in the post-operative period [25]. Intravenous iron supplements may be administered pre-operatively in severe anemia to avoid complications related to anemia and reduce or avoid intra-operative blood replacement.

9.10.3 Effects of Tobacco Chewing and Smoking

Tobacco has known adverse effects on multiple organ systems. Chewing of tobacco has increased the risk of cardiovascular diseases like myocardial infarction (MI), and increased risk of stroke. Apart from oral cancer, it also increases the risk of pancreatic, esophageal, and stomach cancer. Cigarette smoking contains many particulate and gaseous irritants like hydrocyanic acid, carbon monoxide, carbon dioxide, etc. Cardiovascular effects of smoking involve hypertension, MI, atherosclerosis. Irritants can increase mucous secretions, increase airway reactivity, may lead to emphysema and bronchitis. Increased levels of carboxyhemoglobin levels may alter oxygen binding capacity of the blood, reduce 2,3 diphosphoglycerate levels, and lead to hyperbolic oxyhemoglobin dissociation curve thereby leading to tissue hypoxia. Also, these patients are at increased risk of deep vein thrombosis, as smoking increases the number of red blood cells, white blood cells, platelets, and fibrinogen levels in the blood [26]. Smoking cessation is to be advised to patients at the first contact in the pre-operative evaluation as smoking increases the risk of perioperative complications. Though the period of at least 8 weeks is desirable in oncosurgeries, such time may not be available, but the adverse effects of smoking start recovering as early as 24 h. Current smoke should be advised to stop smoking at least 12 h or the evening before surgery to reduce levels of carboxyhemoglobin. As the period of cessation is increased further, mucociliary function improves and airway reactivity decreases.

9.10.4 Effect of Chemotherapy

In the case of extensive disease or borderline resectable lesions, patients are given cisplatin-based chemotherapy [27]. Cisplatin has known adverse renal effect [28] and hence renal function tests should be performed in these patients to rule out pre-existing renal injury and appropriate measures to optimize renal function in the perioperative period should be planned. Any form of myelosuppression should be corrected before surgery either by transfusion or using granulocyte stimulating drugs [29]. Surgeries in patients with neutropenia should be deferred until the counts recover, to avoid the risk of post-operative infections.

9.10.5 Pre-operative Pain Management

Oral and oropharyngeal regions of the head and neck are richly innervated and hence are the source of both somatic and neuropathic pain. As the tumor grows in size, along with intensive treatment regimens, pain starts to hamper day to day life especially neuropathic pain. Between 25 and 60% of patients with pain due to head and neck cancer experience neuropathic pain [30]. Tumors of the oral cavity, tonsillar region follow a glossopharyngeal and vagal nerve distribution with referred pain-causing otalgia, tinnitus, and dental pain. The treatment includes the use of NSAIDS, paracetamol for mild pain, and changing to weak or stronger opioids as the intensity of pain increases. Adjuvants like anti-depressants (amitriptyline, nortriptyline), anticonvulsants (gabapentin, pregabalin) are typically useful for the treatment of neuropathic pain [31]. While assessing these patients in the pre-anesthetic check-ups, the anesthetist should take a good clinical history and if required send appropriate investigation to rule out any complications secondary to long-term use of analgesics like NSAIDs. A careful history of the type and duration of the analgesic therapy is important for perioperative pain management, as the analgesic requirements in these patients may be higher.

9.11 Intra-operative Management

9.11.1 Pre-medication

Most often head and neck cancer patients posted for surgery may have a difficult airway and in some cases, a compromised airway also. Hence, the anesthesiologist should be very careful while administering any sort of sedative agent before securing the airway, keeping in mind the risk of losing a potentially compromised airway. At the same time, awake intubation procedures like fiber-optic intubation and awake video laryngoscopy require patient cooperation and occasionally sedation may be essential. The two most frequently used drugs are dexmedetomidine and remifentanil infusions, primarily because of their favorable pharmacokinetics and margin of safety. However, they do not provide amnesia. Titrated doses of propofol provide the advantage of amnesia, but the risk of airway compromise is much higher and should be used very judiciously. A combination of good counseling and topical preparation with local anesthetic drugs may obviate the need for sedation during these procedures and be a safer approach in some situations.

9.11.2 Monitoring

Standard American Society of Anesthesiologist (ASA) monitoring should be used. Continuous ECG monitoring, pulse oximeter monitoring, non-invasive blood pressure monitoring should be instituted before the induction of anesthesia. Invasive blood pressure monitoring is generally not required in these patients unless excess blood loss is expected which is mostly in cases of maxillectomies and glossectomies [10] or during long-duration reconstructive procedures like free flap surgeries. The arterial line is cannulated post-induction of anesthesia. In some situations, stroke volume optimization, using an invasive cardiac output monitor can be used to guide fluid therapy with a goal-directed approach [32]. This is especially useful in high-risk cases and long-duration surgeries. Temperature monitoring is desired since these are long-duration surgeries, which may involve significant blood loss and hence temperature fluctuations may be expected. Efforts should be taken to ensure that patients are adequately warmed during the surgery, using forced-air warmers and fluid warming set.

9.11.3 Role of Peri-intubation Oxygenation

Pre-oxygenation is vital in these patients. These are anticipated difficult airways and efforts

should be made to prolong apnea time during attempts at securing the airway. During minor procedures like direct laryngoscopy, examination under anesthesia, where intubation is not required, pre-oxygenation and apneic oxygenation can ensure prolonged apnea periods and avoid hypoxia during the procedure.

Oxygen administration during the apneic period, termed "apneic oxygenation" can safely prolong the duration of apnea without desaturation and by maintaining oxygen saturation at safe limits for a longer period. This is especially useful in oral cancer patients who have an anticipated difficult airway, where securing the airway may take time with a significant risk for airway loss. Apneic oxygenation is a physiological phenomenon, if a patent airway is maintained between the lung and the pharynx, there will be a continuous oxygen uptake from the environment even without any diaphragmatic or lung movement, provided that the patient has been adequately pre-oxygenated. There is a continuous flux of oxygen from the alveoli into the pulmonary capillaries at the rate of 200–250 ml/min while at the same time, carbon dioxide diffuses into the alveoli at a much lesser rate, 20 ml/min. This generates a negative pressure of up to 20 cm H_2O which drives gases containing oxygen into the lungs from the pharynx (Aventilatory mass flow).

An apneic oxygenation technique is NODESAT (Nasal Oxygen During Effort Securing A Tube) [33, 34]. This technique provides non-humidified, cold, dry oxygen at the rate of 5–15 l/min using a simple nasal cannula. This technique is used to avoid hypoxemia while attempts are made at tracheal intubation. It increases the apnea time to 10–15 min however it has little effect on CO_2 clearance. Another apneic oxygenation technique, which uses high flow nasal oxygen is called THRIVE (Transnasal Humidified Rapid-Insufflation Ventilatory Exchange) [35]. THRIVE technique uses high flow oxygen for the exchange of gases and creates a PEEP effect to keep alveoli open, and should be routinely used in managing and securing the airway during head and neck cancer surgeries. THRIVE has shown to prolong safe apnea time to as much as 14–65 min in a study conducted by Patel et al. [35]. THRIVE uses a specialized wide-bore nasal cannula to deliver a complete range of gas flows up to 70 l/min. It has a specialized humidifier which allows for delivering gases at optimal temperature and humidity (44 mg/dl). This increases the patient's tolerance and also improves mucociliary clearance [35]. The rise in the end-tidal carbon dioxide concentration was reported to be less as compared to NODESAT, only 0.15 kPa/min SponTaneous Respiration using IntraVEnous anesthesia and Hi-flow nasal oxygen (STRIVE Hi) [36]. This is a novel technique that describes the use of High Flow Nasal Oxygenation at 50 l/min in spontaneously breathing patients undergoing intravenous anesthesia for tubeless surgery. This has been described by Booth et al. in patients undergoing microlaryngoscopy surgeries. Physiologically it ensures a higher FiO_2, a positive airway pressure that maintains a patent airway, favorable respiratory mechanics, and decreased upper airway resistance. This significantly decreases the desaturation episodes while ensuring surgeries could be performed without the need for intubation.

9.11.4 General Anesthesia

After confirming adequate starvation, the patient should be wheeled into the operation theater. Using appropriate monitoring, induction of anesthesia should commence based on the airway plan. In case, the plan is to secure the airway post-induction of anesthesia, an appropriate dose of opioids, propofol with depolarizing or non-depolarizing muscle relaxant should be used. An adequately relaxed patient is important to obtain the best glottic view during laryngoscopy. And if the airway plan is to allow for awake intubation, then induction of anesthesia should commence after securing the airway. Maintenance of anesthesia is usually a balanced approach with a combination of opioids and inhalational agents. Since this is surface surgery, profound muscle relaxation is not required and the anesthesia is largely an opioid-based approach with less use of neuromuscular blocking agents.

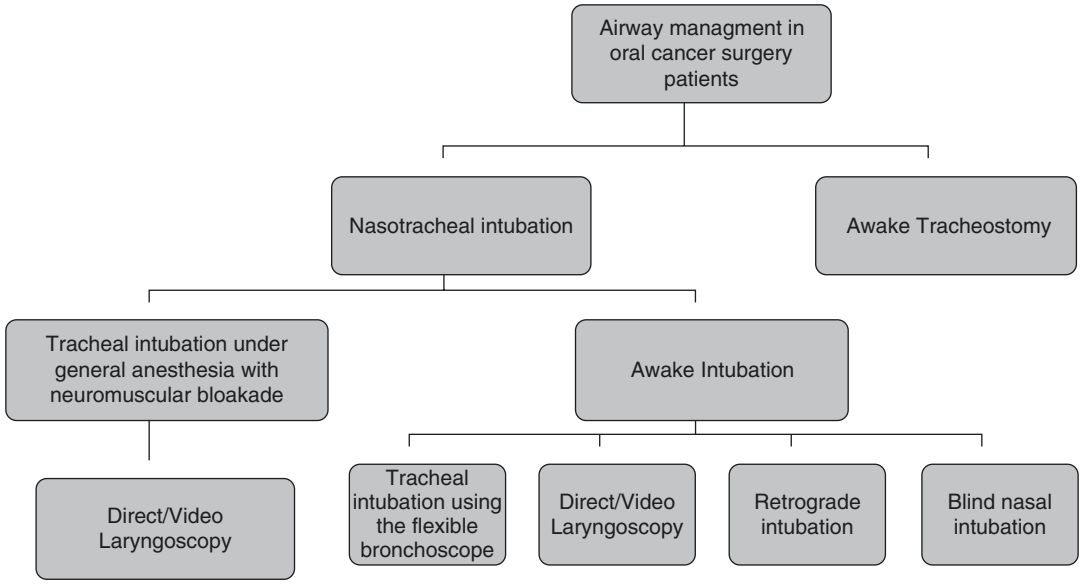

Fig. 9.4 Airway management in patients undergoing surgery for oral cancer

9.11.5 Securing the Airway

Different methods of airway management for head and neck cancer surgeries are described in Fig. 9.4. The plan of airway management should be tailor-made for the individual patient and the decision to secure the airway using either awake or under anesthesia should be taken after careful consideration of previously mentioned factors. With the advent of newer video laryngoscopes (VLs) airway management has undergone a paradigm shift. However, their role may be limited in head and neck cancer surgeries, where the blade insertion might itself be difficult or impossible due to the presence of trismus and intubation using the flexible bronchoscope, which may be a better option. The presence of intra-oral or oropharyngeal pathology might hinder glottic view during direct laryngoscopy due to mechanical obstruction in which case video laryngoscopy might be useful. However, if there is a risk of bleeding during manipulation, the first choice for securing the airway should be by using an awake intubation technique preferably with a flexible fiber-optic bronchoscope.

9.11.6 Awake Intubation

Awake intubation requires planning and availability of equipment along with requisite expertise [21].

9.11.6.1 Pre-medication for Awake Intubation

The topical solution of oxymetazoline is used for vasoconstriction. It causes vasoconstriction of nasal mucosa which reduces the chances of epistaxis during nasal intubation. Anti-sialagogues like intravenous glycopyrrolate should be given at least 15 min before the procedure. This creates a dry field that improves visibility for the procedure [37]. Furthermore, it also facilitates the action of local anesthetics as they do not get diluted or suctioned out during fiber-optic intubation by the performing anesthesiologist.

9.11.6.2 Methods of Anesthetizing the Airway for Awake Intubation

1. Preparation of both the nares with 2% lignocaine jelly before insertion of the endotracheal tube.

2. Viscous lignocaine gargle—Anesthesiologists can tropicalize the oral cavity by asking patients to gargle using 2% lignocaine for a period of 5–10 min. One could also anesthetize the oral cavity using a 10% lignocaine spray supplied in pressurized bottles (10 mg lignocaine per activation).
3. Atomizers—One of the methods of topically anesthetizing the respiratory mucosa using the spray technique. The advantage of atomizers is that they reduce the drug into fine particles(spray/aerosol) which helps to deliver medicine to the nose and throat.
4. Trans-laryngeal injection—In this technique, anesthesiologists pierce the cricothyroid membrane using a 22G intravenous cannula. Once the position of the cannula in the trachea is confirmed by aspiration of air, the anesthesiologist removes the stylet, leaving the cannula in-situ. Then the operator injects 4% lignocaine at the end of deep inspiration. This induces vigorous cough which allows the spread of the local anesthetic solution onto the vocal cords from below and anesthetizes the subglottic part of the airway.
5. "SprAY as you GO" technique (SAYGO)—In this technique, the operator instills local anesthetic through the suction channel of the fiberoptic scope, using a syringe or through an epidural catheter, thus anesthetizing the part distal to the scope before it is approached.
6. Glossopharyngeal nerve block—The posterior one-third of the tongue and the oropharynx up to the vallecula including the anterior surface of the epiglottis is supplied by the glossopharyngeal nerve. It can be blocked intra-orally, injecting local anesthetic at the base of the tonsillar folds on either side.
7. Superior laryngeal nerve (SLN) block—The SLN supplies the posterior surface of the epiglottis and larynx up to the level of the vocal cords. The superior laryngeal nerve is blocked at the level of the hyoid bone. A 24/25G needle is passed inferiorly to greater cornu of hyoid bone such that it lies superior to the thyroid cartilage. At this point, the operator injects 2–3 ml of local anesthetic. It is done on both sides.

The glossopharyngeal and SLN blocks are rarely performed these days as a combination of topical preparation techniques using local anesthetic agents is usually enough and avoids inconvenience to the patient with multiple needle pricks.

9.11.6.3 Types of Awake Intubation

Although Fiberoptic bronchoscope guided intubation is generally considered the gold standard in most cases, one should be familiar with all three techniques of securing the airway awake and be able to use them depending on the available infrastructure.

Intubation with using a Flexible Broncoscope (FB)

After lubrication of the fiber-optic endoscope, the endotracheal tube is mounted over the bronchoscope. The bronchoscope is introduced through the lower nasal meatus. While identifying the nasal septum, the floor of nose superior, and turbinates laterally, the bronchoscope is steered into the nasopharynx and the oropharynx. Once in the oropharynx, the epiglottis is identified as the first landmark. The bronchoscope is then advanced under the epiglottis to see the glottic opening and trachea which is the second landmark. Fiber-optic bronchoscope then needs to be advanced into the trachea to identify the carina which is the third landmark. With carina in vision, endotracheal tube (ETT) is then gently advanced over the scope with a gentle rotating motion through the nose, naso/oropharynx, pharynx, and larynx.

Retrograde Intubation

One of the main advantages of retrograde intubation is one which does not need to visually identify laryngeal inlet. The main indications for retrograde intubation are tumors of the tongue, mandible, the floor of mouth, larynx, and pharynx, maxillofacial trauma, burns, microstomia, cervical spine injury. In cases of retropharyngeal abscess, acute epiglottitis also, retrograde intubation can be extremely useful. Although in cases of complete trismus, retrieval of the guide may be difficult and hence also achieving nasotracheal

intubation. However, retrograde intubation requires a lesser area to maneuver the guide, and hence it can still be used in patients with limited mouth opening where insertion of laryngoscopy blade might still be difficult.

An epidural catheter is passed through the cricothyroid membrane, through an epidural needle or intravenous cannula puncture, in the cephalad direction until it comes out of the nose or mouth. In some cases, it might be necessary to grasp the catheter in the mouth using Magill forceps, then tie it with another wire while pulling it out of the nose for nasal intubation. An ETT is then inserted into the trachea from either nasal or oral route, railroading it over the catheter. Alternately the epidural catheter may be tied or looped around Murphy's eye, a gentle pull of the catheter at the neck end is used to guide the tip of the ETT into the trachea (pull-through technique). This is usually more successful than the railroading technique.

One may also perform retrograde intubation, using an anterograde guide over the retrograde guide. This makes the retrograde guide stiffer for easier passage of the tracheal tube. This helps in negotiating acute or-pharyngo-laryngeal angles. These anterograde guides could be suction catheters, guidewire sheaths, multi-lumen catheters, etc. These help in the easier passage of endotracheal tube over the retrograde guide and help to overcome the problems with looping of the catheter and difficulty in railroading the ETT, due to discrepancy in the diameter of the ETT and the epidural catheter.

Complications of retrograde intubation [38] include injury to vocal cords secondary to puncture at the cricothyroid membrane, bleeding secondary to aberrant vessels from superior thyroid artery [39], injury to the thyroid gland which can be avoided by going close to cricothyroid cartilage. Other complications include sore throat, minor bleeding at the puncture site, local surgical emphysema, inability to guide endotracheal tube in the airway, broken piece guidewire left in the airway. Using an intravenous cannula instead of an epidural needle for cricothyroid puncture can avoid injury to the vocal cord.

Although fiber-optic intubation takes precedence over retrograde intubation in most cases, few conditions like a bleeding tumor, excess secretions can make FOB intubation extremely difficult, and here retrograde intubation might be preferable. However, this technique needs patient cooperation to bring out the epidural catheter and at least 0.5 cm. of mouth opening to bring the catheter out [38].

Blind Nasal Intubation

This technique is guided either by breath sounds or an $EtCO_2$ trace. A nasal endotracheal tube is passed through the nose towards the larynx. The tube is then passed in direction of the loudest breath sounds by moving the patient's head until the larynx is entered. This technique is useful in patients with trismus but normal oropharyngeal and laryngeal anatomy in centers where fiber-optic bronchoscopes are not available. However, this technique can cause trauma to oral and laryngeal structures.

Though one should be familiar with both blind nasal and retrograde intubation, these techniques are performed blindly with low success rate and higher complications than FOB guided intubation and hence should be discouraged when FOB is available.

Awake Video Laryngoscopy (VL)

Video laryngoscopy is a much simpler procedure as compared to fiber-optic bronchoscopy having a much faster learning curve. However, a randomized controlled trial comparing FOB and awake VL to assess the success and ease of intubation in patients with expected difficult airway, did not find any difference when performed by an experienced anesthetist [40]. On the other hand, a recent meta-analysis by Alhomary et al. comparing VL and FOB for awake tracheal intubation, found VL to be associated with shorter intubation time [41]. They did not find any difference between the two techniques in terms of first attempt success rate, rate of complication, and level of patient satisfaction. However, most studies in their review did not include patients with trismus or intra-oral tumors, as the insertion of

the blade would be difficult in these group of patients and they argued that FOB should still remain method of choice for securing the airway awake.

Once the airway is secured and confirmed using sustained waveform capnography, anesthesia can be induced, using an appropriate anesthetizing agent like intravenous fentanyl (2–6 mcg/kg), propofol (2 mg/kg) followed by a muscle relaxant of choice. Intermediate-acting muscle relaxants like vecuronium or rocuronium may be used intra-operatively.

Nasal Endotracheal Tubes

The major consideration while choosing the variety of ETT for intubation is interference in the surgical field. Amongst the most commonly used ETT is the North-Pole pre-shaped tube made up of ivory (Fig. 9.5). It is specifically designed to be curved away from the surgical site [42]. Also, it is much softer than the polyvinyl chloride tubes while it is advantageous in terms of causing less nasal trauma at the time of insertion, suctioning through the device, opacity obscuring tube blockade, and resistance during spontaneous breathing if left uncut post-surgery are a few of its disadvantages as compared to standard the polyvinyl chloride tubes [43]. The insertion of North-Pole ETT over the fiber-optic bronchoscope is also difficult due to the curvature. The North-Pole tube needs to be held in a straightened position to be loaded over the bronchoscope. If the patient is kept intubated overnight with a north-pole tube in-situ, the anesthetist can cut the north-pole tube at the designated mark over the tube, to bypass the curve of the north-pole tube and reduce the length of the tube thereby decreasing resistance to spontaneous breathing. The flexometallic tubes may also be passed nasally and have the advantage of bringing non-kinkable and less traumatic during insertion, however, their opacity obscures tube blockage.

9.11.7 General Measures

Major blood may occur during the resection of the primary tumor, especially if it involves the tongue or the maxilla [10]. These are long-duration surgeries, and hence temperature monitoring along with fluid and forced-air warming sets are essential in these patients to avoid hypothermia

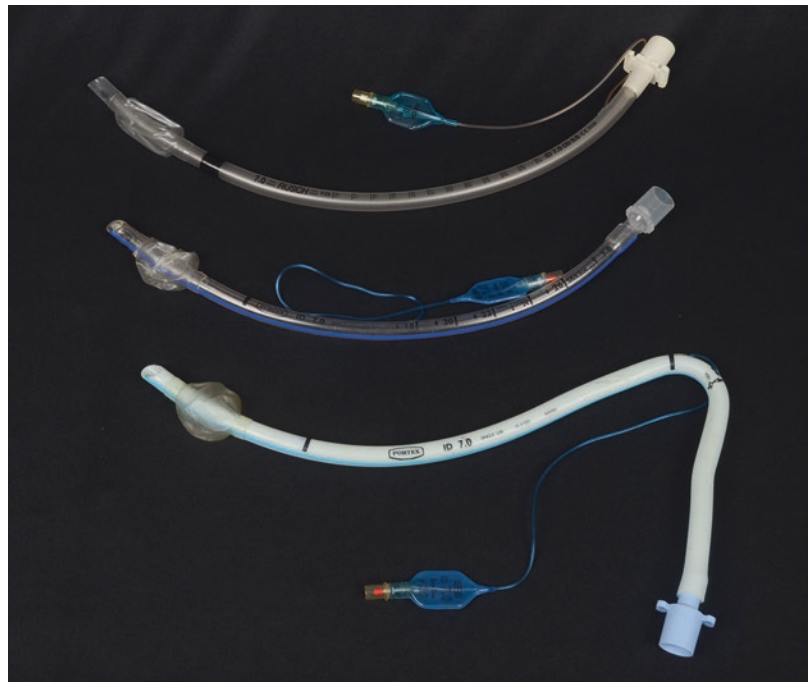

Fig. 9.5 Endotracheal tubes used for nasotracheal intubation: north-pole tube, polyvinyl chloride tube, and flexometallic tube

[9]. Intra-operative pain is generally somatic and hence tends to respond well to NSAIDs like diclofenac. Opioids apart from providing effective analgesia or high-intensity surgical pain also facilitate better tube tolerance.

9.11.8 Fluid Management

These patients are pre-operatively fluid depleted secondary to poor oral intake due to painful intra-oral lesions and trismus, in addition to poor nutrition and cancer cachexia. They may develop a precipitous fall in blood pressure once anesthesia is induced. Hence, careful assessment of fluid status should be performed before surgery and these patients may even require fluid boluses before induction of anesthesia to avoid hypotension. With the advent of Enhanced Recovery After Surgery (ERAS) protocols for head and neck cancer surgery patients, the emphasis is now on using Goal-Directed Fluid Therapy (GDFT) [32]. Chalmers et al. [44] reported that the use of cardiac output monitor LIDCO™ rapid and Pulse Contour Cardiac Output monitor (PiCCO) reduced the amount of fluid given during major head and neck cancer operations. It resulted in shorter hospital stays and reduced morbidity related to fluid balance [44]. Ringer Lactate and normal saline are generally used as the maintenance fluid of choice. Occasionally colloids may be used during acute periods of blood loss to maintain the volume status. Intra-operative replacement of blood and blood products should depend on the pre-operative hemoglobin and extent of blood loss. It is essential to take into account concealed blood loss in the operating field while assessing the need for blood replacement.

9.11.9 Intra-operative Analgesia

A multimodal analgesia technique should be used. Opioids like morphine and fentanyl should be used intra-operatively to maintain analgesia. Non-opioid analgesics like paracetamol and diclofenac may be used unless contraindicated, for both intra-operative and post-operative analgesia.

9.11.9.1 Nerve Blocks

Inferior alveolar nerve block [45, 46] may be given intra-operatively for mandibular surgeries. This involves depositing local anesthetic within the oral cavity in the region of the infra-alveolar nerve before it enters the mandibular foramen.

9.11.10 Intra-operative Airway Management

Tracheostomy is commonly performed after radical head and neck cancer resections provide a secured airway. Proponents of routine tracheostomy argue that since the risk of airway edema and loss of structural patency of the airway exist after extensive HNC resection and/or reconstruction, tracheostomy is a safer mode to maintain the airway post-operatively. However, recent studies have emphasized [47–52] that a delayed extubation strategy which involves retaining the tracheal tube post-operatively and performing tracheal extubation after 12 hours or on the following morning, is an equally safe and a less invasive method of perioperative airway management. The delayed extubation strategy is associated with fewer complications and faster recovery as compared to tracheostomy.

Despite the benefits of the delayed extubation strategy, there is a potential for airway compromise after extubation due to edema, altered anatomy after extensive resection, and bulky flaps encroaching into the airway. Also, quick access to the airway in the event of airway obstruction may be extremely difficult. Thus, careful patient selection is very important while making a post-operative airway management plan. Gupta et al. found “tracheostomy to be preferred if radiation was previously received in the same region of surgery, resection of two more sub-sites of oral cavity or oropharynx, bilateral neck dissection, extended hemi mandibulectomy or central arch mandibulectomy, bulky flap for reconstruction: latissimus dorsi;

double-skin island pectoralis major myocutaneous flap and flap with a compressing element: intact mandibular rim; use of a concomitant reconstruction plate" [53]. In all these cases, they advised tracheostomy to be preferred over overnight intubation [53].

There still exists insufficient data to guide optimal management of the airway in the perioperative period. The studies comparing the two methods (elective tracheostomy and a delayed extubation strategy) have been either retrospective or prospective with a small sample size, and inadequate to make a definite conclusion and guide perioperative airway management. The decision to perform tracheostomy in these cases is often based on the surgeon's experience, and dependent on the training and comfort level of the surgical and anesthesia teams and available infrastructure, rather than the type of surgery or reconstruction [54].

Nevertheless, delayed extubation is not a universal substitution for tracheostomy and it is very essential to identify the particular subset of patients in whom delayed extubation strategy is safe or those patients in whom tracheostomy is warranted. The presence of bulky flaps and extensive resection should be taken into account before deciding on the plan for post-operative airway management.

9.11.10.1 Intra-operative Loss of Airway

Surgical manipulation, change of head position, use of retractors during surgery can all be potential causes of ETT displacement or tube malposition. This may often be missed under the surgical drapes. Hence continuous monitoring of EtCO2 is crucial. Also, intra-operative endotracheal tube cuff rupture secondary to intra-nasal spurs, or use of Magill's forceps while intubating or due to surgical handling during tracheostomy, can all lead to loss of secured airway and serious complications. Hence, the anesthetist needs to be vigilant throughout the surgery and be ready with a back-up plan. A plan for emergency cricothyroidotomy followed by a tracheostomy and equipment for the same should always be accessible in case of accidental extubation, especially when the anesthetist is unable to secure the airway by traditional methods or mask ventilate the patients during surgery. Insertion of a supraglottic airway for rescue ventilation is often impossible in this setting. Performing an intra-operative FOB may be extremely challenging and sometimes impossible, as the blood in the surgical field may obscure the view. In case of cuff rupture and minor air leak, one could do throat packing, however, the best option is to replace the ETT using a tube exchanger as reintubation during surgery may often be difficult or impossible due to bleeding, inability to mask ventilate or even perform laryngoscopy depending on the extent of resection performed.

9.12 Post-operative Management

9.12.1 Post-operative Airway Management

At the end of the procedure, it is important to independently confirm the removal of the throat pack by the surgeon, anesthetist, and nurse and document the same. It is important to ensure that the patients have been adequately reversed from neuromuscular blockade, have a patent airway, and are pain-free at the end of surgery. The patient will have either a tracheostomy or nasal ETT at the end of surgery. On the table, extubation is rarely feasible due to concerns about airway edema, bleeding, and the inability of the patient to maintain a patent airway immediately after surgery. Hence these patients are usually extubated on the following morning or at least 8–12 h after surgery until airway patency is not anticipated to be a concern. Ensure that the ETT/tracheostomy is patent, free of secretions, properly positioned, and well-secured before leaving the operating room. These patients should be transferred to a monitored area in the post-operative recovery room or surgical ICU. These patients can be oxygenated using a T-piece post-surgery or can be on pressure support ventilation, depending on the existing infrastructure and institutional protocols. Irrespective of either method of ventilation, basic ECG, pulse oxime-

try, and blood pressure monitoring must be instituted in all patients post-operatively. The patients should be nursed in a semi-recumbent position. Vigilant monitoring is essential, when sedation is given to these patients, due to the potential risk of hypoventilation and apnea with sedation, especially when they are not ventilated. The use of pressure support ventilation is advantageous as it gives a greater margin of safety while using sedation; however, this may not be feasible in all settings due to patient load in the ICU, staffing, cost, and infrastructural constraints. All patients should be closely monitored for airway patency, tube malposition, bleeding, cardiorespiratory stability, and pain.

9.12.1.1 Sedation

Both patients kept on the overnight endotracheal tube or tracheostomy tube may require sedation for tube tolerance. The requirement of sedation is more in patients managed with a delayed extubation strategy. Use of opioids like morphine, along with lignocaine nebulization can be given for sedation and tube tolerance. However, opioids should be used judiciously and the patient monitored closely, especially when not ventilated to avoid complications.

9.12.1.2 Humidification

Patients with a tracheostomy or those kept intubated overnight should receive humidified oxygen therapy. Giving dry oxygen might irritate the airway causing coughing, sloughing of the mucosa, thickening, and retention of secretions with impaired mucociliary clearance, increasing the risk of tube blockage [55]. Humidification may be provided passively using heat moisture exchanger (HME) filters or actively via using nebulizers [56].

9.12.1.3 Extubation

A pre-existing difficult airway may be further compromised intra-operatively due to surgical handling leading to laryngopharyngeal edema and bulky flaps encroaching into the oral cavity reducing the airway caliber, both of which may make re-securing the airway after extubation of the trachea extremely difficult. Extubation of a patient following oral cancer surgery should be considered as high-risk extubation [57]. Although there are many guidelines for difficult airway extubation, these guidelines may need to be modified and tailored for the individual patient based on clinical judgment and the expertise of the anesthetist.

Most of the weaning criteria do not take into account the ability of the patient to maintain a patent airway post-extubation. Airway edema, a bulky flap obstructing the airway, or hematoma may lead to loss of airway patency and thereby extubation failure. These patients already had a pre-existing difficult airway, now following surgery, reintubation, or mask ventilation may be challenging and can potentially lead to serious morbidity. Furthermore, airway handling is associated with hemorrhage, hematoma, and edema which may lead to increased post-operative airway deterioration.

9.12.1.4 Assessing and Treating Airway Edema

Oral surgeries may be associated with airway edema secondary to the surgery itself, flap reconstruction in addition to the additive effect of preoperative radiation therapy. Airway edema may be checked either by doing direct laryngoscopy before extubation [58]. The purpose of this exercise is to check the airway patency/ease of reintubation and also suction oropharyngeal airway secretions.

The other method is the cuff leak test. However, the role of the cuff leak test in oral surgeries is limited. If the airway edema is due to the surgery or flap reconstruction, maintaining the patient in a head elevated position with the tracheal tube in situ, might decrease the intensity of the airway swelling. Corticosteroids have been advocated to prevent and treat airway edema, but the results are conflicting [59, 60]. Some centers advocate that the use of corticosteroid 4 h before extubation improves outcomes. This should be continued at least till 12 h post-extubation [61]. However, steroids are not routinely required in all patients and may be used in select cases. Adrenaline nebulization may be used in select patients.

9.12.1.5 Performing Extubation

Extubation in these patients can be extremely challenging and should be done with complete readiness for reintubation using a FOB or surgical access to the airway in form of cricothyrotomy or tracheostomy. Patients are usually extubated the following morning only after confirming that the surgical site is satisfactory and the patient is wide awake with intact reflexes. Extubation may be deferred if bleeding from the surgical site, severe edema around the face, or the patient is unlikely to maintain his airway. In select borderline cases, where there is a high possibility of extubation failure, it is preferable to extubate difficult patients in presence of ENT or head and neck surgeons, so that a surgical tracheostomy can be performed for a definitive airway [57] if there is airway obstruction post-extubation. The extubation should be performed over a tube exchanger/bronchoscope or one may even consider elective tracheotomy if required. A flexible fiber-optic bronchoscope or cricothyrotomy set should be kept handy if the need arises to rescue the airway in these patients. Extubation should be performed under the supervision of anesthetists, with complete monitoring including continuous ECG monitoring, continuous pulse oximeter monitoring, and non-invasive blood pressure monitoring. The All India Difficult Airway Association (AIDAA) guidelines for difficult extubation emphasize the need for a back-up plan, which includes surgical airway access if required and accessible at all times following extubation of the difficult airway [57].

One should perform thorough suctioning of the trachea followed by oropharynx to remove any secretions, confirm throat pack removal, and perform a visual examination of the oral cavity before extubation. Anesthesiologists should then deflate the cuff of the ETT and remove the tube in an anatomical configuration at the peak of inspiration while the patient takes a deep breath. Removing the ETT at peak inspiration increases cough effectiveness. Ask the patient to cough to expel secretions. In presence of stridor due to edema, nebulization with a racemic solution of epinephrine should be performed. This reduces glottic edema and the swelling caused by the tube and its removal. Intravenous steroids may be continued if edema persists post-extubation. Auscultate the patient for any upper airway noise or any adventitious sounds. Patients should receive oxygen therapy after extubation and be monitored for airway compromise. Patients should be encouraged to take deep breaths and cough.

9.12.1.6 Use of Airway Exchange Catheters

An airway exchange catheter (AEC) should be used in high-risk extubations, where there is a potential for extubation failure due to the inability to maintain a patent airway post-extubation. The airway exchange catheter should not be inserted beyond the 25 cm mark, at the level of the incisor. They should be secured and kept in place following extubation for up to 4 h in case reintubations are required. Certain studies have given an arbitrary number of 1 h post-extubation, it can be tolerated up to 72 h [62]. The anesthetist should topicalize AEC with lignocaine jelly to improve patient tolerance of the catheter. Staged extubation sets use a guidewire instead of a hollow catheter and are better tolerated by the patients. Commonly used AEC is Cooks' airway exchange catheter of size 11Fr and 14Fr [62–64]. These are compatible with ETT >4 mm and >5 mm, respectively. AEC is made semi-rigid to minimize trauma [62–64] and at the same time, they are hollow and can be used to give oxygen to the patient (up to 4 l/min). Jet ventilation should not be attempted through the AEC, due to the risk of barotrauma [65, 66]. While re-introducing ETT over an AEC, laryngoscopy should be performed to retract the soft tissue [67].

9.12.2 Nutrition

A Ryles tube (RT) is generally inserted at the beginning of surgery. Due to extensive resection and probable reconstruction, the chewing and swallowing function in these patients is severely compromised [68]. Hence it is extremely essential that RT is placed and confirmed preoperatively as altered anatomy in the post-operative period along with the risk of disrupting surgical sutures might make it difficult to

insert RT later. Post-operatively, an X-ray chest should be performed to confirm that the tip of RT is below the diaphragm, before starting RT feeds. Ryles tube feeding should be instituted in these patients within 24 h of surgery [68]. Till the time RT feeding is started, these patients should receive maintenance fluid in the post-anesthesia care unit in form of dextrose containing isotonic fluids.

9.12.3 Rehabilitation

These patients require both vocal and swallowing training post-surgery to improve the quality of life. These rehabilitation programs are focused, depending on the type of surgery and the extent of tissue removed. The therapist will assess the ability to swallow, to start drinking by around day 8 [49], though this does vary from person to person. The emphasis is to start eating again early, and it must be done as normally as possible. It helps in wound healing, reduces the risk of infections, and results in early recovery. These programs also focus on mouth opening exercises using jaw stretchers in case of patients with pre-existing or post-operative trismus. Generally, patients managed with delayed extubation have a faster return to daily activities as compared to patients managed with a tracheostomy [49, 69].

9.12.4 Post-operative Pain Management

Despite a very high prevalence of post-operative pain in head and neck cancer surgery patients, the management is generally sub-optimal [70]. The maximum pain score is generally reported on the day of surgery, and it decreases considerably after that [71]. The intensity of the pain depends on multiple factors such as duration of surgery, the extent of surgery, and the presence of pre-operative pain [72]. The approach to post-operative pain should be multimodal. Recent French guidelines for the management of post-operative pain management in patients undergoing head and neck cancer surgery emphasize the importance of intra-operative positioning and the use of multimodal analgesia along with intravenous morphine, patient-controlled analgesia (PCA) for post-operative pain management. They specifically emphasize on care-related pain management in terms of use adequate analgesia and sedation in appropriate doses when performing procedures like tracheostomy tube change and nasogastric tube insertion [73].

9.12.5 Enhanced Recovery After Surgery (ERAS)

This is a multi-disciplinary approach that involves surgeons, anesthetists, ward teams, physiotherapists, speech and language therapists, and dieticians to work on a standardized pathway [32]. It includes pre-operative, intra-operative, and post-operative components. Nutrition should be built up before surgery. It improves wound healing and reduces the risk of infection. The fasting period should be limited to pre-surgery. Intra-operatively, the standard anesthesia technique should be used with special emphasis on goal-directed fluid therapy, glucose, and temperature control. Post-operative emphasis must be on a specific pain management protocol, early feeding, and early mobilization.

Dort et al. [4] gave the best practice guidelines for perioperative care of patients undergoing major reconstructive head and neck cancer surgeries using a free flap. These guidelines however need to be further clinically evaluated. These recommendations include “preoperative carbohydrate treatment, pharmacologic thromboprophylaxis, perioperative antibiotics in clean-contaminated procedures, corticosteroid and antiemetic medications, short-acting anxiolytics, goal-directed fluid management, opioid-sparing multimodal analgesia, frequent flap monitoring, early mobilization, and the avoidance of preoperative fasting” [4].

9.12.6 Post-operative Complications

The overall incidence of airway complications is far more in patients with a tracheostomy as compared to patients with delayed extubation [49].

The most common airway complications in the case of tracheostomy in the immediate post-operative period involve obstructed tube, displaced tube, infection at tracheostomy site, and lower respiratory tract infection [49]. Long term complications include a trachea-cutaneous fistula or a blocked tube [74]. Most of these tracheostomies are temporary. The cuffed tracheostomy tubes are changed to uncuffed tubes by the 3rd–5th day, depending on the risk of aspiration. The tracheostomy tubes are corked by approximately 5th–7th day after surgery. For patients managed with delayed extubation technique, the risk of acute airway compromise post-extubation or blockade of ETT in the immediate post-operative period remains the two most common airway complications. If these patients are posted for surgery again, securing the airway might be extremely difficult, and awake intubation or upfront tracheostomy should be considered over standard induction technique, based on the anesthetist's clinical judgment and experience.

9.13 Care of the Patient with a Tracheostomy

Ensuring patency and proper position of the tracheostomy is paramount during the post-operativecare period. Accidental displacement or extubation of a fresh tracheostomy under 7 days may result in loss of the tract and airway loss, resulting in serious complications. Astute observation, routine care, prompt management of post-operative complications, and quick access to proper equipment during an emergency can reduce morbidity significantly.

9.13.1 Daily Checks by Nursing Staff

Tracheostomy related complications can be easily prevented by training of nursing staff concerning tracheostomy care and identification of problems [75]. Patients with a tracheostomy need to be diligently observed and during the change of shift every day, special attention to following details like why and when was the tracheostomy performed. The technique used to perform the tracheostomy, percutaneous or surgical, may affect the ease of reinsertion of the treacheostomy tube. A same and smaller size tracheostomy tube along with surgical instruments should always be kept ready near the patient in case of an emergency [75]. Bedside signs must be available for the patient to signal distress of any sort. Nursing staff on every shift change should emphasize the ability of patients to swallow, the sputum characteristics quantity, color, and odor for early identification of infection. The tracheostomy site should be kept clean and healthy. This assessment should be documented in the care plan at the start of every shift.

9.13.2 Humidification

Patients on tracheostomy requiring oxygen therapy should receive some form of humidification. Dry oxygen therapy may lead to retention of viscous and tenacious secretions, impaired mucociliary transport, and impaired ciliary activity [56]. Also, the epithelium may show inflammatory and necrotic changes, ulceration, and bleeding. It also increases the risk of bacterial infection.

9.13.3 Suctioning

Suctioning as required is an essential part of tracheostomy care in the recovery room and also in the ward, ETT should be suctioned as blockade of the tube may lead to catastrophic morbidity. Sputum is continuously produced in the human airway, which is aggravated in presence of infection or inability of the patient to cough effectively. This may lead to airway obstruction, desaturation, and lung consolidation.

9.13.4 Assessment of a Patient with a Tracheostomy Inwards

A blockade of the tracheostomy tube secondary to thick secretions may lead to respiratory distress and even failure. This can be prevented by regular suctioning, humidification, inner

cannula care, and patient assessment at regular intervals. Early identification of warning signs should prevent inadvertent tube blockage [75]. Patient assessment should include frequency of suctioning and/or cleaning or inner cannula, the thickness of airway secretions, airflow evidence from a tracheostomy, signs of respiratory distress like respiratory rate, use of accessory muscles, need for supplemental oxygen, and strength of coughing whether ineffective or excessive should be routinely checked during ward rounds.

9.13.5 Equipment to Be Kept at the Bedside of a Patient with a Tracheostomy

- The tracheostomy tube of the same size and one smaller size and type currently in place
- Surgical instruments—tracheal dilator, cricoid hook, right angle tracheostomy retractors, the knife with 11 no. blade, plain forceps, mosquito forceps, and syringe with a needle to confirm trachea.
- Endotracheal tube and intubation equipment
- Manual resuscitation bag with an oxygen source
- Obturator
- Suction catheters (usually 12F or 14F)
- Yankauer suction catheter
- Functional suctioning system, canister
- Tracheostomy cleaning kit
- Syringe for ETT cuff inflation
- Tracheostomy holder or ties

9.13.6 Obstructed Tracheostomy Tube

This is an emergency with potentially disastrous complications. If a patient with a tracheostomy is found breathless or in respiratory distress in the ward, the nursing staff should immediately raise the alarm and call for help first. As the first step, the patient should be provided with 100% oxygen. Any cap or inner tube must be immediately removed. Simultaneously one staff member must prepare the suction catheter to perform suction in case of a blocked tube. If distress persists, one could try deflating the tube cuff which might allow the patient to breathe from around the tracheostomy tube. If the respiratory distress persists, the tracheostomy tube must be removed and the tracheal stoma site should be suctioned thoroughly and another tracheostomy tube must be placed. In emergencies, one could also attempt to put an endotracheal tube through the stoma site to ensure a patent airway.

9.14 Summary

Patients with oral cancers are challenging for perioperative care for anesthesiologists. It requires a thorough assessment and meticulous planning for an uneventful recovery. The airway management in such patients requires not only knowledge of various airway management tools but also expertise in skills related to airway management. These patients may have received radiotherapy before surgical intervention and hence its assessment for its impact on airway management should be kept in mind.

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Anaesthesia for Head and Neck Cancer Surgeries

10

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10.1 Introduction

Head and neck cancer occur at various locations in the upper part of the aerodigestive tract, most commonly in the larynx, pharynx, salivary gland, and thyroid. Head and neck cancer pose major anesthetic challenges because of the impact of cancer itself, its local and systemic effect, the treatment like radiation therapy or prior surgery, or by a group of the paraneoplastic syndrome in an age group of patients who are already burdened with comorbidities. The anesthetic plan is tailored according to the characteristics of surgeries performed, which ranges from a minor procedure like panendoscopy and tracheostomy to more extensive laryngectomy, extensive resection, dissections, and reconstructions.

10.2 Preoperative Assessment

The patient is assessed for comorbidities, to identify potential difficult airway, stratify risk, and to optimize the patient before taking up for surgery. The patients may have associated cardiac and respiratory comorbidities and nutritional deficiencies. They are in a high-risk category for perioperative cardiac and pulmonary complications. The perioperative risk increases with advanced age and associated comorbidities. The preoperative assessment helps in formulating the systematic anesthetic plan for the optimal intraoperative outcome with enhanced postoperative recovery.

10.2.1 Airway Assessment

Assessment includes a detailed history, clinical examination, and review of relevant radiological imaging and endoscopy findings (Tables 10.1 and 10.2). In conjunction with the surgeon, the assessment allows the anesthesiologist to make individualized perioperative planning and to identify those patients where the predicted degree of difficulty is so great that they may require awake intubation or tracheostomy under local anesthesia by the surgeon.

Table 10.1 Post-radiotherapy sequelae

Tissue	Sequelae
Jaw	Reduced mouth opening
Neck	Reduced neck extension or forced flexion
Larynx	Fixed and immobile larynx
Apex of lung	Restrictive ventilator defect
Head and neck area	• Distortion of airway • Hypothyroidism • Chemoreceptor and baroreceptor damage • Stenosis of carotid artery • Impaired wound healing

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Table 10.2 Sequalae of previous surgery on tissues

Previous surgery	• Difficult mask seals • Difficult nasal access • Contracture of temporalis muscle • Pseudoankylosis of temporomandibular joint (TMJ)
Laryngeal surgery	• Stenosis of larynx • Impaired swallowing reflexes • Aspiration risk
Floor of mouth and tongue surgeries	• Trismus • Firm immobile tongue • Narrow mandibular space
Neck dissections	• Damage to cranial nerves 9, 10, and 11 • Impaired swallowing reflexes • Vocal cord paralysis • Aspiration risk

History of stridor, change in voice, difficulty in breathing particularly on lying flat, snoring, dysphagia should alert anaesthesiologist to potential difficulty in airway management. In long-standing, progressive cancer particularly in subglottic and tracheal compression, narrowing of the airway may have adapted respiratory muscles and hence patients may have fewer signs and symptoms of obstruction of airway particularly in subglottic and tracheal compression.

In supraglottic and tongue base tumors, bedside screening test and physical characteristics that suggest difficult laryngoscopy are unable to predict likely airway obstruction after induction of anesthesia.

Radiological imaging with soft tissue neck X-ray anteroposterior and lateral view, contrast-enhanced computerized tomographic scan (CECT), and/or magnetic resonance imaging aids in delineating size, site, the extent of disease, and potential airway obstruction. All available imaging should be reviewed together by the anesthesiologist in liaison with the surgeon keeping in mind the sequelae of head and neck cancer treatment (Tables 10.1 and 10.2). Anaesthesiologists should study the findings of imaging and endoscopy to delineate the site and extent of these tumors and the degree to which the airway is obstructed.

Preoperative assessment should assess the possibility of mask ventilation, whether laryngoscopy or tracheal intubation is difficult and which airway management technique should be applied - awake intubation or asleep techniques or surgical airway. The Indian and International airway management guidelines stress the importance of a pre-planned strategy along with alternate plans for airway management with increased emphasis on oxygenation.

10.3 Risk Stratification and Optimization of Comorbidities

There is an increasing focus on risk prediction and risk stratification of patients undergoing the major surgical procedure. The POSSUM (Physiological and Operative Severity Score for Enumeration of Mortality and Morbidity) score and revised Lee's cardiac risk index are useful aids in predicting morbidity and the probability of major cardiac events related to non-cardiac surgical procedures, respectively. Both these tools are extensively proven in general and vascular surgery, but their effectiveness is yet to be demonstrated in head and neck surgeries.

Relevant diagnostic tests should be included in the preoperative workup. Baseline investigations include complete hemogram, renal/liver function tests, blood sugars, 12 lead electrocardiography, and chest radiograph. Based on history, clinical examination, and routine tests, additional investigations like prothrombin time (PT), echocardiogram, cardiopulmonary exercise testing (CPET) are done.

Patients' clinical status and functional capacity need to be optimized preoperatively. Preoperative nutritional deficiency solitarily correlates with infection, poor wound healing, and a high risk of postoperative complications. Malnourishment can be because of poor dietary habits, dysphagia, cancer cachexia, systemic side effects of chemotherapy, and radiotherapy-induced mucositis. Nutritional support should be given according to the guidelines ranging from peroral supplementation to Ryle's tube feeding to feeding jejunostomy or gastrostomy.

10.4 Operative Laryngoscopy and Microlaryngeal Surgery

Operating laryngoscopes provide high quality, spacious laryngeal view which helps in performing the diagnostic evaluation, biopsy, and surgery on structures that are in the pharynx and larynx, without causing much distortion (Fig. 10.1) [1, 2]. The assessment of the pharynx and larynx is done using suspension laryngoscopy added with the use of telescopes (angles, straight) (Fig. 10.2) [3, 4]. This provides a gross evaluation of the structures. In case of findings requiring further assessment, microlaryngoscopy using the operating microscope is performed for finer assessment, biopsies, or laser surgeries [2].

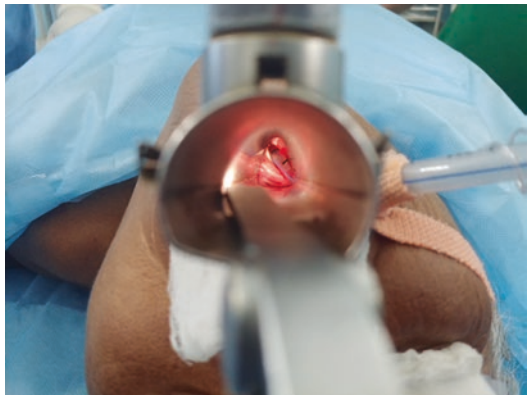

Fig. 10.1 Gottic tumor seen under operating laryngoscope

The basic principle for optimal surgical outcomes after a microlaryngeal surgery (MLS) is the provision of a clear and still surgical field during the intervention. The duration remains variable for the surgical intervention and such immobile patient status needs to be uniformly maintained [5–8]. The surgical intervention requires the use of fluid irrigation and debris and/or blood that may accumulate at the surgical site. So, the airway needs to be well protected and secured from these extraneous materials. Also, the surgical requirement may mandate a change in airway management strategies during the procedure. So, good communication between the surgical team and anaesthesiologists is paramount [6, 7, 9]. The procedure induced systemic changes like cardiovascular system response resulting in tachycardia, arrhythmias, hypertension (arterial and pulmonary) due to laryngeal manipulation needs to be adequately obtunded [9–11]. Though these responses are transient but may lead to increase morbidity and cardiovascular events, especially in high-risk patients like having coronary artery disease [12–14].

Fig. 10.2 Suspension laryngoscopy

Precautions are also required to protect eyes, teeth, arms, and facial damage or compression due to the use of the large surgical equipment in their vicinity [4]. Use of appropriate padding, tooth guard, and proper closure of the eye must be ensured [15]. The goal of anesthetic care includes maintaining the study plane of anesthesia with adequate neuromuscular blockade during the surgical intervention and faster recovery along with full recovery of airway protective reflexes [7, 8].

10.4.1 Airway Concerns for Microlaryngeal Surgery (MLS)

10.4.1.1 Airway Management

The choice of airway management primarily depends on the patient's assessment and the type of surgical intervention planned. The choice among various available airway management techniques, the individual choice depends on the expertise of the anaesthesiologists, type of equipment, and the institutional protocols. However, understanding the various concerns and thus choosing appropriate airway management becomes paramount.

Based on airway assessment with notable attention directed towards the predictors of obvious and potential difficult face mask ventilation, laryngoscopy, tracheal intubation, a decision needs to be taken for airway management under anesthesia or awake. Because of predicted difficult airway, planning needs to be deciphered based on structured difficult airway algorithm formulated by any airway society from around the world [16]. Good communication with the surgical team helps in better coordination and successful airway management. Because of predicted difficult airway, airway management under awake patients is the preferred approach. This requires adequate patient counseling and the topicalization of the airway as well. In case an asleep technique of airway management is planned, various plans should be made and required expertise and equipment are available before the start of the case. The use of video laryngoscopes has allowed successful airway management in such situations as it consistently increases laryngeal view by at least one grade, provides a better view of the pathology, and successful intubation without trauma to the lesion [1, 16–18]. In all situations, equipment and expertise related to emergency surgical access should be ready [1, 14, 17, 19, 20]. Patients with extensive airway pathology and/or critical airway compromise are the most challenging [17]. The airway management in such patients would depend upon the extent (size, the involvement of adjoining structures) site (supraglottic, glottic, tracheal, bronchial), and nature (vascular, cystic, pedunculated) of the lesion. There is no specific and definite plan for airway management in these patients. Awake flexible videoendoscopic, intravenous induction, inhalational induction with/without neuromuscular blockade has been used in these patients [17, 21]. These patients require various plans (primary, rescue, and failure) and at times preoperative awake tracheostomy under local anesthesia may also be one of the options [16, 22].

The various options and key points as per reported literature with regard to airway management in patients with critically obstructed airway include [16, 17]:

- Patients with critical airway compromise and with severe stridor, consider awake surgical access like tracheostomy under local anesthesia. Avoid the use of sedative drugs.
- Patients with pathology and compromising the airway to some extent as assessed with nasal endoscopy or check flexible endoscopy and with a moderate degree of stridor may be considered for airway management either under awake or under inhalational induction. This would depend on the airway assessment and expertise of the anaesthesiologists. The awake flexible endoscopic tracheal intubation shall be preferred in case of any concerns of airway compromise. For airway management under inhalational induction, ensure an optimal depth of anesthesia to prevent cough, laryngospasm but without loss of airway. The use of neuromuscular blockade needs to be

avoided during the securing of the airway to prevent the sudden collapse of the airway and complete airway obstruction. It may be administered once the correct placement of the endotracheal tube has been confirmed.

The insertion of the airway equipment and the endotracheal tube should be inserted carefully to prevent any trauma to the pathology. This can cause bleeding or lesion fragmentation and its distal passage in the airway causing airway compromise. Because of these concerns, the use of a flexible endoscope or video laryngoscope has emerged as an acceptable airway gadget for airway management. Also, the size of the endotracheal tube should be appropriately chosen and small size endotracheal tubes or microlaryngeal surgery tubes are preferred usually. Precautions should be taken to avoid multiple attempts as this may lead to the possibility of bleeding and edema leading to complete airway obstruction. It needs to be emphasized that the need for surgical airway can arise at any time during airway management. So, it is prudent to keep the equipment and personnel ready for the performing surgical access immediately in case the need arises. The use of a rigid bronchoscope is also a useful tool specifically in mass lesions around the airway or even for mass lesions in the airway. At times, the mass lesion can be core through to make the airway patent, especially for tracheal lesions.

Caution should be taken when awake fiberoptic intubation is the modality of airway management. Due to the following reasons, sudden complete obstruction of the airway can occur during awake fiberoptic tracheal intubation:

- Effect of local anesthetic agents:
  - Inhibit the function of the musculature of the tongue and upper airway
  - Precipitate laryngospasm
  - The depressant effect of local anesthetics over the central nervous system
- Friable tumors can bleed due to the impaction of the endoscope or endotracheal tube.
- The fiberoptic endoscope itself can obstruct the airway in the critically narrowed airway, like the "cork in the bottle" effect.
- Tumor fragments during airway manipulation and its distal lodgment leading to airway obstruction
- "Sucking in" of the mobile, pedunculated lesion during airway management which can be aggravated in the apprehensive and agitated patient.

The additional rescue plans for airway management also need to be ensured. Use of transtracheal jet ventilation (TTJV) or use of supraglottic airway device and high-frequency jet ventilation (HFJV) through it are other options. However, caution needs to be ensured with jet ventilation that upper airway should be patent to allow unobstructed expiration and to avoid air trapping and barotrauma.

The extubation also remains challenging and needs to be well planned in consultation with the surgical team. Though after the surgery, the airway is expected to get cleared the surgical intervention itself may lead to the development of airway edema and the possibility of bleeding. So, based on preexisting pathology and surgical procedure done, extubation strategies need to be executed. Elective ventilation for 24–48 h may be required in certain cases wherein airway edema and inflammation are expected postoperatively. The use of an airway exchange catheter (AEC) for extubation allows reintubation in case the need arises. The extubation should be done in a controlled environment with the availability of a difficult airway cart and expertise as well.

10.5 Intraoperative Ventilation Strategies for MLS

The ventilatory strategies to maintain oxygenation during MLS needs to be planned. The various options include MLS under conscious sedation, general anesthesia with or without endotracheal intubation. The MLS endotracheal tube which has a microcuff and has a smaller external diameter is suggested for its use during MLS. The tubeless techniques for MLS include the use of inhalational anesthesia, total intravenous anesthesia with the maintenance of sponta-

neous ventilation, or use of jet ventilatory techniques. At times, apneic intermittent ventilation techniques are also followed for short-duration procedures.

10.5.1 MLS Under Conscious Sedation

Certain selective laryngoscopic procedures may be performed under daycare safely and effectively. These procedures include laser surgery, diagnostic endoscopy, panendoscopy for cancer screening and biopsies, and therapeutic vocal cord injections [2–5, 16]. Patients undergoing these procedures are usually performed under conscious sedation with the use of optimal topicalization with local anesthetic agents. The use of sedatives should be used cautiously in these patients with airway compromise and as per the need of the patient.

10.5.2 MLS Under General Anesthesia

The selective group of patients undergoing MLS would require general anesthesia either using IV induction or inhalational induction. These patients have to reassure the airway without any obvious signs and symptoms of the difficult airway. However, because of pathology, these should be considered as difficult airway and all cautions should be taken for airway management. The anesthesia can be maintained with or without a tracheal tube.

- **Tracheal tube**: The MLS tubes are of small caliber with smaller cuffs and are preferred for MLS. The concerns of increased work of breathing and thus retention of carbon dioxide remains an inherent issue and controlled ventilation is preferred when using this modality for airway management. The majority of glottic tumors are anteriorly placed, so MLS tube can be easily positioned between arytenoid cartilage giving a wide unobstructed laryngeal view [4, 13, 16, 20]. Because of small external diameter, it can be positioned anteriorly as well for posterior lesions. Because of the sharing of the airway, ensure that the tracheal tube is secured properly to avoid its accidental dislodgement.

Various modalities are known for tubeless techniques:

- **Spontaneous ventilation**: In this technique, spontaneous ventilation is maintained while anesthetic gases are delivered through the side port of the bronchoscope, a tracheal tube placed in the nasopharynx, or an operating laryngoscope. The other option of maintaining the depth of anesthesia is the use of total intravenous anesthesia using propofol. These techniques provide an assessment of dynamic airway function, complete view of laryngeal, and adjoining structures. However, this technique lacks the protection of the airway from blood and tissue debris during surgical intervention. A deeper plane of anesthesia is required to blunt laryngeal response otherwise it can precipitate respiratory compromise and cardiovascular instability.
- **Apneic intermittent ventilation**: It involves induction using face mask ventilation following which a suspension laryngoscope is inserted. A small diameter endotracheal tube is used to intubate the trachea through the suspension laryngoscope. The endotracheal tube is removed intermittently to provide an unobstructed surgical field. There is a possibility of the retention of carbon dioxide. Disadvantages include possible trauma because of repeated removal and insertion of the tracheal tube, surgical trauma, laryngospasm, and unprotected airway.
- **Jet ventilation**: The use of jet ventilation (supraglottic or subglottic) helps in MLS by providing a clear, and unobstructed laryngeal view. This technique provides ventilation by delivering intermittent high-pressure oxygen or oxygen-air mixture along with entrainment of atmospheric gases. The risk of barotrauma remains and can cause surgical emphysema, pneumomediastinum, and pneumothorax

because of the use of jet which delivers oxygen at high driving pressures.

10.5.3 General Anesthetic Management for MLS

- **Premedication:** Premedication is optional and is individualized for each patient. Administration of antisialogogue like glycopyrrolate may be required to ease the surgical field visualization by its drying action on oral secretions [3, 10]. Corticosteroids are also used to prevent or decrease tissue swelling postoperatively.
- **Monitoring:** Standard operating room (OR) monitors are to be used. Additional monitoring like invasive blood pressure may be required in patients with comorbidities like coronary artery disease. The prolonged surgical procedures or use of jet ventilation for a long duration may also mandate monitoring of oxygenation using blood gas analysis [1, 20]. Neuromuscular monitoring is recommended during microlaryngeal surgery ideally over the orbicularis oculi because it correlates with the laryngeal adductors.

10.5.4 Anesthesia Induction and Maintenance

In most patients with reassuring airway, intravenous induction can be done safely. Inhalational induction can be done in a selected group of patients like patients having airway granulomas, cysts, pedunculated lesions, etc. [14] Sevoflurane remains the agent of choice for inhalational induction [20]. Target minimum alveolar concentration (MAC) needs to be attained for achieving intubating conditions [19, 22]. This may take variable time to attain this MAC with airway difficulty. The use of continuous airway pressure (CPAP) helps in maintaining a patent airway and may be used specifically in the postoperative period. The use of total intravenous anesthesia (TIVA) using propofol and opioids is another option in patients with a reassuring airway [20, 21]. TIVA provides stable anesthetic depth wherein inhalational agent use is not possible as the use of jet ventilatory strategies. TIVA is also useful for providing hypotensive anesthesia and thus aids in providing the bloodless field for MLS. It provides a good recovery profile including return pf protective reflexes, faster awakening, decreased nausea, vomiting as well and remains desirable for such surgical interventions [23–27].

Maintenance of proper neuromuscular relaxation to provide a still surgical field and also to prevent the occurrence of sudden coughing or bucking response is recommended for microlaryngeal surgery [1, 20, 22]. Such condition also facilitates effective use of jet ventilation by improving lung compliance [20].

The use of direct or suspension laryngoscopy precipitates various cardiovascular responses. The reflex bradycardia and asystole may occur at the insertion of the laryngoscope. The management includes stopping the procedure, and the use of intravenous anticholinergics agents like atropine, glycopyrrolate [28, 29]. The use of a local anesthetic agent or increasing depth of anesthesia is also the options for obtunding such a response. In severe cardiovascular response with hemodynamic compromise, cardiopulmonary resuscitation is required, occasionally isoproterenol infusion or external cardiac pacing may be required [28, 29]. The sympathoadrenal response due to various precipitating responses of laryngeal manipulation may be lead to myocardial ischemia [30, 31]. A incidence of 10–17% has been reported for the same [30, 31]. Timely assessment and appropriate management avoids any serious sequelae. The use of short-acting blockers has been advocated for preventing such adverse events. Esmolol at a dose of 1.5–2 mg/kg intravenous bolus followed by 100–300 μg/kg/min is useful [1, 32].

10.5.5 Extubation and Emergence from Anesthesia

Smooth and non-stimulating emergence from anesthesia after endotracheal intubation is one

of the most challenging goals [1, 26]. Additional trauma of the vocal cords occurs if the patient strains, bucks, or cough when the endotracheal tube is still in situ [1, 28, 32]. The decision of the extubation shall depend on the surgical intervention performed and the status of the airway (pre-procedure and post-procedure). Emergence responses like agitation, excessive body movement, laryngospasm at the time of extubation may compromise the surgery and its outcome [7, 33].

The various strategies to ease the smooth tracheal extubation of a reassuring airway need to be followed. The deep vs awake extubation decision needs to be balanced based on patient needs. The deep plane of anesthesia avoids many of the emergence response but can compromise the airway. Hence maintenance of the airway using appropriate adjuncts like airways, or mask ventilation till patients regains full consciousness. The other hybrid extubation techniques like the Bailey maneuver may also be used for extubation. Herein another airway device, the supraglottic airway device is placed either with a tracheal tube or after removal of the endotracheal tube. The supraglottic airway device is removed once the patient is awake with spontaneous ventilatory efforts [1, 34]. In the case of airway edema, humidified oxygen, and nebulized epinephrine may be administered. With the recent advances, Trans-nasal High-flow Rapid Inspiratory Ventilatory Exchange (THRIVE) has emerged as a useful tool for maintaining oxygenation [12].

The use of an airway exchange catheter (AEC) has been used in difficult airway setting [15]. The AEC, which is long hollow bougie, can be negotiated through the tracheal tube and tube remover over it. The AEC can be kept for the variable duration as per need and removed once the airway remains patent and clear [16, 17]. Ensure that the tip of the AEC remains above the carina and it should be well secured at the nostril to prevent its accidental extubation. Avoid insufflation of oxygen through it as it can lead to barotrauma, pneumothorax, etc.

At times, delayed extubation may also be planned, in case of airway edema exists or there is a risk of bleeding. The patient should be monitored in a controlled environment like that of the intensive care unit and extubated once airway related concerns have been managed. The patient should be provided with sufficient sedation and analgesia to tolerate the tracheal tube. Ensure that the difficult airway cart and expertise are available at the time of extubation.

The need for tracheostomy depends on the airway lesion and may be performed in case the safe mode of airway management is not feasible. Also, in cases, wherein the airway is not patent even after surgical intervention, then tracheostomy may be performed.

10.6 Postoperative Airway Problems

The postoperative period remains a challenge after airway related surgeries. These concerns are related not only due to the primary pathology but also related to the surgical intervention performed. Various concerns include:

- Post-extubation stridor: The usual etiology for post-extubation stridor is edema due to surgical intervention [1]. The other possibility may be a blood clot, surgical throat pack, and should be taken care of at the time of extubation itself. At times, it warrants the examination of the airway under anesthesia.
- Laryngospasm: Airway surgeries have more chances of laryngospasm due to stimulation in lighter planes of anesthesia and may further be precipitated by the presence of blood clots or debris.
- Obstruction of the tracheal tube or tracheostomy tube due to blood clot or mucus plug. Ensure proper suctioning and humidification of the tubes to prevent such blockage. At times, airway obstruction may also lead to post-obstructive negative pressure pulmonary edema.
- Dysfunctional glottis may lead to laryngeal compromise and requires immediate airway management as it is one of the causes of imminent airway obstruction [14].

- Surgical factors like bleeding leading to airway compromise, hematoma related carotid blow out, edema after vocal cord lesion biopsy, radical neck dissection with ligation of venous drainage, residual tumor, etc. need to be assessed.

It is prudent to have good and clear communication between all the team members and all advice needs to be documented. The key planning and any special considerations need to be communicated and documented. The postoperative care of such patients should be in a monitored area.

10.7 Anaesthetic Management for Laser Airway Surgeries

The precision of laser in targeting lesions has revolutionized airway surgeries. Apart from precision, the laser causes minimal bleeding and edema and preserves the adjacent structures, aids fast healing, and thereby reduces hospital stay [30]. The invisible beam of light aids in clear surgical field vision during resection. The most common laser used is the carbon dioxide (CO_2) laser. Water contained in blood and tissues absorbs the energy emitted by CO_2 laser leading to a rapid increase in the temperature causing denaturing of protein and vaporization of the target tissue leading to minimal bleeding and postoperative edema. Laser therapy is being extensively used for laryngeal papilloma, laryngeal web, and hemangioma.

Though the laser surgeries may be done using various anesthetic techniques, the selection of a particular technique depends on the primary lesion, type of proposed surgical intervention, type of laser, duration of intervention, expertise, availability of equipment, and the need for airway protection (Figs. 10.3 and 10.4). Broadly the techniques are described as closed vs open system

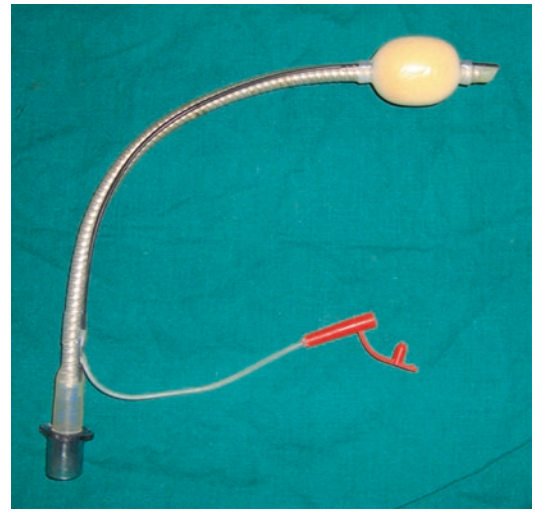

Fig. 10.3 Laser tube

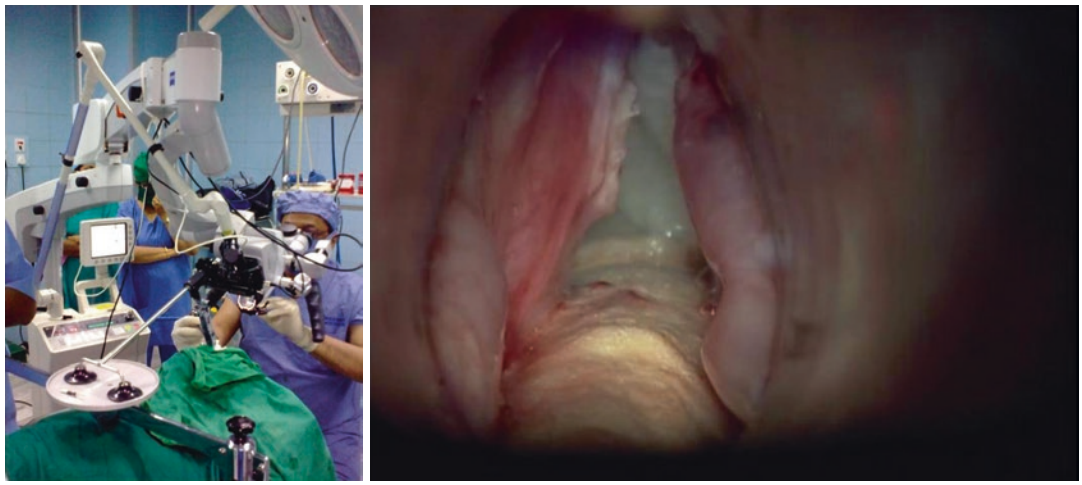

Fig. 10.4 Operating microscope connected with CO_2 laser

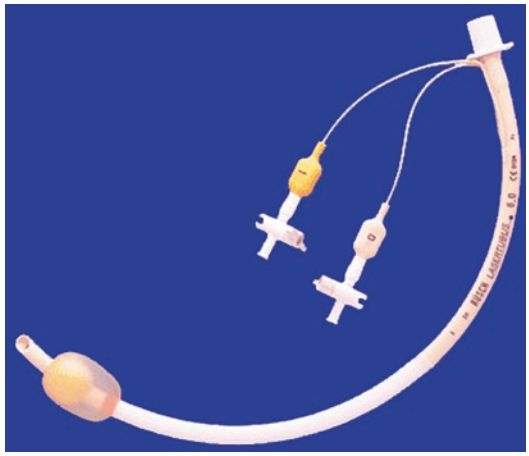

Fig. 10.5 Laser tube

techniques. The closed system techniques involve the use of a cuffed laser tracheal tube while the open technique is performed under spontaneous ventilation or the use of jet ventilation. At times, these may be changed intermittently for the same surgery as per surgical need.

The laser surgeries require laser resistant tubes as the laser can damage the conventional tracheal tubes leading to airway burn. The required tracheal tubes can be either laser proof (Norton tube) or laser resistant. The laser proof tubes do not catch fire even with direct laser in 100% oxygen. The laser resistant tracheal tubes provide some degree of protection according to their protective coating, its material, and type of cuff. The various tubes used include Norton laser endotracheal tube, Xomed laser shield I/II endotracheal tube, Bivona laser endotracheal tube, Mallinckrodt laser-flex endotracheal tube, Sheridan laser-trach endotracheal tube, and Lasertubus endotracheal tube (Fig. 10.5).

10.8 Laser Hazards

The laser therapy for airway procedures is associated with adverse events not only related to the primary lesion but also related to the laser itself. The various laser-related hazards include:

- *Eye and skin injuries*: Laser beams can cause injuries to other organs including the skin cornea and retina of the eye. It may be related to direct laser exposure or indirect effect. All preventive measures to protect the eye like proper closure of eye, eye taping, and the use of saline-soaked eye pads should be taken during laser treatment. Similarly, cover the exposed skin including the face with wet towels and drapes. Also, protection needs to be ensured for damage due to other equipment like suspension laryngoscope with its direct pressure on facial structures.
- *Lung injuries due to laser plumes*: The plumes comprising of microdebris generated to laser destruction of cells can be inhaled and deposits in lung alveoli [34]. This can affect both the patients and operating room personnel. Hence protective laser masks and an efficient smoke evacuator should be used.
- *Misdirected laser and injuries*: Equipment failure or usage of laser equipment by personnel with inadequate knowledge may result in misdirected laser. The misdirected laser beam can cause damage to the striking surface which may be surrounding structures in the operative field or operating room personnel working in proximity of the laser [35–39]. The use of signboards at the areas of laser being used shall prevent unauthorized or unprotected personnel from entering.
- *Airway injuries and fire*: The high energy laser has the potential for airway wire. The laser can damage the tracheal tube and in the milieu of the oxygen-rich environment, airway fire can occur. This blow torch-like fire has dreaded complications [3]. Laser surgical intervention has all the required ingredients for fire if cautions are not followed. Fuel sources like endotracheal tubes, sponges, drapes; oxidant sources like oxygen, nitrous oxide, and ignition source like laser itself.

10.9 Preventing Airway Fires

The airway fires during laser surgery can be prevented by following preventive strategies related to the use of endotracheal tube:

- Use of metallic foil tapes over the tracheal tube.
- Laser tube with a laser-guard protective coating.
- Tracheal tube cuff filled with saline or methylene blue -the cuff remains the most vulnerable part during laser surgery for burn due to laser strikes being thin and large size. The use of saline in the cuff protects as it acts as the saline will flood the field and extinguish any airway fire as soon as it is ruptured. The use of colored solution aids in early detection of its rupture and thus further protective action. The use of moistened pledgets above the cuff also helps in preventing cuff rupture.
- Commercially available dedicated laser tubes.

The other preventive strategies include appropriate caution for the use of various anesthetic gases including oxygen. The use of inert gases like helium and nitrogen will reduce the incidence of airway fire. The inspired concentration of oxygen should be kept low during laser surgery. The newer volatile agents like sevoflurane have low flammability. The drapes should be meticulously used and ensure the anesthetic gases flow away from the surgical site. Close communication between the surgeon and anaesthesiologists should be maintained throughout the surgery. The surgeon needs to inform the anesthesiologist before the actuation of the laser to bring the attention and lower the inspired oxygen concentration.

10.9.1 Airway Fire Management During Laser Surgery

The preventive measures for airway fire during laser surgery remain paramount. The preparation includes the availability of additional laser and polyvinyl chloride (PVC) endotracheal tube, sterile isotonic saline, or water, and plan for tracheal reintubation along with required equipment for a potentially difficult airway (fiberoptic video endoscope, laryngoscopes, preferably video laryngoscopes, airway exchange catheter, etc.).

In case airway fires occur, the surgery should be immediately stopped, switch off all anesthetic gases, and remove the endotracheal tube. Ensure all flammable and burning substances are removed from the patient. Pour saline or water into the patient airway. Once the fire is controlled, establish mask ventilation. Examine the airway for any debris or fragments and remove them gently. Examine the airway simultaneously for the extent of the injury. Based on the assessment, plan for further airway management and other injuries sustained by the patient. The extubation plan again should be based on the extent of airway injury due to fire. Extensive burns require elective mechanical ventilation with a secured airway as chances of edema and oozing remain in such a situation. The use of antibiotics, analgesia, and steroids should be considered based on patient assessment.

10.10 Anaesthetic Management of Laryngectomy

Laryngectomy is the surgical procedure for laryngeal cancers either as the primary treatment or in some cases as a salvage procedure after concurrent chemo-radiotherapy or radiotherapy. It includes the removal of laryngeal structures including epiglottis, hyoid bone, and part of the larynx. Laryngectomy may also involve neck dissections for the removal of lymph nodes and flap reconstruction. This is followed by the repair of the pharynx and permanent tracheostomy (Fig. 10.6).

Preoperative counseling is very important as the patient needs to learn a new method of communication and get accustomed to neck breathing. Preoperative assessment and optimization with special concerns for patients with associated comorbidities involving cardiovascular and respiratory system should be taken up. Laryngectomy belongs to intermediate risk for major adverse cardiac events and hence optimization of cardiovascular and respiratory comorbidities with stress on nutrition for better outcomes of the patient is considered preoperatively. Airway assessment should include a history of radiation therapy, clinical assessment, radiological imaging, and nasal endoscopic findings. These patients usually have CECT and nasal endoscopy done by the sur-

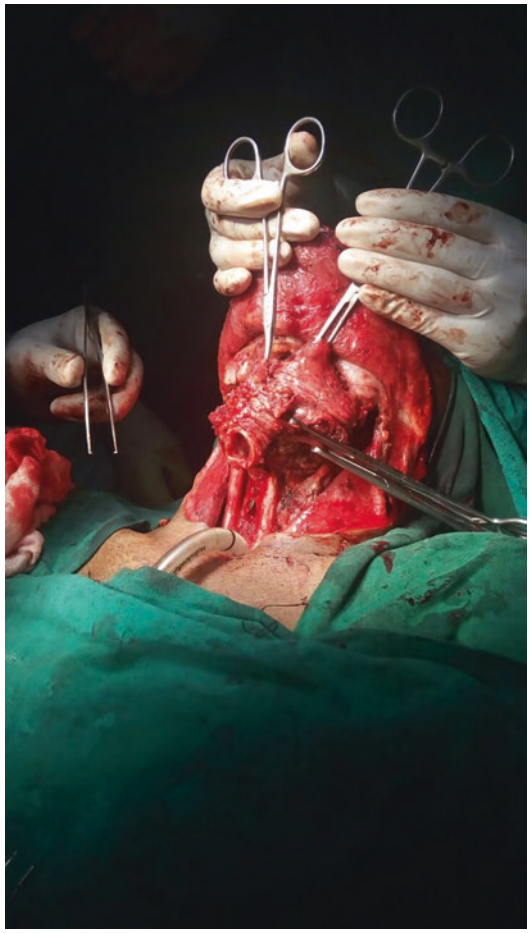

Fig. 10.6 Wide field laryngectomy

gical team and should be reviewed. A collaborative discussion among the perioperative team for an airway management strategy is essential.

10.10.1 Intraoperative Management

Standard monitors are to be used as per guidelines. As the procedure takes a long duration, invasive blood pressure monitoring can be used which also helps in blood gas analysis. The central venous line is rarely required. Temperature monitoring is required, proper care to be given for positioning, and pressure points must be padded adequately.

The difficult airway cart and the alternate and rescue plans for airway management should be ready. Oxygenation strategies during airway management include the use of high-flow nasal oxygen [16]. The face mask ventilation may be difficult as well and depends on the extent of the disease and thus decision between awake vs asleep airway management should consider holistic airway assessment. The use of video laryngoscopes in recent times has provided a safe airway management tool in such patients. The surgical access need and its preparation should also be considered during airway management. The plan of airway strategy needs to be individualized and the most common techniques include:

1. Awake flexible fiberoptic bronchoscope/video endoscope.
2. Inhalational induction maintaining spontaneous ventilation and use flexible fiberoptic bronchoscope/video endoscope or video laryngoscope.
3. Intravenous induction and use flexible fiberoptic bronchoscope/video endoscope or video laryngoscope.
4. Awake video laryngoscopy [12].
5. Awake tracheostomy, in a patient with high risk for failed intubation.

The selection for the appropriate size of the tracheal tube is essential which remains based on airway assessment on imaging. The use of reinforced tubes; the tube is preferred, but a standard tracheal tube may also be used. Once the surgical resection has been performed, the changeover of the tracheal tube is required. Once the tracheostome has been created on the skin, the initially inserted tracheal tube is withdrawn, laryngectomy tube (J tube, Montando tube), or flexometallic tube is inserted through the tracheostomy stoma. At this juncture, correct placement in the trachea needs to be confirmed, and thereafter proper fixation of the tube is to be done. In patients, who have tracheostomy done before the surgery itself, a change of tracheostomy tube with a laryngectomy tube or flexometallic tube is required.

The surgical neck dissection leads to the carotid sinus and stellate ganglion stimulation which causes hemodynamic perturbations like blood pressure, heart rate fluctuations, prolonged QT intervals, and even sinus arrest. In such cases, surgery is stopped, depth of anesthesia is ensured and local anesthetic infiltration of the carotid sheath can also manage these events. These patients may have surgery-related complications like bleeding, ligation of internal jugular vein related increase intracranial pressure, and various nerve palsies. The nerve injuries include the hypoglossal nerve, the marginal mandibular branch of the facial nerve, or the accessory nerve. Injury to the thoracic duct is also a possibility of leading to chyle leakage.

The extubation strategies need to be planned as per the patient status. These patients are shifted in the monitored areas. In case, the flap has been created, then the patients require elective ventilation for 12–24 h and adequate sedation should be maintained. In case, the airway appears to be maintained without any expected edema or bleeding, and extubation criteria are met, the tracheal tube may be removed.

10.11 Juvenile Nasopharyngeal Angiofibroma (JNA)

Juvenile nasopharyngeal angiofibroma (JNA) is a rare benign fibrovascular, locally aggressive tumor which arises from the posterolateral wall of the nasal cavity and extends anteriorly into the nasal cavity, inferiorly to infratemporal fossa through sphenopalatine foramina, and superiorly to orbit [8]. It occurs in adolescent males. The surgical excision remains the treatment of choice. Preoperative embolization of feeder vessel and deliberate intraoperative hypotension are the options to improve the outcome with decreased blood loss.

10.11.1 Clinical Presentation

The usual presentation of patients with nasopharyngeal angiofibroma is recurrent nasal bleed and nasal obstructive features [1, 2]. With the extension of tumor, the other features like diplopia, anosmia, etc. also manifest. The diagnosis is based on clinical presentation along with MRI, CT angiography, and endoscopy.

10.11.2 Anesthetic Consideration

The patient of JNA receives preoperative tumor embolization of feeder vessel usually 24–72 h before planned surgery, especially for a hypervascular JNA as assessed with imaging. Commonly used material includes polyvinyl alcohol particles, microfibrillar collagen, gel foam, gelatin microspheres, and n-butyl cyanoacrylate [40]. This provides selective devascularization of the tumor mass and helps in surgical resection with reduced blood loss and improved overall surgical outcome. At times embolization may be incomplete due to the inaccessibility of feeding vessels by microcatheter approach. Or in some cases, the safe placement of the embolic material in the specific feeder vessel is not possible to the presence of other branches. The percentage of intratumoral ischemia is evaluated by post-embolization contrast CT or MRI. Complications associated with preoperative embolization like cerebrovascular accident due to accidental embolization of one of the carotids, blindness due to embolization of ophthalmic artery, cranial nerve palsies to be assessed preoperatively. Radiotherapy may lead to complications like mucositis, temporal bone radionecrosis, and difficult laryngoscopy due to fibrosis.

10.11.3 Preoperative Blood Conservation Strategies

Autologous blood transfusion:- Preoperative donation should be combined with the administration of iron and erythropoietin. Autologous blood transfusion is not feasible if the patient has anemia due to severe epistaxis.

10.11.3.1 Anaesthetic Management

In addition to standard monitoring like an electrocardiogram, blood pressure, capnography, pulse oximetry; invasive hemodynamic monitoring is also required in such cases. Invasive hemodynamic monitoring is essential considering the expected massive blood loss, and to facilitate hypotensive anesthesia with the beat to beat blood pressure measurements. Because of the possibility of blood loss, two large-bore intravenous access must be secured before surgery. The anesthetic technique is not very specific but in patients with active bleed or risk of bleed, Rapid sequence induction, and intubation with cricoid pressure are suggested. Balanced anesthesia to be maintained to provide a good surgical field. Endotracheal intubation is followed by throat pack insertion to prevent aspiration.

Massive bleeding in JNA resection is due to the inherent vascularity of the lesion, inadvertent vascular injury, and coagulopathy. The coagulopathy is multifactorial and is most commonly due to the consumption and dilution of coagulation factors. This is further worsened due to concomitant hypothermia and acidosis. This can be managed with adequate surgical hemostasis, blood conservation strategies, maintaining normothermia, and transfusion of blood products.

10.11.4 Various Strategies Employed to Decrease Intraoperative Loss

1. Selective arterial embolization of the feeding vessel to be performed preoperatively to decrease blood loss intraoperatively and adequate resectability.
2. Endoscopic approach [3, 14, 15].
3. Reverse Trendelenburg position (15–30°) also facilitates better surgical exposure.
4. The deliberate hypotensive technique using various pharmacological measures [1, 14].
5. Antifibrinolytics agents like tranexamic-acid or epsilon-aminocaproic acid.

10.11.5 Intracranial Extension of JNA

Due to locally invasive characteristics, the tumor can extend into the cranium via superior /inferior orbital fissure to the mid cranial fossa. In case of suspicion, the signs and symptoms of raised intracranial pressure need to be assessed. This should be followed with a thorough neurological examination to evaluate consciousness, neurological deficit followed by a discussion of procedure in detail with neurosurgeon [41].

Precautions should be taken for smooth induction of anesthesia, smooth laryngoscopy, and intubation making sure the intracranial pressure (ICP) should not rise. Cerebral perfusion pressure should be maintained. Anti-edema measures like mannitol and dexamethasone administration should be considered intraoperatively. Drugs like ketamine that may increase ICP and cerebral metabolic rate should be avoided.

10.11.6 Extubation of Trachea

Extubation of the trachea should be based on the extent of surgical intervention, risk of surgical ooze, presence of residual tumor due to inaccessibility. Extubation should be considered ensuring adequate hemostasis and positive leak test. Cases with endoscopic resection of JNA can be extubated more safely [41–43].

Patients should be closely monitored as the patient can have bleeding in the postoperative period requiring elective ventilation and delayed extubation.

The pack should be removed preferably under general anesthesia with securing the airway in the operation theater as there can be bleeding. Resuscitation equipment should be readily available in case of torrential bleeding.

10.12 Summary

With the advancement in medicine, more and more head and neck cancers which were deemed non-resectable are operable now. With this, the anesthesiologist has to be diligent in handling challenges in head and neck cancer cases. Assess patients for airway difficulty, risk stratification, and optimization of comorbidities preoperatively. All airway imaging should be reviewed in liaison with the operating surgeon. The anesthetic plan should be tailored according to the lesion, nature of the surgery, personal expertise, and institutional protocol. The anesthesiologist must be adept at handling difficult airway and various ventilatory strategies as and when required. Irrespective of the primary airway strategy, a pre-formulated fallback should be ready and the surgeon should be ready for surgical airway at a moment's notice. Video laryngoscopes, jet ventilation have greatly influenced the anesthetic technique in head and neck cancer operative procedures. Fibreoptic intubation must be done cautiously as it can cause a "cork in bottle" effect when used in patients with critically narrowed airway. Airway management strategy should continue into the postoperative period as well as some of the most dreaded complications that occur in the postoperative period. The anesthesiologist should be vigilant in preventing and managing airway fires in laser surgeries. Juvenile nasopharyngeal angiofibroma is notorious for its torrential bleeding potential. Preoperative embolization and blood conservation strategies have revolutionized the management of JNA.

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Anesthesia for Lung Cancers

11

Brent MacLellan and Peter Slinger

11.1 Introduction

Globally, lung cancer remains the most common cancer and the most common cause of cancer-related death [1, 2]. Smoking tobacco is the attributable etiology of 90% of lung cancer patients. Other carcinogens include asbestos and radon gas. Cessation of smoking reduces the risk of lung cancer with time but it never equates to that of non-smokers. With increasing incidence, death due to cancer shall surpass cardiac-related death in North America in this decade [2].

Most thoracic surgical procedures are performed for malignancy [3]. Given the variety of physiologic and anatomic implications of each lung cancer, the anesthesiologist must understand the patient's pathologic diagnosis obtained through bronchoscopy, mediastinoscopy, or trans-thoracic needle aspiration. Lung cancer is broadly divided into small cell and non-small cell lung cancers. The management strategies and outcomes differ among these types.

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11.2 Non-small Cell Lung Cancer (NSCLC)

Non-small cell lung cancer (NSCLC) is the predominant type (approximately 80%) and the rest 20% are under the small cell lung cancer (SCLC) category. NSCLC includes adenocarcinoma (most common), squamous cell, and large-cell carcinoma. Overall 5-year survival approaches 40% with surgery compared to 10% without surgery [2].

Adenocarcinoma spreads locally and tends to invade the chest wall, diaphragm, and pericardium while metastasizing early to the brain, bones, liver, and adrenals. Most Pancoast tumors are adenocarcinomas. Associated paraneoplastic syndromes include growth hormone, corticotropin, and hypertrophic pulmonary osteoarthropathy (HPOE). Bronchioloalveolar carcinoma (BAC) is a subtype of adenocarcinoma. The etiology of BAC is unrelated to smoking, with limited metastatic spread, therefore can be treated by lung transplantation [4].

Squamous cell carcinomas are large tumors strongly linked to cigarette smoking with delayed metastases. The presenting features of squamous cell lung cancer are primarily related to mass effects. They manifest as hemoptysis, obstructive pneumonia, superior vena cava (SVC) syndrome, cavitation, and large airway or vessel involvement. Hypercalcemia results from parathyroid-like factor.

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The rare large cell undifferentiated carcinoma commonly involves a rapidly growing and metastasizing peripheral lung mass.

11.3 Small Cell Lung Cancer (SCLC)

This neuroendocrine tumor is considered metastatic on presentation and generally warrants medical not surgical management. Unlike NSCLC, it is simply staged as limited or extensive. Up to 80% of patients with localized disease may respond to chemotherapy such as etoposide/cisplatin or cyclophosphamide/doxorubicin/vincristine. Additional treatment includes radiation to the lung mass and radiation prophylaxis to the brain. Nonetheless, recurrence is common and overall survival is generally below 10%. Patients with the advanced disease typically receive chemotherapy and palliative radiation [2].

SCLC has been found to have characteristics of paraneoplastic syndromes. The features include hyponatremia due to a syndrome of inappropriate anti-diuretic hormone (SIADH) and Cushing syndrome through ectopic production of adrenocorticotropic hormone (ACTH). Lambert-Eaton or myasthenic syndrome is a rare associated paraneoplastic syndrome caused by an impaired release of acetylcholine from nerve terminals in these patients of SCLC [2]. The usual manifestation is typically proximal limb weakness, and this weakness improves with physical activity. Electromyography (EMG) confirms the presence of this syndrome [5]. Like myasthenia gravis, the use of non-depolarizing neuromuscular blocking agents should be used cautiously as these patients are very sensitive to its effects. And also they have a poor response to anticholinesterase reversal agents [6]. These factors need to be considered during anesthetic planning for surgical interventions.

11.4 Carcinoid Tumors

Carcinoid tumors form a spectrum of neuroendocrine tumors from malignant SCLC to the more benign typical carcinoid. Bronchial carcinoid tumors are usually asymptomatic and discovered on screening chest radiographs [7]. Five-year survival following typical carcinoid resection is over 90%. Metastases are rare with these tumors. These tumors may be associated with the ectopic synthesis of vasoactive mediators and such a phenomenon is labeled as carcinoid syndrome. The occurrence of carcinoid syndrome is less common in SCLC as compared to tumors of gut origin with liver metastases. Resection of bronchial carcinoid tumors rarely leads to intraoperative hemodynamic instability or coronary vasospasm [8]. However, the anesthesiologist should consider specific antagonists such as octreotide to manage refractory intraoperative hypotension [9].

11.5 Pleural Tumors

The primary pleural tumors are not common and include fibrous tumors of pleura (benign mesotheliomas) and malignant pleural mesothelioma (MPM). The fibrous tumors may be benign or malignant. The localized large fibrous tumors encroach on the visceral or parietal pleura.

Asbestos exposure is implicated in up to 80% of MPM cases. The window period from exposure to asbestos and tumor manifestation is usually long and thus eliciting history for its causative factor may be missed. The incidence of MPM has been reported to double in the last two decades [2]. MPM invades the visceral and parietal pleura, usually leading to a bloody effusion and exertional dyspnea. The diagnosis requires pleural biopsy and video-assisted thoracoscopy guided biopsy remains the acceptable modality. Diagnosis cannot be confirmed by thoracentesis. The symptom management includes the tapping of pleural fluid and simultaneous talc pleurodesis is performed to minimize the recurrence of the effusion.

MPM is typically refractory to therapy with expected survival under 1 year. Extrapleural pneumonectomy for the early disease may decrease mortality. The management strategies include a multidisciplinary approach including radiation therapy, chemotherapy, and surgery. The surgical intervention includes extrapleural

pneumonectomy, which is a major surgery with perioperative complications. In addition to the standard risks of a pneumonectomy, patients are at risk of extensive hemorrhage from dissection of the chest wall and major vessels, as well as the risks of pericardial and diaphragm dissection [10]

11.6 Preoperative Assessment

Preoperative assessment for surgical intervention for lung cancer surgery requires an understanding of cancer and its effects on body physiology and tools for its assessment. With evolving concepts and tools, thorough updated knowledge is paramount [2]. With the improvement in surgical techniques, a greater number of patients are scheduled for surgical excision of the tumor. The various surgical procedures for lung cancer include "lung-sparing" resections such as sleeve-lobectomies or segmentectomies, with minimally invasive techniques such as video or robotic-assisted thoracoscopic surgery (VATS/RATS). Anesthesiologists need to identify patients at elevated perioperative risk by thorough multimodal assessment and to prepare not only a holistic plan for preoperative optimization but also a strategy for perioperative care. The anesthesiologist must consider the patient's medical comorbidities and perioperative complications for lung resection [3].

11.6.1 Assessment of Lung Cancer

The basic assessment tool using "4-Ms" in cancer patients is applicable for lung cancer as well. It needs to be elicited using a thoroughly targeted history, physical examination, and investigations (Box 11.1).

In terms of medications, bleomycin is a commonly used chemotherapeutic agent for germ cell tumors and these patients may be scheduled for lung surgery for metastasectomy. The exposure to bleomycin is associated with pulmonary toxicity which can be exaggerated with a high fraction of inspired oxygen concentrations (FiO_2). Risk factors include increased age, renal insufficiency, high inspired fraction of oxygen, fluid overload, and pulmonary fibrosis [11]. The safest strategy in the patient who received bleomycin is to administer the lowest fraction of inspired oxygen in perioperative management with appropriate monitoring. Non-steroidal anti-inflammatory drugs (NSAIDs) need to be avoided in the patient who received cisplatin to avoid renal toxicity.

Box 11.1: Anesthetic Considerations in Lung Cancer Patients (the 4 "Ms") [2]

1. ***Mass effects***: obstructive pneumonia, lung abscess, superior vena cava (SVC) syndrome, tracheobronchial distortion, Pancoast syndrome, recurrent laryngeal or phrenic nerve paresis, chest wall or mediastinal extension
2. ***Metabolic effects***: Lambert-Eaton syndrome, hypercalcemia, hyponatremia, Cushing syndrome
3. ***Metastases***: brain, bone, liver, adrenal glands
4. ***Medications***: chemotherapy—pulmonary toxicity (bleomycin, mitomycin), cardiac toxicity (doxorubicin), renal toxicity (cisplatin)

11.6.2 Assessment of Respiratory Function Before Lung Resection

The thorough assessment, optimization, and appropriate planning are important as major respiratory complications like atelectasis, pneumonia, and respiratory failure have been seen in almost 15–20% undergoing lung cancer surgeries. These complications account for 3–4% mortality post lung cancer resection [12]. The assessment should include a detailed history of the patient's quality of life and objective measures of pulmonary function guide anesthetic management. A single test to predict the perioperative outcome after lung cancer surgery is not known. So, a combination of assessment

strategies needs to be used for risk assessment. The "three-legged stool" approach including respiratory mechanics, pulmonary parenchymal function, and cardiorespiratory interaction is one of the useful strategies for assessment before lung cancer surgeries [3].

11.6.2.1 Lung Mechanical Function

The various respiratory mechanics' parameters like forced expiratory volume in one second (FEV1), forced vital capacity (FVC), maximal voluntary ventilation (MVV), and residual volume/total lung capacity ratio (RV/TLC) are useful in predicting postoperative outcomes after lung surgeries. Predicted postoperative FEV1 (ppoFEV1 %) remains an independent predictor of postoperative morbidity and mortality [13, 14], which is calculated as:

- *For lobectomy*: ppoFEV1 % = preoperative FEV1 % × (1– # of functional lung segments being removed/total # of functioning lung segments). (Typically, the number of lung segments is divided as follows: right upper lobe 6, right middle lobe 4, right lower lobe 12, left upper lobe 10, left lower lobe 10).
- *For pneumonectomy*: ppo FEV1% = preoperative FEV1 × (1 – a fraction of total perfusion of the resected lung)

The American College of Chest Physicians (ACCP) guidelines argue that patients with a ppo FEV1 <30% require formal cardiopulmonary exercise testing (CPET) to further stratify risk (Fig. 11.1) [14]. Patients with a PPO FEV1 of 30–60% should undergo a low technology exercise test (stair climb, shuttle walk). Those who can walk greater than 400 m or climb greater than 22 m are deemed low risk. However, patients not attaining these thresholds should undergo formal CPET [14]. Patients with a ppo FEV1 >60% do not require further testing [14]. Patients previ-

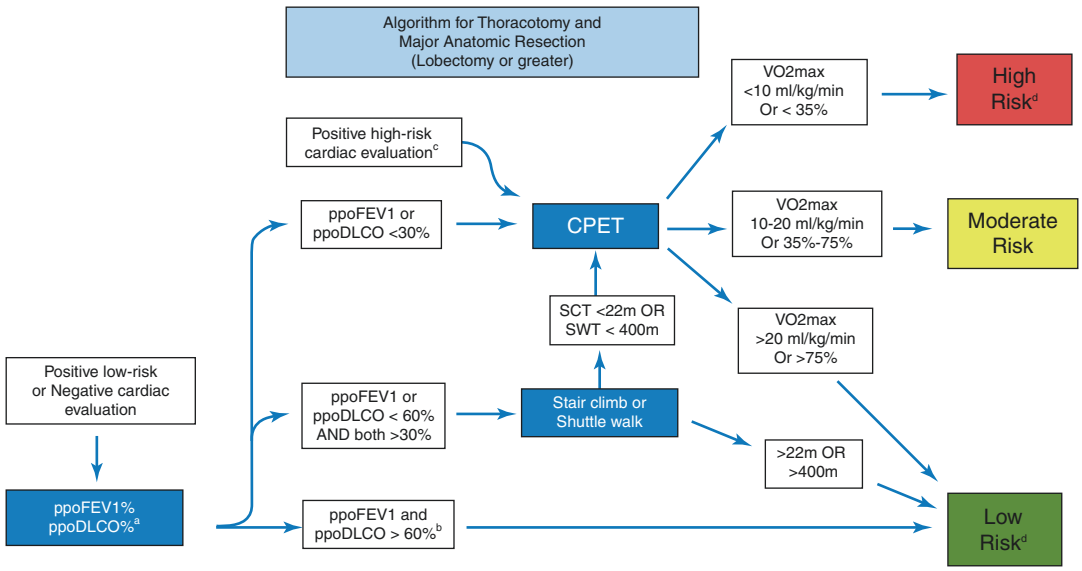

Fig. 11.1 Physiologic evaluation resection algorithm. Definition of risk: Low risk: The expected risk of mortality is below 1%. Major anatomic resections can be safely performed in this group. Moderate risk: morbidity and mortality rates may vary according to the values of split lung function tests, exercise tolerance, and extent of resection. Risks and benefits of the operation should be thoroughly discussed with the patient. High risk: The risk of mortality after standard major anatomic resections may be higher than 10%. Considerable risk of severe cardiopulmonary morbidity and residual functional loss is expected. Patients should be counseled about less invasive surgical or non-surgical options. ppoDLCO%, percent predicted postoperative diffusing capacity for carbon monoxide; ppoFEV1%, percent predicted postoperative forced expiratory volume in 1 s; SCT, stair climb test; SWT, shuttle walk test; VO_2 max, maximal oxygen consumption. Reproduced with permission from Brunelli et al. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery. *CHEST 2013;143(5)(Suppl):e166S–e190S*

ously deemed too high risk can be operated on with acceptable morbidity and mortality, ideally using epidural analgesia and VATS approach in a high volume thoracic center [15–17]. Emphysematous patients have a lung-volume reduction effect on the residual lobe(s) and may exceed their ppoFEV1 if a hyper-inflated lobe is resected [18].

11.6.2.2 Parenchymal Lung Function

The assessment for gas exchange capacity of the lung is usually done by measuring the diffusing capacity for carbon monoxide (DLCO). The DLCO reflects the total functioning surface area of the alveolar-capillary interface. Predicted postoperative (ppo) values are calculated using the same formulae as for the FEV1. Numerous studies have shown that ppo DLCO is an equal or stronger predictor of perioperative morbidity and mortality than ppo FEV1, including in patients with a normal FEV1 [14, 19]. The 2013 ACCP guidelines use the same thresholds for DLCO as for FEV1 to stratify a patient's perioperative risk and pursue additional investigations (Fig. 11.1) [14]. When there is a discrepancy between the ppo FEV1 and ppo DLCO, the lower of the two values should determine risk [13].

11.6.2.3 Cardiopulmonary Interaction

The assessment of the cardiopulmonary interaction remains one of the crucial assessments before lung cancer surgeries. The "gold standard" assessment tool for this function is by laboratory exercise [20]. The estimated maximum oxygen consumption (VO_2max) as per the patient's age, sex, and height is no more useful than the absolute value [21].

VO_2 max is an excellent tool to predict a patient's risk of morbidity and mortality post lung resection, independent of FEV1 and DLCO [14, 22, 23]. The ACCP guidelines state that patients with a VO_2 max below 10 mL/kg/min have an unacceptably high risk, 10–20 mL/kg/min moderate risk, and >20 mL/kg/min low risk requiring no additional testing [14]. European guidelines recommend performing CPET on all patients with an FEV1 or DLCO <80%, then performing ppo FEV1 and DLCO on patients with values below 20 mL/kg/min [24].

Formal CPET is too time-consuming and expensive for routine use before pulmonary resection. The six-minute walk test (6MWT) is a low-tech assessment of exercise capacity with excellent correlation to VO_2 max and similar prognostic value [25, 26]. The 6MWT distance assessment is a valuable tool to estimate the VO_2max by dividing by a figure of 30 (i.e., 600 m distance is equivalent to a VO_2max of 600/30 = 20 mL/kg/min) [27]. Climbing five flights of stairs correlates with a VO_2max >20 mL/kg/min while climbing two flights corresponds to a VO_2 max of 12 mL/kg/min. The patient's inability to climb 2 flights of stairs indicates restricted cardiorespiratory function and surgical management remains extremely high-risk [28, 29].

11.6.2.4 Ventilation Perfusion Scintigraphy

The ventilation-perfusion (V/Q) lung scanning is an important assessment modality in lung cancer patients scheduled for lung resection surgeries. This aids in the prediction of the post-resection pulmonary function. At times, the lobe or region of the lung involved with cancer may be already non-functional, therefore calculating PPO values based on perfusion rather than lung segments may be more accurate [13, 14]. V/Q scanning is likely more beneficial in pneumonectomy than lobectomy patients [30].

11.7 Intraoperative Monitoring

Generally, lung cancer resections are major procedures of moderate duration (2–4 h). The patient is positioned in a lateral position with the opening of the hemithorax. Anesthesia induction and airway management are initially done in the supine position, so on turning the patient laterally, the rechecking of monitors and airway is required. Also, the vitals and respiratory parameters should be checked soon after the change of position. The choice of invasive monitoring is usually based on patient assessment but the placement of these invasive monitoring after the

positioning of the patient for surgery is difficult. So, in patients with cardiorespiratory compromise, placement of the invasive monitoring like arterial catheter is advisable.

11.7.1 Oxygenation

Significant desaturation (SpO_2 <90%) is seen in almost 1–10% of patients undergoing lung surgeries during one-lung ventilation even with FiO_2 of 1 [2]. The arterial P_aO_2 via arterial blood gases (ABG) provides better oxygenation status as compared to the use of pulse oximeter (SpO_2) in these situations. Considering the sigmoidal shape of the oxyhemoglobin dissociation curve, the P_aO_2 may better indicate how much buffer exists before the patient rapidly desaturates to dangerous levels

11.7.2 Capnometry

The gradient of arterial (P_aCO_2) to end-tidal ($P_{ET}CO_2$) increases during OLV. The $P_{ET}CO_2$ signifies lung perfusion during OLV, though it does not correlate well with the alveolar minute ventilation [31]. The $P_{ET}CO_2$ briefly decreases at the initiation of OLV due to a higher ventilation/perfusion ratio to the dependent lung. Subsequently, it tends to increase as hypoxic pulmonary vasoconstriction (HPV) shunts blood from the non-dependent to the dependent lung. Severe (>5 mmHg) or prolonged falls in $P_{ET}CO_2$ is a good indicator of perfusion maldistribution among the two lungs and thus can predict desaturation [2].

11.7.3 Arterial Line

Surgical compression of major vascular structures may cause sudden decreases in cardiac output manifested as hypotension. This emphasizes the need for arterial line placement for ABG sampling in patients undergoing major lung surgeries. Maintaining a catheter position intraoperatively may be easier in the dependent arm, but using either side is feasible.

11.7.4 Central Venous Line

The utility of central venous access for purpose of pressure monitoring to guide fluid status remains grossly restricted due to lateral positioning an open chest. It is indeed not an acceptable tool to guide fluid management. However, it provides access for administering vasopressors and inotropes in cases where limited intravenous fluids are administered (e.g., pneumonectomies) or excessive blood loss is anticipated (re-do thoracotomies, decortications).

11.7.5 Pulmonary Artery Catheters

Intraoperative pulmonary artery (PA) pressure may also not accurately reflect left-heart preload. Given the variable distribution of lung perfusion, the use of thermodilution cardiac output measurements during OLV is controversial [32].

11.7.6 Fiberoptic Bronchoscopy

The lung surgeries require OLV and thus need airway devices for lung separation like double-lumen tubes or bronchial blockers. The placement of these devices requires flexible bronchoscopic guidance and should be reconfirmed after in the lateral position due to frequent migration of these devices, which can be missed by auscultation alone [33, 34].

11.7.7 Continuous Spirometry

Side-stream spirometry provides valuable data during OLV including inspiratory and expiratory volumes, pressures, and flow interactions. Sudden discrepancies between inspired and expired tidal volumes may provide an early signal of migration of the lung isolation device, as well as air leaks post lung resection. Auto-PEEP manifests as persistent end-expiratory flow during OLV, with potential hypoxia due to increased shunt to the non-dependent lung and hypotension due to decreased venous return.

11.7.8 Transesophageal Echocardiography (TEE)

TEE provides a dynamic monitor of myocardial function and cardiac preload, which may be more reliable than other hemodynamic monitors [35]. Potential indications for TEE during lung cancer surgery include hemodynamic instability, pericardial effusions, cardiac involvement by a tumor, air emboli, and detecting a patent foramen ovale during refractory hypoxemia.

11.8 Lung Isolation

The OLV is required for lung surgeries for various reasons including better surgical exposure, prevention of contralateral lung soiling from blood, infected material, whole lung lavage, and isolate ventilation in cases of bronchopleural fistula, tracheobronchial trauma, and severe bullous disease [36]. At times, in conditions like lung transplantation or pulmonary thromboendarterectomy, lung isolation aids in the provision of differential ventilation to lungs to avoid unilateral reperfusion injury. The methods for lung isolation include double-lumen tubes (DLTs), bronchial blockers, or single-lumen endobronchial tubes (SLTs) (Table 11.1).

11.8.1 Double-Lumen Tubes

The most common technique for lung isolation is with a DLT, which contains both endotracheal

Table 11.1 Options for lung isolation [2]

Options	Advantages	Disadvantages
Double-lumen tube 1. Direct laryngoscopy 2. Via tube exchanger 3. Fiberoptically	Easy to place successfully Repositioning rarely required Bronchoscopy to isolated lung Suction to isolated lung CPAP easily added Can alternate one-lung ventilation to either lung easily Placement still possible if bronchoscopy not available Best device for absolute lung isolation	Size selection more difficult Difficult to place in patients with difficult airways or abnormal tracheas Not optimal for postoperative ventilation Potential laryngeal trauma Potential bronchial trauma
Bronchial blockers (BB) 1. Arndt 2. Cohen 3. Fuji 4. EZ blocker	Size selection rarely an issue Easily added to regular ETT Allows ventilation during placement Easier placement in patients with difficult airways and children Postoperative two-lung ventilation by withdrawing blocker Selective lobar lung isolation possible CPAP to isolated lung possible	More time needed for positioning Repositioning needed more often Bronchoscope essential for positioning Limited right lung isolation due to RUL anatomy Bronchoscopy to isolated lung impossible Minimal suction to isolated lung Difficult to alternate one-lung ventilation to either lung
Univent tube	Same as BBs Less repositioning compared with BBs Rarely used	Same as BBs ETT portion has higher airflow resistance than regular ETT ETT portion has a larger diameter than regular ETT
Endobronchial tube	Like regular ETTs, easier placement in difficult airways Longer than regular ETT Short cuff designed for lung isolation	Bronchoscopy necessary for placement Does not allow for bronchoscopy, suctioning, or CPAP to isolated lung Difficult one-lung ventilation to right lung
Endotracheal tube advanced into the bronchus	Easier placement in patients with difficult airways	Does not allow for bronchoscopy, suctioning, or CPAP to isolated lung Cuff not designed for lung isolation Extremely difficult right one-lung ventilation

CPAP, continuous positive airway pressure; ETT, endotracheal tube; RUL, right upper lobe

Table 11.2 Comparative diameters of single- and double-lumen tubes [2]

Single-lumen tubes		Double-lumen tubes			
ID (mm)	ED (mm)	French size (Fr)	Double-lumen ED (mm)	Bronchial lumen ID (mm)	FOB size (mm)
6.5	8.9	26	8.7	3.2	2.4
7	9.5	28	9.3	3.4	2.4
8	10.8	32	10.7	3.5	2.4
8.5	11.4	35	11.7	4.3	≥3.5
9	12.1	37	12.3	4.5	≥3.5
9.5	12.8	39	13.0	4.9	≥3.5
10	13.5	41	13.7	5.4	

ED, external diameter; FOB, fiberoptic bronchoscope; ID, internal diameter
Double-lumen ED is equal to the approximate external diameter of the double-lumen portion of the tube. FOB size is equal to the maximum diameter of the fiberoptic bronchoscope that will pass through both lumina of a given size of a double-lumen tube

Table 11.3 Selection of double-lumen tube size based on adult patient sex and height [2]

Sex	Height (cm)	Size of double-lumen tube (Fr)
Female	<160 (63 in.)[a]	35
Female	>160	37
Male	<170 (67 in.)[b]	39
Male	>170	41

[a]For females of short stature (<152 cm or 60 in.), examine the bronchial diameter on CT; consider a 32-Fr double-lumen tube
[b]For males of short stature (<160 cm), consider a 37 Fr double-lumen tube

and endobronchial lumens with corresponding cuffs capable of isolating the right or left lung. Table 11.2 lists the different sizes of DLTs, corresponding fiberoptic bronchoscope size, and comparable SLT diameter.

11.8.1.1 Size Selection

Ideally, the bronchial lumen of the left-sided DLT should be 1–2 mm smaller in diameter than the patient's left mainstem bronchus (LMSB) to accommodate the bronchial cuff. In addition to reviewing chest imaging to detect abnormal airway anatomy, a simplified guide can assist appropriate DLT sizing (Table 11.3) [37].

11.8.1.2 DLT Placement Method

The various methods have been described in the literature for DLT placement. The traditional blind technique of DLT placement includes placing it using the direct laryngoscopy method and when once the endobronchial cuff crosses the vocal cords, the DLT is turned 90–180° counterclockwise (for a left-sided DLT placement) and advancing it further to place it in the bronchial lumen in the left mainstem bronchus (LMSB). Since the diameter at the level of the cricoid ring is not smaller than that of LMSB, so the DLT should negotiate the site without obstruction if an appropriate size DLT is selected [38]. In the direct vision technique, the placement of DLT in the respective bronchial lumen is guided by a flexible fiberoptic bronchoscope once the initial placement is across the glottis. Bronchoscopy must ultimately confirm placement with either technique.

11.8.1.3 Right-Sided Double-Lumen Tubes

The left-sided DLT is mostly used for lung surgeries. However, in some specific situations, a right-sided DLT is required [39] (Box 11.2). The right-sided DLT cuff is different from the left-sided DLT cuff due to the anatomy of the right bronchus. The right mainstem bronchus is shorter and the right upper lobe originates only 1.5–2 cm from the carina. Given this anatomical variation, to keep the right upper lobe patent for ventilation, the cuff of right-sided DLT has a slot [40] (Fig. 11.2).

11.8.2 Bronchial Blockers

Bronchial blockers occlude the mainstem bronchus of the operative lung to allow distal lung collapse. More distal placement can achieve selective lobar collapse. Currently, available devices are either within a modified SLT (Torque Control Blocker Univent®; Vitaid, Lewiston, NY) or are used independently within (intraluminal/coaxial) a conventional SLT: the Arndt® wire-guided endobronchial blocker (Cook Critical

Box 11.2: Indications for a Right-Sided Double-Lumen Tube [2]

- Distorted anatomy of the entrance of left mainstem bronchus
  - External or intraluminal tumor compression
  - Descending thoracic aortic aneurysm
- Site of surgery involving the left mainstem bronchus
  - Left lung transplantation
  - Left-sided tracheobronchial disruption
  - Left-sided pneumonectomy[a]

[a]It is possible to manage a left pneumonectomy with a left-sided DLT or bronchial blocker; however, the DLT or bronchial blocker has to be withdrawn before stapling the mainstem bronchus

Care, Bloomington, IN), the Cohen® tip-deflecting endobronchial blocker (Cook Critical Care, Bloomington, IN), the Fuji Uniblocker® (Vitaid, Lewiston, NY), and the EZ Blocker® with right and left mainstem balloons sitting at the carina (Teleflex, Dresden, Germany) (Fig. 11.3).

Bronchial blockers are a good alternative to DLT in situations of the difficult airway, contralateral pulmonary resection, or anticipated need for postoperative mechanical ventilation. The Cohen and Fuji Uniblocker can also be placed extra-luminal in patients with small airway dimensions (pediatrics or tracheostomy sites).

Table 11.4 describes the characteristics of current bronchial blockers. For standard 9-Fr blockers, an ETT greater than or equal to 7.0 mm ID can be used with a bronchoscope less than 4.0 mm in diameter. Larger bronchoscopes

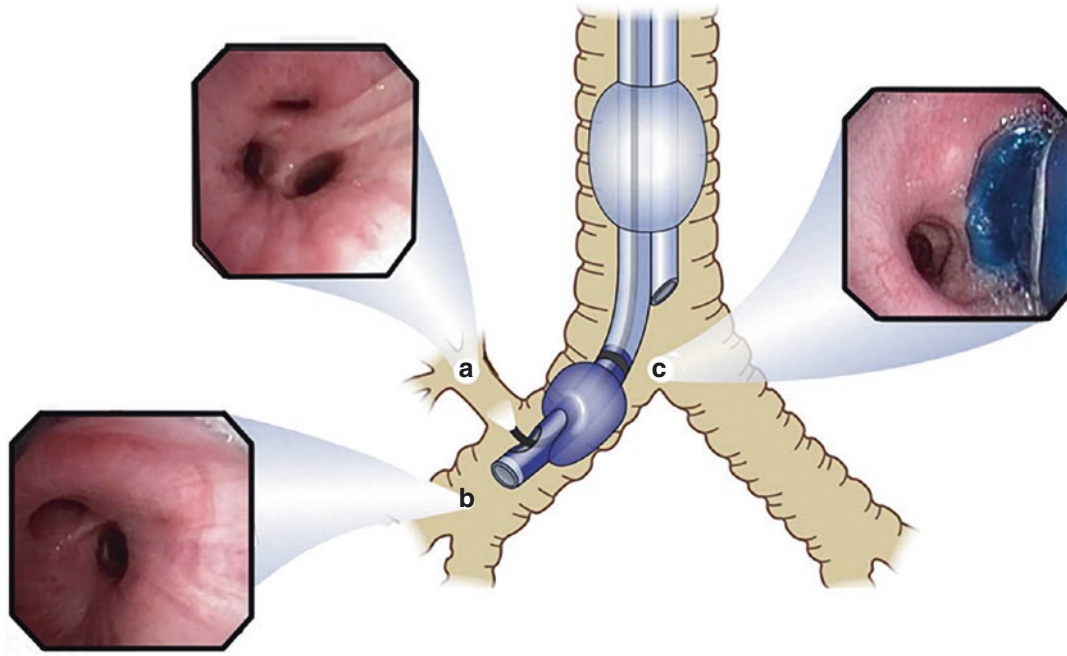

Fig. 11.2 The optimal position of a right-sided DLT is seen from the endobronchial or endotracheal view with a fiberoptic bronchoscope. (**a**) Shows the take-off of the right upper lobe bronchus with three segments (apical, anterior, and posterior) when the fiberoptic bronchoscope emerges from the opening slot located in the endobronchial lumen. (**b**) Shows an unobstructed view of the entrance of the right middle and right lower lobe bronchus when the fiberscope is passed through the endobronchial lumen. (**c**) Shows a view of tracheal carina to the right edge of the blue balloon fully inflated, to the left unobstructed view of the entrance of the left mainstem bronchus when the fiberscope is advanced through the tracheal lumen. Reproduced with permission from Slinger P: *Principles and practice of anesthesia for thoracic surgery,* New York, Springer, 2011

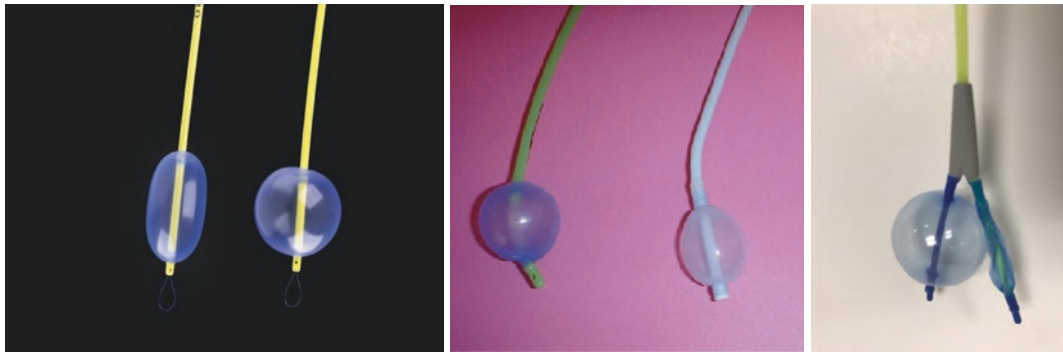

Fig. 11.3 Currently available bronchial blockers. Far left: The original elliptical and the newer spherical Arndt designs (Cook Critical Care, Bloomington, Ind). Middle: The Cohen (left, Cook Critical Care) and Fuji Uniblocker (right, Vitaid, Lewiston, NY). Right: The Rusch EZ Blocker (Teleflex, Dresden, Germany). Reproduced with permission from: Slinger P and Campos J. *Anesthesia for Thoracic Surgery. In: Miller's anesthesia*. Eighth ed. Philadelphia, PA, 2015

Table 11.4 Characteristics of the Cohen, Arndt, Fuji, and EZ bronchial blockers [2]

	Cohen blocker	Arndt blocker	Fuji uniblocker	EZ blocker
Size	9 Fr	5 Fr, 7 Fr, 9 Fr	5 Fr, 9 Fr	7 Fr
Balloon shape	Spherical	Spherical or elliptical	Spherical	Spherical × 2
Guidance mechanism	Wheel device to deflect the tip	Nylon wire loop coupled with the fiberoptic bronchoscope	None, pre-shaped tip	None
Smallest recommended ETT for coaxial use	9 Fr (8.0 ETT)	5 Fr (4.5 ETT) 7 Fr (7.0 ETT) 9 Fr (8.0 ETT)	9 Fr (8.0 ETT)	7.5
Murphy's eye	Present	Present in 9 Fr	Not present	Not present
Center channel	1.6 mm ID	1.4 mm ID	2.0 mm ID	1.4 mm ID

ETT, endotracheal tube; ID, internal diameter

require greater than 7.5 mm ID. Prior lubrication of the blocker is essential.

Current evidence shows that compared to double-lumen tubes, bronchial blockers require slightly more time for insertion, provide comparable timing and quality of lung isolation, decrease the risk of sore throat and airway trauma, but require more frequent repositioning which may affect surgical exposure [41–43]. The inflated balloon may lodge in the trachea, causing complete airway obstruction and potential cardiorespiratory arrest unless the blocker is immediately deflated [44]. The presence of abnormal airway anatomy or inadequate seal within the bronchus has been reported for the failure of this device [45]. Clear communication about the placement of blockers should be ensured with surgeons to prevent surgical stapling during lung resection [46].

11.8.3 Endobronchial Tubes

The use of single-lumen tubes (SLT) for OLV requires advancing tube in the respective bronchus under flexible bronchoscope guidance. This technique is usually reserved for difficult airways, carinal resection, post-pneumonectomy, or uncuffed SLTs in small children.

11.8.4 Difficult Airways and Lung Isolation

Patients requiring OLV may present with an anticipated or unanticipated difficult airway. Carcinoma of the head and neck with previous radiation or surgical resection may greatly complicate lung isolation. Anatomy may be distorted in the distal airways due to compression by a tho-

racic aortic aneurysm or an obstructing tumor near the tracheobronchial bifurcation.

Difficult airways should be secured with an SLT by awake fiberoptic intubation or asleep intubation with airway adjuncts immediately available. Under general anesthesia, lung isolation can subsequently be achieved by passing a bronchial blocker, advancing the SLT into the mainstem bronchus, or changing the SLT to a DLT over an airway exchange catheter (through the bronchial lumen) with visualization by video laryngoscopy. A 14 Fr exchange catheter should be used for 41 Fr and 39 Fr DLTs; for 37 Fr or 35 Fr DLTs, an 11 Fr exchange catheter is required. Soft tipped exchange catheters may be less traumatic (e.g., Cook Exchange Catheter, Cook Critical Care, Bloomington, IN).

11.8.5 Summary

The "ABCs" of lung isolation are:

- Anatomy—The understanding of the tracheobronchial airway anatomy is essential for ensuring the appropriate placement of airway devices for achieving OLV [47].
- Bronchoscopy—The fundamental knowledge and skill of the use of fiberoptic bronchoscopy for positioning and correctly identifying the correct placement of lung isolation devices is mandatory. The virtual online bronchoscopy simulator is available to familiarize themselves with the lung isolation devices (www.thoracicanesthesia.com).
- Chest imaging—The airway imaging basics should also be clear to anesthesiologists involved in providing OLV. Known airway abnormalities can guide optimal methods for lung isolation.

11.9 One-Lung Ventilation

11.9.1 Hypoxic Pulmonary Vasoconstriction (HPV)

In response to low alveolar oxygen tension (PAO_2), hypoxic pulmonary vasoconstriction (HPV) diverts pulmonary blood to well-ventilated lung regions to optimize ventilation/perfusion matching [48]. HPV decreases perfusion to the non-ventilated lung by approximately 50% [49]. HPV has a biphasic temporal response to alveolar hypoxia, plateauing at 20–30 min then again at approximately two hours [50]. The biphasic offset of HPV implies surgeries where bilateral thoracic surgeries are being performed and the collapse of the contralateral lung is required. Preconditioning leads to a greater response to a second hypoxic challenge [51].

All volatile anesthetics, especially older agents, inhibit HPV in a dose-dependent manner (halothane > enflurane > isoflurane) [52]. In doses under 1 MAC, current volatiles (isoflurane, sevoflurane, and desflurane) are weak and equipotent inhibitors of HPV [53–55]. Theoretically, the volatile agent can only access the hypoxic lung pulmonary capillaries during its return through mixed venous blood. Total intravenous anesthesia does not provide superior oxygenation than modern volatile anesthetics provided less than 1 MAC is used [56, 57]. Nitrous oxide is generally avoided in thoracic anesthesia because it can increase postoperative atelectasis and increase pulmonary pressures (inhibit HPV) [2].

11.9.2 Acute Lung Injury

Acute respiratory distress syndrome (ARDS), also known as acute lung injury (ALI), is the leading cause of morbidity and mortality after thoracic surgery [2, 58]. Its incidence of post-thoracotomy is 4–15% and associated mortality is up to 40% [58, 59]. The consensus "Berlin Definition" for ARDS defines mild, moderate, and severe ARDS, which apply post lung resection [60]. Risk factors for ALI post lung resection include peak airway pressures >40 mmHg, plateau airway pressures >29 mmHg, pneumonectomy, excessive intravenous fluids, and preoperative alcohol abuse [61].

The pathophysiology of ALI post OLV mirrors that of ARDS [62]. Modifiable triggers, including barotrauma, volutrauma, atelectrauma, hyperoxia, surgical manipulation, and ischemia-reperfusion, contribute to the inflammatory response capable of causing multiorgan failure

[58]. Therefore, an expanding body of literature guides anesthetic interventions that mitigate the risk of postoperative ALI, most notably "lung-protective ventilation."

11.9.3 Tidal Volumes

Low tidal volume ventilation (4–6 mL/kg of ideal body weight—IBW) compared to conventional high tidal volume ventilation (10–12 mL/kg IBW) during OLV decreases the incidence of ALI post lung cancer resection, especially pneumonectomy [59, 61–66]. To decrease the risk of barotrauma and volutrauma, ventilation should be with a tidal volume of 4–6 mL/kg of IBW during OLV and 6–8 mL/kg of IBW during TLV [62].

11.9.4 Positive End Expiratory Pressure (PEEP)

There is no consensus for optimal PEEP during OLV because patients sit at various points on the alveolar compliance curve. However, in most patients, PEEP is a crucial component of lung-protective ventilation. Inadequate PEEP can de-recruit the dependent lung and cause intraoperative hypoxia and atelectrauma. Excessive PEEP can divert blood to the operative lung and increase shunt fraction. Auto-PEEP averages 4–6 cm H_2O in lung cancer patients and is likely higher in emphysema [2]. Its measurement involves an end-expiratory hold, typically with an ICU ventilator. It is recommended to begin OLV with a PEEP of 3–10 cm H_2O, titrating to oxygenation and monitoring for inadequate expiration. Patients with COPD often require lower or zero PEEP [62].

11.9.5 Airway Pressures

While there are no clear thresholds for safety, minimizing peak and plateau airway pressures during OLV are key strategies to reduce the risk of lung stress. A recent review recommends maintaining peak airway pressure below 30 cm H_2O and plateau pressures below 20 cm H_2O [62].

11.9.6 Alveolar Recruitment Maneuvers (ARM)

To decrease atelectasis and shunt fraction, it is recommended to perform an ARM at a pressure of 30 cm H_2O for at least 10 s at the onset of OLV [67]. Additional ARMs should be performed as needed to improve oxygenation and optimize PEEP.

11.9.7 Fraction of Inspired Oxygen (FIO_2)

Reactive oxygen species are a known contributor to the inflammatory cascade preceding acute lung injury [58]. While an FIO_2 of 1.0 is recommended before lung isolation to decrease atelectasis, thereafter the minimal FIO_2 required to maintain a saturation of 92–96% should be used. Hyperoxia is particularly toxic as a component of ischemia-reperfusion injury. Therefore initial re-expansion of the operative lung should be performed with the lowest FIO_2 possible [62].

11.9.8 Ventilation Mode

Despite being associated with a lower peak airway pressure, pressure-controlled ventilation (PCV) does not improve oxygenation compared to volume-controlled ventilation (VCV) [2]. It is reasonable to use either mode, recognizing that with PCV tidal volumes can vary drastically.

11.9.9 Maintenance of Anesthesia

Studies demonstrate that volatile anesthetics (desflurane and sevoflurane) enhance ischemic preconditioning and attenuate lung injury in OLV compared to propofol infusion [58]. Therefore, anesthesia should be maintained

with volatile anesthetics during OLV unless contraindications exist.

11.9.10 Postoperative Care

Chest physiotherapy, incentive spirometry, and early mobility are crucial in minimizing postoperative pulmonary complications. Early extubation minimizes the risk of ventilator acquired pneumonia (VAP). Acute respiratory failure is managed supportively (oxygenation, ventilation, antibiotics if indicated) to support vital organs while minimizing further lung damage [2].

11.9.11 Hypoxemia During One-Lung Ventilation

Hypoxemia during OLV is rapid and predictable in most cases (Box 11.3) [68]. Patients with long-standing unilateral disease tolerate OLV relatively well with the decreased shunt. Right-sided procedures usually have a larger shunt and hypoxemia during OLV because the right lung normally receives 10% more perfusion than the left [69]. Patients with obstructive airway disease may tolerate OLV better than restrictive lung disease due to auto-PEEP [2]. For bilateral pulmonary surgery such as metastectomies, it is recommended to operate on the lung with better ventilation (usually the right) first because surgical trauma temporarily impairs gas exchange [70].

Box 11.3: Risk Factors for Oxygen Desaturation During One-Lung Ventilation [2]

1. Relatively high ventilation or perfusion (VQ) to the operative lung on the preoperative VQ scan
2. Low PaO_2 during two-lung ventilation, including while in the lateral position
3. Right-sided procedure
4. Normal preoperative FEV1 or FVC
5. Supine position during one-lung ventilation

Management of hypoxemia during OLV should follow a sequence of steps tailored to the individual patient, procedure, and acuity (Box 11.4). These measures can be used prophylactically in high-risk patients.

Box 11.4: Treatments for Oxygen Desaturation During One-Lung Ventilation [2]

- **Severe desaturation:**
  - Resume two-lung ventilation on FIO_2 of 1.0 (if possible)
- **Gradual desaturation**
  - Increase FIO_2 to 1.0
  - Verify the position of lung isolation device with fiberoptic bronchoscopy
  - Optimize cardiac output—inotropes/vasopressors, ensure volatile <1 MAC, minimize IVC compression by the surgeon
  - Recruitment maneuver to the ventilated lung (may briefly increase shunt to non-dependent lung)
  - Apply PEEP at ≥5 cm H_2O to the ventilated lung (after a recruitment maneuver; except in patients with emphysema)
  - Apply CPAP 1–2 cm H_2O and FIO_2 1.0 to the non-ventilated lung (after recruitment)
  - Intermittent re-inflation of the non-ventilated lung
  - Partial ventilation techniques of the non-ventilated lung
    - Passive oxygenation
    - Lobar insufflation (see Fig. 11.4)
  - Lobar collapse (with a bronchial blocker)
  - Surgical obstruction of blood flow to operative lung

IVC, inferior vena cava; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure

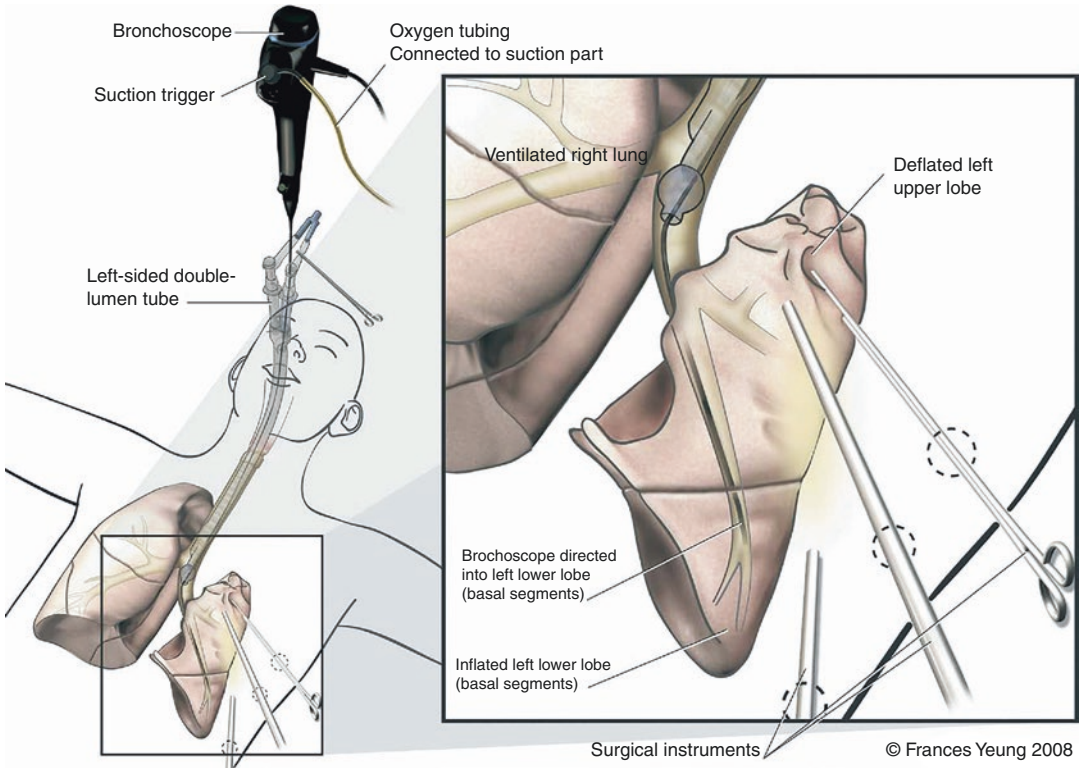

Fig. 11.4 Intermittent oxygen insufflation during thoracoscopic surgery to segments of the non-ventilated lung on the side of surgery using a fiberoptic bronchoscope. Reproduced with permission from: Slinger P. *Principles and practice of anesthesia for thoracic surgery*, New York, Springer, 2011

PEEP to the dependent lung is as effective as CPAP to the non-dependent lung for increasing PaO_2 levels during OLV [71]. CPAP can be applied through a DLT or bronchial blocker and interferes less in open than thoracoscopic surgery [72].

In refractory hypoxemia, intermittent partial ventilation of the operative lung can be administered through the DLT or blocker lumen. Selective insufflation of non-operative segments of the surgical lung is possible by directing the bronchoscope tip into such segments and intermittently compressing the suction port attached to oxygen tubing flowing at 5 L/min (Fig. 11.4) [73]. This technique is particularly useful in thoracoscopic surgery where surgical exposure is more affected by lung recruitment. A third technique is to selectively collapse the surgical lobe by the placement of a bronchial blocker into that lobar bronchus through an SLT or a DLT [74]. To limit shunt, the surgeon can obstruct blood flow to the non-ventilated lung, temporarily in emergencies or definitively in pneumonectomy or lung transplantation [75].

Avoiding potent vasodilators such as nitroglycerin, halothane, and large doses of volatiles will improve oxygenation during OLV [2]. Intravenous almitrine enhances HPV, prevents, and treats hypoxemia during OLV when anesthesia is maintained with propofol [76–78]. Inhaled nitric oxide (iNO) combined with intravenous phenylephrine improves oxygenation in ventilated intensive care unit patients with ARDS, which may translate to OLV [79].

11.10 Intravenous Fluid Management

Due to hydrostatic effects, endothelial and lymphatic dysfunction, intravenous fluids during lung cancer resection may lead to increased shunt

Box 11.5: Fluid Management Recommendations in Pulmonary Resection [2]

- Postoperative fluid balance in the first 24 h less than +20 mL/kg
- Administer under 3L of crystalloid to the typical adult patient in the first 24 postoperative hours
- Do not replace theoretical third-space losses
- Do not strive for urine output over 0.5 mL/kg/h
- Postoperatively, consider treating hypotension or hypoperfusion with inotropes rather than intravenous fluids

and pulmonary edema of the dependent lung. Excessive intravenous fluids are a well-established risk factor for postoperative acute lung injury, especially in pneumonectomy (Box 11.5) [59, 61, 80–82].

11.11 Surgical Procedures

11.11.1 Flexible Fiberoptic Bronchoscopy

Flexible fiberoptic bronchoscopy is performed perioperatively to confirm the cancer diagnosis, determine airway invasion by the tumor, and intraoperatively to verify airway anatomy during a test clamp of the surgical bronchus. Options include awake vs. general anesthesia and oral vs. nasal approaches. Effective topical anesthesia is crucial for the awake approach, with or without sedation or antisialogogues. Under general anesthesia, advantages of a supraglottic airway (SGA) technique include visualization of the vocal cords and subglottic structures, lower airway resistance versus an endotracheal tube, and the potential to maintain spontaneous ventilation in a patient with a difficult airway [83].

11.11.2 Rigid Bronchoscopy

Interventional rigid bronchoscopy with laser, tracheobronchial dilation, or stent placement is a common treatment of airway malignancies [84]. There are five basic methods of ventilation for rigid bronchoscopy:

1. **Spontaneous ventilation**—adults are much less likely than children to breathe effectively under this deep anesthetic
2. **Apneic oxygenation (high flow nasal prongs)**—requires thorough pre-oxygenation; still requires frequent surgical pauses for ventilation to clear CO_2 and maintain oxygen saturation
3. **Positive pressure ventilation via a ventilating bronchoscope**—attach the anesthesia circuit to a side port on the rigid bronchoscope; surgeon usually must interrupt the procedure and occlude the eyepiece; consider throat packs to limit air leaks.
4. **Jet ventilation**—via a handheld injector or with a high-frequency ventilator; risk of barotrauma and pneumothorax
5. **Intermittent rigid bronch removal**—ventilate by bag-mask ventilation, SGA, or ETT

These techniques are most useful with total intravenous anesthesia (often propofol and remifentanil) because volatile anesthetics involve unpredictable dosing and environmental contamination. It is crucial to maintain a deep plane of anesthesia, often with muscle relaxation, to mitigate risks of awareness, laryngospasm, bronchospasm, hemorrhage, and perforation in a tenuous, unprotected airway. In cases where a neodymium-doped yttrium aluminum garnet (Nd: YAG) laser is used, the inspired fraction of oxygen should be limited to mitigate the risk of airway fire. At induction, the surgeon must be present and prepared to establish airway control with the rigid bronchoscope. Effective team communication is paramount. Consider serial arterial blood gases to monitor oxygenation and ventilation. Highly edematous

airways may require systemic steroids, helium, racemic epinephrine, or intubation at the end of the case [2].

11.11.3 Mediastinoscopy

Cervical mediastinoscopy is the traditional method for staging mediastinal lymph nodes in NSCLC. Chest imaging should be carefully reviewed preoperatively to assess airway compromise. Given the risks of coughing during this stimulating procedure, patients are typically managed with a deep general anesthetic, including paralysis, with an SLT. To monitor innominate artery compression and cerebral hypoperfusion, the pulse oximeter is typically placed on the right hand with the blood pressure cuff on the left arm.

The most feared complication of mediastinoscopy is hemorrhage. When mild this usually responds to tamponade by the surgeon, head-up position, and avoiding hypertension. Severe hemorrhage requires emergency management including invasive hemodynamic monitoring, volume and possibly blood transfusion (consider lower body venous access), and thoracotomy or sternotomy. Lung isolation can be achieved with a bronchial blocker or double-lumen tube [2]. Other potential complications include airway obstruction, pneumothorax, recurrent laryngeal or phrenic nerve injuries, esophageal injury, chylothorax, and air embolism [85].

11.11.4 Endobronchial Ultrasound-Guided Biopsy

Endobronchial ultrasound-guided biopsy (EBUS) has replaced mediastinoscopy for preoperative lung cancer staging [2, 86]. EBUS employs a radial probe through a channel of the fiberoptic bronchoscope to allow fine needle aspiration under direct vision [87]. In general, these patients are managed in a bronchoscopy suite with topical anesthesia, intravenous sedation, and possibly an anesthesiologist, depending on the complexity of the case.

11.11.5 Minimally Invasive Thoracoscopic Surgery

Advantages of pulmonary resection by video-assisted thoracoscopic surgery (VATS), compared to open thoracotomy, include: (1) decreased pulmonary complications and mortality in high-risk patients, (2) reduced hospital length of stay, (3) less blood loss and transfusion, (4) less pain (less rib spreading), (5) improvement in pulmonary function, (6) less atrial fibrillation, and (7) less inflammatory response [17, 88–91]. VATS lobectomy is performed with a limited number of incisions, the largest approximately 5 cm in length [92]. Bilateral VATS metastectomies may be performed in the supine position. The anesthesiologist must discuss with the surgeon the potential for conversion to open thoracotomy. While most VATS procedures are done under general anesthesia with lung isolation, minor procedures can be done under intercostal blocks or thoracic epidural with TLV [93, 94].

11.11.6 Robotic-Assisted Thoracic Surgery

Robotic thoracic surgery has been a logical advancement of VATS due to the perceived improve 3D vision and instrument mobility in the chest [95]. Anesthetic considerations are outlined in Box 11.6.

Box 11.6: Anesthetic Considerations for Robotic Thoracic Surgery [2]

- Establish a protocol for immediate undocking (<60 s) of the robot in case of intraoperative emergency
- Given limited patient access, confirm the position of the lung isolation device before docking the robot
- Extensions to intravascular lines and anesthesia circuit
- Increased intrathoracic CO_2 insufflation with hypercarbia and hemodynamic compromise

- Take measures to prevent movement of the OR table during the robotic procedure
- Risk of neuropathies if lateral position prolonged
- Judicious intravenous fluids

11.11.7 Lobectomy

Lobectomy is the standard approach to lung cancer resection to reduce local recurrence. Lobectomy is being increasingly performed via a VATS approach vs. an open thoracotomy. The local invasion may be required that an elective lobectomy be converted intraoperatively to a bilobectomy (right lung) or pneumonectomy (left lung). Surgeons may request that a variable degree of positive airway pressure be used to assess the integrity of the bronchial stump. Uncomplicated patients can usually be extubated in the operating room [2].

Sleeve lobectomy is a parenchyma-sparing mainstem bronchial resection, typically for bronchogenic carcinoma. This technique has lower morbidity and mortality as compared to pneumonectomy in patients with lung cancer [96, 97]. The airway management requires the placement of a contralateral DLT or an endobronchial tube. For carinal resections, options include cross-field ventilation with a sterile circuit and endobronchial tube or high-frequency jet ventilation. For resection of major vessels, heparinization may be necessary. Hence, epidural catheter manipulation needs to be avoided for around 24 h. During pulmonary arterioplasty, massive hemorrhage may occur.

11.11.8 Pneumonectomy

Pneumonectomy for lung cancers requires posterolateral thoracotomy. After removing the lung, it is crucial to test for air leaks from the lung before reconstructing the bronchial stump which should be kept shorter to minimize the accumulation of secretions. The empty thoracic cavity after pneumonectomy remains a potential source of complications like a mediastinal shift with hemodynamic collapse. Surgical drain and application of suction may lead to exacerbation of mediastinal shift. The management of post-pneumonectomy thoracic space is not well elucidated. The management options for preventing complications related to the empty thoracic space include either not placing a chest tube or placing a dedicated post-pneumonectomy chest drainage system. This is a specially designed drain which has both high- and low-pressure under-water relief valves and thus prevents mediastinum shift [2]. A postoperative chest X-ray should be done after pneumonectomy.

Pneumonectomy carries significantly greater risk than a lobectomy. The perioperative mortality rate after pneumonectomy for NSCLC is approximately 5–8% [98, 99]. The risk of complications increases with lesser surgical case volume and patients more than 65 years of age [100]. The risk of complications increases fivefold in patients over age 65. The greatest morbidity post pneumonectomy is ALI, with an incidence of 4–18% and mortality greater than 50% [58, 66]. The risk is greater after right-sided pneumonectomy due to increased pulmonary vascular resistance and right ventricular failure after right pulmonary artery ligation [101].

Airway management strategy includes the use of a DLT on the contralateral side. In case same sided DLT is required, then it should be withdrawn during bronchial stapling. Extubation should be done after surgery and postoperative mechanical ventilation should be avoided to prevent the dehiscence of the bronchial stump. Anesthetic strategies to mitigate the risk of perioperative acute lung injury (ALI) are especially critical to pneumonectomy patients (see Sects. 11.9 and 11.10). The preventive strategies include lower tidal volumes, airway pressures along with an optimal PEEP and FiO_2. The fluid management should be done judiciously using restrictive fluid administration (prevention of fluid overload) and judicious vasopressors/inotropes to maintain hemodynamics if required.

Extrapleural pneumonectomy is typically performed for malignant pleural mesothelioma but

may have a role in the pleural spread of other cancers [102]. This is an extensive procedure requiring clearance of lymph nodes, pericardium, diaphragm, parietal pleura, and chest wall. The key points for anesthetic management include the potential for significant bleeding, coagulopathy, and appropriate blood product use. Postoperative cardiac herniation can cause severe hemodynamic instability. In cases of postoperative mechanical ventilation due to extensive surgery, a single endotracheal tube should replace the DLT at the end of the surgery.

11.11.9 Limited Pulmonary Resections: Segmentectomy and Wedge Resection

Segmentectomy in lung cancer patients refers to resection of a segment of the lung lobe along with its artery, vein, and bronchus. It is an indicated technique in primary lung cancer patients with limited cardiorespiratory reserves. The other pulmonary resection includes wedge resection which is a non-anatomical resection of the part of lung parenchyma having the tumor lesion. These types of resections are usually reserved for the patient with associated comorbidities and peripherally located tumor masses [2]. Limited resections are best performed for peripheral cancers, especially in patients with previous contralateral pulmonary resections [2]. The principles of perioperative care including anesthetic management remain the same as for other major lung resections with the additional strategy for management of associated comorbidities. **A** selective lobar collapse with a bronchial blocker may be considered in patients with poor cardiorespiratory reserves [103].

11.12 Postoperative Analgesia

Various sensory afferents transmit nociception following thoracotomy. The pain generators during thoracotomy for lung cancers are intercostal nerves T4-6 due to surgical incision; vagus nerve due to surgical handling of pleura; phrenic nerve due to the handling of diaphragmatic pleura; and brachial plexus [104]. Therefore, analgesia should be multimodal. Compared to thoracotomy, there is very little consensus on analgesic techniques for VATS procedures [105, 106]. Effective perioperative analgesia is crucial for the prevention of pulmonary complications and chronic post-thoracotomy pain and a multimodal approach of analgesics is preferred [107].

11.12.1 Systemic Medications

11.12.1.1 Opioids

The patients of cancer may have basal pain and may be managed using pharmacological agents as per pain assessment and its severity. The surgical interventions require additional analgesics. Cautious use of opioids is desirable to avoid respiratory sedation in lung cancer patients after lung resections. The dynamic nature of pain due to breathing movements needs to be managed using appropriate measures [108].

11.12.1.2 Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs and acetaminophen remain an important component of the perioperative analgesia in lung cancer patients. It has an opioid-sparing effect and is devoid of respiratory depressive effect. These agents are effective for ipsilateral shoulder pain frequently missed by epidural analgesia. The side effects of NSAIDs platelet dysfunction, gastric erosions, increased bronchial reactivity, and renal dysfunction need to be kept in mind when being used in patients for pain management [2]. Acetaminophen has weak COX inhibition and remains useful with a good safety profile for analgesia [109].

11.12.1.3 Ketamine

Ketamine is an NMDA antagonist with an established role in multimodal post-thoracotomy analgesia through both intravenous and epidural routes. However, the evidence is mixed on its

ability to prevent chronic post-thoracotomy pain [110]. Potential psychomimetic effects can be minimized by using sub-anesthetic doses and supplementing with benzodiazepines.

11.12.2 Local Anesthetic Drugs and Regional Nerve Blocks

11.12.2.1 Intercostal Nerve Blocks

Intercostal nerve blocks remain an easy and effective analgesic technique for thoracotomies or VATS. The block can be administered either percutaneously or under direct vision during surgical exposure. Ultrasound has emerged as an important modality for these blocks. These are good for acute pain but may be limited by short duration. The use of a continuous approach using catheter placement is reported but catheter placement is difficult [111]. Also, the systemic absorption remains a concern and thus doses should be appropriately calculated.

11.12.2.2 Epidural Analgesia

Thoracic epidural analgesia (TEA) technique is one of the most studied, well-proven, and considered as the gold standard techniques for the management of pain during thoracotomy [12, 112]. While the paramedian approach may facilitate insertion, ultrasound guidance has not established its place for mid-thoracic epidurals [113]. Local anesthetics and opioids (e.g., sufentanil or fentanyl) synergistically improve perioperative analgesia [114]. More hydrophilic opioids such as morphine should be considered for procedures spanning a large number of dermatomes due to greater CSF spread. Fortunately, bupivacaine 0.25% via TEA does not impair respiratory mechanics, including patients with severe COPD [115].

There is an ongoing debate about the merits of TEA for VATS procedures. Despite smaller incisions, patients report a similar rate of chronic postoperative pain to thoracotomy. This may be related to similar intercostal nerve trauma [116]. Current evidence does not support a single regional analgesic strategy for VATS procedures [106]. Patients with low pulmonary reserve, chronic pain issues, or a high chance of converting to a thoracotomy may benefit most from TEA.

11.12.2.3 Paravertebral Block

Paravertebral blockade (PVB) involves the injection into a wedge-shaped potential space bordered anteriorly by the parietal pleura, medially by the vertebral bodies and intervertebral foramen, and posteriorly by the superior costotransverse ligament. Local anesthetics cause ipsilateral somatic and sympathetic blockade of multiple spinal levels [117]. Co-administration of paravertebral dexmedetomidine can augment analgesia [107]. The block can be performed under direct vision by the surgeon and/or a percutaneous approach from behind the patient, usually with catheter placement to prolong analgesia. Ultrasound guidance for the percutaneous approach has the potential to increase efficacy and decrease complications such as pneumothorax [118, 119].

For thoracotomy, multiple studies claim that PVB provides comparable analgesia to TEA with fewer complications including hypotension, urinary retention, nausea and vomiting, block failure, arrhythmia, ICU admission, and neuraxial hematoma [120–122]. However, a recent Cochrane Review demonstrated that compared to TEA, PVB is associated with comparable perioperative mortality and major complications [123]. The relative impact on postoperative respiratory function and chronic pain is unclear [120, 121, 123, 124]. For VATS procedures, single-shot paravertebral local anesthetics can reduce pain for up to six hours [125].

11.12.2.4 Erector Spinae Plane (ESP) Block

ESP block has emerged as an effective fascial plane block in recent times with potential application to acute pain management for both thoracotomy and VATS procedures (Fig. 11.5) [126]. It involves ultrasound-guided injection of local anesthetics into the tissue plane deep to the erector spinae muscle superficial to the transverse process to cover the dorsal and ventral rami of thoracic spinal nerves [127].

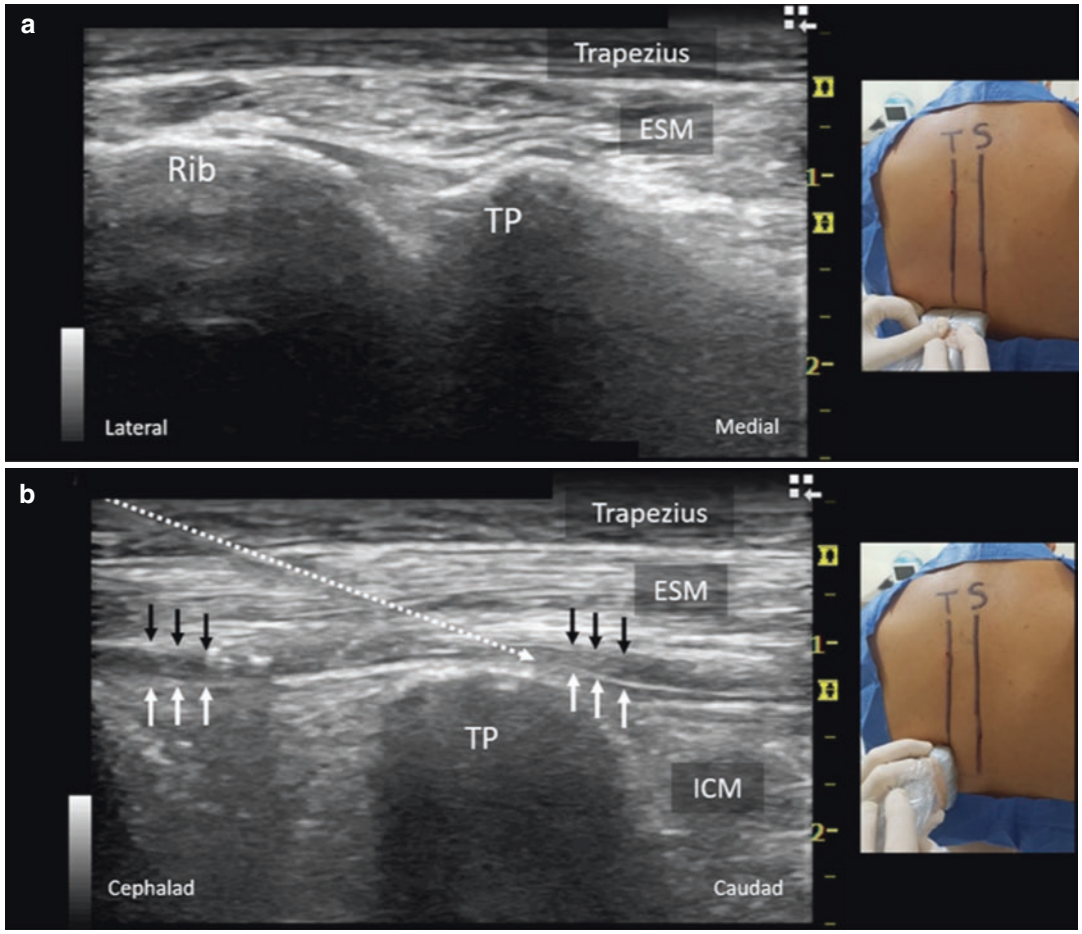

Fig. 11.5 Sonoanatomy and technique of the erector spinae plane (ESP) block. (**a**) The probe is placed lateral to the spinous processes (line S) to obtain a transverse view of the tip of the transverse process (TP) and rib with the overlying trapezius and erector spinae muscle (ESM). (**b**) The probe is rotated into a longitudinal orientation to obtain a parasagittal view of the tips of the TPs (line T), and the block needle (dotted arrow) is advanced in a cephalo-caudad direction to contact the TP. Correct needle tip position is signaled by the linear spread of local anesthetic (solid arrows) deep to the ESM and superficial to the TP and intercostal muscle (ICM). Reproduced with permission from Forero M, Rajarathinam M, Adhikary S, Chin KJ. *Erector spinae plane (ESP) block in the management of post-thoracotomy pain syndrome: A case series*. Scand J Pain. 2017

11.12.3 Postoperative Pain Management Problems

11.12.3.1 Shoulder Pain

Postoperative ipsilateral shoulder pain is very common after VATS and thoracotomy, even with a functioning epidural. It is thought to be caused primarily by diaphragmatic irritation referred to by phrenic nerve afferents [109]. Other causes of shoulder pain should be considered, including chest drains placed too deeply, inadequate coverage of the posterior thoracotomy incision by TEA, chronic pain, and referred pain from myocardial ischemia [2].

Pre-emptive acetaminophen decreases postoperative shoulder pain scores [109]. Increasing epidural medications is usually ineffective. Low volume interscalene block and phrenic nerve injection are effective but carry significant respiratory risks [104, 128]. Otherwise systemic opioids and/or NSAIDs should be considered.

11.12.3.2 Opioid Tolerant Patients

Opioid tolerant patients present significant challenges in lung cancer surgery. Patients may be using prescribed opioids for thoracic pathology, other chronic pain syndromes, be active narcotic abusers, or in rehabilitation receiving daily methadone. Patients should take their regular analgesics perioperatively, otherwise, substitute opioids must be provided. Perioperative opioid requirements are variably increased.

Multimodal analgesia is optimal. Typically, both epidural and systemic opioids are increased to mitigate withdrawal. Fixed dosing is likely superior to patient-controlled techniques, which can lead to the escalation of doses and challenges discharging patients. It is crucial to set realistic expectations that pain scores will be limited by baseline pain levels. Supplemental analgesia options include adding epinephrine 5 ug/mL to the epidural solution and low dose intravenous ketamine [129].

11.12.4 Postoperative Complications

11.12.4.1 Empyema

Empyema is one of the postoperative complications after lung surgeries and is observed in 2–16% of cases of lung cancer resections. It is associated with increased mortality by around 40% as well which is more commonly seen in patients who develop a bronchopleural fistula [2]. Treatment options for empyema include open or VATS decortication, open window thoracostomy, and in less severe cases, tube drainage and systemic antibiotics [130].

Anesthetic management for invasive procedures includes early lung isolation in the supine position to protect from contralateral soiling. A DLT is preferable to facilitate bilateral pulmonary toileting. The risk of massive hemorrhage mandates large-bore IV access, an arterial line, and potentially a central venous line for vasopressors. Patients frequently present with sepsis. Therefore, one must carefully weigh the risks and benefits of a thoracic epidural.

11.12.4.2 Bronchopleural Fistula

A bronchopleural fistula (BPF) may be caused by (1) rupture of a lung abscess or airway into the pleural space, (2) erosion by cancer or inflammation, or (3) dehiscence of a bronchial stump suture line. BPF occurs in 4–20% of pneumonectomy patients compared to <1% of lobectomy patients, with a mortality of up to 70% [131, 132]. BPF is a clinical diagnosis which may include acute dyspnea, subcutaneous emphysema, persistent air leak, contralateral deviation of the trachea, and purulent drainage. The diagnosis is confirmed by bronchoscopy, and less commonly bronchography, sinograms, indicator injection into the pleural space, or inhaled gases to detect transfer across the fistula [133].

Early post-pneumonectomy BPF can be life-threatening and require re-suturing of the bronchial stump. Late post-pneumonectomy BPF is managed with chest tube drainage or a Clagett procedure, which also includes a muscle flap to reinforce the stump. In non-pneumonectomy cases, if the lung fully expands, chest tube suction can usually resolve the air leak. However, in large fistulae with a persistent pneumothorax, surgical resection is usually necessary. Non-surgical treatments include OLV and differential lung ventilation, including high-frequency ventilation, PEEP to the pleural cavity equal to intrathoracic PEEP, unidirectional chest tube valves, and one-way endobronchial valves (for patients unfit for surgery) [134].

Preoperatively, a large BPF is detected through continuous air bubbling through the chest drain or discrepancies in inhaled versus exhaled tidal volumes through spirometry in an intubated patient. The larger the leak, the more crucial it is to establish early and effective lung isolation.

A pre-induction chest drain is mandatory. The main anesthetic goal is to achieve lung isolation before positive pressure ventilation to minimize the risk of tension pneumothorax and contamination of the contralateral lung. One general option is to maintain spontaneous ventilation, either through an inhalational induction, titrated intravenous induction, or awake fiberoptic intubation with airway topicalization. Another general

option is to perform "rapid sequence lung isolation," which includes thorough pre-oxygenation, pre-calculated doses of induction drugs and muscle relaxants, then immediate intubation without bag-mask ventilation. Patients are likely to desaturate rapidly and subsequent bag-mask ventilation can be ineffective due to oxygen passing through the fistula instead of the contralateral lung. Therefore, the "rapid sequence" method should be reserved for experienced hands with airway adjuncts (e.g., video laryngoscope) in patients with generally reassuring airway exams.

A DLT is ideal for lung isolation, airway toileting, and visualization of the affected bronchus, but likely too traumatic for awake fiberoptic intubation. Patients with difficult airways may be better managed with a single-lumen awake intubation, with either a contralateral endobronchial tube or a bronchial blocker pushed into the affected bronchus. Airway placement should always be guided by bronchoscopy to ensure accuracy and minimize trauma. Bronchial blockers are generally not compatible with the bronchial stump post pneumonectomy. Early extubation avoids prolonged positive pressure to the stump.

The thoracic epidural anesthesia with intravenous sedation has been used for minimally invasive BPF repair post pneumonectomy [135]. Pitfalls include incomplete visceral coverage by the epidural and potential contamination of unprotected contralateral airways. An alternative method is high-frequency oscillatory ventilation with permissive hypercapnia, which can minimize barotrauma to the non-operative lung, decrease bronchopleural fistula air leak, and optimize the operative outcome [136].

11.12.4.3 Atrial Fibrillation

Atrial fibrillation (AF) is one of the common cardiac complications and is seen in almost 46% post pneumonectomy patients [137]. Theoretical mechanisms include surgical inflammation, catecholamine surge, myocardial ischemia, and autonomic imbalance [138]. Postoperative AF is associated with increased length/cost of hospital stay, morbidity, mortality, and stroke risk [139, 140].

A recent systematic review and meta-analysis determined that the most effective pharmacologic AF prophylaxis, in descending order, is through: beta-blockers > ACE inhibitors > amiodarone > magnesium > statins > calcium channel blockers > digoxin [137]. Intraoperative prophylaxis can be complicated by hemodynamic instability including epidural use and the risk of residual neuromuscular blockade, therefore should be administered on a case-by-case basis.

11.12.4.4 Cardiac Herniation

An acute cardiac herniation is one of the rare complications after lung surgeries especially pneumonectomy or with pericardial involvement [141]. It usually manifests with pericardial closure dehiscence within 24 h postoperatively. This is associated with increased mortality by almost 50% [142]. It typically results from pressure differences in the two hemi-thoraces after chest closure. The superior vena cava syndrome and profound shock may be seen in cardiac herniation after right lung removal [143]. Herniation after left pneumonectomy may manifest arrhythmias and features suggestive of ventricular outflow tract obstruction.

A cardiac herniation is a surgical emergency. Also, the differential diagnosis like massive intrathoracic hemorrhage, tension pneumothorax, and pulmonary embolism needs to be considered with patients manifesting acute symptoms in the postoperative period. While mobilizing the patient to the operating room for thoracotomy and definitive repair, management includes securing the airway with a single-lumen tube (address lung isolation once surgical control is established), positioning the patient lateral decubitus with the surgical side up, hemodynamic support with inotropes and invasive monitors, and minimizing suction to the affected hemithorax. Intraoperative TEE can help prevent excessive compression of heart chambers by surgical repair [2]. These patients should remain intubated to recover in the intensive care unit.

11.13 Summary

Resectable lung cancers are associated with various regional mass effects, paraneoplastic syndromes, and neoadjuvant therapies which greatly impact anesthetic management. Anesthesia for lung cancer surgeries involves many challenges including one-lung ventilation in patients with limited pulmonary reserve, complex airway management, and critical analgesia to facilitate postoperative recovery. Preoperative assessment of the patient's mechanical and parenchymal lung function, as well as cardiopulmonary interaction, stratifies the risk of perioperative complications. The thoracic anesthetist requires strong knowledge of bronchoscopic anatomy for effective lung isolation and surgical exposure. It is crucial to have an organized approach to managing hypoxemia during one-lung ventilation, both during thoracoscopic and open chest surgery.

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12 Anesthesia for Esophageal Cancer Surgeries

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12.1 Introduction

Esophageal neoplasms, constitute an aggressive disease requiring surgical intervention for treatment. Surgery often involves extensive resection and therefore leads to significant perioperative complications both medical as well as surgical. Patients are frequently diagnosed late in the course of the disease with distant metastasis occurring in about 50% of the patients at the time of presentation. Esophagectomy or surgical resection of esophageal cancer remains the main modality of treatment both as a curative therapy and for palliation after neoadjuvant therapy. Esophageal resection for malignant pathology is a complex surgery and poses major challenges to the surgeon, the anesthesiologists as well as to the patient. The role of anaesthesiologist in the perioperative management of the patient undergoing esophagectomy may have a significant impact on the clinical outcome of the patient.

12.2 Epidemiology

The reported new cases of esophageal cancer in 2012 were estimated to be 455,800 and 40,400 deaths due to esophageal cancer [1–3]. The increased incidence of esophageal adenocarcinoma in patients with Barrett's esophagus is observed [1]. Also, overweight and obesity are the established risk factors for esophageal adenocarcinoma [1].

Histologically, esophageal malignancy is classified commonly as adenocarcinoma or squamous cell carcinoma, and global trends in incidence vary for these histological esophageal cancers. Small cell carcinomas and sarcomas are less frequently encountered in clinical practice. The occurrence of squamous cell subtype is decreasing due to increased awareness and reduction of alcohol and tobacco consumption. According to the anatomical location, most of the increased incidence involves tumors at the gastroesophageal junction (GEJ) and gastric cardia [4].

12.3 Risk Factors and Pathophysiology

The risk factors and pathophysiology vary for the histologically different esophageal cancers.

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Squamous Cell Esophageal Carcinoma The major risk factors for squamous cell carcinoma include smoking and intake of alcohol. In the "esophageal cancer belt" of Iran and Asia, factors such as poor nutritional status, inadequate intake of fruits and vegetables, and consumption of very hot liquids have been identified as risk factors [1]. The most common location of squamous cell carcinomas (SCCs) is the mid-esophagus [5]. The origin of SCC starts with small polypoid excrescences, denuded epithelium, or plaques [5]. Though lesions like this are the precursor of carcinomas, its early detection may be missed on endoscopy due to their unsuspicious appearance. Staining with Lugol's iodine solution due to the presence of glycogen may facilitate early detection during endoscopy; however, this technique is rarely used. The invasion of the submucosal layer occurs early, and it goes on the extent in a cephalad direction along the wall of the esophagus [6]. The lymphatics of the gastrointestinal tract are located beneath the muscularis mucosa layer; however, the lymphatics in the esophagus are present beneath the lamina propria. This accounts for the early lymph node involvement of esophageal malignancy. Regional lymph node metastasis occurs along the paraesophageal, para-aortic regions and in the celiac area. Distant metastases may be seen in almost one-third of the patient at presentation [4].

Adenocarcinoma The pathology of adenocarcinoma of the esophagus is more clearly understood because of the recognition of early cancer in patients with the presence of Barrett's esophagus [7]. Gastroesophageal junction is the most common location for most adenocarcinomas. Adenocarcinoma of the esophagus is often associated with Barrett's esophagus where it may manifest as an ulcer, a nodule, an altered mucosal pattern, or no visible endoscopic abnormality [8]. In the absence of Barrett's esophagus, endoscopic evidence of an ulcer, plaque, or nodule near the gastroesophageal junction may point towards early adenocarcinoma [9]. As in SCC, metastases to regional lymph nodes occurs early. Involvement of celiac and perihepatic nodes is more common with adenocarcinoma because of the involvement of the gastroesophageal junction [10].

12.4 Preoperative Assessment

Esophagectomy is a major surgery performed in poorly nourished often debilitated patient. In addition, the procedure involves extensive dissection in multiple regions of the body such as abdomen, thorax and the neck which increases the perioperative risk manifold. Neoadjuvant chemoradiation (radiation therapy and chemotherapy regime of 5-fluorouracil, cisplatin, and epirubicin) is usually offered to most patients preoperatively. Its role is primarily to allow the complete resection after reduction in tumor size and optimal clearance of micro- and macrotumorous cells. However, persistence of inflammation or development of chronic fibrotic changes may obliterate the tissue planes, thus complicating the surgical resection.

With the changing global profile of patients being taken up for major surgeries, the patients presenting for esophagectomies are older, and comorbid conditions like ischemic heart disease, diabetes, and obesity are being encountered more than ever before. Another point to be considered in the preanesthetic assessment includes the history of smoking, alcohol intake, and the presence of gastroesophageal reflux disease. Owing to the nature of their illness, patients are usually debilitated due to poor nutritional intake. Investigations frequently reveal anemia and hypoalbuminemia.

Predicting risk factors for major morbidity is not easy; however, certain risk factors have consistently been associated with poor outcomes. These include poor general health, cardiac and hepatic dysfunction, age, tumor stage, presence of diabetes, and poor cardiopulmonary reserve [11–13].

Assessing the efficacy of multidisciplinary treatment for preoperative optimization of high-

risk patients is important. The usual assessment tool like climbing two flight stairs for assessing exercise tolerance is a well-accepted screening tool. Various models like Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) and Acute Physiology and Chronic Health Evaluation (APACHE) II may be used to predict the risk of morbidity and mortality [14]. Multiple adaptations of the available tools have been made for the specific surgery-related outcome. One such modification is O-POSSUM which is being used for risk prediction in patients undergoing esophageal and upper gastrointestinal surgery [15]. Though exercise tolerance and surgical risk scoring systems offer convenient triage and risk stratification of patients, nevertheless, a detailed objective evaluation of each patient is subsequently required before surgery. Evaluating the patients' cardiopulmonary reserve by assessing the functional capacity, objectively by cardiopulmonary exercise testing, may help in identifying individuals who are at increased perioperative risk. Cardiopulmonary complications develop in about 42% of patients with an anaerobic threshold of less than 9 ml/min/kg and 20% of patients with an anaerobic threshold of greater than 11 ml/min/kg [16]. Snowden et al. suggested that maximal oxygen consumption (VO_2max) of less than 800 ml/min/m^2 is associated with fewer complications and these patients may safely undergo esophagectomy [17, 18].

The best approach to decide patient suitability for esophagectomy would be a combination of clinical evaluation, morbidity prediction scores, and cardiopulmonary exercise testing. This along with multidisciplinary evaluation and treatment of the patient may lead to improved outcomes though further research is warranted in this direction.

Patients with esophageal pathology remain at risk of pulmonary aspiration because of lesion-associated abnormality including stricture or achalasia. Expecting a full stomach is the norm since esophageal contents are unknown and retained ingested food may be present despite adequate fasting. Rapid sequence induction and intubation (RSII) technique or awake endotracheal intubation may be a prudent option.

Smoking cessation should be advised, and patients should be offered nicotine replacement therapy since smoking is associated with higher postoperative morbidity. Intensive preoperative physical therapy and inspiratory muscle strengthening may improve lung function and functional capacity [19].

It is not uncommon for these patients to have chronic obstructive pulmonary disease (COPD) because of frequent association with smoking. Patients with findings of forced expiratory volume in 1 s (FEV1) < 65% of the predicted normal and reduced peak expiratory flow rate in the preoperative pulmonary function tests remains at increased risk of postoperative pulmonary complications. Perioperative, inhaled beta-agonists and/or steroids along with chest physiotherapy remain the mainstay of treatment and their use should be implemented in the perioperative period.

The other lung-related complication seen after esophagectomy includes acute respiratory distress syndrome (ARDS) and is seen in almost one-third of the patients [20]. Excessive fluid administration is one of the most cited causes for post esophagectomy ARDS. Overdistension of capillaries causes damage to the endothelial glycocalyx resulting in increased vascular permeability. In addition, release of inflammatory mediators – both local as well as systemic along with cellular infiltration may contribute to the lung injury. Various studies have evaluated the efficacy of certain drugs in reducing the incidence of ARDS after esophagectomy. The BALTI-P (The Beta Agonist Lung Injury Prevention Trial) and the VINDALOO (Vitamin D to prevent Acute Lung injury folLOwing Oesophagectomy) have identified the risk factors and management strategies for the occurrence of ARDS after esophagectomy [21–23]. Pretreatment with statins has also been suggested for a reduction in the systemic inflammation arising out of this extensive surgery [24].

12.5 Anesthesia Technique

For most surgical procedures involving the esophagus, general anesthesia with endotracheal intubation, with or without supplemental epidural analgesia, is used as the primary anesthetic technique. A balanced anesthetic technique using either inhalation anesthetics or intravenous anesthetics is recommended. There is evidence to suggest that inhalational anesthetic agents confer a lung protective effect by producing an anti inflammatory and anti oxidative effect in patients undergoing one lung ventilation for thoracic surgery thereby improving post-operative outcomes [25, 26].

Proper airway assessment with all provisions to manage a difficult airway should be in place especially when there is a need for lung isolation. If a thoracic approach for esophagectomy is planned, the airway management equipment should be of appropriate size, and its availability should be ensured. The airway assessment and plans for airway management should be decided. The double-lumen endotracheal tubes, bronchial blockers, and a Univent tube are the various options for one-lung ventilation (OLV). Inadequate lung isolation could be very challenging in a minimally invasive technique as compared to an open technique where the lung can be manually retracted off the surgical field [27, 28]. The placement of a left- or right-sided tube for lung isolation does not impact the incidence or duration of hypoxemia, hypercapnia, and high airway pressures [28]. The correct placement should be confirmed using a fiberoptic bronchoscope and should be rechecked after positioning of the patient as well [29]. Surgeries done in the prone position may be possible even with the use of a tracheal endotracheal tube (single-lumen endotracheal tube). The use of low tidal volumes or pressure-controlled ventilation should be implemented during OLV to limit the alveolar injury arising out of inflammatory insult [30]. Lung-protective ventilation also promotes early extubation [31].

Thoracic epidural analgesia (TEA) for perioperative analgesia is a widely accepted practice for open and minimally invasive surgical interventions across various centers. Its beneficial effect includes not only adequate analgesia, but also decreased respiration-related complications, early extubation, decreased length of hospital stay, and lesser surgical complications like the reduced incidence of anastomotic leakage [32–35]. Extensive surgery in the region of the thoracic cavity and upper abdomen leads to proinflammatory mediators upregulation and subsequent immunosuppression. Major tissue injury has also been associated with dysfunction of the innate immunity [36]. Epidural analgesia suppresses the activity of the neuroendocrine-immune axis possibly by its ability to cause sympathetic nerve block, thereby limiting inflammation and improving the immune function [37]. Thoracic epidural analgesia has a beneficial effect on surgical outcomes by causing the sympatholytic induced increase in perfusion of the anastomotic surgical site. Other regional analgesia techniques being used include a thoracic paravertebral block for esophageal resection with results comparable to that of TEA [38, 39]. It may be particularly useful in patients with spine abnormalities where access to the epidural space is challenging [40].

The positioning of the patient is a team approach and requires the utmost care as the surgery is often prolonged. In the transhiatal approach, the patient remains supine with arms on the side, and a pillow is placed under the shoulder with neck extension to facilitate esophageal anastomosis in the neck (Fig. 12.1). In the

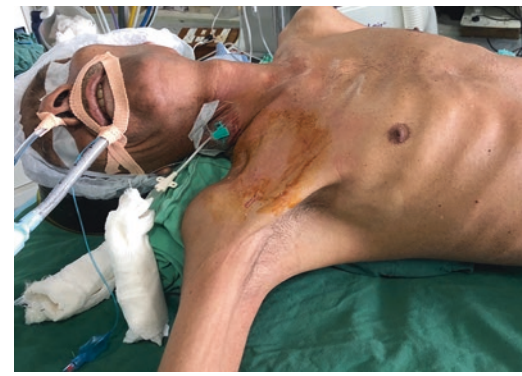

Fig. 12.1 Patient positioned for a transhiatal approach to esophagectomy

thoracotomy approach, the patient is initially placed in the supine position for the abdominal part of the surgery and later positioned in the left lateral position for the right thoracotomy whereas in the thoracoabdominal approach the left chest is elevated with a small pillow. Minimally invasive thoracoscopy was devised to facilitate fast-tracking for faster recovery with minimal perioperative morbidity. This requires the patient in the left lateral decubitus position usually, but some surgeons prefer the prone position of the patients. Cuschieri et al. first described the prone position for thoracoscopic surgery and suggested that it is associated with better postoperative outcomes [41]. This is primarily related to better space for surgery as lungs remain away from the surgical field due to gravity itself. This mitigates the need for single-lung ventilation. The prone position is beneficial because of minimal ventilation-perfusion mismatch, increased functional residual capacity by preventing atelectasis, and better lung secretion drainage. All these factors contribute to minimizing lung injury. This is the likely explanation for reduced pulmonary complications in the prone position described by Cuschieri. The occurrence of various complications like pneumonia and adult respiratory distress syndrome (ARDS) has been variously reported for different positions and techniques of esophageal surgery [42, 43].

Esophagectomy requires a very careful intraoperative fluid therapy as both liberal and restrictive therapy in their extremes may be detrimental. Liberal administration of fluids can lead to tissue edema resulting in compromised perfusion as well as pulmonary interstitial edema. This remains one of the commoner reasons for postoperative pulmonary complications [44]. On the other hand, strict implementation of restrictive fluid therapy can result in hypovolemia which may cause decreased perfusion of tissues, end-organ dysfunction, and even anastomotic leak [45]. Therefore, fluid administration for esophagectomies should be planned based on goal-directed therapy (GDT). Fluid administration based on GDT has been associated with better intraoperative hemodynamic parameters and reduced intensive care unit admissions, leading to reduced morbidity and mortality [46]. GDT aims to administer fluids and inotropes to optimize the cardiac output to maintain tissue perfusion by using static or dynamic parameters.

The guide to fluid administration has conventionally been the use of static parameters like pulse rate, blood pressure, and urine output. The use of central venous pressure remains the poor indicator of fluid status. More recently, other dynamic parameters are being preferred. Parameters like pulse pressure and stroke volume variation are being increasingly used, especially in patients with associated comorbidities. These tools have been prevented over or under fluid resuscitation with better outcomes in high-risk surgical patients [47]. However, adequate data is lacking in patients undergoing open and laparo-thoracoscopic esophagectomy, and most of the data is extrapolated from vascular or intra-abdominal surgeries. Minimally invasive monitoring technique using pulse contour analysis is a commonly used technique to assess GDT. The pulse contour analysis-based parameters use stroke volume variation (SVV), pulse pressure variation (PPV), and stroke volume index (SVI) for fluid status assessment and response to fluid administration [48–50]. However, these parameters are affected in the open chest cavity [45]. Therefore, the use of these parameters in such patients remains controversial. Extra vascular lung water (EVLW) has been used as a marker for the prediction of development of pulmonary edema after esophagectomy [51]. The dilemma remains regarding the reliability of these markers in minimally invasive esophagectomy as there is a paucity of large prospective studies evaluating the same.

12.6 Monitoring

The monitoring for esophageal surgeries includes standard American Society of Anesthesiologists (ASA) monitors. Additional monitoring may be required as per patient assessment and associated comorbidities and includes invasive monitoring like intra-arterial blood pressure and a urinary catheter to monitor urine output. The central

venous catheter (CVC) may be placed for an anticipated need for vasoactive medication. The monitoring of central venous pressure (CVP) is a static parameter and unreliable marker of assessing fluid responsiveness, and trends of CVP are monitored whenever it is in situ, to provide additional hemodynamic data.

Monitoring microcirculatory perfusion has also been described in esophageal surgeries. One of the reasons for the postoperative anastomotic leak has been attributed to compromised regional microcirculatory perfusion [52]. The monitoring tools to detect such compromised perfusion include sidestream darkfield microscopy (SDF), laser Doppler flowmetry, near-infrared spectroscopy (NIRS), laser speckle imaging (LSI), fluorescence imaging (FI), and optical coherence tomography (OCT) [53–59]. The clinical utility of these novel tools has yet to be proven, is difficult to interpret, but appears promising, and whether any of these techniques have an impact on the clinical outcome is yet to be ascertained. The utility of LSI to identify ischemic vs perfused tissue before anastomosis improves the outcome [59]. At this juncture, the anesthesiologist may guide the hemodynamics by using vasopressors or fluids titrated to effect. Postoperatively, the microcirculation techniques that monitor oxygenation or flow may be of greater advantage.

It has been reported that the hypotensive events requiring fluid administration or vasopressors intraoperatively were correlated to a greater occurrence of anastomotic leakages postoperatively [60, 61]. Also, such hypotensive events were more commonly observed in surgeries in the prone position and local anesthetic-based epidural analgesia techniques. Sugasawa et al. studied the monitoring of the stroke volume index (SVI) and its impact on the outcome of the surgery and observed that lower SVI was related to the occurrence of acute kidney injury [50]. Although there is adequate evidence to confirm that hypotension causes reduction of flow over the gastric conduit [52, 54, 56, 58, 62], increasing mean arterial pressure above normal values is unlikely to prove advantageous. Additionally, venous congestion may further contribute to decreasing flow over the gastric conduit. The topical application of nitroglycerin has been propagated in certain studies to deal with the same [52, 55].

Significant hemodynamic perturbations are anticipated such as dysrhythmias, hypotension during manipulation of the pulmonary vasculature, and mediastinal dissection. This should be communicated to the surgeon who may need to halt the mediastinal manipulation until the hemodynamics are restored. Hemorrhage is encountered infrequently, and blood transfusion is rare. Efforts should be made to prevent hypothermia from the time of induction of anesthesia, especially in open surgeries.

Historically, several arguments and observations led to the practice of delayed extubation in patients undergoing esophageal resection. Prolonged surgery, overzealous fluid therapy and systemic inflammation may occasionally lead to airway edema and the risk of airway obstruction. Postoperative pain due to extensive dissection and wide incision compromised respiratory mechanics. Bile reflux in the postoperative period may predispose the patient to aspiration pneumonitis. Thus, patients were electively ventilated in the post-operative period. In current practice, attempts are made to extubate the patient at the end of the surgery since there is no evidence to suggest that postoperative ventilation would result in reduced pulmonary complications after an elective surgery in the high-risk patient [63]. A well-planned perioperative care improves the overall outcome after esophageal surgeries (Table 12.1).

Table 12.1 Summary of anesthetic technique for esophagectomy

Anesthetic considerations for esophagectomy
• General ASA standard monitors
• Invasive monitoring—arterial blood pressure, trends of central venous pressure
• Minimizing aspiration risk
• Thoracic epidural analgesia
• One-lung ventilation—lung-protective strategy
• Goal-directed fluid therapy
• Maintaining adequate perfusion to optimize anastomotic blood flow
• Fast-track extubation

The emphasis needs to be followed for meticulous perioperative fluid management, optimal analgesia, and the use of appropriate analgesia techniques and attempts to minimize blood loss [64–67].

12.7 Postoperative Course

The postoperative course of these patients requires monitoring in a high-dependency unit. Priorities include adequate analgesia, respiratory therapy, avoidance of respiratory complications, early mobilization, and appropriate nutritional therapy.

Anastomotic leakage occurs in approximately 10–15% of the patients of esophageal surgery. The clinical signs suggestive of septicemia need to be monitored for suspicion of such an adverse event [68]. Early anastomotic dehiscence is attributed to inappropriate surgical technique, whereas late breakdown is possible because of poor perfusion of the gastric conduit. It usually presents with features of septicemia arising out of mediastinitis. Anastomotic breakdowns are usually managed with conservative measures such as intravenous antibiotics, nasogastric aspiration, and drainage of the focus of infection, but some may require surgical re-exploration.

Pulmonary complications are one of the postoperative concerns after esophageal surgeries. They occur in approximately 20–40% of patients and negatively impact clinical outcome [69]. A complex interaction of factors including preoperative lung function, age of the patient, preexisting comorbidities, anesthetic technique, adequate analgesia, aggressive respiratory therapy, and surgical approaches influences the incidence of pulmonary complications [70]. An interdisciplinary approach is required to prevent and manage the same [71, 72].

Cardiovascular complications occur in approximately 15–25% of cases. These include hypotension, acute coronary syndromes, and arrhythmias. The most frequent arrhythmia encountered is atrial fibrillation and its occurrence is an ominous sign [73]. It should prompt the search for the underlying cause and contributable factors like hypotension and dyselectrolytemia, and acid-base disturbances should be corrected [74]. Screening for sepsis should be done. Perioperative myocardial ischemia may be prevented by aiming to attain a favorable myocardial demand-supply ratio. Should there be evidence of ischemia, antiplatelet and anticoagulation therapy should be started after evaluation by a cardiologist.

Adequate pain relief is challenging to achieve after esophagectomy, owing to the wide distribution of the multiple surgical incisions. The cervical incision may not be appropriately covered by the thoracic epidural. Good analgesia is vital for improved pulmonary function and compliance with physical rehabilitation as well as for early postoperative mobilization. The persistent postsurgical pain especially post-thoracotomy pain is a concern and mandates optimal acute pain management perioperatively using a multimodal approach [75]. The use of regional techniques and/or patient-controlled analgesia (PCA) using various pharmacological agents needs to be individualized. Recently, the re-emergence of the use of subanesthetic doses of ketamine has shown promising results. Other agents like gabapentin, dexmedetomidine, and lidocaine as an adjuvant analgesic are also being used for providing perioperative analgesia [75–77]. A morphine PCA in conjunction with epidural local anesthetics may sometimes be required to cover for inadequate pain relief because of an extended incision or incisions at sites other than those covered by neuraxial analgesia.

Delirium in the postoperative period is an important concern, especially in elderly patients undergoing major surgeries, and has been variably reported [78]. The risk factors for the occurrence of delirium in the postoperative period (which includes advanced age, smoking, and alcoholism) overlap with established factors for esophageal malignancy [79]. Detection of hypoactive delirium is particularly challenging and is often misdiagnosed as a “calm and comfortable” patient. Delirium renders a patient uncooperative and disrupts physical therapy and mobilization goals. Delirious patients are poorly compliant toward activities intended to facilitate their

recovery. Additionally, it may require constant restraining or constant supervision especially if the patient's behavior is suggestive of the intent of self-harm. A patient with hyperactive delirium can suffer from other complications related to premature or accidental removal of various drains and tubes e.g surgical drains, intercostal tubes, intravenous catheters etc. [80]. All of these increase both morbidity as well as the length of hospital stay.

The postoperative nutritional regime is usually based on the prevalent institutional practice. It is not unusual to start with total parenteral nutrition (TPN) and then advance to enteral jejunostomy feeding. However, with the popularity of enhanced recovery protocols, most of the high-volume centers have evolved to incorporate early enteral nutrition (EN) protocols after esophageal resection. Enteral nutrition has been found to have a lesser risk of associated complications including infections and shorter lengths of hospital stay as compared to parenteral nutrition [81–84]. The TPN may be considered only in a selected group of patients wherein the EN is contraindicated. The modalities of EN after esophageal surgeries include jejunostomy and nasojejunal feeding. Of these, jejunostomy feeding is commonly used, and its safety is well reported but may be associated with risk of leakage, occlusion, or infection [85]. On the other hand, nasojejunal feeding is lesser invasive but its accidental removal is more common [86, 87]. Neither of the routes is superior to the other, and hence the choice between the two needs to be individualized [87].

12.8 Enhanced Recovery After Surgery

The enhanced recovery after surgery (ERAS) and fast-track surgery (FTS) are the emerging concepts in many surgical interventions including esophageal surgeries as well [88, 89]. Though implemented successfully in many gastrointestinal surgeries, its acceptance in esophagectomies was relatively late due to complex major surgical intervention. This approach is patient centered and includes various aspects not only in the intraoperative period but also in the pre- and postoperative period. These protocols remain multidimensional and multidisciplinary. It has many benefits with regard to reduced perioperative complications, lesser hospital stays, and increased patient satisfaction. However, these advantages may not be easily evident in clinical-practice because of difficulties in the introduction as well as implementation of the components of the ERAS protocol [90–94].

After oesophagectomy, the patients may be transferred to a post-anesthesia care unit or a high dependency unit depending on the patient's condition (hemodynamic instability/ Mechanical ventilation) and availability of beds. This may also influenced by the established protocols in the hospital. It seems logical to nurse patients in high dependency units to detect anastomotic breakdown, inadequate analgesia, ongoing hemodynamic instability and evidence of infection at the earliest. Experience with complications specific to this surgery is essential for the post-operative care of these patients.

12.9 Evolution of Surgical Technique

Surgical approaches described for esophagectomy are a transhiatal, transthoracic, combination of both, and recently the minimally invasive technique. The Ivor Lewis approach is a combination of a laparotomy for mobilisation of the stomach and a right thoracotomy for esophageal resection and anastomosis [95]. Laparotomy may be done using a midline or a bilateral subcostal (roof-top) incision. The advantage of roof-top incision over a midline laparotomy incision is that the thoracic epidural is able to provide effective analgesia for both the thoracic as well as abdominal incisions. The McKeown tri-incisional technique involves a right thoracotomy, laparotomy, and left neck incision for creation of a cervical anastomosis [96]. In the transhiatal esophagectomy, a laparotomy is done to remove the esophageal tumor via the diaphragmatic hiatus followed by esophagogastric anastomosis in the left side of the neck

thus avoiding a thoracotomy [97]. The hybrid techniques have also evolved wherein a combination of open and minimally invasive techniques are used. This approach may be utilized for resection of thoracic and cervicothoracic esophageal malignancies with no tracheobronchial or aortic involvement. Minimally invasive oesophagectomy (MIE) consist of either a laparoscopic transhiatal or thoracoscopic resection or a combination of both known as the hybrid technique. Minimally invasive surgery limits surgical trauma, decreases peri-operative complications and promotes early recovery [98]. It is currently incorporated as a part of most ERAS programs for esophageal resections. The MIE has been reported to have decreased perioperative complications including lesser hospital stay, lesser blood loss, and reduced pulmonary complications [99]. However, there was no difference in the stage-specific outcome or incidence of anastomotic leakage. Robotic techniques have also been described and are being performed successfully [100].

12.10 Summary

Esophageal surgeries are complex major surgical interventions, often associated with various perioperative morbidities. Despite improvements in neoadjuvant therapy and refinement of surgical technique, it remains a challenge for both the anesthesiologist and the intensivist. The course of perioperative care should be focused on patient pre-optimization and prevention and early management of the known complications of this surgery. ERAS protocols would greatly help in reducing patient morbidity and bringing down associated costs of health care. Future directives should aim at further reducing the postoperative complications and improving patient outcomes.

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Autologous Free-Flap Reconstruction After Oncosurgery

13

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13.1 Introduction

The resection of tumors may cause large aesthetically and functionally unacceptable defects. Similarly, adjuvant therapies may leave functional tissue impairment or chronic nonhealing wounds requiring excision and reconstruction. Reconstructive surgery aims to obliterate the space created by tissue resection, structural support for remaining tissues, fill the tissue gap and ensure adequate wound closure and healing, and maintain an aesthetically acceptable appearance.

Flap surgery has improved markedly over the last few decades, with success rates of greater than 95% reported. This is the result of enhanced microsurgical techniques and an evolving appreciation for perioperative optimization. In this setting of progress, however, anesthetic perioperative management of free-flap surgery is varied [1], reflecting the paucity of high-level evidence guiding best practice. A continued critical review of current flap surgery literature and extrapolation from other surgical fields is imperative to optimize outcomes.

13.2 Surgical Concepts

Autologous flap reconstructions can be categorized as "pedicled" or "free." A pedicled flap remains partially connected to the donor site via an intact vascular pedicle. The pedicle is at most 5 cm long, limiting reconstruction to local defects. A latissimus dorsi flap, used in breast reconstruction, is a commonly used example. Free flaps are completely detached from the donor site and constitute any combination of the skin, fat, fascia, muscle, bone, nerves, bowel, or omentum. These flaps are used for more distant reconstructions.

There are several distinct phases during free-flap surgery. In the initial phase, donor tissue and its vascular pedicle (artery and vein) are dissected or raised. The clamping and division of the pedicle lead to cessation of blood flow to the donor tissue. This primary ischemic phase varies in time but typically lasts between 60 and 90 min. Donor blood vessels are then anastomosed to distant recipient blood vessels using microsurgical techniques. Restoration of blood flow and reversal of the effects of anaerobic metabolism occurs during this reperfusion phase. This phase

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also called the secondary ischemic phase, predisposes tissue to ischemic-reperfusion injury.

There is a single surgical anastomosis of each vascular pedicle, making free flaps extremely vulnerable to hypoperfusion and venous congestion. Common causes of impaired blood flow include arterial or venous thrombosis at the anastomotic site, arterial vasospasm, and insufficient venous drainage. Ruptured anastomosis with hematoma formation, tightly applied dressings, and poorly positioned equipment can cause external compression on the pedicle. Some vascular pedicles are prone to kinking or stretching with changes in patient positioning. Prolonged ischemic times and flap hypoperfusion secondary to low cardiac output states may exacerbate the secondary ischemic injury.

13.3 Pathological Concepts Associated with Free-Flap Complications

The endothelial glycocalyx (EG) is a gel-like structure lining the intraluminal surface of the endothelial cells of all blood vessels and organs. It has several well-defined functions and plays an integral role in blood vessel wall integrity. It is a delicate structure and can rapidly change under certain metabolic and inflammatory conditions. Lifestyle risk factors (obesity, smoking), neo-/adjuvant treatments (radiotherapy), and chronic pathological conditions (hyperglycemia, renal and cardiovascular disease) predispose this delicate structure to pathological insults [2, 3].

Flap surgery has the potential to cause major systemic inflammatory perturbation in the postoperative period. Large, multisite tissue disruption and ischemic-reperfusion injury (IRI), seen within the flap microvasculature, can disrupt the composition and structure of the fragile EG. Degradation leads to loss of the barrier function between blood components and the underlying vessel wall. The adhesion of circulating immune cells and the activation of several pro-inflammatory pathways cause further disruption and dysfunction within this layer. These pathological processes may progress and lead to localized effects (flap complications, organ dysfunction) or systemic effects (systemic inflammatory response syndrome, coagulopathies) [2, 4].

Following IRI, deactivation of some of the protective antioxidative enzymes within the EG leads to oxidative stress. This includes the deactivation of superoxide, a natural antioxidant activity within the EG, which keeps reactive oxygen species (ROS) and free radicals in equilibrium under physiological conditions. It also has a role in the functionality and release of other antioxidants, such as a nitric oxide (NO). NO causes localized vasodilatation in response to increases in shear stress (increased blood flow). A reduction in NO levels will result in loss of microvascular autoregulation, possibly compromising reperfusion. Also, a degraded and exposed endothelium is vulnerable to platelet adhesion and activation of the coagulation cascade with subsequent thrombus propagation. As previously mentioned, venous and arterial thrombosis can be detrimental to flap viability. Venous thrombosis is more prevalent than arterial thrombosis. After the flap reconstruction, any increase in local interstitial tissue pressure compromises the blood flow and delivery of oxygen to the reconstructed tissue. Several factors predispose free-flap tissues to this pathological process.

In its physiological state, the EG is a protein-rich layer that contributes significantly to intravascular oncotic pressure. According to the revised Starling equation [4], this oncotic pressure is an important factor opposing fluid filtration across the endothelial layer into the interstitium. With degradation and loss of the protein content of the EG, the layer becomes more permeable with increased filtration of fluid and other intravascular molecules into the interstitium. This is commonly seen in inflammatory states and contributes to a decrease in the half-life of intravenous crystalloids and colloids alike [3, 5, 6]. Reabsorption of interstitial fluid relies exclusively on intact lymphatic flow and not on reabsorption from the venous capillaries as previously stated by the original Starling equation. Transplanted free-flap tissues are devoid of an intact lymphatic system and therefore vulnerable to an increase in fluid accumulation.

Acute hypervolemic hemodilution causes EG injury by mechanical stress on the vascular wall and via the secretion of atrial natriuretic peptide (ANP). The atrial stretch from the rapid administration of intravenous fluid leads to ANP secre-

tion. ANP also increases microvascular permeability permitting fluid and colloid extravasation into the interstitium [3]. Studies have shown that when 5% human albumin or 6% hydroxyethyl starch are infused into a normovolemic patient, 60% of the colloid rapidly extravasates into the interstitium [4].

The combination of the abovementioned pathological processes is likely the reasons why multiple studies specific to flap surgery have linked high volumes of intravenous fluids with worse surgical (wound healing, flap failure) and medical (pulmonary congestion) outcomes [7–10].

Relevant to cancer surgery, the EG layer also acts as a barrier to prevent interaction between the ligands on circulating tumor cells (CTC) and the adhesion receptors on the endothelial cells. Following surgical tissue damage, inflammatory activation of procoagulant and prothrombotic pathways may cause clot formation in the microvasculature and platelet adhesion onto CTC. This pathological process has two consequences. The platelet coat on the CTC decreases detection by host defense mechanisms such as natural killer cells. Also, microvascular occlusion promotes adhesion of the CTC onto the degraded endothelium, enabling migration across this layer. In effect, inflammatory mediators may contribute to CTC colonization and lymphatic spread, promoting metastasis [6, 11].

Hyperoxia causes increased levels of ROS with increased tissue destruction after IRI. Studies looking at outcomes after ischemic events such as cerebral vascular accidents and myocardial infarction have linked hyperoxia with the expansion of infarct size and worse outcomes [12, 13]. Intraoperative inspired oxygen concentrations should be carefully titrated to the arterial partial pressure of oxygen (PaO2) deemed appropriate for the clinical setting. Perioperative measures to improve pulmonary function should be employed to reduce the need and duration for oxygen therapy.

In conclusion, seemingly safe routine perioperative therapies such as intravenous fluid and oxygen therapy can potentially cause harm by exacerbating the degradation of the EG seen during surgery. Possible strategies to reduce EG breakdown are discussed in Sect. 13.5.

13.4 Physiology of Flap Perfusion and Relevant Perioperative Factors

The blood supply and drainage of free-flap tissue can be complex. One cannot assume that an isolated understanding of the physiological laws governing blood flow is sufficient. Instead, there is a dynamic and complex interplay between the pathological and other physiological processes requiring more complex consideration.

The Hagen-Poiseuille law is frequently used to describe the determinants of flap perfusion/flow:

$$Q = \Delta P \times \pi \times r^4 / 8 \times \eta \times l$$

where Q (flow) is directly proportional to ΔP (perfusion pressure), the fourth power of r (radius), and inversely proportional to η (viscosity) and l (the length of the tube).

The radius of the blood vessels is an important determinant of blood flow but is not constant and homogenous within the flap. This can be due to several independent factors. Irregularities in the endothelial layer close to the surgical anastomosis will invariably cause turbulence in blood flow and a decrease in the radius of the blood vessel. Reperfusion injury causes localized vasospasm, as well as shedding of the endothelial cells and glycocalyx with resultant microthrombus formation and propagation. Surgical manipulation and cold exposure of the vascular pedicle may also cause vasospasm. Also, acute denervation of pedicle blood vessels causes an attenuated vasoconstrictor response to systemic catecholamines. As a result, normal physiological laws do not hold, and medical interventions aimed at altering the radius of the blood vessels might not reliably lead to improvements in blood flow.

The Hagen-Poiseuille law states that cardiac output is directly related to a pressure differential across a vascular bed. This is one of the reasons why routine intraoperative blood pressure (macrovascular) monitoring is used as a surrogate for tissue perfusion (microvascular). This has several limitations:

Cardiac output or blood flow is also dependent on systemic vascular resistance, as seen in the following equation:

$$\text{Cardiac output} = \left(\text{mean arterial pressure} - \text{right atrial pressure}\right) / \text{systemic vascular resistance}$$

An increase in peripheral resistance seen after the administration of a vasopressor agent may lead to an increase in blood pressure but a decrease in flow or cardiac output. This may compromise the free-flap tissues. Additionally, the physiological response to a hypovolemic state is to preserve perfusion pressure to vital organs at the expense of non-vital organs (skin and fat in the free flap). As a consequence, a predetermined target blood pressure may not reflect adequate flap perfusion and may be falsely reassuring.

Under physiological conditions, there is an expectation that microvascular perfusion will improve in parallel with macrovascular optimization. This is referred to as hemodynamic coherence [14]. Loss of hemodynamic coherence has been described in states of infection, inflammation, and reperfusion injury. The resultant impaired function of the endothelium and the endothelial glycocalyx leads to microvascular obstruction, vasoconstriction, and interstitial edema, despite the correction of the macrovascular parameters. Regardless, optimization of the macrovascular parameters should be primarily achieved before targeting the microcirculation.

Noninvasive intraoperative optical techniques may be used in real time to assess the microcirculation of free-flap tissue. Novel techniques under investigation include optical coherence tomography (vessel density and decorrelation), sidestream darkfield microscopy (velocity, microvascular flow index, total vessel density, perfused vessel density), laser speckle contrast imaging (perfusion units), and fluorescence imaging (time constant and time to peak measured) [15]. Once integrated into standard practice, these bedside measurements may allow for dynamic assessment of medical interventions to optimize macrovascular parameters and flap tissue perfusion.

13.5 Strategies for Hemodynamic Optimization

Surgical intervention leads to an increase in oxygen consumption and metabolic demand. Hemodynamic optimization aims to reduce tissue hypoperfusion and meet the increased metabolic demands of the tissues. These measures should be instituted in the early preoperative period and may be continued postoperatively to overcome potential oxygen debt.

13.5.1 Preoperative Carbohydrate Drinks

Adequate preoperative hydration starts with the minimization of fasting times. Complex carbohydrate drinks up to 2 hours before surgery is safe and improves metabolism and decreases insulin resistance and postoperative nausea and vomiting [16]. Postoperatively, early transition to oral hydration should be encouraged, and intravenous fluids should be discontinued once the patient is hemodynamically stable.

13.5.2 Goal-Directed Therapy (GDT)

Perioperative administration of intravenous fluid plays a pivotal role in patient management and has a direct impact on outcomes. The principles of intravenous (IV) fluid administration are to maintain central normovolemia for optimal cellular perfusion and avoid interstitial edema from salt and water excess [17]. The utilization of GDT allows for tailored IV fluid, inotropic, and vasoactive agent administration. Contemporary, minimally invasive devices derive measurements such as cardiac index, stroke volume, or stroke volume variation from pulse power analysis, pulse contour analysis, and esophageal Doppler monitoring [18]. Medical therapy is titrated according to these explicit targets that reflect end-organ blood flow. A recent meta-analysis of 95 randomized controlled trials comparing GDT versus standard hemodynamic care showed a reduction in mortality and complications (wound infection, pneumonia, respiratory failure, and prolonged ventilation). Also, the length of hospital stay (LOHS) was reduced by almost 1 day [19]. Studies specific to autologous breast flap surgery comparing standard care with GDT in

combination with an enhanced recovery after surgery (ERAS) protocol have shown a reduction in length of hospital stay with no difference in complications [20–23]. The average amount of intraoperative fluids used in the GDT group averaged 3.85 l vs 5.5 l in the pre-implementation group.

There is insufficient evidence to preferentially direct the choice of fluid for flap surgery. The amount, timing, and duration of fluid therapy are more likely to have an impact on outcomes.

Central line placement in free-flap surgery is not indicated unless prolonged vasoactive infusions are anticipated. Central venous pressure monitoring does not improve hemodynamic optimization and has been associated with worse outcomes and complications from line placement [22, 24].

Intraoperative oliguria defined as urine output of less than 0.5 ml/kg/h has not been correlated with acute kidney injury in noncardiac surgery. Oliguria should not be interpreted in isolation. Careful consideration of the patient's comorbidities, the clinical context, and other hemodynamic parameters should be used as a guide for fluid resuscitation [25].

13.5.3 Vasoactive and Inotropic Drugs

The use of vasoactive and inotropic drugs during flap surgery remains contentious. Concerns exist that these drugs may cause anastomotic and flap microvascular vasoconstriction, limiting flap tissue perfusion. Multiple studies have demonstrated no link between perioperative vasoactive/inotropic agent use and flap complications, including flap failure [9, 26–30]. The acute denervation of pedicle blood vessels changes their response upon exposure to vasoconstrictor agents. Specifically, they have an attenuated response; hence, vasoconstriction may not occur at these sites despite the administration of a vasoconstrictor such as noradrenaline. This is in contrast to the vasoconstriction seen in innervated skin blood vessels [31]. Another contributory explanation is the anticipated increase in the cardiac index with appropriate inotropic drug administration in normovolemic patients. This may result in increased flap perfusion.

Concerning the choice of agent, noradrenaline increases the blood flow to reconstructed flap in hypotensive patients in a dose-dependent manner. Dobutamine increases free-flap blood flow to a lesser extent without increasing the mean arterial blood pressure. The use of dobutamine may be limited by tachycardia, especially in patients predisposed to ischemic heart disease [31]. Adrenaline and dopexamine both decrease free-flap skin blood flow and are not suitable agents for flap surgery. Milrinone, an inodilator, does not improve free-flap outcomes and is associated with increased intraoperative use of vasopressor support [32].

13.5.4 Therapies Targeting the Endothelial Glycocalyx

Therapeutic approaches aimed to protect or restore the EG against injury represent a promising direction in clinical medicine. Strategies to reduce oxidative stress and inflammation may include the perioperative use of glucocorticoids, human plasma, plasma augmented with albumin [2], and intravenous lidocaine [33]. There is currently insufficient evidence supporting the routine integration of these modalities into clinical practice.

13.6 Perioperative Considerations for Microvascular Free-Flap Transfer Procedures

Patient outcomes are broadly determined by an interplay of three major variables: the extent of the surgical insult, the patient's risk factors as determined by the acute and chronic medical disease, and the quality of the perioperative care they receive.

The extent of tissue injury during flap reconstruction can be considerable. There may be numerous surgical sites, including the area of

cancer ablation surgery, and one or more donor sites for flap harvesting. This may result in significant metabolic and physiological derangements. Anticipating these disturbances is important for anesthetic planning and potential patient optimization.

Patient risk factors, as determined by their comorbidities and diseases of lifestyle, should be identified and modified where possible. There is emerging evidence that risk factors, such as smoking and hyperglycemia, affect the endothelial glycocalyx and predispose patients to inflammatory processes in the perioperative period [2]. Also, the cancer burden and neoadjuvant therapies may further contribute to adverse outcomes. Adequate optimization might not be possible in the setting of time-pressured cancer surgery.

Perioperative care is ideally provided by a multidisciplinary team. The implementation of perioperative care bundles reduces variation in practice and aims to address modifiable factors leading to incremental and cumulative improvements in outcomes [23, 34] (see Sects. "Autologous Breast Reconstruction" and "Enhanced Recovery After Surgery for Autologous Breast Reconstruction").

13.6.1 Preoperative Considerations: Identification and Optimization of Risk Factors Associated with Poor Flap Outcomes

13.6.1.1 Smoking and Nicotine Replacement Therapy

Smoking has been reported as an independent predictor for the occurrence of various complications related to reconstructive procedures. It has been linked to deep surgical-site infections, incisional dehiscence, and a higher return to theater rates [8, 35–37]. Smoking causes harm via several pathways. Carbon monoxide alters the oxygen-carrying capacity of hemoglobin. Nicotine causes vasoconstriction and promotes the formation of microthrombi via catecholamine and thromboxane A2 release, respectively. Hydrogen cyanide impairs the function of enzymes implicated in cell metabolism. Combined, these factors contribute to impaired wound healing. Each week of abstinence allows the reversal of some of these processes, with a significant benefit demonstrated at approximately 4 weeks [38]. Preclinical animal studies link nicotine replacement therapy with wound healing complications; however, it is unclear if this translates into worse outcomes for reconstructive procedures. While nicotine replacement therapy is preferred to active smoking, complete cessation of both is preferable in the perioperative period.

13.6.1.2 Diabetes Mellitus and $HbA1_C$

There is little research specifically assessing the impact of diabetes in patients undergoing reconstructive surgery. In the field of reconstructive breast surgery, studies have demonstrated a greater incidence of adverse outcomes in diabetic patients undergoing autologous breast reconstruction. This has not been demonstrated with implant-based breast reconstruction [39]. The specific recommendations for diabetes and outcome after reconstructive surgery are not reported. However current guidelines for other major surgeries may be extrapolated, in which there is a demonstrable increase in both morbidity and mortality. It appears that for any reconstructive surgeries, optimal blood glucose levels would reduce perioperative complications along with decreased mortality and shorter duration of hospital stay [40].

13.6.1.3 Radiotherapy

Preoperative radiation to the recipient site causes fibrosis to the vasculature and surrounding tissue. Given decreased vascularity, uptake of the flap is compromised and thus related complications. Complications include poor wound healing, fat necrosis, and flap loss [36, 41].

13.6.1.4 Anemia

Anemia is defined as hemoglobin of <13 g/dl for men and 12 g/dl for women. It is diagnosed in almost 50% of cancer patients during their disease [42]. It is an independent risk factor for

increased 30-day morbidity and mortality in patients undergoing major noncardiac surgery [43]. In the setting of oncosurgery, the causes of anemia include impaired production of red blood cells (systemic inflammation, chemotherapy-related bone marrow suppression, and renal tubular toxicity with decreased erythropoietin production) and iron deficiency anemia (occult bleeding, decreased iron absorption) [42].

Studies specifically assessing preoperative anemia in autologous reconstructive surgery did not show an association with surgical complications, including flap thrombosis or flap loss. Postoperative hemoglobin levels of less than 10 g/dl are associated with increased LOHS and medical complications but did not increase flap-related complications [37, 44]. Intraoperative blood transfusion correlated with postoperative medical complications (mostly respiratory-related), but again no surgical complications.

Anterolateral thigh free flaps were associated with more blood loss and have higher rates of intraoperative blood transfusion when compared with radial forearm free flaps and fibular free flaps [45].

Specific management of the preoperative anemic patient involves a multidisciplinary approach, targeting the likely causes of anemia. Proven successful therapeutic interventions include diet modification and intravenous iron therapy. Oral iron supplementation has reduced efficacy and inadequately meets the time constraints of planned surgery [43]. Treatment of anemia with recombinant erythropoietin has been associated with symptomatic venous thrombosis in the setting of chronic inflammation in cancer patients [46]. It is unclear if this translates into a risk for flap thrombosis. The modest benefit in treating anemia with erythropoietin in the short term may not justify this theoretical risk for flap thrombosis. Expert opinion should be sought.

In conclusion, preoperative anemia should be optimized to minimize the risk of transfusion-related medical complications. Anemia and perioperative blood transfusions are not independently associated with flap complications and therefore should not influence the consideration for blood transfusion.

13.6.1.5 Malnutrition

The prevalence of malnutrition in cancer surgery is reportedly as high as 47%. Causation can be multifactorial: secondary to the inflammatory or neoplastic disease, altered metabolic state, poor access to nutrition, or gastrointestinal tract dysfunction. The Nutrition Risk Screening Tool-2002 (NRS-2002) and the Subjective Global Assessment tool (SGA) are currently the most validated nutrition screening tools in the surgical population. The NRS-2002 is a good predictor of postoperative complications and can be used to predict mortality, morbidity, and length of hospital stay.

Key elements of nutritional optimization involve the provision of protein and micronutrient supplementation to increase muscle mass and support metabolic functions. There is currently no consensus on the duration of nutritional support. However, a 5–7-day duration of preoperative nutrition therapy is reported to reduce postoperative morbidity by 50% [43]. The European Society for Clinical Nutrition and Metabolism guidelines advocate a 7–14-day supplementation period for severely malnourished patients.

13.6.1.6 Surgery-Specific Considerations

Autologous Breast Reconstruction

General

Breast cancer is the most frequently diagnosed cancer worldwide, accounting for 23% of the world's cancer cases [47]. Most will undergo lumpectomy or mastectomy as part of their treatment. Reconstruction timing and type (implant versus autologous) will vary geographically.

Commonly used free flaps for breast reconstruction include DIEP (deep inferior epigastric perforator) and TRAM (transverse rectus abdominis musculocutaneous) flaps. The donor sites for these methods are from the inferior abdominal area with vascular pedicles dissected from the

deep inferior epigastric vessels. The internal mammary vessels form the recipient vascular pedicle.

The risk of developing complications after reconstruction depends broadly on patient comorbidities, type of reconstruction, and additional adjuvant therapies. Any combination(s) of risk factors seems to dramatically increase the risk of having poorer outcomes [36].

Comorbidities

Data extracted from the ACS-NSQIP database (USA) identified that the majority of patients having immediate reconstruction after mastectomy were ASA class II. Twenty-three percent of patients had hypertension and almost 5% were diabetic. Thirteen percent were active smokers. In this study, factors linked with increased surgical complications were smoking, hypertension, diabetes, and obesity [37].

Obesity

Obese patients undergoing breast reconstructive procedures experience higher rates of wound-related complications and reconstructive failure [36, 37, 48]. There is an appreciable increase in complication rates in patients with a body mass index (BMI) of >30 kg/m^2, with a significant increase beyond a BMI of 40 kg/m^2. Notably, obese patients having implant-based reconstruction have a greater failure rate than autologous breast reconstruction, especially if the BMI is >35 kg/m^2. Obese patients undergoing delayed breast reconstruction should be encouraged to lose weight until their BMI is within an acceptable range.

Type of Reconstruction

Compared with implant-based reconstruction, autologous reconstruction involves a more substantial operation with a longer recovery time. It is associated with an increase in surgical complications in the short term, but compared with implant-based reconstruction, this risk diminishes over time [37].

Adjuvant Therapies

Radiotherapy

Postmastectomy radiotherapy (PMRT) for node-positive breast cancer reduces the risk of local recurrence and improves overall survival [49]. It is unfortunately associated with increased reconstruction failure and complications, regardless of the reconstructive method. Compared with implant-based reconstruction, autologous reconstruction is associated with significantly less wound-related postoperative complications. In a study comparing bilateral autologous reconstruction, there was an increase in complications on the irradiated side. Common complications associated with recipient site radiotherapy include flap fibrosis, fat necrosis, and wound dehiscence [49].

Radiation-Induced Heart Injury

Radiotherapy to the chest area can cause pathological changes to the heart, blood vessels, and lung tissue. It causes an acute increase in reactive oxygen and nitrogen species and can lead to acute endothelial dysfunction and long-term tissue fibrosis. Patients who received postoperative radiotherapy for breast cancer have higher rates of mortality associated with ischemic heart disease and may have signs and symptoms of congestive cardiac failure [50]. Further investigation and referral may be needed.

Hormone Inhibitors

Adjuvant therapy for estrogen receptor-positive breast cancers includes hormone inhibitor (HI) agents such as tamoxifen (selective estrogen receptor modulator) and letrozole (aromatase inhibitors). These drugs decrease the constitutive effects of estrogen in the skin, impacting wound healing and increasing rates of high-grade prosthetic capsular contractures [51]. HI agents have additionally been implicated in microvascular thrombotic events resulting in thrombotic flap complications and total flap loss. There is conflicting evidence regarding the systemic thromboembolic phenomenon; how-

ever, there is likely to be a contributory role. Temporary cessation of these agents is recommended, although there is currently no consensus regarding the timing of this. Considering the pharmacodynamic properties of these drugs and timing of postoperative complications, cessation 2–4 weeks before surgery and recommencement 2 weeks postoperatively have been suggested. No studies have demonstrated a decrease in cancer survival rate with temporarily discontinuing HI [52].

Chemotherapy-Induced Cardiac Toxicity

Systolic dysfunction may develop in breast cancer patients treated with anthracyclines (doxorubicin) and trastuzumab (targets human epidermal growth factor receptor 2 or HER2) [53]. Further investigation and referral may be needed.

Enhanced Recovery After Surgery for Autologous Breast Reconstruction

There is mounting evidence demonstrating the benefits of ERAS implementation within several surgical fields. Currently, there are only a few quality studies [20, 21, 23] evaluating the outcomes after ERAS implementation in autologous breast reconstruction. These studies had several common findings and are summarized below:

- Fasting periods were limited to 2 h preoperatively with early resumption of eating and drinking in the postoperative period. There were no incidences of aspiration reported.
- Multimodal analgesia included regular paracetamol and a nonsteroidal anti-inflammatory agent. Regional techniques such as transverse abdominis plane (TAP) blocks were used. The decreased reliance on parenteral opioids and earlier transition to oral analgesia resulted in a reduction in total opioid and antiemetic use. A common finding in these studies was a positive correlation between the total amount of opioids used and LOHS.
- GDT resulted in a reduction in the number of intraoperative fluid volumes administered. The average amount of intraoperative fluids used in the GDT group averaged 3.85 l vs. 5.5 l in the non-GDT group.
- Thrombo-prophylaxis was started in the early postoperative period with no significant difference in hematoma formation.

There was no difference in major complications between groups, implying that the above measures are safe and effective. The length of hospital stay was decreased by an average of 1 day.

The ERAS Society has published consensus recommendations about reconstructive procedures. This includes head and neck [54] and breast surgery [55], respectively.

Head and Neck Cancer Resection with Immediate Flap Reconstruction

General

Head and neck (HN) neoplasms form the fifth most common cancer worldwide and originate most frequently from the mucosa of the upper aerodigestive tract (oral cavity, pharynx, nasal cavity, sinuses). Less frequently, neoplasms originate from the salivary glands, thyroid, soft tissue, bone, and skin. Squamous cell carcinoma and papillary thyroid cancer are commonly seen [56].

Etiology

The etiology of head and neck cancers is an interplay between host and environmental factors.

Host Factors

- Immunosuppression (human immunodeficiency virus infection, chronic immunosuppression after organ transplantation)

Environmental Exposure

- Alcohol abuse
- Tobacco
- Infection with human papillomavirus and Epstein-Barr virus
  Ionizing radiation

Demographic

On review of the literature, it was noted that the average HN reconstruction patient was 64 years of age. The average overall complication rate was 48% with flap success rates nearing 95%. The mortality rate was between 1 and 2%. The incidence of complications was found to be directly related to the comorbid state of the patient, rather than the age. Several comorbidity scores can help predict flap survival rates and complications. The Kaplan-Feinstein Index (KFI), the Adult Comorbidity Evaluation-27 (ACE-27), the American Society of Anesthesiologists (ASA) score, and the Index of Coexistent Diseases (ICED) score correlated well with flap survival and complication rates [57]. Pertinent comorbidities that are strongly associated with flap failure rates include diabetes and chronic obstructive pulmonary disease. Hypertension was prevalent in 64% of patients but was not associated with worse outcomes. Pulmonary and cardiac complications were frequently seen in the postoperative period [8, 58, 59].

Commonly Used Free Flaps in Head and Neck Reconstruction

Resection of complex tumors in the HN area can have major functional and aesthetic consequences. Flap reconstruction plays a major role in the restoration of form and physiological function. Commonly utilized free flaps are the radial forearm free flap (RFFF) and anterolateral thigh (ALT) flap. Fibular free flaps are used to repair mandibular defects.

Airway Planning and Postoperative Destination

Patients undergoing surgery for HN tumors should have a thorough airway assessment [54].

Distortion of the upper airway by prior surgery, irradiation, and bulky tumors may cause airway compromise after induction of anesthesia. HN patients may also be at risk of postoperative airway occlusion. Surgical procedures that carry the greatest risk include bilateral neck dissection and resections of the mandible, tongue, and floor of the mouth. Free-flap edema may cause additional narrowing of the aerodigestive tract. The radial forearm free flap (RFFF) is smaller and more pliable than other commonly used flaps and poses less risk. The Cameron tracheostomy scoring system [60] considers surgical risk factors with a threshold score of more than five points prompting consideration for elective tracheostomy placement. It does not take into consideration the cardiopulmonary reserve of the patient, and this should be evaluated in conjunction with surgical risk factors for the planning of appropriate postoperative destinations and ventilation. Patients with adequate cardiopulmonary reserve undergoing free-flap reconstruction for unilateral neck dissection may be considered for overnight sedation and delayed extubation, instead of elective tracheostomy placement [61].

It should be noted that not all HN reconstruction patients will require postoperative ventilation in an intensive care unit (ICU). Carefully selected patients may recover in wards with specialized nursing staff trained to identify flap and airway compromise and escalate management where appropriate. Comparing routine admission to an intensive care unit (ICU) with specialized ward-based care, the ward cohort showed less respiratory-related complications, with no increase in flap-related complications [62].

Postoperative Delirium

Postoperative delirium (POD) is commonly seen after HN reconstruction. It is defined as a reversible neurological deficit and is characterized by fluctuations in the conscious level and a change in cognition. Several risk factors have been identified and include age above 70 years, male gender, prolonged surgery, intraoperative blood transfusions, tracheostomy placement, and American Society of Anesthesiologists (ASA) physical status of more than III [63]. It is commonly seen within the first 3 days of surgery. Postoperative agitation and disorientation seen with POD may lead to surgical anastomotic disruption and flap compromise. Early identification and specialized intervention is imperative and may include a short period of intubation and ventilation in an ICU setting.

Patients presenting with HN tumors may have a history of alcohol abuse. Acute alcohol withdrawal may present in the postoperative period as confusion, agitation, and generalized seizures, putting the patient at risk for surgical anastomotic disruption. Patients should be screened and managed appropriately.

13.6.2 Intraoperative Considerations

13.6.2.1 Patient Positioning and Pressure Care

The duration of free-flap surgery can be long and may exceed 8 h. This brings unique challenges about positioning, access to patient, and pressure care [64]. To avoid peripheral nerve injury of the brachial plexus and ulnar nerve, shoulder abduction should be less than 90°, and arms in the neutral position, respectively. The patient needs to be adequately positioned and secured to allow for intraoperative assessment of symmetry. Attention should be paid to avoid focal areas of pressure caused by cables, gown knots, or inadequate cushioning. Vulnerable areas include the heels, sacrum, and occiput [65]. Consider passively moving joints for extended procedures to avoid joint stiffness and pressure areas.

Free-Flap Breast Reconstruction

For delayed reconstruction, the patient will be supine with the arms adducted for the duration of the surgery. For patients undergoing simultaneous mastectomy and immediate reconstruction, the arm position may start in the abducted position to allow access to the axilla. The arms are then adducted for the reconstruction part of the procedure.

Distal venous and arterial line access points will not be readily accessible during surgery; therefore extension lines and/ proximal access points will be needed. For the same reason, two peripheral venous access sites are advised. Care should be taken to avoid pressure injuries secondary to lines and access points. Central venous access is not routinely used unless the prolonged use of inotropes or vasoactive drugs is anticipated. When the total intravenous anesthetic is used for maintenance of anesthesia, it should be noted that peripheral venous access points will not be visible and readily accessible during the case. There is an ongoing debate if this is an acceptable practice and whether a central venous line with its potential placement complications is justified.

The anterior superior iliac spine should be in line with the break of the table to allow table flexion to assist donor site closure. To minimize tension on the donor site wound, the patient will remain with their hips in flexion for 24–48 h postoperatively. For this reason, the ward bed should be appropriately positioned before transfer from the operating table.

Head and Neck Reconstruction

Theater layout will depend on the location of the flap donor site, the backup donor site, and the area of tumor excision. Generally, the head and neck area of the patient will be away from the anesthetic machine with the flap donor site exposed and accessible to the surgical team(s). The eyes should be occluded with a watertight dressing and appropriately shielded. A head ring and shoulder roll are frequently needed to gain adequate access to the head and neck area. The endotracheal tube and airway connectors will not be readily accessible during the case and should be adequately secured. Long airway circuits are frequently used and arranged either cephalad or caudally. Pressure areas caused by the endotracheal tube, circuit, connectors, and heat and moisture filter should be avoided. The head may be slightly elevated to avoid venous congestion and venous bleeding from surgical sites.

Central venous access is not routinely placed for head and neck surgeries. If prolonged use of vasoactive agents is anticipated, femoral central lines on the contralateral side to the surgical site are advised. If an RFFF is considered, vascular access and invasive monitoring should be placed on the contralateral arm.

13.6.2.2 Surgical Equipment

Key surgical equipment for microsurgery may include loupes for low magnification and operating microscopes for higher magnification. Given the duration of surgery, surgeons need to operate with the correct ergonomics to minimize fatigue. Commonly, surgeons will operate in the seated position with elbows at approximately 90° and their hands and forearms supported to minimize tremors.

13.6.2.3 Monitoring

Routine intraoperative monitoring should be used during free-flap reconstruction procedures. Also, invasive arterial blood pressure monitoring allows for arterial blood gas analysis. The arterial partial pressure of oxygen and carbon dioxide should be kept within physiological limits. Urine output should be measured via an indwelling catheter. Core temperature measurement may be measured via an indwelling catheter or a temperature probe placed in the esophagus. Optional equipment includes depth of anesthesia monitoring, peripheral nerve stimulation, pulse contour analysis systems, or esophageal Doppler monitoring.

13.6.2.4 Anesthetic Maintenance

Concerning free-flap outcomes, maintenance of anesthesia using propofol as total intravenous anesthesia (TIVA) agent has not been proven to be superior over inhalational anesthesia. However, anesthetic maintenance with propofol reduces the incidence of postoperative nausea and vomiting (PONV) [55, 66], possibly reducing the risk of anastomosis disruption due to retching and vomiting. In the setting of oncosurgery, propofol may have a cancer survival benefit by inhibiting cancer cell migration and by preserving the function of natural killer and T cells [11]. In a single-center retrospective study of more than 7000 cancer surgery patients, there was an increased risk of death in patients receiving an inhalational compared with propofol-based anesthetic [67].

13.6.2.5 Multimodal Analgesia

Good analgesia mitigates the surge of stress hormones as well as the vasoconstrictive response to pain. The paradigm of multimodal analgesia is advocated and widely practiced for postsurgical pain [68]. The concept involves the use of combinations of analgesic agents with different modes of action to achieve improved analgesia and reduced opioid requirements. This includes the use of anti-inflammatory agents, regional techniques, and other adjuvants in addition to opioids. The concept of preemptive analgesia describes the reduction in magnitude and duration of postoperative pain by applying antinociceptive techniques before tissue injury. While there is no definite evidence to show improvement in postsurgical pain control, there may be a role in reducing the development of chronic postsurgical pain [69].

Lignocaine Infusions

The incidence of chronic postsurgical pain is high in breast surgery with an incidence of up to 65% [70, 71]. Even minor breast surgeries such as lumpectomy and sentinel lymph node dissection have a 40% incidence, with mostly a neuropathic component [72]. Perioperative lignocaine infusion is associated with a modestly decreased incidence of chronic postsurgical pain in the setting of mastectomies [73]. Postulated mechanisms include its sodium channel-blocking mechanism of action, as well as anti-inflammatory and anti-hyperalgesic properties. Intraoperative intravenous lignocaine infusion combined with postoperative subcutaneous lignocaine infusion reduces pain at rest, cumulative morphine consumption, and hospital length of stay in the setting of major colorectal, urological, and neuropathic cancer pain settings [74–76].

Nonsteroidal Anti-inflammatory Drugs and Cyclooxygenase-2 Inhibitors

In a retrospective cohort study of autologous breast reconstruction comparing perioperative ibuprofen versus celecoxib, celecoxib was not associated with an increase in flap failure rates. There was a threefold increase in postoperative hematoma formation in the ibuprofen group. It should be noted that patients in both groups received additional aspirin as an antiplatelet agent [77]. Another autologous breast recon-

struction study did not show a correlation between perioperative ketorolac administration and postoperative hematoma formation [21].

Gabapentinoids

The administration of gabapentinoids such as gabapentin and pregabalin preoperatively improves postoperative acute pain with an opioid-sparing effect, although there is no evidence regarding the prevention of chronic postsurgical pain [78].

Regional Anesthetic Techniques for Autologous Breast Reconstruction

The abdominal donor site is the major contributor to pain in autologous breast reconstructions [79].

Epidural

Intraoperative epidural use has been described in a small study of 99 patients [80]. In this study, the group receiving general anesthetic with an intraoperative epidural had improved pain scores, a decrease in opioid consumption, and less PONV, compared to the general anesthetic alone. The need for vasopressor support was marginally higher in the epidural group, presumably to correct epidural-associated vasodilatation and hypotension. Unfortunately, this study did not compare the total volume of perioperative intravenous fluid used. There was no significant difference in postoperative complications. Postoperative hypotension and delay in mobilization associated with epidural use may make this technique less favorable.

Transverse Abdominis Plane Blocks and Rectus Sheath Block

Transverse abdominis plane (TAP) and rectus sheath blocks with or without catheter placement resulted in reductions in postoperative opioid consumption, better PONV scores, and a reduction in length of hospital stay [20, 21, 23, 79, 81].

13.6.2.6 Postoperative Nausea and Vomiting (PONV)

PONV remains common with an incidence ranging from 25 to 60% [82]. Vomiting can have several detrimental effects on flap outcomes. Complications include wound dehiscence, hematoma formation, and reduced patient satisfaction. The Apfel risk score is a useful tool that predicts the increasing prevalence of PONV risk based on the number of patient risk factors. These risk factors include the use of postoperative opioids, nonsmoking status, female gender, history of PONV, or motion sickness [83]. Based on the score, the patient would be categorized as low (0–1 risk factor), medium (2 risk factors), and high risk (3 risk factors). The recommendation from the Australian and New Zealand College of Anaesthetists is to monitor for low risk, one to two interventions for medium risk, and more than two interventions for high risk [84].

13.6.2.7 Temperature Management

While there is theoretical evidence to suggest hypothermia reduces pedicle thrombosis [85, 86], this has not been proven in the clinical setting. It has been observed that the occurrence of intraoperative hypothermia is associated with an increased risk of flap infection and simultaneously no benefit is observed for anastomotic patency for the graft [87]. Preoperatively, patients should be actively warmed. Exposure for surgical-site marking by the surgical teams should be kept to a minimum or should be completed the day before surgery. Intraoperatively, the patient should be actively warmed and intravenous fluid warmers should be utilized.

13.6.2.8 Venous Thromboembolism Prevention

The 2005 Caprini Risk Assessment Model has been used for risk stratification in reconstructive surgeries with regard to the occurrence of 60-day venous thromboembolism (VTE) risk [88]. Individualized measures to prevent VTE are recommended according to the risk category and include mechanical (compression stockings) and chemical (enoxaparin/heparin) prophylaxis. Contraindications and potential risk of bleeding should be assessed before determining the appropriate method of prophylaxis. Most patients undergoing free-flap reconstructive procedures in the setting of malignancy will fall into the high-risk category of developing.

On review of the literature, it was noted that there was variation in practice in terms of dosing, duration, and timing of administration of VTE prophylaxis. Doses ranged from 30 to 60 mg of enoxaparin daily, adjusted for weight and renal function. The timing of drug administration ranged from 1 h preoperatively to 12 h postoperatively [89]. The duration of drug administration varied according to the risk stratification score. A review of these protocols did not provide sufficient evidence to dictate administration protocols.

In the setting of flap reconstruction, the observed rates of significant re-operative hematoma are not clinically increased with the use of perioperative enoxaparin or unfractionated heparin [89–91]. Dextran is associated with increased hematoma formation, cardiac and respiratory complications, anaphylaxis, and flap loss [92]. Aspirin is associated with increased hematoma formation [92]. Of note, postoperative administration of aspirin, dextran, heparin, and low-molecular-weight heparin has no protective effect against the development of pedicel thrombosis and no significant effect on flap survival overall [92].

13.6.2.9 Antibiotic Regimen

Systemic antibiotic prophylaxis given 1 h pre-incision and continued for 24 h postoperatively is recommended for breast surgery and clean-contaminated surgery of the head and neck. The most commonly isolated organisms in plastic surgery are *Staphylococcus aureus* and streptococci. In clean-contaminated head and neck surgery, organisms include anaerobic and gram-positive aerobic organisms. Patients with wound infections may have polymicrobial colonization with gram-negative aerobic and anaerobic organisms. Cefazolin has emerged as the drug of choice in most institutions, covering gram-positive aerobic organisms. Clindamycin plus gentamicin covers gram-positive and gram-negative aerobic organisms; however, gentamicin toxicity may be a limiting factor. Intravenous amoxicillin-clavulanate and clindamycin plus gentamicin are as effective as cefazolin. Administration of repeat doses of intravenous antibiotics should be considered in prolonged procedures. The overall duration of antibiotic therapy should be limited to less than 24 h as the benefit beyond this has not been demonstrated [93, 94].

13.6.3 Postoperative Considerations

Key aspects for optimal postoperative flap care include:

- Gentle anesthetic emergence
- Optimization of flap perfusion
- Postoperative flap monitoring
- Safe and comfortable recovery

13.6.3.1 Anesthetic Emergence

Any sudden increases in intrathoracic pressure may disrupt the surgical anastomosis with potential hematoma formation. Measures to minimize coughing, vomiting, shivering, and excessive movement should be employed. Any blood or secretions should be cleared from the airway while the patient is still anesthetized. A slow emergence with the patient already transferred onto a ward bed is advised. Humidified air and oxygen might reduce airway irritation and coughing post-extubation.

13.6.3.2 Optimization of Flap Perfusion

Careless postoperative IV fluid administration can negate the meticulous steps taken intraoperatively to optimize the hemodynamic status of the patient. IV fluids can be discontinued once a patient is stable and tolerating oral fluids. A degree of postoperative oliguria can be expected in the early postoperative period. It is a normal neurohormonal response to surgical stress and is a poor indicator of overall fluid status. A low urine output interpreted in isolation should not trigger unnecessary IV fluid administration.

Cardiovascular complications occur commonly in postoperative HN reconstruction patients [95] and should be excluded in hemodynamically unstable patients. Clinical assessment includes an urgent review of vital sign trends, wound sites, drain output, and fluid balance charts. The pas-

sive leg raise (PLR) test is a useful bedside maneuver to assess fluid responsiveness [96]. It has been validated in non-ventilated patients with or without arrhythmias. Fluid-responsive patients are defined as having an increase in cardiac output (or its surrogate) of more than 15% after the PLR test. These patients may benefit from fluid resuscitation to improve hemodynamic status. Ongoing hypotension or low cardiac output despite fluid resuscitation warrants specialist review and treatment.

Specific attention is required to ensure that the flap pedicle is not compressed by equipment or dressings. Head and neck reconstructions may be compromised if neck vessels are kinked, stretched, or compressed by adjacent structures or drains. The head should therefore be maintained in a neutral position postoperatively.

13.6.3.3 Postoperative Flap Monitoring

Postoperatively, patients require dedicated nursing staff with experience and expertise to diagnose early flap compromise. Microvascular thrombosis occurs most frequently within the first 72 h, reflecting the need for more frequent and intensive flap observations during this time [55]. Subjective assessment of flap health includes observation of color, temperature, turgor, and changes of appearance. More objective monitoring methods include the use of Doppler devices, near-infrared spectroscopy, and indocyanine green fluorescence video angiography [54, 97–99]. Insufficiencies of arterial inflow and venous congestion should be diagnosed promptly and may warrant urgent surgical exploration.

13.6.3.4 Pulmonary Function and Early Mobilization

Postoperative pulmonary complications can be reduced by implementing a multidisciplinary perioperative respiratory care bundle [100]. Components of this bundle include perioperative incentive spirometry, cough, and deep breathing exercises, oral care including perioperative chlorhexidine mouthwashes, patient education, early mobilization, and head of the bed elevation. Adequate pain management, prevention of PONV, and timely removal of catheters and drains may promote early mobilization.

13.7 Summary

Outcomes after autologous free-flap reconstruction depend on the interplay of multiple factors. The implementation of perioperative care bundles reduces variation in practice by addressing modifiable factors known to alter outcomes. This may lead to incremental and cumulative improvements in care. Perioperative appreciation of the pathophysiological determinants of flap perfusion and the consequence of therapeutic interventions will permit a more considered approach.

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Anesthesia for Gastrointestinal Cancer Surgeries

14

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14.1 Introduction

The incidence of gastrointestinal cancer is increasing globally. The perioperative management remains challenging for this group of cancers. Obtaining a favorable outcome in the gastrointestinal onco-surgeries requires a sound understanding of the basics of bowel anatomy and physiology. Anesthesiologists must be well-versed with the various anatomical considerations, clinical presentations, and treatment protocols of gastrointestinal cancers for planning the optimum perioperative anesthesia care for these complex surgeries. Perioperative care includes preoperative optimization, and various factors are involved for the optimization, including their efforts at smoking cessation [1]. Also, perioperative analgesia and fluid management determine an optimal outcome after the onco-surgery. This chapter focuses on perioperative management of surgery for cancer of the stomach, small intestine, and large intestine.

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14.2 Overview of Preoperative Assessment, Anesthesia, and Pain Management for Bowel Surgery

Gastrointestinal onco-surgeries are usually major operations, which generally involve prolonged general anesthesia with controlled ventilation. Apart from routine pre-anesthetic check-up (PAC) investigations, preoperative evaluation should also focus on patient-related factors like smoking, nutritional status (hypoalbuminemia), comorbidities, electrolyte imbalance, cardiopulmonary function assessment, and systemic examination (Fig. 14.1). The surgery-related factors like incision sites, the extent of resection, presence of metastasis, blood loss, creation of ileostomy/colostomy, and ability to attain a tumor-free margin need to be considered during the PAC. Neoadjuvant chemotherapy and radiotherapy have important implications in the form of organ toxicity [2] (lung, bone marrow, kidney, and heart) and difficulty in dissecting surgical planes due to adhesions or fibrosis. Nutritional and vitamin deficiencies may require optimization preoperatively. Cardiopulmonary exercise testing (CPET) has recently been suggested to provide a holistic objective assessment of the functional reserve of the patient and may be used for predicting the outcome during the surgery. Some of these patients may come to the anesthesiologist for repeat or redo surgeries, completion

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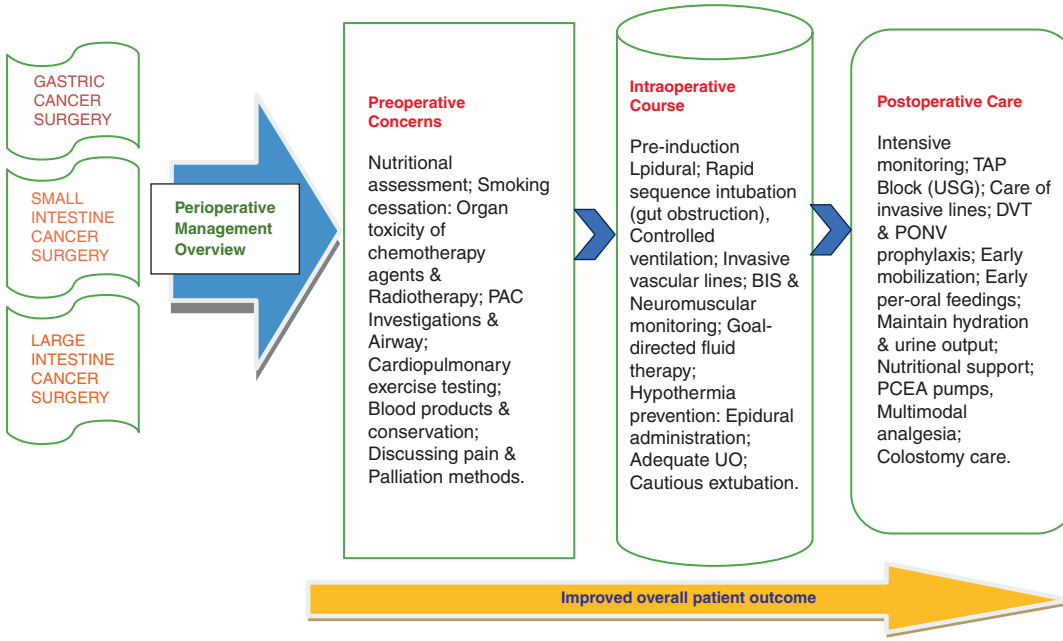

Fig. 14.1 Key concepts of perioperative management for bowel cancer surgeries. (Abbreviations: *PAC* pre-anesthetic check-up, *BIS* bi-spectral index, *UO* urine output, *DVT* deep vein thrombosis, *PONV* postoperative nausea/vomiting, *PCEA* patient-controlled epidural analgesia, *TAP* transversus abdominis plane, *USG* ultrasound-guided block)

surgeries, or palliative procedures. Blood and blood products must be arranged for all these radical surgeries. These patients may already be anemic because of occult or frank gastrointestinal blood loss from tumors as well as due to cancer chemotherapy. There have been several recent concerns regarding blood transfusion in cancer surgery as it is known to cause immunosuppression/immunomodulation resulting in cancer recurrence or cancer metastasis [3]. Transfusion-limiting practices like normovolemic hemodilution and the use of cell savers are coming up in various cancer centers. Discussion and planning about pain management during the perioperative period, its advantages, and techniques must be done in the PAC visit involving the patient as well. Analgesia is multimodal, and systemic agents are combined with regional techniques for improved patient satisfaction and overall outcome. Patient-controlled analgesia (PCA) pumps can be beneficial and used through intravenous routes or applied to epidural catheters for optimal postoperative pain relief. The use of central neuraxial block is beneficial because of beneficial effects like maintenance of bowel blood flow and reducing the bowel oxygen consumption. Also, with the advent of ultrasound [4], truncal blocks like rectus sheath, transversus abdominis plane (TAP) block, and quadratus lumborum (QL) block can be given accurately, with reduced volumes of local anesthetic drugs, and the provision to thread catheters for long-lasting analgesia is also available.

14.3 Anesthesia for Gastric Cancers

Gastric cancer ranks fourth in the world among the commonest causes of cancer-related deaths. Though its incidence has reduced over the years due to awareness regarding smoking cessation and treatment of *Helicobacter pylori* infection, the incidence of proximal gastric cancers is more than distal, resulting in more total gastrectomies than subtotal ones. The stomach begins at the

gastroesophageal junction and ends at the duodenum. It is vital to understand the functions of the stomach to know the perioperative implications of gastrectomy [5]. This includes food storage, mixing of food with gastric juices and breakdown into chyme, controlled release of chyme into the small intestine for digestion, defense against bacteria (acidic pH), and secretion of pepsinogen and intrinsic factor (important for vitamin B12 absorption). Hence gastrectomy can lead to the removal of first defense against pathogens, indigestion, "dumping" of contents into the small intestine [6], and nutrient deficiencies (vitamin B12 deficiency).

Gastric tumors can be benign or malignant, with most of them being of epithelial origin, with the mesenchymal and neuroendocrine origin being less common. The major "alarm symptoms" pointing toward gastric cancer in susceptible population [7] include unexplained weight loss, chronic gastrointestinal bleeding, dysphagia, vomiting, epigastric mass, persistent upper abdominal pain, iron deficiency anemia in the elderly, and obstructive jaundice. Gastric adenocarcinoma accounts for more than 95% of malignant gastric neoplasms. The second commonest malignancy is primary gastric lymphomas, followed by rarer tumors like GIST (gastrointestinal stromal tumors) and carcinoid tumors. The risk factors for gastric cancer include *Helicobacter pylori* infection [8] (commonest cause), smoking, host genetics (pro-inflammatory genetic polymorphisms), dietary factors (smoked or processed foods), atrophic gastritis, and familial syndromes. Those involving the mucosa or mucosa and submucosa are categorized as early gastric cancers, irrespective of lymph node involvement. Those involving the muscularis propria or beyond come under advanced gastric cancers. The *TNM* (tumor, nodes, metastasis) staging determines the management option, with perioperative chemotherapy [9] (with cisplatin, epirubicin, and fluorouracil) playing an important role in gastric cancer treatment. In some cases, a staging laparotomy or laparoscopy may be required before definitive surgery. Standard gastrectomy is the treatment of choice for resectable gastric cancers. Extended gastrectomy for advanced cancers involves resection of adjacent involved organs and extended lymphadenectomy. Non-curative surgery is considered for metastatic gastric cancers for symptomatic relief of symptoms like bleeding and obstruction. This includes palliative gastrectomy, gastrojejunostomy, and cytoreductive excision surgery. Extension of gastric resection [10] depends on the extent of tumor spread. Total gastrectomy involves resection of the entire stomach, including the cardia and pylorus. Distal gastrectomy involves resection of pylorus and cardia is preserved. Pylorus-preserving gastrectomy retains the upper third of the stomach. Proximal gastrectomy includes the esophagogastric junction, preserving the pylorus. Segmental gastrectomy involves circumferential resection of the stomach, preserving both the pylorus and the cardia. Nowadays, splenectomy and distal pancreatectomy are not done as part of radical gastrectomy, to reduce morbidity and mortality.

Anesthesia for gastric cancer surgery depends on a sound preoperative evaluation of the patient, including his nutritional status, functional cardiorespiratory assessment, systemic examination, organ system evaluation, airway examination, chemotherapeutic toxicity assessment, explanation of pain management strategies, and metastatic workup. If the patient had undergone preoperative chemotherapy, then neutropenia (and other markers of bone marrow depression) must be excluded. Hepatorenal toxicity and cardiac function assessment (possible cardiomyopathy) must also be looked for. Baseline echocardiography with bedside functional cardiorespiratory assessment is mandatory in such patients. Both malnutrition and obesity can lead to adverse perioperative outcomes [11]. In malnourished patients, a feeding jejunostomy is made before radical surgery to enable early enteral feeding. Most patients may be smokers and hence may have respiratory problems. A reduced forced expiratory volume in 1 second (FEV1) or abnormal FEV1/FVC ratio (*Tiffeneau-Pinelli index*) on pulmonary function test may point toward the occurrence of postoperative pulmonary complications. Smoking cessation is of paramount importance, and counseling must be

done at the time of the first preoperative visit. Consideration must also be given for coexisting comorbidities of the patient while planning anesthesia. Deep vein thrmbosis (DVT) prophylaxis [12] (both mechanical and pharmacological) along early ambulation is pivotal for enhanced patient outcomes. Antibiotic and postoperative nausea/vomiting (PONV) prophylaxis must be given as per institutional protocols. *H. pylori* infection must be treated preoperatively.

The anesthetic management including monitoring needs to be individualized based on patient assessment and extent of the surgery. Depending upon patient comorbidities and extent of surgical resection, invasive monitoring with arterial and central venous lines may be inserted, in addition to standard American Society of Anesthesiologists (ASA) monitors. Complete asepsis must be followed during all procedures, especially as these patients are immunocompromised due to underlying cancer and chemotherapy. A pre-induction thoracic epidural (TEA) [13] under local anesthesia is the gold standard for perioperative pain management. Also, TEA has beneficial effects on bowel function, DVT prevention, reduction in anesthetic requirements, and prevention of cancer recurrence (as it reduces the stress response of anesthesia and surgery). After adequate preoxygenation, rapid sequence induction (prevention of aspiration) is generally followed for securing the airway. Standard general anesthesia (GA) with a cuffed endotracheal tube and controlled mechanical ventilation is administered. Nitrous oxide [14] is generally avoided to prevent bowel distension and PONV. Blood and blood products must be arranged preoperatively, as dissection may be difficult and prolonged. Bowel perfusion must be adequate by maintaining a fine balance between normal mean arterial pressure and avoiding mucosal edema or fluid overload. Electrolyte imbalances must be detected and corrected early. Long surgical duration and anesthesia exposure times must also be kept in mind. Extubation must be cautious, especially in patients with cardiorespiratory diseases or those developing hemodynamic disturbances during surgery. Postoperative intensive care/high-dependency care unit (ICU/HDU) care is required in most patients. Vigilant monitoring must be done in the postoperative period to look out for cardiopulmonary complications (like arrhythmias, fluid overload, thromboembolism, renal dysfunction) and surgical complications (infections, anastomotic leaks, bleeding, peritonitis). Nutritional deficiencies [15] must be anticipated and appropriately supplemented (methyl-cobalamin and iron preparations). Most centers advocate early enteral feeding on postoperative day 5 or through a feeding jejunostomy on day 1, to enhance patient immunity and aid in the early return of bowel function [16].

14.4 Anesthesia for Cancer of the Small Intestine

The small bowel involves the duodenum, jejunum, and ileum. The major types of small intestinal cancer include [17] adenocarcinoma (commonest), sarcoma (leiomyosarcoma), carcinoid tumors, gastrointestinal stromal tumors, and lymphomas. They may have a sudden presentation in the form of acute or subacute intestinal obstruction or chronic symptoms like unexplained weight loss, nausea, vomiting, alteration in bowel habits, melena, constipation or diarrhea, abdominal pain, and malaise. Risk factors for intestinal cancers include smoking, familial adenomatous polyposis, Crohn's disease, celiac disease, and a high-fat diet [18].

Malignant tumors of the *duodenum* are rare, though they account for 50% of small bowel neoplasms. Most of them are adenocarcinomas, most commonly located in the second part of the duodenum. The most frequent presenting features [19] include abdominal pain, weight loss, jaundice, nausea/vomiting, and hemorrhage (in that order). Surgery remains the cornerstone of treatment for operable tumors. Radiotherapy and chemotherapy along with palliative procedures can be advocated for advanced cancers. The two major surgical options include pancreatoduodenectomy with lymph node dissection or segmental resection (for distal growths). Anesthetic considerations for these surgeries are the same as those for "Whipple's procedure" done for pancreatic tumors. Standard

general anesthesia with preoperative thoracic epidural catheter insertion, cuffed endotracheal tube insertion and controlled mechanical ventilation is the usuall acceptable practice. All anesthetic precautions for obstructive jaundice need to be followed. If cis-atracurium is available, its use is recommended. Peripheral neuromuscular monitoring is desirable. Maintenance of adequate urine output throughout the perioperative period is mandatory to preserve renal function, by stabilizing the mean arterial pressures. Pain management through TEA and use of truncal blocks (bilateral ultrasound-guided transversus abdominis plane block) [20] must be utilized in all cases. DVT, PONV, and antibiotic prophylaxis must be given in all cases. For metastatic tumors, palliative laser photocoagulation of lesions and gastrojejunal anastomosis may be performed.

Jejunal adenocarcinomas are very rare and diagnosed late. They may mimic a stricture resulting in intestinal obstruction [21]. Screening for intestinal tuberculosis and Peutz-Jeghers syndrome may be required. Surgical resection is the treatment of choice. Chemotherapy has limited and may be considered for advanced or residual cancers. Curative resection involves wide excision of the jejunum, mesentery, and the draining lymph nodes. Pre-induction thoracic epidural followed by modified rapid sequence induction (because of intestinal obstruction) and standard general anesthesia with a cuffed endotracheal tube and controlled ventilation is administered.

The ileum is the last part of the small intestine connecting it to the cecum (first part of the large intestine). Not only does it help in further digestion of food particles, but it also aids the absorption of nutrients like vitamins/minerals and water from food. Adenocarcinomas of the ileum are a rare entity, with nonspecific symptoms and hence delayed diagnosis. They may mimic tubercular ileal strictures. Wide ileal resection with negative margins and regional lymphadenectomy is done for proximal ileal tumors. For distal tumors, right radical hemicolectomy with lymph node clearance and a colostomy is done [22]. Nutritional deficiencies must be corrected, and supportive therapy is given, especially in malnourished patients. Blood and blood products must be arranged preoperatively. Chemotherapy does not have a major role in these cancers. For patients undergoing extensive resections and in places where facilities exist, a small bowel transplant may be considered after ruling out advanced or metastatic disease or other contraindications.

14.5 Carcinoma of the Large Intestine

The large intestine is a long tube connecting the small intestine with the anus. It has four parts: cecum, colon, rectum, and anal canal. Large intestinal cancers can present late and may preclude complete surgical resection. The most common feature of these cancers is gastrointestinal blood loss. Right-sided colon cancers generally present with fatigue and weakness due to iron deficiency anemia. Left-sided colon cancers produce occult bleeding or alteration in bowel habits. Losses of weight, anorexia, and bowel obstruction are late features [23]. Risk factors for colon cancer include a personal history of adenomas, family history of cancer, low-fiber/high-fat diet, high intake of processed foods/red meat, smoking, alcoholism, advanced age, and familial [24] syndromes (hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis (FAP), MYH-associated polyposis (MAP), inflammatory bowel disease). The screening tests for these cancers include FOBT (fecal occult blood tests), sigmoidoscopy, colposcopy (most useful), endoscopic-guided biopsy, barium enemas, CEA (carcinoembryonic antigen) essays, and CT (high-resolution and contrast-enhanced computed tomography) scans.

14.6 Colon Cancers

Cancer of the colon generally presents with vague abdominal discomfort, the sensation of incomplete bowel emptying, alternating diarrhea or constipation, per rectal bleeding, nausea/vomiting, unexplained weight loss, and fatigue. The risk factors include African-American race, dietary habits, sedentary lifestyle, genetic or

familial causes (hereditary nonpolyposis colorectal cancer and familial adenomatous polyposis), previous history of cancer and radiation therapy, inflammatory bowel disease, smoking, and alcoholism. The type of surgery depends on the stage and extent of colon cancer. *Colonoscopic polypectomy* with biopsy and local excision can be done for early tumors. Generally, *hemicolectomy* with lymph node dissection is done for colonic cancers. Here, at least one-third to one-fourth of the colon is removed along with nearby lymph nodes. In *total colectomy*, the entire colon is removed along with lymph node clearance. This is done in extensive tumors or multiple polyposis syndrome [25]. Colectomy can be done either by open surgery or by laparoscopic approach.

Anesthesia for radical colon cancer surgery starts from a thorough preoperative evaluation for assessment of nutritional status, baseline cardiorespiratory status, side effects of chemotherapeutic agents (if given), organ system assessment, and routine PAC investigations. The main anesthetic goals [26] concentrate on reducing the catabolic stress response, maintaining systemic and colonic perfusion along with oxygenation, optimizing fluid-electrolyte administration, adequate pain management, and prevention and early management of postoperative bowel dysfunction. A pre-induction lower-thoracic or lumbar epidural catheter insertion is followed by standard general anesthesia and controlled ventilation. Invasive monitoring is advocated in high-risk cases to monitor the intravascular fluid status. End-organ perfusion must be maintained at all stages of the surgery, and bowel ischemia must be prevented. Large incisions exposing long bowel loops and the use of bowel wash can lead to higher chances of hypothermia [27]. Temperature monitoring along with robust external warming devices is mandatory. Goal-directed therapy [28] facilitated by noninvasive cardiac output monitors (Vigileo™) may be beneficial in preventing fluid overload and bowel mucosal edema as well as maintaining adequate hourly urine output. Many of these patients may have preexisting electrolyte disturbances (vomiting, diarrhea, malnutrition), which may manifest or magnify intraoperatively, resulting in serious perioperative complications. ABG (arterial blood gas) analysis may assist the correction of acid-base and electrolyte disturbances.

Numerous scoring systems have been utilized for risk stratification in colorectal surgeries. These are primarily based on the patient-related history, functional assessment, physical examination, blood investigations including serum markers, and surgery-specific parameters. One of the commonly used scoring systems [29] includes the POSSUM (the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity) scoring system which assesses and predicts the perioperative complications and outcome. These have undergone several changes and serial improvements in their scoring assessments over a time period, and the recent one includes Portsmouth-POSSUM (P-POSSUM) and specialty-specific CR-POSSUM. Current studies have questioned the necessity of preoperative mechanical bowel preparation and nasogastric tube insertion for elective colorectal surgeries, as they have been associated with increased complications. Every effort must be made to correct hypoalbuminemia and anemia before surgery. Preoperative oral carbohydrate loading and postoperative use of chewing gum [30] have been shown to have a multitude of benefits. In recent times, the enhanced recovery after surgery (ERAS) protocol has been utilized for improving postoperative outcomes. This enhanced or fast-tracked approach to early recovery must be managed by a multidisciplinary team for effectiveness. Thromboembolism prophylaxis, nutritional support, early ambulation, colostomy care, strict aseptic precautions, and psychological and family support go a long way in ensuring a successful outcome. Early enteral feeding has been advocated in recent times to allow quicker gut healing and reduce infectious complications [31].

Pain management is usually undertaken with epidural infusions of dilute local anesthetics (0.125% bupivacaine or 0.3% ropivacaine), utilizing patient-controlled epidural analgesia (PCEA) pumps [32]. Opioids may be used with caution postoperatively, for fear of delaying the return of bowel function and causing PONV or itching. Also, ultrasound-guided TAP blocks (bilateral) along with continuous catheter tech-

niques can be inserted in patients with contraindications for central neuraxial blocks. Further, intrathecal analgesia wound infiltration and systemic lidocaine infusion can also be used. Analgesia is always multimodal, and systemic agents like paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) (to be used judiciously) need to be continued.

14.7 Carcinoma Rectum

The risk factors and presenting features of rectal cancers are nearly identical to colon cancers. Bleeding per-rectum, incomplete defecation, thin stools, unexplained weight loss, alternating bowel habits, and anemia in the elderly are definite pointers. Staging of rectal cancers [33] aids in planning the line of management (stages 0 to 4). Treatment involves surgery, chemotherapy, and/or radiotherapy. Colonoscopy, polypectomy, and local excision may be planned for benign tumors. Local trans-anal resection is advocated for early, small stage 1 rectal cancers. Trans-anal endoscopic microsurgery is for stage 1 cancer higher in the rectum. Lower anterior resection [34] (LAR) is done for most stage 2 and stage 3 cancers in the upper part of the rectum. If the colon is attached to the remaining rectum, then a permanent colostomy is not needed. If neoadjuvant chemotherapy is given, then a short-term ileostomy is created to allow healing of the rectum. Proctectomy with coloanal anastomosis is performed for stage 2 and 3 cancers in the middle and lower third of the rectum. This is a major surgery where a total mesorectal excision with removal of para-rectal lymph nodes is done. A colonic J-pouch or a coloplasty procedure is done to replicate the stool-storage function of the rectum. A short-term ileostomy followed by ileostomy closure after 8 weeks may be required. Abdominoperineal resection (APR) [35] is done for locally advanced stage 1, stage 2, and stage 3 cancers near the anal verge (lower end of the rectum). A permanent colostomy is needed in these situations. In advanced rectal cancers with metastases to nearby structures, pelvic exenteration is done, which entails the removal of the urinary bladder and prostate (in men) or uterus (in women). This is a major radical surgery with higher morbidity and mortality, which requires a colostomy and a urostomy. In unresectable rectal cancers, a palliative diverting colostomy is done to allow for stool passage, followed by chemotherapy. For isolated distal rectal cancer spread, metastasectomy of the lung or liver nodule may be undertaken, weighing the risk-benefit ratio and after removing the primary cancerous growth. Coloanal anastomosis and LAR are sphincter-sparing procedures. Nowadays, some of these procedures are done laparoscopically, allowing earlier patient recovery and lesser postoperative pain. Anesthetic considerations are the same as for colon cancer surgery. The emphasis is on enhancing early patient recovery, reducing perioperative stress response, infection control, pain management, colostomy care, and preventing gut dysfunction.

Chemoradiotherapy can be given preoperatively for stage 2 and 3 rectal tumors. For stage 4 rectal tumors, extensive radical surgeries can be undertaken after weighing the risk-benefit ratio. In addition to chemoradiotherapy, newer "targeted therapy" with FDA-approved biologics [36] (e.g., *bevacizumab*, *cetuximab*, *panitumumab*) has been administered. Such patients can also present to the anesthesiologist for chemo-port insertion or radiation therapy (Monitored Anesthesia Care) [37] and various other procedures or to the intensivist with any of the complications of multimodal chemotherapy. Dedicated colostomy care and early palliative care are of paramount importance. Perioperative physicians must be geared up for the challenges posed by advances in cancer therapies of all kinds and strive for patient safety with enhanced recovery and minimizing cancer recurrence in these patients.

14.8 Summary

Gastrointestinal cancers have some common risk factors and varied clinical presentations, which can lead to delay in their diagnosis if ignored or due to lack of awareness (Table 14.1). Smoking cessation, alcohol moderation, and intake of a high-fiber diet are required in all cases.

Table 14.1 Key points for gastrointestinal cancer surgeries

S. no.	Cancer site	Types of surgery	Anesthesia
1.	Stomach	Radical gastrectomy: Distal, proximal, subtotal, or total gastrectomy with lymph node dissection and anastomoses along with chemotherapy	Rapid sequence induction, thoracic epidural pre-induction, general anesthesia with controlled ventilation
2.	Small intestine	*Duodenum:* Pancreatoduodenectomy with lymph node dissection *Jejunum:* Wide excision of the jejunum with mesentery and draining lymph nodes *Ileum:* For proximal tumors, wide ileal resection with regional lymphadenectomy; for distal tumors, radical right hemicolectomy with lymph node dissection and colostomy	Pre-induction lower-thoracic epidural, standard general anesthesia or rapid sequence for intestinal obstruction, controlled ventilation; ileostomy care
3.	Large intestine	*Cecum*, *colon*: Partial or total colectomy with colostomy with lymph node dissection *Rectum:* Lower anterior resection (LAR – sphincter sparing); proctectomy with coloanal anastomosis with para-rectal lymphadenectomy with or without coloplasty; abdominoperineal resection (APR – sphincter sacrificing) with colostomy; pelvic exenteration (for advanced rectal cancers); palliative surgery; chemotherapy	Pre-induction lumbar epidural, standard general anesthesia with controlled ventilation, colostomy care

Anesthesiologists may be involved in the care of these cancer patients in various stages of their therapy, including palliative care. Pain management is pivotal for enhanced recovery. Perioperative physicians, by decreasing the stress and immune response of onco-surgery, also help in preventing cancer recurrences. There should be close coordination between the anesthesiologist, intensivist, pain physician, palliative care physician, nurse, nutritionist, physiotherapist, and colostomy-care staff. Future research must be directed in developing validated, fast-track recovery protocols for all gastrointestinal cancer surgeries.

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15 Anesthesia for Hepatobiliary Cancers

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15.1 Introduction

Hepatobiliary cancers are usually highly malignant tumors and include hepatocellular carcinoma (HCC), cholangiocarcinoma, and gallbladder cancers [1]. Chronic inflammation is the most significant risk factor for gallbladder cancer and cholangiocarcinoma. Chronic hepatitis B viral infection is one of the commonest etiologies for the occurrence of HCC. The treatment modality for hepatobiliary cancers is primarily based on the site and extent of the tumor. Partial hepatectomy remains curative for early disease [1]. The radiofrequency ablation of HCC tumors is another curative option for lesions that are 3 cm or less in size [2]. Liver transplantation is a treatment option in select cases of extrahepatic cholangiocarcinoma [3].

15.2 Preoperative Evaluation

The preoperative evaluation of patients presenting for hepatectomy requires not only a routine assessment but also focused assessment as per the status of the individual patient [4]. Patients with minimal to no parenchymal disease will not require as extensive an evaluation as those with severe hepatic impairments. Despite the availability of different hepatic function tests, not all tests can predict cardiovascular, respiratory, or hepatic function fluctuations in the perioperative period [4].

The preoperative evaluation of patients for hepatobiliary surgeries includes a detailed history and clinical examination with additional focus on findings related to liver function such as ascites, jaundice, or hepatomegaly. Physical findings raise suspicion of hepatic or cardiopulmonary impairment and provide indications for further testing and useful information about the potential effects of anesthetic management. For example, the presence of significant ascites or hepatomegaly may be associated with a reduced functional residual capacity (FRC) and diminished intravascular volume status. These findings increase the risk of hemodynamic compromise at the induction of anesthesia due to decreased venous return and also increased risk of pulmonary aspiration. Under such circumstances, a rapid sequence induction (RSI) with an agent that causes minimal hemodynamic changes may be more appropriate.

Shortness of breath and decreased room air oxygen saturation may also be an indication of a ventilation/perfusion mismatch [5]. The significance of this finding may be manifold, as it may impact several aspects of perioperative management. For example, adequate preoxygenation before induction of anesthesia will be necessary

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to avoid hypoxemia, and cautious fluid management will be necessary to avoid fluid overload. This finding may also influence the surgical approach, since patients with baseline hypoxemia may not be able to tolerate the cardiopulmonary effects of pneumoperitoneum and the positional changes associated with a laparoscopic approach [6].

Hematological assessment of liver function needs to be performed preoperatively. These investigations include complete blood count, serum chemistries, coagulation profile, and liver function tests. However, the results of these investigations need to be interpreted cautiously as their nonspecific nature renders the true assessment of liver function difficult [7]. However, elevated bilirubin and hepatic transaminases are usually indicative of some degree of hepatic impairment. Chronic liver disease may also be associated with decreased levels of most procoagulant factors [8]. The basic coagulation tests including prothrombin time and partial thromboplastin times are routinely performed. However, their correlation with bleeding tendencies is not robust [9]. The recent introduction of thromboelastography has enabled the identification of the different types of coagulation abnormalities and thus more focused management. Thus it has emerged as a better modality to identify coagulation abnormality [10]. Elevated prothrombin time may also occur independently of liver function. The administration of vitamin K may be considered before liver resection. However, routine correction of prothrombin time with fresh frozen plasma is not recommended [7].

The necessity of additional laboratory studies may be ascertained based on patient assessment including functional status, associated comorbidities, and extent of surgical intervention. Also, pulmonary function tests are not routinely indicated in patients without significant lung disease. However, the physiologic stress associated with vascular occlusion during liver surgery has led some authors to advocate for pharmacologic or exercise stress testing before hepatectomy [5].

The percentage of functional liver expected to remain after resection is an important consideration during preoperative assessment. The surgical resection of the liver should allow a future liver remnant of at least 20% in a healthy liver and even more in the liver having dysfunction from other associated diseases [6]. Strategies like portal vein embolization which induces liver hypertrophy should be considered when the potential healthy liver remnant will be less then 20% [8].

15.3 Preoperative Holding Area

In the absence of severe hepatic impairment, an anxiolytic such as midazolam may be administered. The presence of severe hepatic dysfunction could impair the metabolism of some benzodiazepines including midazolam and diazepam [9]. Conjugation of other benzodiazepines such as oxazepam and temazepam has been shown to take place without hepatic metabolism. Such drugs may be considered for patients with liver dysfunction. More recently, some enhanced recovery pathways have advocated for the omission of preoperative anxiolytics and the consumption of carbohydrate drinks up to 2 h before surgery [11].

15.4 Intraoperative Management

Several anesthetic techniques have been suggested for the management of patients undergoing hepatectomy. However, the choice of anesthetic agents and management approaches are less important than the care with which they are used. Due to the potential for severe and sudden onset of blood loss, at least two large-bore peripheral intravenous (IV) lines are recommended [12]. A central line is not routinely indicated, but may be considered for complicated resections. An arterial line allows for closer hemodynamic monitoring and frequent blood draws.

The main principle of intraoperative management is to minimize caval distention to minimize blood loss during parenchymal resection. Minimal caval distention may be achieved by the judicious use of IV fluids, diuretics, or vasodila-

tors [6]. The optimal approach to fluid management during liver resection remains undefined. In a reported randomized prospective study of 125 patients undergoing liver resection, the authors reported that lower postoperative morbidity was seen in patients who were administered lesser intraoperative IV fluids [13]. They reported that patients in whom stroke volume variation-guided goal-directed fluid therapy (GDT) received less intraoperative IV fluids. Colloid infusions may be particularly beneficial in cirrhotic patients and in patients who present with significant ascites [14]. An estimate of caval pressure may be attained by central venous pressure or stroke volume variation monitoring [15, 16]. Euvolemia is typically restored after the hepatic transaction has been completed. Increased blood loss in the intraoperative period has been reported to have an adverse effect on outcome and survival in patients undergoing liver resection [13, 14].

The choice of anesthetic drugs depends on the status of liver function. Patients with the compensated liver disease usually tolerate inhalational agents and narcotics, but those patients who have advanced liver disease tend to have a state of hyperdynamic circulation. Such patients manifest increased cardiac output and decreased systemic vascular resistance with blunted compensatory chronotropic and inotropic mechanisms [9]. Because of changes in the physiology of the patient with liver disease, care should be taken during induction, maintenance of anesthesia, and patient positioning for surgical intervention. Concerning the use of volatile agents in patients with liver disease, isoflurane, desflurane, and sevoflurane may be associated with less hepatic impairment than halothane [17, 18]. In patients with decompensated liver disease, the drug metabolism (for drugs which are primarily metabolized in the liver) and volume of distribution of drugs are altered. With a decrease in drug metabolism and increased volume of distribution, the duration and recovery profile of the drugs may be prolonged [12, 13]. Drugs like cisatracurium which undergo non-hepatic metabolism are considered the preferred drugs in such patients [14].

15.5 Pain Management

Multimodal analgesia management remains an acceptable modality. Thoracic epidural analgesia is typically employed during open liver resections as it provides optimal analgesia and has an opioid-sparing effect [15]. Although concerns about the safety and efficacy of epidural analgesia in this setting remain [16], complications associated with epidural catheter placement are relatively rare [19]. Epidural-associated hypotension is most commonly treated with fluid boluses. However, excessive fluid administration may result in fluid overload, and vasopressors should be considered if initial fluid resuscitation is not effective in relieving hypotension. To avoid complications associated with coagulopathy, the coagulation parameters should be checked before epidural catheter placement and its removal [20].

At our institution, a thoracic epidural catheter is placed between the fifth and tenth thoracic interspinous levels. After a negative test dose, a bolus of 10 μg/kg of epidural hydromorphone (maximum of 1 mg) is administered before securing the catheter. Before surgical incision, 3–10 mL of 2% lidocaine is administered incrementally via the epidural catheter to establish a block. The continuous infusion of bupivacaine 0.075% and hydromorphone 5 μg/mL at 5–8 mL/h is started epidurally. A secondary alternative to hydromorphone is fentanyl. Infusion rates on the surgical floor are 5–8 mL/h with an added patient-controlled epidural analgesia dose of 3 mL every 10 min as needed (not to exceed 6 mL/h) [15].

Though epidural analgesia is well known, its failure rate should be acknowledged, and appropriate measures should be taken for providing analgesia in such situations. In a prospective randomized study in 83 patients undergoing open hepatic resection, the failure rate of epidural analgesia was 20%, compared to 4% in patients who received abdominal wound catheters [21]. The authors reported that early postoperative pain scores were greater in the patients who received abdominal wound catheters; however, the pain scores were low at all points. Furthermore, the need for vasopressor was more

in patients who received epidural analgesia as compared to those who received abdominal wound catheters. The length of stay, fluid requirements, nausea, sedation scores, or postoperative complications remained comparable with these two techniques of analgesia. The authors concluded that abdominal wound catheters simplified patient management and could not recommend the routine use of epidural analgesia for open liver resections.

Patient-controlled analgesia (PCA) is also considered an acceptable option for providing postoperative analgesia. It can be used as an alternative to epidural analgesia when it is contraindicated. The use of morphine, fentanyl, and hydromorphone IV PCA has been described in patients undergoing liver resection [15, 22]. Typically, lower starting doses with no basal rates are programmed. For example, a hydromorphone IV PCA regimen with no basal rate, a 0.2 mg of demand dose every 10 min, and 0.5 mg nursing bolus every hour if needed have been described [15].

Fascial plane blocks such as the four-point transversus abdominis plane block (TAP Block) have also been shown to be effective for providing analgesia after laparotomies. The advantages of TAP block include reduced concerns about coagulopathy and the lack of significant sympathectomy. Where available, a mixture of liposomal bupivacaine (266 mg) and 0.25% bupivacaine may be used to provide analgesia for up to 30 hours [23]. The injection of 10 ml of 0.5% ropivacaine at each site has also been described [24]. The use of local infiltrating catheters has also been described by some authors and has variable results as compared to IV PCA and epidural analgesia [25, 26].

15.5.1 Acetaminophen

Acetaminophen is one of the safest components of multimodal analgesia. Its use in patients with liver disease should be avoided as a metabolite of acetaminophen, N-acetyl-p-benzoquinone imine (NAPQI), is hepatotoxic which becomes nontoxic after its conjugation with glutathione. However, levels of glutathione are decreased in patients with liver disease and thus higher levels of NAPQI [27].

The reported literature is conflicting for the safe use of acetaminophen in the perioperative period for patients with liver surgeries. The short-term use has been reported to be safe in patients with nonalcoholic cirrhotic liver disease [27]. However, 2–3 mg/day is the recommended maximum dose in patients with hepatic impairment [28].

15.5.2 Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain a useful component of multimodal analgesia. The pharmacokinetics of the NSAIDs including ibuprofen, etodolac, and diclofenac is not altered in patients with mild to moderate liver dysfunction. However other NSAIDs like naproxen, sulindac, and celecoxib require dose reduction in the patient having mild to moderate liver dysfunction. The use of NSAIDs may be avoided in patients with severe liver dysfunction because of significant adverse effect profile [27].

15.5.3 Opioids

The safe use of opioids is essential for patients with liver disease and depends on the extent of liver dysfunction. The opioids are largely tolerated in patients with compensated liver disease. Since certain opioids are metabolized by the liver, so their clearance will be impaired in patients with liver disease leading to increased bioavailability. The first-pass metabolism is decreased in proportion to the severity of liver dysfunction. After liver resection surgeries, the liver function may get impaired leading to impaired opioid metabolism. This severity of impairment depends on the extent of liver resection [22].

Morphine is metabolized to morphine-6-glucuronide (active metabolite) and morphine-3-glucuronide (inactive metabolite) in the liver. After liver resection surgeries with the decreased hepatic flow and decreased liver function, liver metabolism of morphine is altered with decreased hepatic clearance. The reported literature is conflicting with regard to the clinical effects of various opioids in patients with liver diseases. Some published literature reported decreased clearance of morphine in cirrhotic patients [29], and others have found no significant alteration in morphine metabolism [30]. Differences in study results could be related to differences in the degree of hepatic impairment between subjects in both studies. It was reported that morphine metabolism is affected in patients with liver cirrhosis and the morphine bioavailability was twice in these patients as compared to patients without cirrhosis [31]. So, the dose may be decreased, and the interval of dosing may be increased in patients with liver dysfunction [27].

Fentanyl and sufentanil have high hepatic extraction ratios of 80% and approximately 100%, respectively. Both are primarily metabolized in the liver, and reduced hepatic blood flow shall reduce drug clearance for these opioids [27]. The pharmacokinetics of a single dose of both drugs does not seem to be affected by liver disease. However, significant prolongations in the half-life have been observed in patients on continuous infusions [32]. Similar to morphine, the initial doses may need to be lower in patients with reduced liver function. Dosing intervals may also need to be increased, and patients assessed at more frequent intervals.

Alfentanil is almost exclusively eliminated by the liver, and thus its metabolism is impaired in liver dysfunction leading to decreased plasma clearance and an increased unbound fraction. This delayed elimination raises the possibility of a prolonged effect after the administration of either a single or repeated dose. A dose reduction in a patient with severe liver dysfunction may be necessary [33].

Remifentanil is a synthetic μ opioid agonist and is an ester-based molecule [33]. It is metabolized by the blood- and tissue-nonspecific esterases. The metabolites are inactive and excreted through the kidneys. Patients with liver diseases of any severity do not affect the metabolism or excretion of remifentanil [34, 35]. However, there is evidence to suggest that respiratory depression can occur in patients with severe liver disease with remifentanil administration [34]. Unless the drug is being used as a part of monitored anesthesia care, the respiratory depressant effects may not be as significant in the recovery period since the drug is rapidly metabolized. Patients with severe liver disease require dose adjustments of remifentanil.

Hydromorphone metabolism occurs through the liver, and thus any compromise in liver function shall decrease the metabolism if it is leading to prolonged duration [27]. Patients with moderate to severe liver dysfunction require reduction of the initial dose by 25–50% and close monitoring for respiratory depression.

Meperidine is extensively metabolized in the liver to normeperidine (6-N-desmethylmeperidine) which is further hydrolyzed to meperidinic acid. Normeperidine possesses neurotoxic effects, and its accumulation may lead to neuromuscular irritability and seizures [36]. Additionally, potential decreases in the excretion of normeperidine could increase the risk of central nervous system complications. Patients with cirrhosis have been reported to have decreased plasma clearance and thus increased half-life of meperidine [27]. So, dose reduction and longer dosing intervals are suggested for use of meperidine in patients with liver diseases.

15.6 Summary

Patients with liver disease require cautious selection of various anesthetic drugs used in the perioperative period along with judicious fluid management. General anesthesia can be safely administered to patients undergoing hepatic resection for hepatobiliary cancers.

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16 Anaesthesia for Breast Onco-surgeries and Reconstruction

James Freeman, Aislinn Sherwin, and Donal Buggy

16.1 Introduction

Breast cancer is the most common cancer to affect women [1]. Though breast cancer survival rates have been steadily increasing since the 1990s, with the 5-year survival rate currently approaching 90% [2], breast malignancy remains a leading cause of cancer death in females [3]. The fiscal burden associated with breast cancer is not insignificant. In 2009, the cost of breast cancer across the European Union was €15 billion with only pulmonary cancers having a higher associated expenditure [4].

The potential risk factors associated with developing breast malignancy are legion [5, 6]. Being genetically female is the strongest risk factor, and, across female populations as a whole, the lifetime incidence of developing breast malignancy is one in eight (12%) [7]. Certain populations are at an increased risk. For example, the risk of developing breast cancer is strongly related to increasing age [7]; a 70-year-old woman has almost a tenfold increase in the risk of developing breast cancer within 10 years compared to a 30-year-old (0.43% vs 3.74%) [8]. There is thought to be a strong genetic link in roughly 5% of breast cancers [9], and two genes in particular, BReast CAncer gene 1 (BRCA1) and BReast CAncer gene 2 (BRCA2), account for most cases of inherited cancer. Women affected by a BRCA mutation have a vastly increased lifetime risk of developing breast cancer [9]. Other factors associated with the development of breast cancer include oestrogen exposure [10], smoking [11], obesity [12–14] and alcohol consumption [15].

16.2 Anatomy

The adult female breast functions as an apocrine gland and is located superficial to the pectoralis muscle on the anterior chest wall. Blood is supplied to the breast through branches of the internal mammary, axillary and posterior intercostal arteries.

Venous drainage of the breast is primarily dependent on three principal groups of veins, namely, branches of the internal thoracic, the axillary and posterior intercostal veins.

Initially, lymphatic drainage of the breast flows from the breast lobules into a sub-areolar plexus (Sappey's plexus). From this plexus, three main routes are available: the internal mammary pathway, the axillary pathway and the retro-mammary pathway. Typically, the axillary nodes receive 75% of the lymph drained from the breast.

The nerve supply of the breast comes from several origins. The medial and lateral pectoral

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nerves are branches of the medial and lateral cords of the brachial plexus, respectively. The medial pectoral nerve pierces the pectoralis minor to supply part of the pectoralis major and pectoralis minor. The lateral pectoral nerve runs above the pectoralis minor to enter the pectoralis major and supplies the remainder of the pectoralis major. The long thoracic nerve (LTN) is derived from the ventral rami of C5–C7. It supplies the superficial aspect of the serratus anterior. Damage to the LTN can occur during breast procedures resulting in a "winged scapula". These nerves are the targets of the Pecs block described by Blanco [16]. Cutaneous innervation of the breast is through the lateral and anterior branches of the intercostal nerves which are general sensory branches of dermatomes T1 to T6.

16.3 Types of Breast Cancer Surgery

Trends towards increased survival and reduced mortality rates in breast cancer patients [2] are probably due to more effective and appropriate management strategies, in particular the development of adjuvant therapeutic options [17]. However, breast cancer itself is a major indication for breast surgery, and surgical resection remains a mainstay of any curative management pathway. Surgery is often offered as part of a multimodal treatment regimen which may also include hormonal therapy, chemotherapy, radiotherapy and immunotherapy [18]. Over 80% of breast cancer patients will undergo some form of surgery as part of their treatment [18]. Surgical intervention for breast cancer treatment and disease management can be broadly split into two separate groups: mastectomy, where the entire breast is removed, and less aggressive, breast-conserving interventions such as partial mastectomies and lumpectomies [3].

Surgical management of breast cancer has evolved over the past 40 years, trending away from more mutilating and radical procedures towards a focus on more conservative techniques [19]. In patients with early-stage breast cancer, a breast-conserving surgical technique in combination with adjuvant radiotherapy is now considered to be the "gold standard" approach [20]. The surgeon managing breast cancers in the modern age is not, therefore, concerned with disease clearance alone, but also with aesthetic outcome [19].

16.3.1 Mastectomy

Use of the mastectomy stretches back to antiquity [21]. In more recent times, the mastectomy has evolved since Halsted's description [22] at the end of the nineteenth century. The radical mastectomy, which is a mutilating and painful procedure where the breast, pectoral muscles and axillary lymphatic nodes are removed, has been largely replaced by less disfiguring and more conservative approaches. The *modified radical mastectomy* spares the pectoral muscles, whilst the *simple mastectomy* removes only breast tissue. The lumpectomy is discussed below. Whilst there has been a move towards breast-conservative techniques, in the modern surgical management of breast cancer, mastectomy does continue to play a role in selected cases. Interestingly, in the 2000s, mastectomy rates took an upward turn in the United States [23]. In particular, the rates of "prophylactic" double mastectomies in patients with unilateral disease dramatically increased even though no survival benefit is shown when the healthy breast is removed simultaneously [24]. The reasons for this increase are difficult to ascertain but may reflect patient fear of recurrence.

16.3.2 Wide Local Excision and Lumpectomy

Excision of a breast lesion is commonly performed to obtain a histopathological diagnosis. Though an open biopsy technique might be useful in certain scenarios, minimally invasive techniques such as percutaneous needle biopsy are the current gold standard [25, 26]. Smaller needle aspirations can often be performed under local

anaesthesia in the office or outpatient setting. For non-palpable lesions, a hook wire is usually inserted under radiological guidance to guide the operating surgeon.

16.3.3 Sentinel Lymph Node Biopsy

When treating cancerous breast lesions, obviously diseased lymph nodes are resected simultaneously. Where no clinically diseased nodes are apparent, sentinel lymph node excision is performed. Sentinel nodes, the first nodes draining afferent lymphatics from the breast cancer lesion, can be detected using coloured or radioactive dyes. Many of the coloured dyes (e.g. methylene blue) can interfere with pulse oximetry [27]. The anaesthetist should be aware of potential erroneous saturation probe readings in the perioperative period. Verbal warning should also be provided by the surgeon before infiltration of dye. Dyes used have been associated with anaphylactic reactions intraoperatively. Consideration of dye reactions should occur if acute cardiovascular changes occur.

16.3.4 Axillary Dissection

There are three surgical "levels" of lymph nodes in the axillary region (Table 16.1). In axillary dissections for breast cancer, the level I and II node groups are removed. There does not seem to be any survival advantage in removing the more superficial level III nodes. Ideally, the surgeon should be aiming to identify and preserve the thoracodorsal, long thoracic and intercostobrachial nerves to avoid chronic postoperative dysaesthesia.

Table 16.1 Surgical level of axillary nodes

Level	Location
I	Below the lower edge of the pectoralis minor muscle
II	Underneath the pectoralis minor muscle
III	Above the pectoralis minor muscle

16.4 Types of Breast Reconstructive Surgery

Provided there is no contraindication, all patients undergoing mastectomy should be offered the opportunity to avail of surgical breast reconstruction [28]. There are several options available to refashion the breast, and these options can be placed into two broad categories: implant-based reconstructive procedures or reconstruction using autologous flaps [29] (Fig. 16.1). Reconstruction may be part of the original surgery for tumour removal or be carried out at a remote time to allow for adjuvant therapy to occur.

16.4.1 Implant-Based Reconstruction

Implant-based reconstruction usually involves saline tissue expander insertion. Once sufficient expansion has taken place, the expander is removed and replaced with a definitive silicone implant. Implant-based procedures have the advantage of being less complex and less invasive than flap-based reconstruction. Though implant insertion in isolation is not a long procedure in itself, the overall reconstruction process has the potential requirement for multiple procedures. Over 5 years, one-third of patients availing of implants will require further surgery due to complications such as a scarring reaction or contracture [30].

16.4.2 Flap-Based Reconstruction

Reconstructive autologous flap surgery makes use of the patient's skin, fat and occasionally muscle. This flap of autologous tissue is shaped into a new breast after transfer from a separate anatomical site. The type of procedure determines where the flap is "raised" from. Commonly used donor sites include the abdomen, thigh, back, hip and buttocks. Though flap-based reconstruction methods involve a longer duration of initial surgery, they may be associated with an overall reduction in the number of operations and complication rates. Flap-based reconstruction is

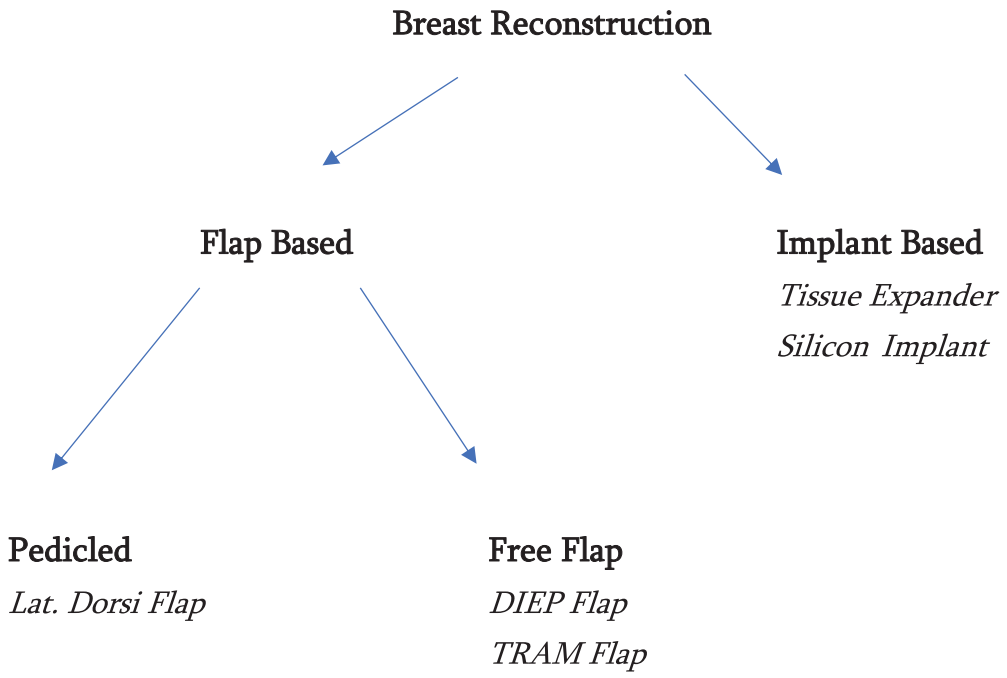

Fig. 16.1 Breast reconstruction pathway with examples

also thought to give a more natural aesthetic appearance.

Autologous flaps themselves can be classified into two types (Fig. 16.1). In pedicled flaps, the donor tissue remains connected to the original donor site via an intact vascular pedicle. Thus, there is no period where the blood supply is interrupted. The most common example of a pedicled flap is the latissimus dorsi flap, where the flap is moved into the breast through a defect in the axilla.

In comparison, free flaps are completely detached from the body with the division of the vascular pedicle. Blood supply to the flap is then re-established using microvascular techniques.

The two most common free-flap procedures for breast reconstruction are the deep inferior epigastric perforator (DIEP) free flap and the transverse rectus abdominis myocutaneous (TRAM) free flap. These procedures involve harvesting an ellipse of tissue from the lower abdomen followed by transfer to the anterior chest. Unlike the TRAM flap, the DIEP procedure spares involvement of the rectus abdominis muscle which helps to preserve abdominal strength, decreases the likelihood of herniation and shortens recovery time [31]. The DIEP flap is now considered the "gold standard" for free-flap breast reconstruction.

16.5 Preoperative Assessment

Alongside the value in identifying and optimising co-existing ailments and planning perioperative management, the preoperative anaesthetic assessment allows for the creation of a dialogue with the patient and an explanation of the conduct of anaesthesia.

16.5.1 General Consideration

Breast reconstruction, when performed apart from solid tumour excision, is an elective procedure, and sufficient time should be taken to optimise any underlying conditions. Conversely, any undue delay in investigating the cancer patient is unlikely to be in the patient's best interest. Those patients with a delay of 12 weeks or

more in presentation or access to treatment have significantly worse long-term survival outcomes [32], and every effort should be made to offer intervention within 3 months.

There are no specific or mandatory investigations warranted in women undergoing breast cancer surgery. Investigations should be guided by patient history and previous therapies. Any intercurrent disease processes should be investigated and optimised appropriately. An allergy history should be elucidated with particular attention to the more common allergens such as latex, antimicrobials, neuromuscular blockers and other anaesthetic agents. Administration of the patient's routine medications should follow appropriate local and national guidance. In those patients undergoing more extensive surgical interventions, a sample should be taken for blood typing and possible cross-match.

16.5.2 Anxiety and Premedication

It should be borne in mind that the diagnosis of cancer can be an extremely stressful experience. Though some element of mental preparation can occur in the period between diagnosis and surgical intervention, anxiety levels can increase in the perioperative period [33]. Aside from the more generalised fears attached to undergoing surgery and anaesthesia, such as "not waking up" or experiencing postoperative pain, breast cancer surgery patients may also have concerns around their physical appearance in the postoperative period and their identity as women [34, 35].

The harm associated with preoperative anxiety does not appear to be limited to preoperative psychological distress, and more anxious patients tend to have increased pain scores in the postoperative period [36] and are more likely to suffer impaired wound healing [33]. Addressing patient concerns and allaying anxiety may thus have beneficial effects extending into the postoperative period [34, 37]. Aside from the provision of simple reassurance at a preoperative encounter, anxiolysis can be augmented with the judicious use of benzodiazepine administration preoperatively. Concerns have previously been raised regarding the carcinogenic potential of long-term benzodiazepine administration [38], but there is no firm evidence to suggest benzodiazepine use in the perioperative period is detrimental to the outcome. Rather, benzodiazepines reduce anxiety, blood pressure and heart rate and facilitate laryngeal mask airway insertion. Typical anxiolytic premedication includes an age-, weight- and morbidity-appropriate oral dose of temazepam, lorazepam or diazepam.

16.5.3 Neoadjuvant Therapy Consideration: Chemotherapy

Chemotherapy, when appropriate, is usually administered in the postoperative period. Occasionally, preoperative (neoadjuvant) chemotherapy is employed to "shrink" large or locally advanced tumours to decrease the extent of surgical resection required [39]. The chemotherapeutic regimens used neoadjuvantly are similar to those prescribed in the postoperative period, and, where surgical intervention is offered, the timing of chemotherapy has no apparent influence on longer-term outcomes [40]. Chemotherapy for primary breast cancer is usually administered over a four- to eight-cycle period (12–24 weeks), and most regimens involve anthracycline [41] and/or taxane administration.

A common side effect of many chemotherapeutic agents is myelosuppression. This is usually (at least partially) reversed within 6 weeks of stopping chemotherapy but may persist for longer periods. In neutropenic patients, fulminant sepsis and rapid clinical deterioration can occur, and the clinical manifestations of infection can be atypical. Pancytopenia will also have effects on perioperative oxygen delivery and haemostasis. A full blood count is mandatory for those patients undergoing surgery post-chemotherapy.

The cardiac side effects of anthracyclines became apparent soon after their introduction in the 1970s. Anthracycline "cardio-toxicity" does not appear to have a standardised definition, and manifestations range from clinical deterioration requiring emergent hospital admission to subclinical structural changes, to new dysrhythmia,

and to asymptomatic cardiac biomarker rise [42]. These changes do not tend to develop immediately, and there is some evidence to suggest that perioperative issues relating to anthracycline administration are quite rare [43]. However, an electrocardiogram and an echocardiogram should be obtained provided they can be performed on time. In particular, left ventricular function and contractility should be assessed with a transthoracic echocardiogram. Depending on the clinical features and investigation results, the patient may need a specialist cardiologist opinion before surgery. The risk of cardiomyopathy is significantly higher when trastuzumab (Herceptin) is administered in combination with anthracyclines [44].

Many chemotherapeutic agents act as cytotoxins and are potential carcinogens. The development of secondary malignancies is a risk, in particular, AML and myelodysplastic syndrome [45]. Other potential complaints from those undertaking a chemotherapeutic regimen include gastrointestinal upset, hair loss, photosensitivity, cystitis and peripheral neuropathy [46].

16.5.4 Neoadjuvant Therapy Consideration: Radiotherapy

When used as part of a multimodal therapeutic regimen, radiotherapy is usually offered after tumour resection in breast cancer patients [47]. As such, consideration of the impact of radiation to the chest wall is unlikely to be required for the breast cancer patient undergoing primary tumour excision. History of radiotherapy may, however, be an issue in those presenting for delayed breast reconstruction after initial tumour resection.

The primary concern for anaesthesia providers with regard to radiotherapy to the chest wall is the development of radiotherapy-induced lung injury (RILI). A 2003 review put the incidence of RILI at 5–15% [48] in those receiving radiotherapy for breast cancer.

RILI has traditionally been divided into two distinct clinical phases: acute pneumonitis and late fibrosis. Radiation pneumonitis typically presents 1 to 6 months after completion of radiotherapy, and symptoms include dyspnoea, nonproductive cough, pleuritic chest pain and a low-grade fever. In patients with underlying chest disease, it can be difficult to differentiate pneumonitis from an exacerbation of underlying disease, and radiographic imaging may not be helpful. Acute pneumonitis usually responds well to steroids and a pronged, tapering course is often prescribed. Pneumonitis can resolve completely or, less commonly, progress to fibrosis.

Fibrosis typically presents months to years after completion of radiotherapy. There is progressive dyspnoea associated with "scarring" of the lung subjected to high-energy radiation. For these patients, treatment is aimed at symptomatic relief instead of cure. There will be radiographic evidence of this scarring, but there does not appear to be a correlation between the degree of radiological abnormality and clinical features. Formal pulmonary function tests may help where a restrictive pattern may be present with a variable reduction in diffusing capacity [48, 49].

16.6 Intraoperative Care

Intravenous, inhalational and regional methods are all acceptable techniques for providing anaesthesia for breast cancer surgeries. Not infrequently, a combination is employed to achieve optimal operating conditions and patient comfort. The potential permutations are many, but the more routine combinations include the use of a regional technique for analgesia and general anaesthesia using inhalational or intravenous agents for maintenance. In our institution, a balanced general anaesthetic with pecs block is the most common method of proving anaesthesia for breast cancer surgeries. Other commonly used combinations include pecs blockade with TIVA and general anaesthesia with a paravertebral blockade.

16.7 General Anaesthesia

General anaesthesia can be maintained with volatile agents or a total intravenous anaesthesia (TIVA) technique. Commonly used agents include sevoflurane, isoflurane, propofol and remifentanil. Though early research in onco-

anaesthesia suggested that TIVA may offer a long-term survival benefit in breast cancer surgeries, at the time of writing there is clinical equipoise [50, 51].

Intravenous induction with propofol is common in our institution, but, depending on the clinical scenario, inhalational agents such as sevoflurane can be used for induction. Intravenous induction with propofol has several advantages. It provides a rapid onset of anaesthesia with induction occurring within one arm-brain circulation time. Propofol blunts the airway reflexes making it the ideal agent for laryngeal mask airway (LMA) insertion. Propofol also has the advantage of rapid emergence [52]. When considering flap-based reconstructive surgeries, all inhalational agents decrease vascular resistance.

Sevoflurane and desflurane are commonly used in longer procedures because both agents provide intraoperative cardiovascular stability and are associated with more rapid awakening after long surgeries [53]. Nitrous oxide should probably be avoided in these procedures as it is associated with gastric distention, nausea and vomiting after surgery and a possible greater risk of postoperative cardiac ischaemia [54, 55]. The effects different inhalational agents have on free-flap blood flow are not completely understood [56], and little is known about how anaesthetic agents interplay with the microvascular parameters involved in fluid distribution [57].

Sevoflurane may have beneficial effects on the microcirculation as it reduces plasma leakage into the interstitial space and can therefore reduce flap oedema [58]. It may also have a protective effect against ischemic-reperfusion injury [59, 60]. However, the anaesthesia provider should recognise that there is little in the way of concrete evidence to suggest the use of one inhalation agent over another, and individual anaesthetists will have their preference. Further studies are needed to compare inhaled and intravenous anaesthesia in microvascular surgery [61], but the use of propofol and remifentanil target-controlled infusion (TCI) is also a popular technique [62].

Provided there are no other contraindications, for short procedures a laryngeal mask airway (LMA) is a suitable device for maintaining the airway perioperatively. There is some controversy regarding the maximum acceptable continuous duration an LMA can be left in place [63–65], but tracheal intubation is probably the most appropriate airway strategy for prolonged procedures, particularly with intraoperative changes of position. Other indications for intubation and initiation of mechanical ventilation include those patients at risk of aspiration and obesity.

16.7.1 Positioning

The impact on physiology and the care requirements of the different positions used in the operative phase can be found in most anaesthesia textbooks. We will not discuss these in detail and only note the more common positions that can be found during surgeries relating to breast cancer. For resection or debulking of a breast tumour, the patient is usually supine. The ipsilateral arm to the tumour may be abducted to facilitate access to the axillary region.

In reconstructive surgeries, a supine positioning is the most frequent. However, depending on the surgery, lateral or prone positions may be required to ensure optimal operating conditions. Both arms may be abducted (the crucifix position) if a bilateral reconstructive procedure is to take place, and varying degrees of reverse Trendelenburg and flexion at the hips can be needed to ensure a good cosmetic result and reduce blood loss. The lateral position may be required for some flap reconstructions. More rarely, a prone position is used to facilitate retrieval of adipose tissue to use in fat grafting of the breast for aesthetic purposes. A re-enforced endotracheal tube is advised if patients are required to be put into a prone position.

16.8 Analgesia

Breast surgery is usually associated with mild to moderate pain scores in the immediate postoperative period. This does not mean that the benefits of effective preoperative analgesia provision should be underestimated. The implications of poorly controlled perioperative pain may extend

beyond ethical and humanitarian concerns, and effective perioperative analgesia provision may play a role in reducing the risk of metastatic progression in cancer surgeries [66] or theoretical risk of vasospasm in flap reconstructions due to catecholamine release.

16.9 Regional Anaesthesia and Analgesia

A variety of techniques utilising local anaesthetic agents have been described as providing effective analgesia and anaesthesia in the operative period. These techniques range from simple infiltration of local anaesthetic to more complex approaches. Some of the more common techniques employed are discussed below.

16.9.1 Local Anaesthetic Infiltration

Perhaps the easiest, quickest and least technically demanding method of administering local anaesthetic for analgesia involves local infiltration. The risks of pneumothorax and significant intravascular injection are minimal. However, evidence for the analgesic impact provided by local infiltration has been, at best, mixed [67–69].

Pain after breast surgery, for the most part, is mild to moderate, and there is no strong evidence that infiltration of local anaesthesia reduces opiate use or side effect profile in the postoperative period [67, 70]. A meta-analysis found that bupivacaine and ropivacaine locally infiltrated in breast cancer surgeries have significant analgesic effects for 2 hours postoperatively, but this effect is not long-lasting and infiltrative techniques might not provide any significant analgesia by 12–24 hours postoperatively [71]. In keeping with this short-lived effect, local infiltration does not appear to influence the longer-term incidence of chronic pain [72], and the timing of infiltration (pre-emptive vs post-procedure) does not appear to have any impact on postoperative pain [73].

Placing a catheter into the surgical site allows for repeated bolus administration of a local anaesthetic agent or a continuous infusion. A 2010 meta-analysis showed no significant difference between placebo and amide local anaesthetic infiltration postoperatively [74], but the authors suggested a well-designed, adequately powered randomised controlled trial be performed to better assess the analgesic effect of wound infiltration. Conversely, a 2014 study of 73 women undergoing radical mastectomy showed improved analgesia at every point postoperatively up to 48 hours [75]. A recent randomised controlled trial from our unit [76] compared local anaesthetic agent infusion via wound infusion pump against single-shot pecs blocks and a combination of both techniques. We found that women undergoing breast cancer surgery had better analgesia over the first 24 postoperative hours when both of these techniques were combined than with either technique individually. Verbal response scores for pain indicated that pecs blocks provide better analgesia in the early postoperative period (first 6 hours), whilst local anaesthetic agent infusion provided better analgesia from the 12- to 24-hour period.

16.9.2 Pecs Block

A growing number of breast surgeries are managed as day cases. The invasiveness of neuraxial, paravertebral and intercostal techniques (and their higher potential for a significant complication) deems them unsuitable for use in the day-case surgery cohort. Pectoral nerve blockade is less invasive, has a lower incidence of complication and is easy to perform. First described in 2011 [16], the ultimate aim is the deposition of local anaesthesia between the thoracic muscles. The pectoral nerve or pecs block has been likened by some to the TAP block of the abdomen, and the quick uptake by anaesthesia providers has probably been facilitated by the increasing availability of ultrasound machines. In comparison to the thoracic paravertebral blockade, the pecs block has no risk of sympathectomy and a lower risk of intravenous injection and may provide better early pain relief for patients undergoing mastectomy [77].

Two types of pecs block have thus far been described, the imaginatively named pecs I and

pecs II. Pecs I is more superficial and involves administration of local anaesthetic into the interfascial plane between the pectoral major and minor muscles, targeting the lateral and median pectoral nerves. It is useful for subpectoral prosthesis or tissue expander insertion and as an adjunct to paravertebral blockade (PVB) in mastectomy.

A modified pecs block (or pecs II block) involves two-needle approaches. Initially, a pecs I block is performed with local anaesthesia deposition between the pectoral muscles. The modification involves puncture of the pectoral minor muscle and administration of LA into the space between the pectoralis minor and serratus anterior muscle. The targets here include the long thoracic nerve, the thoracodorsal nerve and a variable number of thoracic intercostal nerves. In general, pecs blocks are performed on anaesthetised patients which may lead to increased patient and anaesthesia provider comfort.

16.9.3 Pecs Block Supplementation

16.9.3.1 Serratus Anterior Block

The serratus anterior block is performed to provide analgesia to the lateral thorax. A local anaesthetic agent is injected between the serratus anterior and latissimus dorsi muscles, and the block targets the lateral thoracic intercostal nerves, long thoracic nerve and thoracodorsal nerve. This can be done under direct vision by the surgeon or by using ultrasonography. It can be a useful adjunct to the Pecs blocks and may be particularly useful in procedures involving axillary clearance and reconstructive surgeries.

16.9.3.2 Transversus Thoracic Plane Block

The Pecs block alone is not sufficient to provide analgesia for procedures involving the internal mammary region. In this scenario, supplementation with the transverse thoracic muscle plane block can be useful [78]. Using an ultrasound-guided approach, the local anaesthetic agent is administered in the plane between the transversus thoracic muscle and the internal intercostal muscle where the fourth and the fifth ribs connect to the sternum. The block aims to target the anterior branches of the intercostal nerves from dermatomal level T2 to T6.

16.9.4 Paravertebral Blockade

Paravertebral blockade (PVB) was first described more than a century ago by Hugo Sellheim [79]. Though initially in vogue, use of the technique waned through the mid-twentieth century until it was repopularised by Eason and Wyatt [80]. Paravertebral blocks are relatively easy to learn and perform and are a useful technique for patients undergoing unilateral surgery of the thorax and abdomen. The paravertebral block is possibly still seen as the gold standard for the provision of analgesia for breast surgeries. It is not, however, particularly useful in those patients undergoing day cases due to the potential side effect of hypotension.

The paravertebral block is effectively an ipsilateral spinal nerve block with local anaesthetic agents injected into the potential space adjacent to the relevant thoracic spinal nerve. The spinal nerves within the paravertebral space are without a fascial sheath, making them very susceptible to the effects of local anaesthetic agents. It should be noted that the innervation of the anterior chest wall is not exclusive to thoracic spinal nerves. Sensory innervation is also derived from the brachial plexus via medical and lateral pectoral nerves.

The thoracic paravertebral space (PVS) begins at T1 and extends down caudally to terminate at T12, and it is described as being "wedge-shaped" in all three dimensions [79]. The medial wall is formed by components of the axial skeleton, the vertebrae, intervertebral foramina and intervertebral discs. The posterior border is also formed by skeletal structures: the transverse processes of the vertebrae, the heads of the ribs and the superior costotransverse ligament. Anterio-laterally, the parietal pleura and intercostal membrane complete the PVS borders. Structures contained within the space include spinal nerves, intercostal vessels, fat, the sympathetic chain and white and

grey rami communicantes. Within the paravertebral space, the spinal nerve root divides into ventral and dorsal rami.

Blockade can be performed in both awake and anaesthetised patients. Ultrasonographic [81] and anatomical landmarks can be used to determine the site of insertion and to aid successful needle entry to the PVS. Single shot, multiple entry and infusion catheter placement techniques have all been described.

The thoracic PVS, unlike the lumbar or cervical spaces, allows spread in both cephalad and caudad directions. For simple mastectomy, a single administration of local anaesthetic at the T3/4 level is usually sufficient. For those procedures which are likely to involve more than four dermatomal distributions, multiple injections may be required, and it may be more beneficial to insert a catheter (usually a standard epidural catheter) to facilitate spread. For example, a mastectomy with axiallary dissection will require dermatomal distribution T1–T6 to be covered. If a catheter is to be used, it can be beneficial to "expand" the space with the local anaesthetic agent before attempting to thread a catheter. In comparison to epidural space access, threading a catheter can be more difficult. The catheter should also not be inserted more than 2 cm into the PVS to decrease the risk of epidural or intercostal cannulation. The use of bilateral PVBs for surgical analgesia has been described, but there is limited evidence to suggest that this offers any advantage over thoracic epidural placement [82].

Levobupivacaine and ropivacaine are probably the most commonly used local anaesthetic agents. Unfortunately, there does not seem to be a reliable relationship between the volume of injectate and the subsequent spread throughout the paravertebral space. Local anaesthetic agents introduced into the PVS can spread in both caudal and cranial directions but also into the epidural and intercostal spaces as well as the pre-vertebral plane.

In line with any similar type of regional technique, contraindications include patient refusal, local infection, PVS tumours, a true allergy to local anaesthetic and coagulopathy. Caution should be used in those patients relying on intercostal function for adequate gas exchange (e.g. severe respiratory disease), those who have a diaphragmatic paresis on the contralateral side to proposed surgery site and those with severe spinal deformity. Abnormal anatomy is also likely to increase the risk of failure and complication.

When compared to thoracic epidural placement, PVB is postulated as easier to both learn and perform and can be performed safely in anaesthetised patients with less risk of neurological complication, hypotension and urinary retention [79]. In comparison to opioid-based analgesic techniques, PVB has a lower incidence of nausea, vomiting, sedation and constipation. Hypothetically, this should translate to earlier toleration of enteral feeding and mobilisation. PVB has also been associated with a reduction in the incidence of chronic pain after breast surgery [77].

16.9.5 Thoracic Epidural

A well-placed thoracic epidural will provide analgesia to the chest wall bilaterally. With the re-emergence of PVB and the increasing use of pecs blocks, the use of epidurals for breast surgeries has declined. Thoracic epidurals are not suitable for day-case procedures or a single night stay postoperatively. Whilst there is a suggestion that thoracic epidurals do provide superior analgesia in comparison to other modalities [67], we feel that for even more extensive unilateral surgeries where a pecs block is unsuitable, PVB is probably still the preferred technique over epidural. The drawbacks to thoracic epidural placement are well known and include technical difficulty, hypotension, urinary retention and, more rarely, haematoma and neurological damage.

16.10 Systemic Analgesia

16.10.1 Opioids

Systemic opioid administration has traditionally been the backbone of analgesic regimens for breakthrough pain in the postoperative period,

and short-acting oral agents are commonly prescribed for use outside of the immediate postoperative period. Dosing is usually titrated to the level of patient pain, and, on occasion, patient-controlled devices may be required to provide sufficient intravenous analgesia.

More recently, there has been a trend to prescribing scheduled doses of opioid in the postoperative period where the agent is given to the patient regardless of pain score at the time of administration. There are limitations to this strategy. Opioids are not innocuous agents and have some side effects. Scheduled administration probably has an increased likelihood of side effect incidence without significant analgesic benefit. Scheduled opioid administration has been investigated where the first dose is given in the preoperative period, with a second dose given postoperatively and 12 h after the first dose. The evidence for the analgesic benefits of this strategy is mixed [67, 83, 84].

Concerns around perioperative opioid administration arose from a landmark paper by Exadaktylos et al. in 2006 [85]. This publication suggested that using a paravertebral technique and minimising opioid administration in the perioperative period decreased tumour recurrence. Subsequent in vitro investigation showed that opioids have both pro- and anti-tumour effects at the cellular level [86]. However, ensuing clinical studies have shown no definitive association with opioid administration and tumour recurrence [86–88].

Remifentanil is a short-acting synthetic opioid drug which is metabolised by tissue and plasma esterases. Administration of remifentanil can provide for adequate operative analgesia, rapid control of blood pressure and vasodilation and, in particular, provides excellent conditions for microvascular surgery [61].

16.10.2 Paracetamol and NSAIDs

Paracetamol should be used routinely in the perioperative period unless there is a contraindication. It has a proven safety profile in those patients with peptic ulcer disease and asthma and does not interfere with platelet function. Intravenous administration of paracetamol has been shown to have an opioid-sparing effect [89], and a combination of paracetamol and nonsteroidal anti-inflammatory drug (NSAID) administration probably offers superior analgesia compared to either drug alone [90].

Though NSAIDs have a well-established role in multimodal analgesia regimens, they have not been the focus of many randomised controlled trials specifically examining their analgesic efficacy in relation to breast surgery. There is some evidence to suggest that diclofenac reduces pain and opioid use in the postoperative period [91]. This analgesic effect possibly comes at the risk of an increase in postoperative bleeding. In breast cancer surgery, there have been suggestions that NSAID use in the perioperative period is associated with improved disease-free survival in the long term [92].

Traditionally, there has been a reluctance to administer NSAIDs intraoperatively in flap-based reconstructive procedures. This is due to concerns around perioperative bleeding and haematoma formation [93]. However, it appears that NSAID administration is safe to administer in flap surgeries without an increase in bleeding-related complications [94, 95] and may reduce microvascular thrombosis [96]. In spite of this, NSAID use should probably be discussed with the surgical team before administration.

16.10.3 Systemic Analgesia Adjuncts

Lidocaine is the prototypical amide local anaesthetic, and lidocaine's primary mechanism of action involves sodium channel blockade within neural tissues. The exact mechanism of the systemic analgesic effect associated with intravenous administration is unclear but probably involves an element of sodium channel inhibition, at least in part [97]. The usual dose of intravenous lidocaine required for perioperative analgesia involves an initial bolus of 1–2 mg/kg followed by an infusion of 0.5–3 mg/kg/hour. The most widely used dose range for infusion is 1–2 mg/kg/hour [98].

In contrast to well-documented analgesic benefits for thoracic and abdominal surgeries [99, 100], intravenous lidocaine does not appear to provide a significant contribution to analgesia [101] for breast surgery. As yet, an explanation for the discrepancies in effect on the differing surgical sites is found wanting.

An N-methyl-D-aspartate receptor inhibitor and dissociative anaesthetic, ketamine has been used for analgesic purposes since the 1960s [102]. The perioperative potentiation of opioid analgesia and opioid-sparing effects of ketamine have been well described [103–105].

However, there is an insufficient evidence base to support the specific use of intravenous ketamine in breast surgeries. For instance, a randomised controlled trial evaluating pre-emptive ketamine against the administration at the time of skin closure found no evidence of any pre-emptive effect [106] suggesting that ketamine does not contribute a lasting effect to postoperative analgesia. Given the positive analgesic effects of ketamine administration in procedures not involving the breast [107], it seems probable that ketamine would be of benefit in the breast surgery patient cohort. However, this benefit has not yet been determined using well-controlled in vivo trials, and it may well be the case that intravenous ketamine is similar to intravenous lidocaine, whereby the analgesic effect is surgery site dependent.

Intravenous clonidine in patients undergoing breast cancer surgery decreases postoperative nausea and vomiting (PONV) rates but does not appear to have a significant impact on pain [108]. Should a paravertebral technique be employed for perioperative analgesia, the addition of clonidine (in a dose of 75mcg) to the local anaesthesia injectate can improve analgesia and reduce the postoperative opioid requirement [109].

16.11 Postoperative Care

Initial postoperative care should take place in the recovery room with particular attention to haemodynamic stability and detection of significant bleeding. Modern breast surgical practice places a significant emphasis on the cosmetic result. Surgical incisions tend to be small, and haemostasis can occasionally be difficult. In more extensive procedures, blood loss can be significant and occur over a short period.

Oxygen, intravenous fluids, analgesia and anti-emesis are prescribed on an as-needed basis. With significant comorbidity, extensive surgery or perioperative complication, admission to a high-dependency unit may be warranted.

Early mobilisation and enteral nutrition are important. Aside from aiding in postoperative mobilisation, physiotherapy has a role in preventing potential complications specifically associated with breast cancer surgeries such as shoulder immobility and upper limb oedema.

A balanced, multimodal approach to analgesia is advised and might include systemic opioids, NSAIDs and continuous infusions of local anaesthetic agent.

Where a paravertebral or epidural block has been placed, monitoring of the dermatomal level of the block should be performed at regular intervals. Any catheters delivering local anaesthetic agent should be clearly labelled to avoid erroneous administration of other agents through the same line. Ideally, an acute pain service would provide adequate assessment and support for those with indwelling catheters or patient-controlled analgesia devices.

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Anesthetic Concerns in Endocrine Cancers

17

Rajeshwari Subramaniam

17.1 Introduction

Anesthesiologists concerned with the perioperative care of patients scheduled for major oncological surgery have to address many additional issues compared to patients presenting for major non-oncological surgery. The psychological preparation and counseling of both patients and caregivers are more intense given the anxiety related to outcome, quality of life, etc. The provision of effective analgesia is mandatory, and antiemetic prophylaxis has to be planned well. Vascular port placement may be needed. If the disease in question happens to be a functional endocrine tumor, the perioperative care becomes complex, and the anesthesiologist needs to have a thorough knowledge of the systemic effects of the disease so that patients may be optimized and morbidity related to the endocrine disorder minimized.

17.2 Craniopharyngioma

Craniopharyngiomas are rare non-glial intracranial tumors. They constitute 2–6% of all pediatric intracranial tumors [1]. They are postulated to originate from Rathke's pouch in the pediatric population (adamantinomatous variety). In adults, the origin of papillary craniopharyngiomas is from metaplasia of the existing squamous cell rests.

Multiple classifications have been suggested in the literature. These are based on the site of tumor origin, the relationship between tumor and meninges, or their histopathology. The incidence of craniopharyngioma is 0.13–2 per 100000 population per year [2]. It has a bimodal age of presentation, often seen in children aged 5–14 years and elderly 65–74 years of age [3].

Although histologically benign, their strong tendency for local invasion and recurrence makes them one of the most difficult tumors to deal with. It requires multidisciplinary management including the endocrinologist, the anesthesiologist, and the surgeon.

The insidious onset and slow growth often delay diagnosis until severe symptoms manifest. The presentation varies according to the tumor location, size, growth potential, and local invasion. These include:

- Mass effect – symptoms due to increased intracranial pressure leading to its manifestations like nausea, vomiting, convulsions, and cranial nerve palsy [2]
- Endocrine disturbances – signs of hypopituitarism, hypothyroidism, hypoadrenalism that include growth retardation, short stature, lethargy, obesity, precocious puberty, amenorrhea, impotence, diabetes insipidus, hypotension, cerebral salt-wasting syndrome

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- Behavioral and psychiatric disturbances suggestive of hypothalamic damage by tumor invasion [4]
- Compression of optic nerve causing visual field defects –scotoma, bitemporal hemianopia, homonymous anopsia, papilledema, and optic atrophy
- Thalamus and frontal lobe involvement present with short-term memory deficits, hyperphagia, psychomotor retardation, and emotional disturbances [2]

Medical management of endocrine dysfunction includes hormone supplementation and steroid replacement. It should be started in the preoperative period and continued into the postoperative period. After medical optimization treatment primarily includes surgical resection of the tumor and postoperative radiotherapy (RT) for any residual lesion [5].

Historically gross total resection was the treatment of choice. The surgical approach depends on tumor location, size, and patient age [6].

For large tumors extending out of sella turcica, craniotomy is planned in all age groups. For massive tumors, surgery may be planned in two phases with initial debulking of the tumor followed by craniotomy a few weeks later. If the tumor is small and situated within the sella endoscopic trans-nasal, the trans-sphenoidal [7] approach is preferred in adults to reduce the risk of major bleeding and optic nerve injury as seen with craniotomy (avoided in children due to risk of injury to sinuses, small nares). It may be associated with higher incidences of CSF leaks. A keyhole or minimally invasive supraorbital incision may be used for a lesser risk of CSF leaks and better cosmesis [8].

Significant neurocognitive deficits and hypothalamic injury during gross total resection have recently led to a paradigm shift in the treatment choices [5]. More often a conservative approach with subtotal resections is being done to reduce the morbidity of extensive surgery.

Postoperative external beam radiotherapy (EBRT) is often required after subtotal excision or in tumor recurrences. RT may have major delayed side effects especially in children like hypothalamic damage-causing cognitive dysfunction, altered behavior, hyperphagia, obesity, panhypopituitarism, diabetic insipidus, optic neuropathy, secondary malignancies, and the rarely reported cerebral artery stenosis, further worsening the morbidity. This often makes long-term management difficult.

For tumors with large cystic portions causing significant mass effect, RT can be directed into the cyst cavity, and aspiration of the cystic contents may be done to relieve the obstruction to CSF flow, followed by complete resection a few weeks later [9]. Accidental cyst rupture may cause chemical meningitis. Alternatively, an Ommaya reservoir can be placed intraventricular to drain the cyst fluid and to instill the antineoplastic agent. Intracystic chemotherapy with bleomycin has been tried although no randomized controlled trials or systemic reviews are available to support its use. Due to concerns about its central nervous system toxicity, bleomycin has been largely replaced by interferon-α therapy [5].

Patients presenting with hydrocephalus and raised intracranial pressure may require an emergency ventricular shunt to drain CSF and relieve symptoms.

These patients often require repeated surgeries due to the high recurrence rate and thus present with a multitude of neurological and endocrinological symptoms.

Preoperative workup should include:

- A detailed history of symptoms.
- General physical examination.
- Neurological assessment to identify neurological deficits including cranial nerve involvement and signs suggestive of increased intracranial pressure.
- Airway assessment, especially in children and obese patients.
- Preoperative counseling of patient and family.
- Laboratory investigations including complete hemogram, renal function test, liver function tests, serum electrolytes, coagulation profile, blood typing, and crossmatch. Urine routine/

microscopy and osmolality (if symptoms suggestive of diabetes insipidus).
- Endocrine function assessment including thyroid function tests, an assay of growth hormone, serum cortisol levels, sex hormones, adrenocorticotropic hormone, and prolactin levels should be checked and optimized as necessary.
- Ophthalmological examination for visual field defects and papilledema.
- Detailed endocrinological evaluation as per symptoms.
- MRI with or without contrast (diagnostic method of choice) should be done for screening and staging of the tumor. It helps to plan the surgical approach. If MRI is not available, CECT can be done, which shows a heterogeneous tumor with 90% calcification.
- Volume status should be assessed and dyselectrolytemia should be corrected.

17.2.1 Anesthetic Management

The anesthetic management needs to be individualized as per patient assessment. The key features include:

- Anxious patients should be premedicated, if not having altered sensorium due to raised ICP or a difficult airway.
- Optimize volume status, electrolytes, and endocrine function. Hydrocortisone 0.5–1 mg/kg IV should be given preoperatively. Patients on hormonal therapy and anti-epileptics should continue their medicines as per schedule.
- Such patients manifest diabetes insipidus (DI) postoperatively mostly (70–90%), but some patients may present within the preoperative period (8–35%) [10]. It results in large volumes of dilute urine and consequent dehydration. It should be treated with crystalloid replacement. If severe and refractory to fluid therapy, desmopressin (DDAVP) 0.05 mg may be used twice daily orally. Intranasal or subcutaneous lysine vasopressin (2.5–10 units twice/thrice daily) remains one of the management options and being 20 times more potent than the oral form.
- Although craniopharyngiomas are avascular tumors, they may encase or displace major intracranial blood vessels. So, the risk of bleeding entails the arrangement of adequate blood products. Also, two wide-bore peripheral venous access should be secured before surgery.
- In the operation theater, apart from routine monitoring [pulse oximetry (SpO_2), noninvasive blood pressure (NIBP), electrocardiography (ECG), end-tidal carbon dioxide (E_tCO_2), temperature, urine output], invasive BP monitoring should be used to beat-to-beat measurement of BP. Central venous access may be obtained for fluid management and administration of vasopressors if required.
- Goals of anesthetic technique:
  - Maintenance of cerebral oxygenation and perfusion
  - Optimal operative field with brain relaxation
  - Rapid emergence to enable assessment of the neurological status
- The anesthetic plan includes either intravenous or inhalational induction along with shorter-acting opioids and non-depolarizing neuromuscular blocking agents. Obese patients with a history of features suggestive of obstructive sleep apnea may require a difficult airway cart with the use of airway adjuncts like video laryngoscope or fiberoptic bronchoscope. The airway should be secured with an endotracheal tube and mechanical ventilation instituted to ensure an $EtCO_2$ 32–35 mmHg. For maintenance, avoid using high MAC of inhalational agents as it causes cerebral vasodilatation leading to raised intracranial pressures. Total intravenous anesthesia with propofol and fentanyl infusion would be ideal.
- Measure to reduce intracranial pressures should be ensured to provide a good operative field. These include adequate depth of anesthesia and muscle relaxation, neutral neck position if permitted by the surgical approach, 20–30 degree reverse Trendelenburg tilt, mild

hyperventilation to keep $EtCO_2$ 30–35 mmHg, use of total intravenous anesthesia with propofol in place of the inhalational agent, and mannitol 0.25–1 g/kg slow IV before the opening of the dura.

- The position of the patient depends on the surgical approach chosen. For craniotomy, subfrontal, pterional, transcallosal, transcortical, lamina terminalis, and bifrontal approaches [9] may be used depending upon the tumor location and size. For smaller intrasellar tumors, an endoscopic approach in the supine position with the head flexed to one side and reverse Trendelenburg position is required. A Mayfield frame is used to stabilize the head which can cause intracranial bleed, dural tear, or skull fractures in small children. Hence it invites extreme caution! Local infiltration or scalp block may be given. After proper positioning, eyes and all pressure points must be padded.
- Intraoperative bleeding should be managed with fluids, blood, and blood products. Persistent hypotension despite adequate resuscitation should raise suspicion of hypoadrenalism and warrants steroid replacement. Inj. hydrocortisone 0.5–1 mg/kg IV should be given and continued in the postoperative period for at least 72 h.
- Given the proximity of the lesion to vital neurological structures, surgery can lead to damage to the optic chiasm, thalamus, mammillothalamic tract, and forebrain causing neurological deficits in the postoperative period.
- Temperature homeostasis may be disturbed due to hypothalamic injury. Hence temperature should be closely monitored and hypothermia/hyperthermia prevented.
- The trans-sphenoidal approach may lead to CSF leaks which should be watched for in the postoperative period.

17.2.2 Postoperative Management

Postoperative management remains crucial and the following are the important concerns:

- Diabetes insipidus should be suspected if urine output >4 m/kg/h and treated with fluid replacement and desmopressin. Its incidence is highest in the postoperative period (70–90%).
- Adequate analgesia must be provided with multimodal techniques including opioids, NSAIDs, and scalp blocks.
- Steroid and hormone replacement should be continued for at least 72 h or even later as per need.
- Cerebral edema reduction measures should be continued along with seizure prophylaxis.
- Hypopituitarism and hypothalamic dysfunction should be watched for and managed.
- Postoperatively, certain high-risk patients including major blood loss intraoperatively, suspicion of increased intracranial pressures, and extensive tumor resection should be managed in critical care setup and may require the need for mechanical ventilation.
- Postoperative MRI is done to look for residual lesions and to plan adjuvant RT.
- Long-term endocrinology follow-up is required for the management of hormonal imbalances.

In summary, a dedicated multidisciplinary approach toward the management of craniopharyngiomas is essential for successful postoperative outcomes. This requires in-depth knowledge about the associated endocrinopathies and the perioperative involvement of various brain centers. Preoperative optimization of the hormonal dysfunction and dyselectrolytemia with a high index of suspicion for diabetes insipidus in the postoperative period is key to successful management.

17.3 Adrenocortical Tumors

Adrenocortical carcinoma (ACC) may be secretory (producing cortisol and/or mineralocorticoid and/or androgen) resulting in Cushing's or Conn's syndrome or nonsecretory. It is commonly seen in females of less than 40 years. Overt clinical symptoms, due to hypersecretion of the adrenal hormones, are the most common presentation (nearly 60% of cases). ACC hypersecretion is the etiological factor for Cushing's syndrome in almost 10–15% of cases [11]. About

30% of patients of ACC have symptoms related to mass effect without clinical manifestation related to the secretory tumor. Most ACCs resulting in Cushing's syndrome (80%) are ACTH dependent, the source being the pituitary. Adrenal hyperplasia resulting from excess ACTH from the pituitary is termed Cushing's disease. About 10% result from an ectopic ACTH source, usually small cell Ca of the lung. The remaining 10% are ACTH independent.

Conn's syndrome (primary hyperaldosteronism) is manifested usually from a single adenoma. The excessive ACTS production from the pituitary gland may lead to adrenal hyperplasia, and the condition is labeled as Cushing's disease.

Adrenocortical carcinoma (ACC): The commonest etiology of corticotropin-independent Cushing's syndrome is ACC. The majority (80%) are secondary to elevated ACTH from a pituitary tumor. The remaining small proportion is secondary to ectopic ACTH-producing sites (10%). ACC manifests as "metabolic syndrome," and impaired glucose levels, increased blood pressure, hyperlipidemia, hypercoagulability, and central obesity are the usual manifestations [12]. Other important clinical findings include hirsutism, amenorrhea in females, striae, and bruising [11]. High serum cortisol levels lead to hypercoagulability secondary to hyper-homocysteinemia, increased clotting factors, impaired fibrinolysis, and abnormalities in von Willebrand factor (vWF). These factors mandate a thorough preoperative evaluation to identify any of these abnormalities for optimal perioperative planning and risk stratification [12]. An extensive preoperative cardiac evaluation, including assessment of cardiac risk factors, ECG, and echocardiography, is also required.

Hypercortisolism also has an impact on psychological and cognitive abnormalities. Patients have mood fluctuations, depression, and suicidal thoughts. A preoperative psychiatric evaluation may be needed. About 50% have osteoporosis, and so all patients must be questioned about bone pains/backache to rule out vertebral collapse/fractures which can affect perioperative care [13].

Rarely symptoms escalate over a few weeks, leading to a "cortisol crisis," which requires emergent adrenalectomy as a lifesaving measure [14].

Nearly half of the ACCs are functional. The most common hormone secreted is cortisol followed by androgens, aldosterone, and estrogen. Almost 15% of patients of ACC may have raised more than one hormone, and thus biochemical profiling for serum cortisol, plasma ACTH, 24-h free urinary cortisol, and 1 mg dexamethasone suppression test should be done [15]. Also, the elevation of sex steroids and/or their precursors and mineralocorticoids are indicative of malignancy.

Imaging with MRI/CT is the next step and is necessary to see the precise location, size, metastases, homogeneity, contrast enhancement, and contrast washout [16]. Typically malignant lesions have a slower washout time.

17.3.1 Preoperative Optimization

These patients need optimization of blood pressure and glucose, often on an urgent basis, before surgery. The use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor-blocking (ARB) drugs are effective for symptom control. It is important to withhold ARB dose on the day of surgery to avoid the severe and often refractory hypotension seen in these patients following induction [17], neuraxial blockade, or adrenalectomy, compounded by suppression of the HPA axis due to hypercortisolemia. Electrolyte abnormalities should be corrected. Severe metabolic alkalosis (due to intracellular acidosis and HCO_3^-reabsorption) may lead to compensatory respiratory depression, atelectasis, and hypoxemia [14]. Hypokalemia can increase myocardial irritability and predispose to arrhythmias. Preexisting anemia is not uncommon; also, there is a potential for significant blood loss. Blood and blood products should therefore be typed and crossmatched before surgery. Consideration should be also given for DVT prophylaxis preoperatively. In case neuraxial blockade is planned, pharma-

cological thromboprophylaxis can be initiated following surgery. Vascular access may be difficult due to peripheral edema/easy bruisability of skin [18]. Fungal infections are common in the neck/axillae and should be considered before placing central venous access. Stress doses of steroids should be given intravenously in the perioperative period in patients with hypercortisolism, to reduce postoperative adrenal insufficiency.

17.3.2 Induction and Maintenance of Anesthesia

For IV induction in patients with cortisol excess, etomidate is avoided. Both propofol and thiopental are suitable. Depending on the indication, either non-depolarizing or depolarizing muscle relaxants can be used. In patients with predominant cortisol excess, central obesity and "buffalo hump" may cause difficulty with laryngoscopy, which can be overcome by placing the patient in the "ramped" position employed for bariatric patients.

17.3.3 Monitoring and Ventilator Management

Standard monitoring (SpO_2, ECG, noninvasive blood pressure, and E_tCO_2) is usually sufficient for laparoscopic adrenalectomy. After induction, arterial and central lines may be placed which facilitate hemodynamic monitoring, accurate titration of vasopressor therapy, and blood-gas estimation in sicker patients [18]. Invasive hemodynamic monitoring along with the noninvasive cardiac output is useful for goal-directed fluid therapy in patients with a poor preoperative cardiac reserve and large tumors associated with prolonged surgery and blood loss. Intraoperatively, both hypertension (adrenal dissection and mobilization) and hypotension (blood loss, cortisol withdrawal) may occur. Neuromuscular monitoring is useful to guide blockade, given that hypokalemia can prolong blockade.

Preoperative hypoventilation (secondary to metabolic alkalosis and diminished ventilatory drive) and resulting atelectasis can worsen hypoxemia and/or lung compliance after pneumoperitoneum, which can be managed to some extent by using higher FiO_2 and PEEP. All inhalational agents are suitable. Blood sugar levels need to be monitored at frequent intervals [18]. In the case of complex tumors with extensive vascular involvement, vascular isolation procedures and extracorporeal membrane oxygenation may have to be arranged.

17.3.4 Surgical Approach

The surgical excision of these tumors can be attempted via an open or laparoscopic approach. An open approach remains an acceptable standard modality of the management of these tumors, especially when an infiltrating tumor or suspected lymph nodes (presumably stage III) are present. The laparoscopic approach may be preferred in selected patients based on accessibility and respectability [11]. Although pain intensity in the initial postoperative period with either technique is high, requiring frequent opioids, LA has the advantages of better cosmesis, less pain, and reduced analgesic requirement. Further, pneumoperitoneum worsens the effects of general anesthesia in lung mechanics, such as reduced functional residual capacity, increased intrapulmonary shunts, and increased dead space. This may further increase hypoxemia [18].

17.3.5 Analgesia

The provision of adequate analgesia cannot be overemphasized. After open procedures, the large incision, obese body habitus, preoperative compromised lung function, and edema set the stage for the development of postoperative pneumonia [19]. Preinduction placement of an epidural catheter or a single dose of intrathecal morphine (150–200 μg) may provide superior quality analgesia without respiratory depression [14]. Multimodal analgesia with NSAIDs and paracetamol is useful but not as effective. Early ambulation and provision of postoperative thromboprophylaxis are essential [12, 19]. Parenteral

steroids are administered for up to 72 h, with gradual tapering off onto minimal maintenance oral doses.

17.4 Malignant Adrenal Medullary Tumors: Malignant Pheochromocytomas

The malignant pheochromocytoma is seen in 3–13% of the patients of pheochromocytomas [20]. These patients may have metastases to the lung, lymphatic nodes, muscle, or liver. These tumors have a poor prognosis with a 5-year survival of 44%.

17.4.1 Presentation

Malignant pheochromocytomas present with all features commonly found with the non-benign counterparts. Also, they are significantly larger (more than 10 cm), and the 24-h urinary vanillylmandelic acid (VMA) per unit of the tumor is often low. Hyperglycemia is frequent and may mandate therapy with insulin. The etiology for glucose metabolism alteration is related more to alpha-receptor-mediated insulin inhibition than β-insulin-releasing actions.

17.4.2 Investigations

Preoperative investigations must include an ECG, blood pressure (BP) and heart rate (HR) record, and echocardiography [21]. Laboratory tests should include hematocrit, liver and renal function and baseline electrolytes. Blood sugar status needs to be elucidated.

17.4.3 Preoperative Optimization

The pharmacological optimization for the effect of excess circulating catecholamines is desirable before surgery. Prolonged exposure to catecholamines may result in myocardial ischemia, arrhythmias, or congestive failure (catecholamine cardiomyopathy). These patients have pallor and increased hematocrit due to catecholamine vasoconstriction. A vast majority of patients with malignant pheochromocytomas present with severe hypertension, which needs evaluation and control. The alpha-blockers remain the first drug of choice to control blood pressure. Recently the use of doxazosin, terazosin, and prazosin is preferred as compared to conventional phenoxybenzamine [21]. The newer agents are short-acting and easily titratable to the target hemodynamic status with a lesser risk of hypotensive episodes [21]. Urapidil, a peripheral postsynaptic alpha-1 adrenergic antagonist, has been successfully used for rapid preoperative optimization of patients with pheochromocytomas ([22]). Calcium channel blockers and/or clonidine may be required to optimize blood pressure control in case alpha blockers by themselves are inadequate. Once an appropriate alpha-blockade is achieved, beta-blockers may be added for arrhythmia control [21]. Patients with metastatic pheochromocytoma may also require alpha-methyl-para-tyrosine (MPT, which inhibits catecholamine synthesis). Preoperative institution of selective alpha-adrenergic and subsequent beta-blockade has several advantages (Fig. 17.1).

MPT inhibits catecholamine synthesis. Tumor catecholamine stores are reduced by 50% after pretreatment for 3 days. There is a good correlation between catecholamine release from tumor and perioperative cardiovascular instability. A few patients may have refractory hypertension not controlled by alpha-blockers. The tachycardia and precipitous hypotension/QT prolongation caused by alpha-blockade (especially phenoxybenzamine and phentolamine) may not be well tolerated in patients with coronary artery disease. Similarly, patients with LV dysfunction due to catecholamine cardiomyopathy may not tolerate beta-blockade. In these groups of patients, MPT may be useful for blood pressure control. The dose is 250 mg orally, increased by 250–500 mg/day to reach 1.5–2 g/day for 1–3 weeks in extensive metastatic disease. The use of MPT combined with a-blockade (“com-

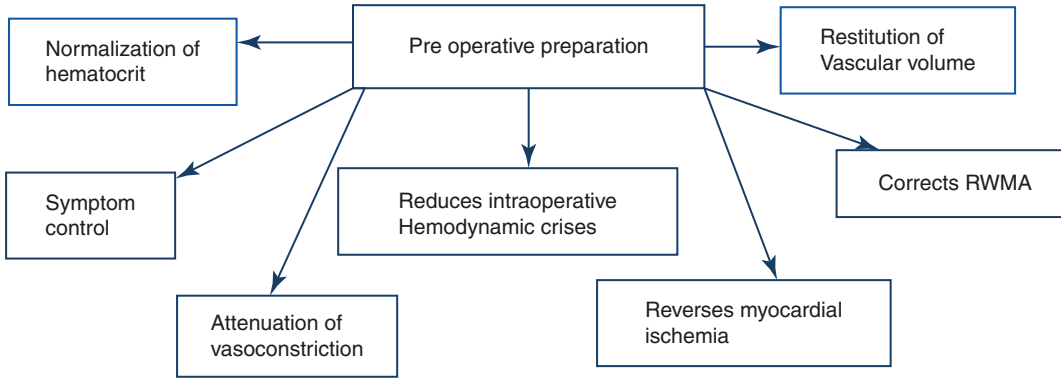

Fig. 17.1 Preoperative institution of selective alpha-adrenergic and subsequent beta-blockade has several advantages

bined medical blockade") is observed to have stable hemodynamics [23]. Diarrhea, crystalluria, galactorrhea, anxiety, and depression are among the many side effects of MPT, frequently leading to poor compliance: rarely extrapyramidal symptoms may need treatment with carbidopa. Appropriate saline hydration (2–3 L) is required in patients who have received alpha-blockers to prevent hypotension post-removal of the tumor. In the face of good hemodynamic monitoring and availability of appropriate drugs for acute intraoperative blood pressure control, the utility of preoperative alpha-blockade has been questioned [24].

17.4.4 Induction and Maintenance of Anesthesia

Probably there is no other surgical condition than pheochromocytoma whose anesthetic management is often described as hazardous and discussed in great detail with a variety of agents; in reality, however, with a better understanding of its pathophysiology, advanced monitoring, availability of a multitude of agents, and anesthetic management are reasonably straightforward.

Propofol and thiopental are both useful for anesthetic induction. Administration of a bolus of magnesium sulfate 30 mg/kg at induction is very effective in preventing blood pressure surges. Vecuronium, due to its cardiovascular stability, is the preferred neuromuscular blocking agent. Fentanyl in doses of 3–5 μg/kg IV attenuates stress response to intubation.

17.4.5 Intraoperative Hypertension

The hypertensive events are observed intraoperatively at various time points like events causing sympathetic stimulation, e.g., laryngoscopy, endotracheal intubation, and orogastric or nasogastric tube insertion. Also, certain drugs have a vagolytic effect; catecholamine secretion, histamine release, or dopamine receptor blockade can induce hypertension. These agents include ketamine, morphine in large doses, atropine, pancuronium, droperidol, metoclopramide, and inhalational agents including halothane and desflurane. Patient positioning or any compression on the abdomen can lead to tumor releases of catecholamines and thus surge in blood pressure. Profound (>10 mm Hg) postural fall in blood pressure after α-blockade, mean arterial pressure (MAP) above 100 mm Hg, symptomatic high blood pressure, high plasma NE concentration, and large tumor size have all been seen to correlate with severe intraoperative hemodynamic instability. The hypertensive episodes are more commonly seen in familial pheochromocytomas. These hypertensive episodes can lead to various cardiac events and thus mandate vigilance. Rhabdomyolysis has been reported as well. Recurrent hypertensive episodes may result in mydriasis.

17.4.6 Management of Hypertensive Crisis

The mainstay is sodium nitroprusside (SNP) infusion which is prepared as a 0.01% solution in 5% dextrose. It is preferably "in-line" and connected to the central venous catheter, to enable small boluses to be rapidly administered during intraoperative hypertensive crises, e.g., in response to tumor handling, pneumoperitoneum, etc. [21, 25]. It brings down the blood pressure rapidly with associated tachycardia. Milder rises in blood pressure can be controlled by boluses of labetalol or 200–500 μg boluses of nitroglycerine. Supraventricular tachycardia can be treated with esmolol 0.5 mg/kg; lidocaine 1–1.5 mg/kg is indicated for ventricular arrhythmia. Nicardipine (5–10 mg/hr) and fenoldopam (0.2 mg/kg/min) are the preferred drugs for patients not responding to conventional drugs. Urapidil infusion (10–15 mg/hr) has also been reported for hemodynamic control during laparoscopic pheochromocytoma excision. More recently, the use of dexmedetomidine (0.3–0.7 μg/kg/min) has been reported [26].

17.4.7 Postoperative Concerns

Pheochromocytoma excision is commonly associated with significant postoperative hypotension due to acute and abrupt catecholamine withdrawal. It is compounded by the residual action of long-acting alpha-blockers, volume loss and inadequate replacement, or relative hypovolemia in the face of vasodilation resulting from catecholamine withdrawal, and "downregulation" of peripheral adrenoceptors. Tumor size >60 mm, urinary norepinephrine levels >600 μg/day, and urinary epinephrine levels >200 μg/day are independent predictors of prolonged hypotension requiring postoperative vasopressor support [26, 27].

After adequate fluid replacement to correct losses, it is advisable to initiate a low-dose norepinephrine infusion which corrects hypotension and allows the adrenoceptors to regain their responsiveness to catecholamines. Hypoglycemia tends to occur and can be severe, resulting in obtundation. It is more common with epinephrine-secreting pheochromocytomas and longer operative times [28].

17.5 Malignant Carcinoid and Carcinoid Syndrome

Carcinoid tumors are uncommon, slow-growing, mostly asymptomatic neuroendocrine tumors of enterochromaffin cells. Despite a benign nature, their similarity to carcinomas gives them their name. The incidence of these tumors is approximately 3.8–5.2/100,000. Carcinoids secrete serotonin, histamine, bradykinin, and other vasoactive peptides that are rapidly metabolized by the liver after their release into the portal circulation. Symptoms are therefore produced by hepatic metastases, and by carcinoids not draining into the liver (bronchial carcinoids), when the vasoactive peptides reach the systemic circulation, producing life-threatening perioperative hemodynamic instability [29].

In 2000, the World Health Organization developed a classical system that recommended "neuroendocrine (NE) tumor" instead of "carcinoid." According to this classification system, these tumors may be grouped into any of three classes based on malignant potential as assessed histologically:

- Well-differentiated NE tumor
- Well-differentiated NE carcinoma
- Poorly differentiated NE carcinoma

The commoner sites of carcinoids are the gastrointestinal (GI) tract (67.5%) and bronchopulmonary system (25.3%). Among the GI tract, the small intestine (40%) is commoner followed by the rectum (27%) and stomach (10%). The symptoms of carcinoid syndrome are due to hepatic metastases occurring from NE tumors in the small intestine. The vasoactive substances released in circulation by the metastatic tumor cells remain the reason for the manifestation of the carcinoid syndrome in 30–50% of the patients [30].

17.5.1 Clinical Features

Carcinoid syndrome manifests with symptoms like flushing, gut hypermotility with diarrhea, wheezing, and shortness of breath. Other findings are abdominal pain (35%) and carcinoid heart disease (30%). Significant diarrhea may result in fluid and electrolyte abnormalities and hypoproteinemia. The classical carcinoid syndrome presents with episodic flushing of the upper torso, head, and neck, diarrhea, and wheezing which is seen in only 10% of patients. Few patients present with abdominal pain and right-sided and left-sided heart disease [29]. Some patients may as a result require parenteral nutrition before major surgery. The release of vasoactive peptides into the portal circulation usually does not lead to classical symptoms of carcinoid syndrome as they are metabolized in the liver. Tumors not draining into the portal vein or liver metastasis that secretes hormones into the hepatic veins allowing them to escape hepatic metabolism and be directly released into the systemic circulation lead to carcinoid syndrome symptoms. Diarrhea, lacrimation, rhinorrhea, and eventually right-sided valvular heart disease are also features of long-standing carcinoid syndrome.

As lungs could metabolize the vasoactive peptides, right-sided carcinoid is seen usually. It manifests with retraction and fixation of the tricuspid valve leaflets caused by fibrous thickening of the endocardium. The severity of symptoms related to the duration of exposure to a high concentration of 5-hydroxytryptamine (5-HT). A high concentration of 5-HIAA (≥300 μmol/24 h) and more than three episodes of flushing are indicative of progress in cardiac disease. The typical finding is a right-sided valvular lesion (commonly regurgitation; occasionally, stenosis). Pulmonary insufficiency and stenosis may also be present. These changes eventually lead to symptomatic right-sided heart failure (fatigue with exertion, edema, hepatomegaly, and low cardiac output). Fibrous tissue growth may distort and interrupt electrical pathways, leading to arrhythmias. Large bronchial carcinoids can produce left-sided heart disease if the tumor output overwhelms the lung's capacity to metabolize these peptides. Still, less than 10% of patients with carcinoid heart disease develop aortic or mitral insufficiency.

A carcinoid crisis related to a sudden and large release of the hormone in the systemic circulation. This may occur during anesthesia administration, tumor manipulation, chemotherapy, hepatic arterial embolization, or radionuclide therapy, mostly in patients with extensive tumor bulk or even spontaneously. Serotonin, bradykinin, histamine, kallikrein, and catecholamines are thought to be the main mediators of carcinoid crises. It is a medical emergency and corrective measures need to be instituted at the earliest.

17.5.2 Investigations

The 24-h urine 5-HIAA (5-hydroxyindoleacetic acid) a serotonin metabolite should be measured in patients who present with flushing and wheezing. It may be used both diagnostically and as an aid to monitoring tumor activity. The test has a sensitivity of 73% and a specificity of 100% for carcinoid tumors. The level of serum chromaffin A, a glycoprotein secreted by neuroendocrine tumor, is also indicative of carcinoid tumors [30, 31].

17.5.3 Preoperative Assessment

A detailed cardiovascular history must be elicited as excessive hormone can lead to pulmonary stenosis or heart failure. The presence of reduced exercise tolerance, orthopnea, paroxysmal dyspnea, and peripheral edema are indicative of carcinoid heart disease. The chest symptoms due to coronary artery spasm may also be observed, especially when flushing episodes occur [30]. These patients should be evaluated with regard to (a) the severity of symptoms (which is usually proportional to tumor burden in terms of metastasis and extent of disease), (b) adequacy of medi-

cal optimization, (c) documentation of known or potential triggering factors, and (d) risk assessment based on cardiovascular compromise. The incidence of cardiac involvement in carcinoids can be as high as 50%. Cardiac investigations should include NT-proBNP measurements, echocardiography, or cardiac magnetic resonance imaging.

Echocardiography is mandatory to delineate RV function and valve morphology and to document the presence of valve abnormalities [30–32]. Pulmonary hypertension, right atrium dilatation, elevated central venous pressures, the severity of tricuspid valve disease, and right ventricular dysfunction are important risk factors seen in these patients. High right-sided cardiac pressures with tricuspid regurgitation and a pulsatile liver may preclude hepatic resection, whereby tricuspid valve repair needs to be done first [30].

17.5.4 Preoperative Optimization

This is aimed at antagonizing or blocking the mediators of carcinoid syndrome and providing symptom relief. Severe diarrhea may lead to dehydration, hypokalemia, hyponatremia, hypochloremia, abdominal pain, and nausea [31].

Somatostatin analogs are the mainstay of treatment and should be readily available during any surgical procedure. Preoperative administration of octreotide (100–200 μg 8 or 12 hourly) is administered in patients at risk of a carcinoid crisis. Recently, telotristat ethyl, an oral tryptophan hydroxylase inhibitor, has shown a significant reduction of symptoms and urinary 5-HIAA in patients with carcinoid syndrome who are not adequately optimized by somatostatin analogs [32].

Patients should ideally be admitted at least 48 h before the scheduled surgery, and fluid and electrolyte status optimized. Octreotide should be initiated at 50–100 μg/h, an additional bolus of 50–100 μg at induction, 20–100 μg boluses intraoperatively, and a 300 μg/h continuous infusion for recurrent symptoms. Anxiolytic premedication is imperative as anxiety can trigger a carcinoid crisis.

17.5.5 Anesthetic Management and Treatment of Intraoperative Carcinoid Crisis

Balanced anesthesia technique is preferred, taking care to avoid light planes. Propofol may produce hypotension; etomidate may not obtund laryngeal reflexes adequately. High-dose opioid anesthesia/TIVA is useful. High serotonin levels are associated with delayed recovery; hence agents with rapid elimination, e.g., desflurane, may be preferable [31].

Invasive hemodynamic monitoring is desirable in these patients [30, 31]. For cardiac procedures and major surgery, TEE is mandated to distinguish between causes of hypotension.

Intraoperatively, agents to be avoided are histamine-releasing drugs (atracurium), long-acting opioids, vasopressors, inotropes, and dexamethasone. Hypercapnia, hyper-/hypotension, and hypothermia can also initiate a crisis. Differentiation between hypotension due to carcinoid crisis and RV dysfunction or CPB-induced vasoplegia (during cardiac surgery) is very important and can be done by TEE examination and by the presence of facial swelling and flushing in carcinoid. It is therefore important to monitor the patient's face [32]. Flushing and bronchospasm are warning signs of the impending crisis. In case of an intraoperative crisis, the volume and electrolyte status should be rapidly optimized. Use of plasma and octreotide (500 μg IV/h), instead of catecholamine vasopressors along with fluid resuscitation, is required [31]. Calcium and catecholamine vasopressor-induced release of mediators from the tumor may worsen the syndrome.

If unresponsive to octreotide, vasopressin, phenylephrine, methylene blue, or calcium may be considered. Right ventricular dysfunction may require dopamine or epinephrine [32].

17.6 Insulinomas

Insulinomas are neuroendocrine tumors and the most common functional neuroendocrine tumors of the pancreas, characterized by insulin hypersecretion. The incidence of insulinomas is 1–4 per million per year [33]. They are usually small (<2 cm), solitary, intrapancreatic, and benign (90% of cases) [34]. These tumors are also associated with hereditary multiple endocrine neoplasias (MEN-1) in 10% of cases [35]. These tumors tend to be multifocal and associated with higher recurrence rates. The duodenal wall is the commonest site for extra-pancreatic insulinomas. The median age of presentation is 47 years with a slight female predominance (1.4:1) [33, 35].

Whipple's triad (described by Whipple and Frantz in 1938) is an important diagnostic tool [34]:

- Recurrent hypoglycemia
- Serum blood glucose levels <50 mg/dl during hypoglycemia
- Immediate relief of symptoms with glucose administration

Patients may present with hypoglycemic symptoms or neuroglycopenic symptoms. Hypoglycemia leads to catecholamine release causing sweating, palpitations, tremor, nausea, vomiting, and anxiety. Neuroglycopenic symptoms include headache, dizziness, blurred vision, diplopia, confusion, and altered sensorium. If severe, it can lead to seizures and coma.

Abnormal weight gain is common due to the overfeeding done to overcome and avoid hypoglycemia. Symptoms are mostly precipitated by fasting or exercise but may also occur without any relation to food. Diagnosis is often delayed due to nonspecific symptomology. Hence, a high index of suspicion and biochemical testing in the form of a supervised 72-h fasting test must be done to confirm the diagnosis. A 72-h fasting test is a gold standard for confirmation of insulinomas [33]. The patient is allowed to drink calorie-free fluids during the 72-h fasting period and physical activity is encouraged. Plasma glucose, insulin, proinsulin, and C-peptide levels are checked every 6 h during a 72-h supervised period of fasting until the plasma glucose level is 60 mg/dl. This interval of testing is reduced to 1–2 h at glucose levels between 45 and 60 mg/dl. The fasting is stopped when the glucose level is less than 45 mg/dl or the patient has signs and symptoms of hypoglycemia. In a patient without insulinoma, serum levels of insulin, C-peptide, and proinsulin are suppressed during fasting. Sulfonylureas can cause hypoglycemia and hence its levels should be measured to rule out as a cause. Due to the better availability of insulin and proinsulin assays nowadays, a 48-h fasting test is also being commonly done with success [35, 36].

Once the diagnosis is confirmed, the localization of the tumor can be done by noninvasive radiological tests like USG, CT, and MRI but with low sensitivities of 9–67%, 16–73%, and 7–45%, respectively [34]. Hence chances of missing a small tumor are often high. Although somatostatin receptor scintigraphy is useful to diagnose many pancreatic neoplasms, it has poor sensitivity to detect insulinomas. Only 30% of insulinomas express somatostatin receptors and bind octreotide [37]. Intraoperative USG with palpation by an experienced surgeon is the best technique for tumor localization with a sensitivity of 75–100% [34, 35, 38].

Treatment includes dietary modification in the form of small, frequent meals to avoid prolonged periods of fasting. Pharmacological management includes drugs like somatostatin analogue octreotide and a benzothiadiazine derivative diazoxide. Octreotide binds to type 2 somatostatin receptor on the insulinoma, to reduce insulin secretion. The dose is 50 μg subcutaneously two to three times daily up to a maximum of 100 μg in 24 h. Side effects include abdominal cramps, gastrointestinal bloating, malabsorption, and cholelithiasis [33].

Diazoxide reduces insulin secretion by alpha-adrenergic-mediated inhibition of beta cells of islets of Langerhans and promotes glycogenolysis by inhibiting cyclic adenosine monophosphate phosphodiesterase. The dose is 150–200 mg in two to three divided doses and titrated to a maximum of 400 mg in 24 h. Nausea, vomiting, edema (due to sodium retention), and hirsutism

are side effects associated with its use [33]. Other drugs like sirolimus, everolimus, phenytoin, prednisolone, calcium channel blockers, and beta-blockers have been used for symptomatic control of hypoglycemia [39].

Surgical enucleation is often curative in small, benign, sporadic tumors. Often a partial pancreatectomy may be planned, which helps preserve some pancreatic function. A more extensive surgical approach is warranted for multifocal, malignant, large tumors and those associated with MEN-1 syndrome. Large (>4 cm), unresectable malignant tumors with diffuse margins and those with metastasis to the liver or lymph nodes are often managed medically along with other modalities. Chemotherapy (with streptozocin, doxorubicin, or 5-fluorouracil), radiofrequency ablation of liver metastasis, EUS-guided alcohol ablation, and embolization of pancreatic tumors can be done in patients who are poor surgical candidates [39]. The drugs rapamycin (sirolimus) and everolimus cause hyperglycemia by inducing hepatic and peripheral resistance to insulin and b-islet cell toxicity [40]. Adverse effects include stomatitis and aphthous ulcers. Their use as first-line medical therapy requires more clinical trials.

17.6.1 Anesthetic Concerns

Apart from routine pre-anesthesia check, a complete neurological examination must be performed. Any previous neurological damage caused due to severe hypoglycemia must be documented. The aim should be to maintain blood glucose above 50 mg/dl throughout the perioperative period. This may require continuous dextrose infusion, especially during preoperative fasting.

Premedication may be considered only if the patients seem very anxious. It may be avoided otherwise as it may mask the symptoms of hypoglycemia. Diazoxide and octreotide are administered on the morning of surgery to reduce insulin secretion during tumor handling. Patients with insulinomas may be obese, with difficult airway and difficult intravenous access. Appropriate preparations should be made for the same.

The surgical procedure may be laparotomy or laparoscopic tumor resection depending on tumor size, location, and surgical expertise. General anesthesia with epidural analgesia provides optimal conditions with adequate postoperative analgesia. Induction agents that reduce cerebral metabolism and oxygen consumption should be preferred (propofol, thiopentone). Propofol is preferred as thiopentone can cause severe hypotension in patients on diazoxide, both being strong peripheral vasodilators [41]. Symptoms of hypoglycemia may be masked under general anesthesia. They may easily be confused with pain and hypovolemia. Hence clinical signs may not be reliable.

Wide fluctuations in blood glucose levels may occur intraoperatively. Point-of-care devices should be used to check blood glucose every 15–30 min, and dextrose infusion must be continued to maintain glucose levels between 50 and 150 mg/dl. An arterial line should be placed for repeated blood sampling for glucose levels. Intraoperative severe hypoglycemia-induced neurological damage may be missed and lead to significant postoperative morbidity. The use of artificial pancreas has been described in the literature, in which a predetermined range of blood glucose is maintained by titrating the insulin and dextrose infusions [42].

Hemodynamic changes associated with pneumoperitoneum can cause significant catecholamine release and lead to a rise in blood glucose levels. The sudden surge in insulin levels and resultant hypoglycemia can occur during tumor handling.

Post-resection, rebound hyperglycemia may occur as insulin levels start to decline as early as within 20 minutes of tumor removal, up to a few hours to days. Hence glucose monitoring should be continued into the postoperative period until the levels stabilize. Insulin infusion may be required to counter the rebound hyperglycemia. Multiple adenomas may be present that may have been missed intraoperatively due to a small size. This can cause persistent hypoglycemia in the postoperative period.

Insulinomas are rare pancreatic neuroendocrine tumors that present with refractory hypo-

glycemia. Drugs like octreotide and diazoxide help in symptomatic management by reducing insulin secretion and preventing severe symptoms associated with hypoglycemia. Intraoperative ultrasound and manual palpation help in better localization of the tumor. With a well-planned surgical resection, recurrence rates in nonmalignant adenomas are very small. Frequent blood glucose monitoring is mandatory in the perioperative period to maintain a safe range of blood glucose.

17.7 Parathyroid Tumors

Two pairs of parathyroid glands situated near the thyroid gland secrete parathyroid hormone (PTH). The main function of PTH is calcium homeostasis in the human body, in close coordination with calcitonin (made in parafollicular cells of the thyroid gland) and vitamin D. Excess PTH increases osteoclast-mediated calcium and phosphate resorption from bone. Up to 99% of calcium stores in the body exists within the bones. Of the remaining 1% free (ionized) extracellular calcium concentration is responsible for all the physiological effects. Normal serum calcium levels are between 8.8 mg/dL (2.1 mmol/L) and 10.4 mg/dL (2.6 mmol/L). Hypercalcemia is defined by levels above 10.4 mg/dL. Hypoalbuminemia and acid-base imbalances affect the total serum levels and may give a false value. Ionized calcium is a better indicator of calcium levels and should be done in such situations. Normal ionized calcium levels are 1.1–1.3 mmol/liter [43].

Hyperparathyroidism can be primary, secondary, or tertiary depending on the cause of excess PTH. Primary hyperparathyroidism is due to excess PTH production in the gland itself mostly due to adenoma, while secondary causes include renal disease, vitamin D deficiency, or low calcium intake which cause hypocalcemia which in turn stimulates PTH production. Prolonged hypocalcemia (often due to renal disease) leading to parathyroid hyperplasia causing excess PTH production constitutes tertiary hyperparathyroidism [44].

Primary hyperparathyroidism (excess PTH) is the third commonest endocrine disorder [45]. Its incidence is highest in postmenopausal women with the average age of diagnosis being 55 years. It is the most common etiology of hypercalcemia in ambulatory patients [46].

Primary hyperparathyroidism is mostly asymptomatic (80%) and is often detected on routine electrolyte assays [45]. Symptomatic patients may present with a myriad of symptoms. A popular pneumonic often used is *painful bones*, *renal stones*, *abdominal groans*, and *psychic moans*. Symptoms may include renal calculi, polyuria, nephrogenic diabetes insipidus, painful osteoporotic bones with pathological fractures, osteitis fibrosa cystica (a rare manifestation in which fibrosis of the bones leads to the formation of cystic brown tumors), proximal skeletal muscle weakness, abdominal pain, constipation, paresthesia, depression, cognitive impairment, and lethargy [47]. As calcium plays an important role in myocardial conduction, patients may present with systemic hypertension, angina, syncope, and palpitations with ECG showing short QT interval due to shortened ST segment. Osborn waves (J waves) may be seen in severe hypercalcemia. It may also mimic an ST-segment elevation myocardial infarction on ECG.

A single parathyroid adenoma is most often the etiology (80–85%). Multiple gland hyperplasia may be present in 10–20% of patients and parathyroid carcinoma is rare (<1%) [46]. Familial syndromes like multiple endocrine neoplasia (MEN) types I and IIa also have parathyroid hyperplasia, and associated anomalies should be looked out for.

A diagnosis of primary hyperparathyroidism is made in the setting of persistent hypercalcemia with elevated or inappropriately normal PTH levels and fractional urinary excretion of Ca >0.02. Ultrasound may show parathyroid gland enlargement. Technitium-99 sestamibi nuclear scan shows increased tracer uptake in parathyroid glands (80–90% sensitivity) [43, 46]. Drug-induced hypercalcemia should be ruled out (lithium, thiazides, vitamin D intoxication, milk-alkali syndrome). Other causes of hypercalcemia like

malignancies, endocrinopathies like thyrotoxicosis, Addison's disease, granulomatous disorders like sarcoidosis, and prolonged immobilization should be looked out for [47, 48].

The extent of medical management depends upon the severity of symptoms, degree of hypercalcemia, and associated comorbidities. Mild and moderate hypercalcemia is often easily manageable with forced saline diuresis, correction of volume status, and bisphosphonate therapy. To prevent fluid overload, loop diuretics (furosemide) which depress the proximal tubular reabsorption of calcium are used, especially in the setting of likely cardiac compromise. They help increase the urinary calcium excretion by 200–250 mEq/day [46]. Diuretics should be used only when the patient is euvolemic. Thiazide diuretics should be avoided as they promote renal tubular reabsorption of calcium. Potassium and magnesium levels should be cautiously monitored. The goal of long-term therapy is to maintain bone mineral density and to prevent osteoclast-induced bone resorption. Drugs used include oral bisphosphonates, raloxifene (a selective estrogen receptor modulator), and cinacalcet (a calcimetric agent that increases the sensitivity of the calcium sarcoplasmic reticulum to extracellular calcium, thereby reducing the production and secretion of PTH) [45].

Hyper parathyroid patients, even if asymptomatic are at risk of continuing bone loss, repeated hypercalcemic crises, renal damage, and a long-term increase in cardiovascular mortality especially in elderly patients. Total parathyroidectomy is the only curative treatment.

17.7.1 Anesthetic Management of Parathyroidectomy

The key points of optimal perioperative anesthetic management include [46]:

1. A careful and detailed history of symptoms and signs should be elicited.
2. Blood investigations should include serum calcium levels (total and ionized), serum albumin, serum magnesium, PTH and calcitonin hormone assay, and vitamin D levels apart from the routine. Any dyselectrolytemia should be corrected.
3. All medical therapy should be reviewed and continued in the preoperative period. Calcium-lowering agents should not be started immediately before surgery as it may lead to severe hypocalcemia in the postoperative period. This is especially true for oral bisphosphonates which take 2–3 days to affect [45].
4. X-ray chest and neck and relevant radiological workup should be done.
5. Documentation of vocal cord movements on indirect laryngoscopy (IDL) must be done preoperatively.
6. Intraoperatively, careful positioning and padding of pressure points must be done because of fragile bones.
7. A thyroidectomy (neck extended) position is required for the surgery, and both hands are kept by the side of the patient. Appropriate intravenous access with extension lines must be secured.
8. Standard monitoring of ECG, NIBP, SpO_2, and temperature should be done.
9. Skeletal muscle weakness warrants the use of neuromuscular monitoring (train-of-four count) for the use of muscle relaxants.
10. A bilateral superficial cervical plexus block can be given to supplement opioid analgesia. NSAIDs should be used only after ruling out renal dysfunction.
11. An intraoperative rapid PTH test may be done to detect any remaining abnormal glands. A decline in PTH levels by more than 50 percent indicates the complete removal of parathyroid glands. A decline of less than 50 percent in PTH level percent warrants bilateral neck exploration to look for other overactive glands [43].
12. Intraoperative recurrent laryngeal nerve injury should be ruled out by a check laryngoscopy during extubation and documentation of bilateral vocal cord movements.
13. Postoperative complications include bleeding and hematoma formation that may cause

sudden respiratory compromise and should be watched carefully. Hypocalcemia can manifest as early as 6–24 h or delayed on postoperative day 3 or 4. Regular monitoring of serum Ca should be done and intravenous or oral supplementation started as per severity [45].

With the advent of newer technology, minimally invasive parathyroidectomies are being performed using gamma-probe localization and video-assisted endoscopes which lead to much smaller scars and minimal dissection. They have comparable surgical success rates and length of hospital stay. The anesthesia concerns are similar to the routine surgical technique.

Hypercalcemic crisis presents with water and sodium loss (natriuresis induced by increased calcium), nausea, vomiting, dehydration, hemodynamic instability, bradyarrhythmias, heart block confusion, agitation, and seizures [47–49]. Calcium levels >3.5 mMol/L (>14 mg/dl) are life-threatening and need immediate management which includes [47–49]:

1. Assess airway, breathing, and circulation and manage appropriately.
2. Fluid resuscitation with 0.9% saline at 75–150 ml/h to achieve a urine output of 200 ml/h. A fluid bolus of 500–1000 ml should be given in the first hour and 2–6 liters over the first 24 h. A 1.6–2.4 mg/dl reduction in the serum calcium may be expected.
3. Bisphosphonates promote osteoclast apoptosis and are highly effective in malignant etiologies. Pamidronate 90 mg or zoledronate 4 mg is used IV as oral bioavailability of these drugs is poor in patients who have significant nausea, vomiting, and anorexia due to hypercalcemia.
4. Calcitonin is an osteoclast inhibitor, given by subcutaneous (SC) or intramuscular (IM) injection – 100 U every 6 h or as an IV infusion in emergencies (10 units/kg over 6 h). A test dose must be given before the full dose as hypersensitivity reactions are common. Tachyphylaxis occurs and can be reduced with co-administration of steroids.
5. Steroids (oral prednisone 40–60 mg once daily or IV hydrocortisone 100–300 mg/day) inhibit calcium absorption from the gut.
6. Phosphate infusion reduces calcium levels effectively within minutes but is associated with deposition of calcium phosphate in the tissues. Thus it should be used only in life-threatening situations.
7. Loop diuretics (furosemide in a dose of 20–40 mg IV given 2–6 hourly) only after euvolemia is achieved, in patients at risk of fluid overload in the setting of cardiovascular compromise. Serum Na, K, Mg, and PO_4 should be monitored.
8. Other anti-osteoclast therapies include gallium nitrate (200 mg/m^2 per day slow IV infusion for 5 days). Mithramycin, a tumoricidal antibiotic, with a narrow therapeutic index, is at present of research value.
9. Hemodialysis should be initiated in refractory cases.

Parathyroid adenomas, occurring alone or as part of MEN syndromes, are associated with hyperparathyroidism with a variety of symptoms involving various organ systems. The key to successful management involves careful preoperative correction of severe hypercalcemia and other dyselectrolytemias and initiation of calcium-lowering therapies. Intraoperative close monitoring for signs and symptoms of hyper- or hypocalcemia and monitoring of electrolytes, acid-base balance, and ECG are essential. Postoperatively hypocalcemia is expected and patients should be started on calcium supplementation.

17.8 Summary

To conclude, a dedicated multidisciplinary approach toward all aspects of endocrine malignancies is essential for the successful management of these tumors. This requires in-depth knowledge about the associated endocrinopathies and the perioperative involvement of various organ systems. Preoperative optimization of hormonal dysfunction, hypertension, catecholamine excess, and dyselectrolytemia with a high index

of suspicion for intraoperative crisis unique to the tumor(s) and focused, monitored postoperative recovery are key to successful management.

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18 Anesthesia for Gynecological and Urological Cancer Surgery

Uma Hariharan and Rakesh Garg

18.1 Introduction

Gynecological and urological cancers are increasing worldwide. Anesthesiologists would be encountering more and more such cases for both elective and emergency surgeries. Neoadjuvant chemotherapy in many such cancers may affect the perioperative course of these patients. Radiation therapy may lead to both difficult airway and surgery, with fibrosis and adhesions with blood loss. Prolonged surgery and anesthesia lead to increased stress and the incidence of perioperative complications. This chapter deals with the anesthetic and perioperative considerations of open gynecological and urological cancer surgeries. The laparoscopic and robotic interventions are discussed elsewhere in this book.

18.2 General Overview of Perianesthetic Management in Urogynecological Cancer Onco-surgery

Urological and gynecological cancer patients may present to the anesthesiologist, either before or after adjuvant chemotherapy and/or radiotherapy. These have important perioperative considerations in the context of organ system dysfunction, fibrosis, immunosuppression, and other toxicities. A thorough pre-anesthetic evaluation, complete systemic examination, airway assessment, organ function tests, and recording of functional capacity are of prime importance. Special investigations may be required, depending on patient comorbidities and surgical considerations. A metastatic workup is essential to decipher the organ system involvement in these cancers. These onco-surgical patients are also prone to deep vein thrombosis (DVT) due to cancer per se, obesity, chemotherapeutic agents, immobility, blood loss, and prolonged surgical times. Major fluid shifts may occur, especially in patients with ascites. Advanced monitoring devices may be required for accurate estimation of intravascular status and for following goal-directed fluid therapy. Blood and blood product availability must be confirmed in the blood bank preoperatively. Since these operations entail large incisions, intra- and postoperative analgesia must be ensured, either by epidural catheter insertion

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(PCEA, patient-controlled epidural analgesia) or by regional/truncal blocks (TAP, transversus abdominis plane blocks) or by systemic agents (PCIA, patient-controlled intravenous analgesia). Pain management remains multimodal for these surgical procedures.

18.3 Urological Cancers

The incidence of urological cancers is increasing worldwide, especially related to increased tobacco usage [1]. They include prostate cancer, renal cancer, bladder cancer, carcinoma of the urethra, and penile cancer. The usual major symptoms [2] include painless hematuria, difficulty in micturition, urinary retention, recurrent urinary tract infections, loss of weight, and fatigue. Delays in diagnosis due to nonspecific symptoms lead to late presentation of cancer and problems associated with advanced disease. Preanesthetic evaluation should be thorough, concentrating on individual organ system function, metastatic workup, baseline functional assessment, airway evaluation, arranging for blood and blood products, and routine preoperative investigations. Lymphovascular invasion can lead to difficulty in surgical resection and blood loss.

18.3.1 Anesthesia for Radical Prostatectomy

Radical prostatectomy is the commonest urological onco-surgery [3]. Nowadays, robotic radical prostatectomy is being done, with improved perioperative outcomes. The treatment options for prostate cancer depend on the stage of presentation. Apart from radical resection, chemotherapy (paclitaxel, docetaxel, mitoxantrone, cyclophosphamide) and radiotherapy can be administered for advanced disease. In metastatic prostate cancer [4], bisphosphonates and hormonal therapy [luteinizing hormone-releasing hormone (LHRH) antagonists and estrogens] are also prescribed. Also, external beam radiotherapy to prostate and pelvic lymph nodes can be administered. Anesthetic considerations start with a thorough preoperative workup for comorbidities, baseline functional assessment, evaluating for local or distant metastasis, and organ system evaluation. Open radical prostatectomy [5] is generally done under standard general anesthesia with endotracheal intubation, combined with a pre-induction epidural catheter insertion. Epidural analgesia leads to reduced anesthetic agent dose, better perioperative analgesia, decreased incidences of thromboembolism, and reduced chances of chronic pain states. This may be avoided in patients with bony metastasis. In recent times, there have been studies that highlight the role of morphine usage in facilitating cancer recurrence [6]. Radical prostatectomy can lead to blood loss which may be difficult to quantitate and can lead to hemodynamic compromise. Blood and blood products must be readily available for transfusion. Opening up of prostatic sinuses can lead to the possibility of air embolism and the spread of tumor cells to the systemic circulation. The main goals are the maintenance of systemic perfusion pressures, adequate oxygenation, normocarbia, and normothermia. Hypothermia and deep vein thrombosis can be a problem in open radical prostatectomies [7], leading to increased patient morbidity and mortality. Early ambulation and perioperative mechanical DVT prophylaxis are recommended.

18.3.2 Anesthesia for Radical Cystectomy

Radical cystectomy with lymph node dissection and bladder reconstruction is the treatment for resectable bladder cancers [8]. Patients can also present for palliative procedures and Bacillus Calmette-Guérin (BCG) injection for advanced bladder cancers. Patients may present late due to nonspecific symptoms. Radical cystectomy is a major surgery with the potential for a reasonable amount of blood loss and prolonged surgery to obtain a tumor-free margin as well as for bladder reconstruction. Standard general anesthesia with endotracheal intubation and pre-induction lumbar epidural catheter insertion is performed. Invasive monitoring in the form of arterial and

central venous catheter insertion is done in indicated cases with coexisting cardiovascular abnormalities. Arterial blood pressure lines can aid in beat-to-beat monitoring and in assessing the blood gas status. Noninvasive cardiac output monitors [9] can be used for monitoring of intravascular status, especially during prolonged surgeries with massive blood loss. Nowadays, these surgeries are done robotically for enhanced postoperative outcomes. Bladder reconstruction or neo-bladder formation is either done open or robotically, by the creation of an ileal conduit or by artificial bladder. Measurement of hourly urine output can be extremely difficult in such surgeries, which can confound fluid therapy. Pain management is achieved with epidural infusions and systemic analgesics. Lymph node dissection reduces future lymphovascular flow, leading to increased chances of lymphedema and DVT in the postoperative period [10]. Mechanical and pharmacologic prophylaxis against DVT may be recommended in open radical cystectomies. Nowadays, robotic radical cystectomies are widely performed, with reduced incidences of these complications.

18.3.3 Anesthesia for Radical Nephrectomy

Surgery for renal cell carcinoma (RCC) depends on the stage of presentation and metastasis. Surgical resection may or may not be combined with ipsilateral adrenalectomy and extended lymphadenectomy. Radical nephrectomy [11] is a major operation, which can be done either by an open, laparoscopic approach or robotically. In stage T1 tumors (less than 7 cm in size) with a solitary kidney or renal dysfunction or hereditary tumors, the nephron-sparing procedure can be advocated instead of radical procedures. Nephron-sparing surgery (NSS) [12] can again be done either by an open, laparoscopic approach or robotically. Robotic NSS has gained wide acceptance, with improved perioperative outcomes, especially in patients with comorbidities. In some localized RCCs, minimally invasive therapy is sometimes given, in the form of cryotherapy, radiofrequency ablation, and high-intensity focused ultrasound (HIFU) therapy [13]. For advanced renal tumors or margin-positive cancers, radical surgery is combined with adjuvant radiotherapy, chemotherapy, and active surveillance. All these procedures have important implications for the attending anesthesiologist. Radiation therapy [14] can lead to loss of surgical planes for dissection, difficulty in surgical access, increased blood loss, prolonged operative times, and greater chances of transfusion with its associated risks. Metastatic tumors that are resectable may be subjected to cytoreductive nephrectomy, minimally invasive therapy for solitary metastases, and palliative therapy for distant metastases (bone). Anesthesiologists may be involved in the care of these patients at any stage of their treatment: diagnostic procedures, definitive resection, cytoreduction, insertion of chemo-port, monitored anesthesia care, and pain management and palliative care.

Open radical nephrectomy (RN) is a major surgery with the possibility of blood loss, prolonged anesthetic agent exposure, hypothermia, and renal dysfunction. Pre-induction incision congruent epidural catheter insertion [15] can be done for perioperative pain management as well as for reducing intraoperative anesthetic agent requirement. PCEA can be instituted in the postoperative period for excellent pain relief, which is important for early recovery. Anesthetic agents which do not depend on the kidney for excretion or which are not known to cause nephrotoxicity can be employed. Atracurium or cisatracurium (non-depolarizing muscle relaxant undergoing Hofmann elimination) is generally preferred in these patients. Nephrotoxic agents like nonsteroidal anti-inflammatory drugs (NSAIDs) and aminoglycoside antibiotics are avoided [16]. In patients with concurrent cardiorespiratory involvement, invasive monitoring of the arterial blood pressure is warranted. An ultrasound-guided central venous catheter insertion can be considered not only for monitoring the central venous pressure but also for infusing fluids and drugs. There are a variety of noninvasive cardiac output monitors available for use in high-risk cardiac cases, to guide fluid therapy and

hemodynamic management. If RN is combined with adrenalectomy, there are more chances of intraoperative fluctuations in blood pressure, and stress doses of steroids (both mineralo- and glucocorticoid cover) need to be administered in the perioperative period according to standard protocols [17]. Complete asepsis must be practiced for all procedures to prevent the occurrence of nosocomial infections. The concurrent use of systemic opioids, steroid supplementation, prolonged anesthesia time, and blood transfusions cause immunosuppression, which can be deleterious in renal cancer patients.

18.3.4 Anesthesia for Carcinoma Urethra

Urothelial tumors are rare and may present late. Early cancerous lesions of the distal urethra are managed with endoscopic or minimally invasive procedures, along with radiation therapy and chemotherapy. Radiation therapy before surgery can lead to difficult dissection, increased operative times, and blood loss. Chemotherapeutic agents can affect various organ systems, including immunosuppression, cardiomyopathies, nephrotoxicity, hepatic dysfunction, and neurotoxicity. A thorough preoperative evaluation and knowledge of the extent of surgery are mandatory for a successful perioperative outcome. Surgery for carcinoma of urethra [18] can be localized excision, partial or total penectomy, anterior exenteration (in females with invasive cancers), pelvic lymphadenectomy, and radical cysto-urethrectomy. The literature describes four modalities of surgical management in male urethral cancer: [1] conservative therapy or local excision, [2] partial penectomy, [3] radical penectomy, and [4] pelvic lymphadenectomy and en bloc resection including penectomy and cystoprostatectomy with the removal of the anterior pubis. Endoscopic laser excision (Nd:Yag laser, CO2 laser, or Holmium:YAG laser) of the tumor may be done in the early stages, which can be performed either under regional anesthesia (spinal or combined spinal-epidural block) or under standard general anesthesia. All precautions about anesthesia for laser surgeries [19] must be taken, especially gearing up operation theatre preparedness to tackle airway fires or endotracheal tube damage due to laser energy. Such interventions are fraught with the possibility of causing urethral stricture, and these patients can present for repeated urethral dilatations. They can also present to the anesthesiologist for cystoscopies and biopsies, both before and after surgical resection. If radical surgery is performed, it needs to be followed up with reconstructive surgeries, both for cosmesis and for creating urinary passage. Urinary diversion procedures can be time-consuming, and measures to preserve microvascular circulation in the graft can be beneficial. It is difficult to accurately measure the hourly urine output in such situations, and fluid management must follow goal-directed therapy [20]. Special attention must be paid to maintaining normothermia, as the hypothermia can set in easily in such prolonged surgeries, leading to a multitude of adverse effects. Pain management is generally multimodal, with patient-controlled epidural analgesia (PCEA infusion with local anesthetics and opioids) for continued postoperative pain relief.

18.3.5 Anesthesia for Testicular Cancer Surgery

Radical inguinal orchidectomy [21] (removal of testicle and spermatic cord) is the surgical treatment of testicular cancer. Treatment depends on the type and stage of cancer. Tumor markers include high AFP (alpha-fetoprotein) and serum beta-HCG (human chorionic gonadotropin) levels. For locally advanced seminomas (germ cell tumors), radiation therapy to the para-aortic lymph nodes and/or chemotherapy (carboplatin analogs) can be instituted after surgery. For non-seminomatous testicular cancers, retroperitoneal lymph node dissection (RPLND) [22] is done in addition to radical inguinal orchidectomy (RIO). Germ cell tumors are highly sensitive to chemotherapy [most commonly BEP (bleomycin, etoposide, cisplatin) or VIP (etoposide, ifosfamide, cisplatin) regime]. RPLND is a complex opera-

tion requiring considerable skill to remove all appropriate lymph nodes and to minimize side effects of the surgery (like erectile dysfunction, infertility, intestinal obstruction, infection, chylous ascites, and lymphedema). Nowadays, this surgery is done either laparoscopically or robotically. External beam radiation can also be given for irradiating lymph nodes, especially for pure seminomas. Chemotherapy is the treatment of choice in metastatic testicular cancers and radiotherapy for brain metastases. Recurrent testicular cancers are treated by high-dose chemotherapy with stem cell transplantation. Fertility issues [23], including sperm banking, must be considered before any treatment for testicular cancers.

Anesthetic considerations for RIO include thorough pre-anesthetic checkup; pre-induction lumbar epidural catheter insertion; invasive monitoring in indicated and high-risk cases; arranging blood and blood products; considerations for chemotherapy-related side effects on various organ systems; metastatic workup; DVT prophylaxis, especially in cases with lymph node dissection; and vigilant postoperative care. Anesthesia for RPLND is by standard general anesthesia with cuffed endotracheal intubation and mechanical ventilation. This procedure can be prolonged, especially in cases with previous radiation therapy, leading to blood loss and prolonged anesthesia exposure. Nowadays, nerve-sparing RPLND is performed to safeguard the *nervi erigentes* to preserve sexual functions [24]. Robotic RPLND is also being done in several centers with good results. Pain management can be accomplished by ultrasound-guided TAP block (bilateral), by epidural infusions, or patient-controlled epidural infusions (PCEA).

18.3.6 Anesthesia for Cancer of the Penis/Vulva

Approximately 95% of penile and vulvar cancers are squamous cell carcinomas. They are infrequent in the developed world. Both penile and vulvar cancers are associated with HPV (human papilloma virus) infection [25], and both are more common in patients with HIV (human immunodeficiency virus) infection. These are lymphophilic tumors, and lymph node involvement is the most important predictor of prognosis. Penectomy/vulvectomy with lymph node dissection is the standard treatment for invasive cancers. Some may require adjuvant radiotherapy and/or chemotherapy. These surgeries may cause a severe emotional impact on the patient and may require preoperative psychological counseling. Urethral reconstruction for facilitating micturition is warranted and may be time-consuming, requiring multistage operations. Nowadays, robotic VEIL (video endoscopic inguinal lymphadenectomy) [26] is performed for invasive penile/vulvar cancers. These patients are prone to lymphedemas, venous thrombosis/thrombophlebitis, and limb cellulitis in the postoperative period. Anesthesia for open surgery of carcinoma of the penis/vulva can be performed either under combined spinal-epidural anesthesia or under standard general anesthesia with endotracheal intubation and mechanical ventilation. Thorough pre-anesthetic assessment, perioperative standard and invasive monitoring, temperature regulation, maintenance of intravascular volumes, and adequate postoperative pain relief with DVT prophylaxis are vital for a successful patient outcome. Viral marker evaluation is mandatory in all cases.

18.4 Gynecological Cancers

Malignancy affecting the female genital tract is increasing in incidence, with probable association with smoking, alcohol consumption, genetic predisposition, human papillomavirus (HPV) infection, and hormone therapies [27]. The major issues with gynecological cancers include difficult surgical access for pelvic malignancy; late presentation due to nonspecific clinical features; the possibility of involvement of adjacent abdominal/pelvic organs; and infiltration of neurovascular bundles and adherent lymph nodes. The major gynecological cancers include cervical cancer, endometrial cancer, ovarian cancer, cancer of the fallopian tube, and vulvar/vaginal cancer. There is an increased propensity to develop DVT [28] in these patients due to a multifactorial etiol-

ogy, including the release of procoagulant tissue factor from tumor cells; compression of pelvic vessels by the tumor mass; immobilization; repeated venous cannulation, especially insertion of a central venous catheter; chemotherapy and radiotherapy; erythropoietin-stimulating agent therapy; and prolonged surgical time, especially with lymph node dissection. In this regard, thromboprophylaxis must be considered in every case, starting preoperatively and continuing into the postoperative period. Also, mechanical thromboprophylactic devices and early mobilization must be encouraged. Adequate pain management, especially with regional blocks, and the adoption of minimally invasive surgical techniques are particularly beneficial. Obesity [29] is one of the major risk factors for gynecological malignancy. Apart from difficult airway considerations, obese patients require special mattresses, operating theater tables, armrests, transfer sheets, and blood pressure cuffs. Thermoregulation is also a major concern in these surgeries, which requires external warming devices, fluid warmers, and continuous temperature monitoring devices.

18.4.1 Anesthesia for Surgery of Carcinoma of the Cervix

Cervical cancer is the second commonest cancer [30] worldwide. The majority are squamous cell carcinomas. Preoperative investigations must focus on baseline patient status, organ system evaluation, airway and spine assessment, and metastatic workup. Local cancer spread is to the vaginal mucosa, myometrium, paracervical lymph nodes, bladder, and rectum. The hematogenous spread can be to the liver, lungs, and bones. Early disease can be managed by simple hysterectomy. Most patients require a radical hysterectomy, entailing the removal of the uterus, vagina, uterosacral and uterovesical ligaments, and parametrium, and pelvic node dissection. With the advent of minimal access surgery, most radical hysterectomies are performed by robotic surgery. Open radical hysterectomy [31] generally requires standard general anesthesia with cuffed endotracheal intubation and controlled mechanical ventilation. Pre-induction lumbar epidural catheter insertion for perioperative pain management goes a long way in reducing intraoperative anesthetic requirements and prevention chronic pain syndromes. Blood and blood products should be arranged beforehand. If the cervix has been irradiated preoperatively, there is a possibility of difficult dissection and blood loss. Some patients with precancerous cervical lesions can be operated upon under regional anesthesia. In advanced cancers with late presentations, the patients may present with painful pyometra or hematometra, due to cervical drainage obstruction by tumor growth. Broad-spectrum antibiotics with anaerobic cover must be administered preoperatively, along with fluid resuscitation, maintaining urine output, and postoperative intensive monitoring in HDU (high-dependency unit).

18.4.2 Anesthesia for Endometrial Cancer

Carcinoma of the endometrium is the commonest cancer of the female genital tract in the developed world. Patients may present for a multitude of operative procedures [32], including diagnostic hysteroscopy and biopsy; staging surgeries; or definitive resections; or palliative procedures. Adenocarcinomas are the commonest endometrial cancers. Spread can be local, tubal (peritoneal), lymphatic, and by bloodstream (lungs, liver, brain, and bone). Definitive surgery consists of total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. In centers where facilities exist, these surgeries are performed robotically, with improved postoperative outcomes. Open radical surgery for uterine cancer is a major procedure with the possibility of blood loss, prolonged operative time, and damage to surrounding structures during tumor mopping/pelvic dissection. Invasive monitoring can be instituted in high-risk cardiac cases. The pre-induction lumbar epidural can be instituted for adequate pain relief. Adjuvant chemo-/radiotherapy also has concurrent anesthetic implications. Metastatic and inoperable cases can present for palliative procedures. Complete pre-anesthetic

evaluation, including metastatic workup, must be performed, before regional or general anesthesia or monitored anesthesia care (*MAC*).

18.4.3 Anesthesia for Ovarian Cancer

Ovarian cancer is the fifth commonest cancer among females in Europe. It has the poorest prognosis among gynecological cancers mainly due to late presentation and peritoneal carcinomatosis. The four major cell types of origin of ovarian cancer [33] include surface epithelium (carcinomas), germ cell tumors, stromal tumors, and primary peritoneal carcinomatosis. Management depends on the stage of presentation, with a recent focus on the side of curative rather than palliative approach. Surgical treatment is the backbone consisting of staging laparotomy, hysterectomy with bilateral salpingo-oophorectomy, peritoneal/pelvic biopsies with the search for metastatic deposits, lymphadenectomy, peritonectomy, omentectomy, and tumor debulking. In cases with extensive spread to other abdominal and pelvic organs, a greater extent of cytoreductive surgery may be required. These include splenectomy, appendicectomy, cholecystectomy, bowel resection anastomosis, colectomy with stoma formation, and partial liver resections. The ultimate aim is to remove as much tumor and cancerous deposits as possible, within acceptable patient safety limits. Some patients may present for interval debulking [34], defined as the cytoreductive surgery performed after a short course of induction chemotherapy (2–3 cycles). With the increasing incidence of ovarian cancer in the reproductive age group, fertility issues and the possibility of ovum preservation for future use have to be discussed preoperatively. Radiotherapy, though rarely given in ovarian cancer, may be helpful for metastasis.

Ovarian laparotomy is a major surgery, which entails extensive resections, blood loss, increased surgical and anesthesia time, massive fluid shifts, and organ system affliction. The main perioperative concerns [35] include the anesthetic implications of neoadjuvant chemotherapy; evaluation of organ system involvement by malignancy or metastasis; management of problems due to ascites; deep vein thrombosis prophylaxis; and adequate pain management protocols. Advanced ovarian cancer with ascites mandates goal-directed therapy for cytoreductive surgery, with individually tailored perioperative fluid management, guided by the use of cardiac output monitoring devices. Preservation of end-organ perfusion along with stroke volume optimization can go a long way in improving overall outcomes. Invasive monitoring, especially arterial line, is advantageous in such surgeries for beat-to-beat monitoring and repeated arterial blood gas analysis. A pre-induction thoracic epidural catheter is recommended to reduce the stress of anesthesia and surgery as well as continued postoperative pain relief. Sudden hemodynamic decompensation which can occur during ascitic fluid drainage can be minimized by adequate fluid therapy and slow surgical drainage/suctioning. Patients with massive ascites need to be intubated using rapid sequence induction with cricoid pressure (after adequate pre-oxygenation), due to increased chances of aspiration and oxygen desaturation (reduced functional residual capacity). Inspired oxygen fraction may need to be limited in patients who have received chemotherapy with bleomycin [36] analogs. Some patients may have concurrent pleural effusions, which may require preoperative pleural tapping, to improve perioperative respiratory mechanics. Those patients who are on preoperative diuretics for ascites may have preexisting electrolyte derangements, which need to be corrected before induction. Preoperative liver dysfunction may occur due to liver deposits or severe ascites. A pre-induction thoracic epidural catheter must be inserted under local anesthesia for perioperative stress reduction and pain relief. Two large-bore intravenous lines and central venous access are required, as there are both fluid and blood loss in ovarian laparotomies. Ultrasound guidance can be utilized for securing invasive lines. Active external and internal warming measures must be utilized. An hourly urine output of at least 0.5–1 ml/Kg/hour should be maintained. The estimation of blood loss can be confounded by mixing with ascitic fluid and serous fluid. Metabolic and electrolyte derange-

ments are common in such extensive surgeries, warranting frequent arterial blood gas analysis and instituting corrective measures. In recent times, serum lactate levels have been utilized as an indicator of tissue perfusion and metabolic acidosis. Special attention must be paid toward complete asepsis during all procedures as these patients are immunosuppressed due to cancer and concurrent chemotherapy. Coexisting diabetes may lead to vitiation of glycemic control, requiring intravenous insulin infusion and hourly blood sugar charting.

Hyperthermic intraperitoneal chemotherapy (HIPEC) [37] is being practiced in major cancer centers and has been discussed in detail in other chapter. HIPEC entails filling the peritoneal cavity with a high-dose, heated chemotherapeutic solution, resulting in a large and direct exposure of malignant cells to chemotherapeutic agents. When HIPEC is combined with cytoreductive surgery, it has produced better results than the use of intravenous chemotherapy. Anesthesia considerations are mainly related to alterations in thermoregulation, coagulation disturbances, hemodynamic abnormalities, and respiratory gas exchange perturbations. Hyperdynamic circulation sets in due to thermal stress. Coagulopathy occurs due to dilution of platelets and coagulation factors by large-volume fluid infusions. Also, there are protein loss (leading to increased free fraction of protein-bound drugs), increased intra-abdominal pressures (leading to increased airway pressures, reduced renal perfusion, reduced functional residual volume (FRC), and greater propensity to cause abdominal compartment syndrome), increased basal metabolic rate, and exposure of the body to extremes of temperature. The resultant increase in end-tidal CO_2 causes a fall in systemic vascular resistance and peripheral vasodilation. It is recommended to keep the core temperatures between 35 and 36 °C before starting hyperthermic chemotherapy to maintain core temperatures below 38 °C during the procedure. All patient and fluid warmers should be turned off before starting HIPEC. The ultimate goal is to maintain normothermia, normoxia, normotension, and normocarbia. It is imperative to ensure adequate intravenous fluid hydration as well as good urine output during the procedure.

Postoperative care of patients undergoing ovarian laparotomies [38] can be quite challenging. Some patients may require vasopressor infusions to support their circulation. Hemodynamic instability and respiratory gas exchange derangement may necessitate continued postoperative mechanical ventilation till stability is achieved. Pain management, thromboprophylaxis, vigilant monitoring, and PONV (postoperative nausea vomiting) prophylaxis are the cornerstones of improved outcomes. PCEA (patient-controlled epidural analgesia) is preferred, which has multiple patient benefits. In patients with coagulopathies or on systemic anticoagulation, PCIA (patient-controlled intravenous analgesia with opioids) or ultrasound-guided bilateral TAP (transversus abdominis plane) block can be administered, along with a multimodal pain management protocol. Perioperative epidural analgesia has been shown to reduce tumor recurrence after ovarian cancer surgery. The summary of the major concerns related to urological and gynecological onco-surgeries is based on the site of surgery and associated comorbidities (Table 18.1).

18.5 Future Prospects

With tremendous research focusing on cancer worldwide, anesthesiologists caring for onco-surgical patients are not far behind in their contribution toward the global cancer control program. Open surgery for urological and gynecological cancers is still considered for complete tumor excision, especially in developing countries. Open radical surgeries are dwindling with the advent of minimally invasive cancer surgeries. The future lies in the era of robotic onco-surgery, facilitated by the da Vinci robotic system. Nevertheless, open onco-surgeries have not lost their importance and may still be required in difficult cases. There should be close liaison between the anesthesiologist, urologist, gynecologist, plastic surgeon, intensivist, nutritionist, oncologist, psychologist, and physiotherapist for a successful perioperative outcome in these

Table 18.1 Perioperative anesthetic concerns in urological and gynecological onco-surgeries

S. no.	Surgery	Position	Anesthesia technique	Special monitoring	Specific concerns	Special observations in perioperative period
1.	Radical prostatectomy	Lithotomy and supine	Standard general anesthesia (GA) with pre-induction lumbar epidural	Blood loss; serum electrolytes; temperature monitoring	Venous embolism; thromboprophylaxis recommended	Prolonged surgery; elderly patient; vertebral metastasis
2.	Radical cystectomy with bladder reconstruction	Supine; Trendelenburg	Standard GA with pre-induction lumbar epidural	Blood loss; estimation of urine output difficult	Difficult dissection and bowel handling for neo-bladder formation; deep vein thrombosis	Extensive and prolonged surgery; risks of blood loss and transfusion risks
3.	Radical penectomy/ vulvectomy	Supine	Regional anesthesia (CSEA) or standard GA	Blood loss; sexual function loss; urethral reconstruction	Urinary diversion; prolonged procedure; previous radiation therapy	Adequate pain management; difficulty in attaining tumor-free margins
4.	Radical hysterectomy	Supine and lithotomy	Standard GA with pre-induction lumbar epidural	Blood loss; deep vein thrombosis	Previous radiotherapy causing difficult dissection and metastasis causing prolonged procedures	Risks of blood transfusion; positioning concerns
5.	Radical lymph node dissection	Supine, limb abduction	Regional anesthesia (CSEA) or standard GA	Redo surgeries, difficult dissection	Risk of neurovascular injury; sexual dysfunction	Lymphedema and its attendant complications
6.	Radical orchidectomy	Supine	Standard GA with pre-induction lumbar epidural	Blood loss, fertility issues; previous radio- and/or chemotherapy-induced changes	Blood loss; vagal stimulation	May be combined with retroperitoneal lymph node dissection
7.	Radical nephrectomy	Lateral	Standard GA with pre-induction thoracic epidural	Blood loss; renal dysfunction; adjuvant radiotherapy effects	Positioning issues; early vascular tumor invasion	Avoid nephrotoxic drugs

surgeries. The use of cell savers and blood transfusion-limiting agents must be investigated further in onco-surgery [39]. Adequate pain management (multimodal therapy, nerve blocks, and patient-controlled analgesia) is the cornerstone for reducing anesthetic requirements and prevention of chronic pain. In recent times, there has been concern regarding systemic opioid use causing cancer recurrence or progression [40]. Further research is required in this gray zone, and consensus guidelines need to be developed for pain management in onco-anesthesia.

18.6 Summary

Anesthesia for open urological and gynecological surgeries can be quite challenging, especially in advanced cancers and patients with comorbidities and metastases. A thorough pre-anesthetic evaluation, assessing all organ systems is pivotal. The effects of concurrent chemotherapy and radiation therapy must be kept in mind while anesthetizing such patients. Radical surgery entails blood loss and hence blood/blood products must be arranged beforehand. Antibiotic, DVT, and PONV prophylaxis are mandatory in all cases. Prevention of pressure sores and peripheral neuropathies due to prolonged surgical positioning must be given special attention. Cancer patients may have pre-existing myopathy or neuropathy, secondary to previous chemo- and/or radiotherapy. Pain relief must be given a phenomenal importance, especially in the era of ultrasound-guided regional blocks. Anesthesiologists need to gear up for the challenges placed by various radical cancer surgeries and reconstructive procedures, whether open or minimally invasive.

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Anesthesia for Mediastinal Tumors

19

Ravinder Kumar Pandey, Dalim Kumar Baidya, and Ankur Sharma

19.1 Introduction

The mediastinal masses are increasingly being recognized and scheduled for surgical excision. The perioperative care of these patients poses many challenges to the anesthesiologists. These are related to many concerns including the site of a mediastinal mass, relation to adjoining structures, airway management, perioperative analgesia, etc.

The mediastinum is bounded by important structures. Its superior boundary is formed by the thoracic inlet, inferior boundary is formed by the transverse thoracic plane, lateral boundary is formed by the pleura, anterior boundary is formed by posterior surface of the manubrium sternii and posterior boundary by T1-T4 thoracic vertebra [1]. A hypothetical plane made by the line from the sternal angle anteriorly to the lower border of the fourth thoracic vertebra divides the mediastinum into the superior mediastinum and inferior mediastinum. The inferior mediastinumis divided in to three parts: (Table 19.1) [2].

Anterior mediastinum—It extends from posterior surface of the lower sternum to the anterior surface of the pericardium and great vessels, it lies between pleural cavities and extend from thoracic inlet to the diaphragm.

Middle mediastinum—It lies between the anterior mediastinum and the anterior border of the vertebral bodies.

Posterior mediastinum—It lies posterior to the middle mediastinum.

19.2 Overview of Concerns for Mediastinal Tumors

Perioperative management of mediastinal masses has peculiar concerns for perioperative management [3]. The mediastinal masses for surgical intervention may have substantial morbidity and mortality because of the vicinity of vital structures around [4]. The collapse of these mediastinal masses on the trachea, chambers of heart, pulmonary veins, or the superior vena cava could have disastrous cardiovascular and pulmonary outcomes [5]. Primarily prevention of such complications and hence appropriate planning remain paramount. Its early recognition and management are equally important. This requires understanding the anatomical relation and planning of perioperative care accordingly. The collapse of the endobronchial tree is the most dreaded complication, especially when the point

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Table 19.1 Division of the mediastinum, its boundaries, and contents

Mediastinum divisions		Boundaries	Contents
Superior mediastinum		Extend superiorly by thoracic inlet, inferiorly transverse thoracic plane, laterally by pleura, anteriorly by the posterior surface of manubrium sterni, and posteriorly by T1-T4 thoracic vertebra	Thymus, trachea, esophagus • Arteries: aortic arch, brachiocephalic trunk, left common carotid artery, left subclavian artery, superior vena cava, brachiocephalic veins, the arch of the azygos, thoracic duct
Inferior mediastinum	Anterior	From the posterior surface of the lower sternum to the anterior surface of pericardium and great vessels, lies between pleural cavities, extend from thoracic inlet to the diaphragm	Thymus, trachea, esophagus, large veins, large arteries, thoracic duct, sympathetic trunk, lymph nodes, ectopic thyroid gland, and parathyroid tissues
	Middle	Between the anterior mediastinum and the anterior border of the vertebral bodies	Heart and pericardium, great vessels, vagus, and phrenic nerves
	Posterior	Posterior to the middle mediastinum	Intercostal nerves, thoracic spinal ganglion, and sympathetic chain

of tracheobronchial compression or collapse is distal to the tip of the endotracheal tube [6]. Thorough preparation can decrease the risk of significant perioperative complications and postoperative morbidity [7].

19.3 Evaluation of the Patient

The patient should be thoroughly assessed including history, signs, symptoms, clinical examination, biochemical parameters, and relevant imaging. Special tests may be required based on the initial assessment outcome.

Signs and Symptoms The signs and symptoms related to mediastinal mass lesions vary according to size and nature of the lesion. It can remain asymptomatic as well and is an incidental finding [8]. The anterior and superior mediastinal masses causes following symptoms which can be categorized as: asymptomatic difficulty in swallowing; heaviness in chest with pain; sweating; headache; neck and facial swelling; venous distention in the neck, arms, and upper chest; and posture-related symptoms. The severe symptoms which have associated high risk to the patients' outcome include dyspnea at rest, stridor, orthopnea, syncope, or cough when supine [9].

The severity of a symptom is graded by how it is affected by lying in the supine position [10]. The symptoms due to mediastinal masses at anterior and superior locations may be graded as:

- Asymptomatic – Patient without any symptoms.
- Mild – These patients can lie supine but have a mild cough and/or pressure symptoms due to mediastinal lesion.
- Moderate – These patients can lie supine only for a short duration due to increasing manifestations of symptoms.
- Severe – These patients can not lie supine at all.

In cases wherein the patient cannot lie supine, the inquiry related to head up position using a pillow (number, height) for relief of symptoms should be done. The patient should be enquired for his most comfortable position with minimum symptoms (head up and its degree, sitting upright, forward bending, lateral decubitus) and should be documented. This helps during the positioning for anesthesia induction and airway management to prevent the occurrence of airway compromise or cardiovascular collapse [11].

The patient may experience systemic symptoms from the tumors. These may be related to other medical conditions and the results of previous therapies. Patients with mediastinal mass diagnosed as thymoma may have associated myasthenia gravis in almost 30% of cases [12]. Patients with mediastinal lesions may have received radiation therapy and/or chemotherapy. These may lead to various changes in the chest due to edema, fibrosis leading to distortion of the airway, kinking of vessels, etc. [13]. These may further complicate the conduct of general anesthesia.

Clinical Examination Patients with mediastinal examinations not only require general physical examination, but focused assessment for eliciting findings specifically related to mass and its impact on surrounding structures needs to be done. The findings related to any airway, respiratory, and cardiovascular compromise are important to elicit. Cardiovascular examination should focus on evaluating for hemodynamic stability and on a concern for possible pericardial effusion. In addition to the examination of the lungs, respiratory evaluation should assess the patient's most comfortable position without or with minimum symptoms.

19.4 Investigations

Preoperative testing should be used to aid in the diagnosis of the mass and the assessment of the severity of the disease. These mediastinal lesions are classified according to location as anterior, middle, or posterior mediastinum tumors [13]. The commoner benign lesions of the anterior mediastinum are thymic cyst, hyperplasia, thymoma, and cystic hygroma. The malignant lesions at this site include lymphomas, germ cell tumors, thyroid cancers, and thymic cancers. The commoner lesions in the middle mediastinum include benign (adenopathies, cysts, hernias, etc.) and malignant (lymphoma, thyroid cancer, esophageal cancer, etc.) lesions. Lesions in the posterior mediastinum are usually neurological lesions and include benign (neurofibroma, schwannoma, etc.) and malignant (neuroblastoma) lesions.

Imaging The radiological imaging is done preoperatively for assessing the location of the mass and its relation to the adjacent structures. It is also done to assess the resectability of the tumor if the lesion requires surgical resection. The anesthesiologists should review these imaging modalities before surgery to make a perioperative anesthetic plan. Chest x-ray remains a screening imaging modality, but computed tomography (CT) scan is useful to assess various important findings that are important for perioperative care [14].

The CT scan is a useful to identify compressive effect of the mass on airways or vascular structures including great vessels and the heart. If the pericardial effusion is found, it can be associated with higher chances of perioperative complications [15]. Compression of the main stem bronchi, particularly in combination with tracheal compression, can increase perioperative risk significantly. The extent of tracheobronchial compression signifies not only the symptomatology but also the risk of complete obstruction during airway management under anesthesia [16]. It has been reported that the severity of tracheal compression on CT scans cannot be considered as a good predictor of respiratory complications, as 8% of patients with more than 50% diameter also had respiratory complications under general anesthesia. The cross-sectional area of the trachea is an important parameter to predict airway compromise, and it has been reported that more than 50% reduction of the cross-sectional tracheal area is a predictor of serious anesthetic problems related to the airway.

Another parameter that has been used as an assessment tool for perioperative planning of anesthesia includes mediastinal thoracic ratio (MTR) [17]. This parameter compares the mediastinal mass size to the diameter of the thoracic cavity. The perioperative respiratory complications are increased with an increase in MTR >50% [18]. The "mediastinal mass ratio" (MMR) measured by CT scan has been described by King et al. [19] as a maximum mediastinal mass width relative to maximum mediastinum width. They have graded mediastinal masses as small (MMR < 30%), medium (MMR 31% to 41%), and large (MMR > 45%). It has been reported that MMR > 56% correlates with increased perioperative respiratory complications.

Pulmonary Function Tests (PFT) These should be performed in an upright and supine position. These provide more objective data in identifying high-risk patients. The Shamberger risk assessment box using two parameters of peak expiratory flow rate (PEFR) and the tracheal area has been proposed to identify patients at risk of respiratory compromise [20]. This risk assessment tool shall be useful to plan periopera-

tive care including airway management (Table 19.2) [20]. The box is divided into four sections (A, B, C, and D). Patients in sections "A" (tracheal area less than 50% and PEFR more than 50% of the predicted values) and "D" (a tracheal area more than 50% and PEFR less than 50% of the predicted values) have moderate risk and therefore should receive local anesthesia (LA), if possible [20]. If general anesthesia (GA) is necessary, it is safe to use spontaneous inhalational anesthesia and avoid the use of muscle relaxants. However, patients in section "B" (tracheal area as well as PEFR more than 50% of the predicted) have "low risk" and can receive GA without any complications. But, patients in section "C" (tracheal area and PEFR, both less than 50% of the predicted) have "high risk" and should receive LA only [20].

Flow Volume Loops This test is thought to aid in the diagnosis of intrathoracic versus extrathoracic masses (Fig. 19.1) [21]. Patients with intrathoracic airway obstruction will present with reduced expiratory flow rate, demonstrated by the appearance of expiratory flow truncation (expiratory limb plateau). The patients having extrathoracic airway obstruction due to the mediastinal masses manifest reduced flow in the inspiratory phase (inspiratory plateau) [22]. Various studies have shown a poor correlation of the flow volume loops with the level of airway obstruction, and this test may not be beneficial for patient management [23, 24].

Transthoracic Echocardiography (TTE) It can aid to detect pericardial effusion and cardiovascular compression [25]. Any patient with cardiac symptoms should have a TTE before the procedure. Identification of a pericardial effusion preoperatively can significantly impact patient management [26].

Tissue Sampling Many modalities are utilized to make and confirm the diagnosis of the mediastinal masses. For definitive management strategies, at times, a tissue sample is required for testing. Attempts should be made to obtain a biopsy with the assistance of a CT scan. If it is not technically possible, or the patient is not able to tolerate the procedure, or insufficient samples

Table 19.2 Shamberger risk assessment box

	Tracheal area < 50%	Tracheal area > 50%
Peak expiratory flow rate (PEFR) > 50%	A (moderate risk)	B (low risk)
Peak expiratory flow rate (PEFR <50%	C (high risk)	D (moderate risk)

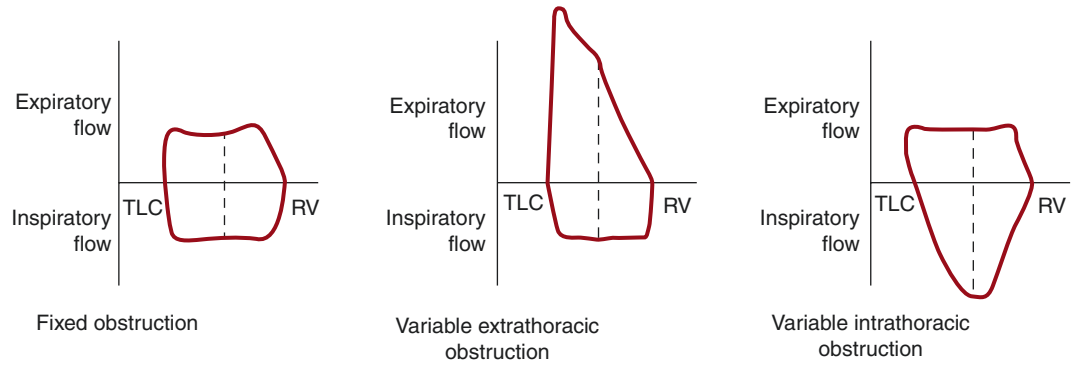

Fig. 19.1 Flow volume loops for thoracic airway obstruction

are obtained, the surgical biopsy should be tried next.

19.5 Anesthesia Management

An individualized anesthetic plan needs to be formulated for every patient presenting with a mediastinal mass primarily based on the medical and radiological features (Table 19.3) [27]. The plan also needs to be made based on the proposed technique of surgical intervention and extent of surgery.

The various perioperative anesthesia strategies include the following:

Table 19.3 Anesthesia goals for mediastinal mass

Strategy	Remarks
Multidisciplinary optimization and planning	Optimize medically before the procedure (steroids, radiation, chemotherapy) Perform procedures/biopsies under local anesthesia if possible Guide approach by CT findings (> 50% tracheobronchial obstruction) and positional symptoms (supine dyspnea, presyncope)
The cautious approach to general anesthesia, if it is necessary	Maintain spontaneous ventilation and awake during ETT placement distal to the obstruction
Planning for an intraoperative crisis	Preoperative cardiopulmonary bypass Invasive monitors and lines, venous access in lower extremities Rigid bronchoscopy and thoracic surgeon immediately available during anesthetic induction Stretcher immediately available for repositioning: prone, decubitus
Complications	Complete airway obstruction with dynamic hyperinflation, cardiac arrest from obstructive shock, hemorrhage from superior vena cava (SVC) syndrome, cardiac tamponade

Regional/Local Anesthesia The small minimally invasive procedures like biopsies can be performed under regional anesthesia techniques [28]. The position-related respiratory compromise should be assessed, and care should be taken for such positions during the procedures. Various analgesic and anesthetic techniques include the use of regional blocks like intercostal, paravertebral, and epidural blocks. Local infiltration techniques may also be supplemented. The sedative drugs should be cautiously used; in fact, they should be avoided at most. The emerging use of dexmedetomidine and ketamine may be used in selected patients, if required [29].

General Anesthesia With the large mediastinal masses, there may be a significant risk of a total or near-total airway obstruction secondary to dynamic airway collapse caused due to various reasons under general anesthesia [30, 31]. The airway compromise may be related to general anesthesia-related decreases in lung volumes and thus the related decrease in tracheobronchial diameters. Also, the general anesthesia reduces the muscular tone including smooth muscles of the airway leading to airway compromise. The impact of general anesthesia on diaphragmatic mobility remains another cause as the caudal movement of the diaphragm is restricted under anesthesia. These cause a reduction in the transpleural pressure gradient which is one of the parameters for keeping the airway dilated [30]. If general anesthesia is required, preserving spontaneous respiration would maintain the normal gradient of transpulmonary pressure that helps to keep the airway stretched and patented, thus preventing the collapse of the airway.

The patients with mediastinal masses can be stratified for perioperative risk based on symptoms and tracheal diameter as “safe, unsafe, and uncertain” [10]. Such risk stratification shall aid in appropriate perioperative care planning, especially during the induction of anesthesia. Adult patients who are asymptomatic with a tracheal diameter of >50% may be considered “safe”; with severe symptoms irrespective of tracheal diameter as “unsafe”; and mild or moderate

symptoms with tracheal diameter < 50% or with an uncertain history of tracheal diameter not known as "uncertain".

The concern for cardiovascular collapse after induction or bleeding due to mass invasion mandates the presence of wide-bore venous access in a patient with a mediastinal mass. It is prudent to secure two large-bore peripheral venous accesses before the induction of anesthesia. An arterial line may also be secured for blood pressure monitoring. The use of cardiac stable drugs like etomidate is preferred for the induction of anesthesia. The choice between propofol-based intravenous versus sevoflurane-based inhalational induction techniques needs to be individualized as per patient assessment. The shorter-acting neuromuscular blocking drugs are desirable for an optimal surgical field; however, its need may be discussed along with surgeons based on surgical interventions. If a patient has dyspnea while lying supine, a semi-recumbent or a lateral decubitus position should be used during anesthesia induction and airway management to alleviate the patient's symptoms. At times, turning the patient laterally or use of rigid bronchoscope is required if airway compromise occurs during anesthesia induction. Awake tracheal intubation under topicalization should be planned in patients with tracheal compression. The endotracheal tube should be negotiated beyond the compression [32]. Microlaryngeal surgery tube (MLS) can be handy in such a situation as it has more length with the narrow diameter and adult size cuff. The rigid bronchoscope can be used for the rescue oxygenation even if it is crossed into only one main stem bronchus to negotiate the compressed obstructed trachea. In such a situation, the endotracheal tube can be placed either by inserting an airway exchange catheter through the rigid bronchoscope or railroading the endotracheal tube over it after removal of the rigid bronchoscope. A double-lumen tube is the other option in cases of distal tracheal compression [33].

In patients with features suggestive of superior vena cava (SVC) syndrome, the peripheral venous access should be secured in lower limbs [34]. In patients with significant cardiovascular compromise, the arrangement of cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO) is suggested [35, 36]. If it is impossible to place an endotracheal tube (ETT) or to do an awake tracheostomy due to the location of the mass, then CPB may be a useful alternative. The initiation of ECMO in individuals with low-lying mediastinal tumors should be considered as a component of the airway management strategy [35].

The postoperative concerns include lung atelectasis, infections, and airway edema with associated airway compromise. The postoperative mechanical ventilation and care in the critical care unit are desirable if the resection is lengthy, complicated, or technical hard or if the patient has undergone major fluid shifts or blood loss.

19.6 Anesthetic Concerns for Thoracic Robotic Surgery

Robotic surgery for mediastinal tumors has peculiar perioperative anesthetic concerns. It usually requires patient positioning in such a manner that the robot can be docked, its arms optimally aligned, and freely moved (Fig. 19.2). Such a position has the concern of airway and neurovascular compression of the upper limb. The pressure points need to be properly padded to prevent such neurovascular injuries [36]. The surgical procedure of robotic thymectomy requires dissection of major vascular and neural structures in the thorax [37]. This may lead to hemodynamic compromise and arrhythmias. Recurrent nerve palsy has been observed after surgical removal of ectopic thymus from the aortopulmonary window [38].

The other issues are docking the robot from one side and covering the patient's torso and face from the other side, limiting access to the airway of the patient (Fig. 19.3). Thus, double lumen tube (DLT) should be properly secured and in cephalad direction as the migration of DLT after the creation of capnomediastinum has been reported (Fig. 19.4). Surgical injury can cause pleural rent on the opposite side with a risk of

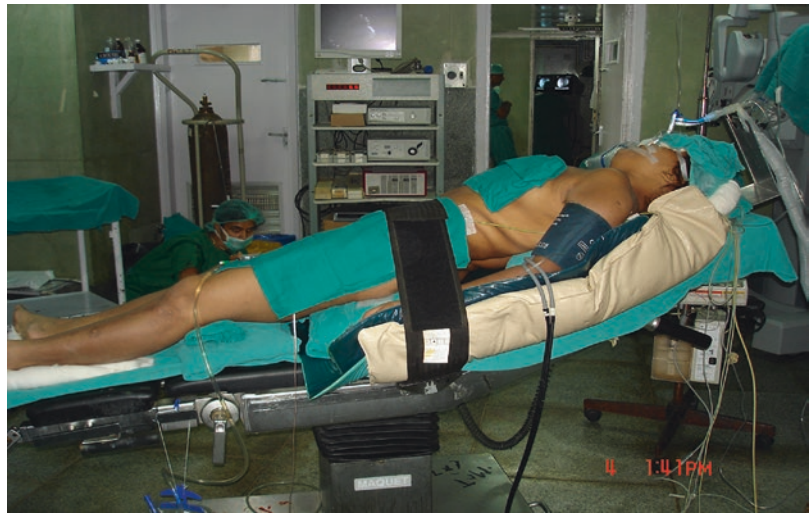

Fig. 19.2 Patient's position during thoracic robotic surgery

Fig. 19.3 The robot docking covers the patient's torso and head, limiting access to the airways of the patient

tension capnothorax. This is manifested by a sudden increase of end-tidal carbon dioxide ($EtCO_2$) and a rise in airway pressures (Paw). This can be treated by increasing the size of the rent surgically for the escape of the collected gases. Neuromuscular blockade is needed to adequately ventilate and maintain normocarbia. Besides care for patients with myasthenia gravis, thorough observation is needed for blood loss and postoperative nerve injury.

Postoperative Pain Management Postoperative analgesia is not only important for patient satisfaction but also for minimizing pulmonary complications, enabling the patient to breathe deeply, cough effectively, and ambulate. Opioids can be titrated during emergence from anesthesia to achieve adequate analgesia, avoiding respiratory depression. This can be continued postoperatively by patient-controlled analgesia (PCA), often in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDs). For video-assisted or robotic-assisted thoracoscopic surgery, postoperative PCA in combination with NSAIDs or paracetamol should be sufficient. However, for sternotomy or thoracotomy, con-

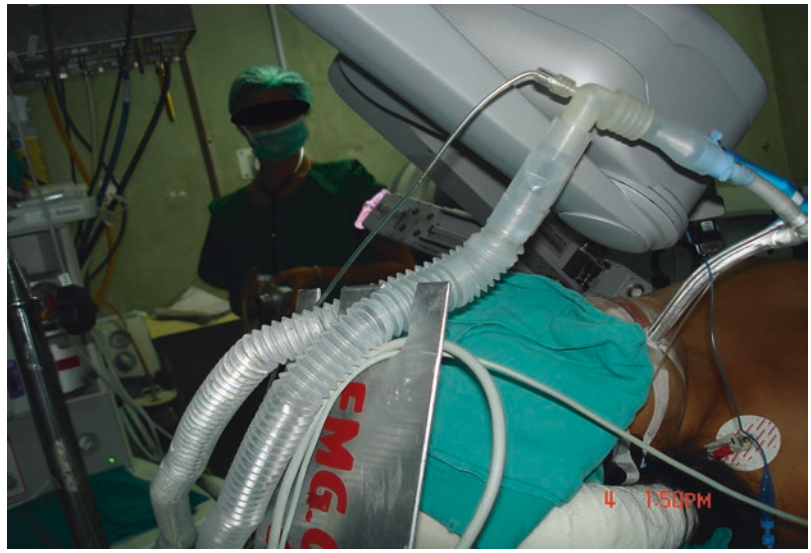

Fig. 19.4 Cephalad fixation of DLT to avoid any obstacle in the field of robotic arms

gruent thoracic epidural infusion or paravertebral infusion of local anesthetic will provide suitable postoperative analgesia. Other techniques of pain management are intrathecal opiates, intercostal nerve block, cryoanalgesia, and intrapleural regional analgesia. As robotic surgeries are minimally invasive, neuraxial analgesia should be avoided, and the use of multimodal analgesia techniques including short-acting opioids and NSAIDs is sufficient for pain control.

19.7 Anesthetic Concerns in Pediatric Patients with a Mediastinal Mass

As children have the compressible cartilaginous structure of the airway [39] and it is difficult to obtain a history of positional symptoms, deaths are mainly been reported in children with mediastinal mass during anesthesia induction. Anesthetic management of such children is challenging because of the risk of compression of the airway and great vessels after induction of anesthesia [40]. Moreover, signs/symptoms may not correlate with the size of the tumor, and it is difficult to find out from history as they cannot express symptoms. Pre-biopsy steroid treatment is justifiable in high-risk children without extrathoracic lymphadenopathy or pleural effusion. Coordinating the timing for the biopsy is essential in these situations, with the oncology, surgery, and anesthesia team. Another option to preoperative steroids is to irradiate the tumor while leaving a tiny region covered by lead for subsequent biopsy in the cooperative high-risk person.

Inhalational induction with spontaneous ventilation is advisable as children may not be cooperative under local/topical anesthesia. For thoracotomy of VATS, lung isolation with one-lung ventilation may be achieved with an appropriate size DLT or bronchial blockers. The smallest size DLT available is 26Fr which can be used only in children >8 years. In children below 8 years, the other option is to use univent tube with a bronchial blocker. The smallest univent tube available is size 3.5 mm ID which can be used in children >6 years. However, fiber-optic bronchoscopy is required to place bronchial blockers in the appropriate place, and univent has a high resistance to gas flow due to small internal diameter. Other bronchial blockers like Arndt, Cohen, and EZ blockers can be used in children if appropriate sizes are available. Fogarty embolectomy catheter has been used for lung isolation in small children and infants [41]. This also requires fiber-optic bronchoscopy for the appropriate placement of the Fogarty catheter. Moreover, the high-pressure, low-volume cuff can cause bron-

chial mucosal injury, and there is a risk of displacement of Fogarty intraoperatively.

Appropriate analgesia is of paramount importance for thoracotomy or sternotomy. Inserting a thoracic epidural catheter in an anesthetized child may not be considered safe. The epidural catheter can be inserted via lumber or caudal route and advanced till thoracic dermatome under ultrasound guidance [42]. Alternate modes of analgesia are paravertebral block or intravenous opioid analgesia supplemented by paracetamol/NSAIDs.

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20 Anesthesia for Robotic Gynecologic and Urogenital Cancer Surgery

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20.1 Introduction

Robotic surgeries are increasingly being used in various domains of medical practice. Urologic and gynecologic surgeries can be performed robotically to reduce morbidity and mortality. Robotic-assisted urologic surgeries can be used for diseases involving the kidneys, adrenals, bladder, ureter, prostate, and pelvic floor. Some of the urologic surgeries which can be accomplished using the da Vinci™ robotic system include pyeloplasty, partial nephrectomy or nephron-sparing surgery (NSS), radical nephrectomy, sacro-colpopexy, radical prostatectomy (transperitoneal or retroperitoneal), radical cystectomy, neobladder formation, retroperitoneal lymph node dissection (RPLND), robotic laparo-endoscopic single-site surgery (LESS), and robotic natural orifice transluminal endoscopic surgery (NOTES) [1, 2]. The common gynecologic robotic procedures include hysterectomy; radical hysterectomy for endometrial and cervical cancer; robotic-assisted vaginal hysterectomy; pelvic and inguinal lymphadenectomy; and sacro-colpopexy; and the list is ever increasing. Anesthetic considerations include those common to all robotic surgeries as well as those specific to each surgery, apart from patient-specific concerns. This chapter would focus on concerns related to robotic interventions specifically in urologic and gynecologic onco-surgeries. The overview of laparoscopic and robotic surgeries is discussed elsewhere in this book.

20.1.1 Advancement in Robotic Surgery for Urology

Robotic surgery in urology has become popular as its indications have increased with better perioperative outcomes. The main surgical advancement for robotic urology includes advances in equipment, advances in reconstructive techniques including pelvic repairs, and advances in structured robotic surgery training. The wristed robotic arms improve dexterity especially in confined areas like the pelvis [3]. Robotic surgery has certain limitations like cost factor, lack of tactile feedback of the structures during the surgical intervention, and dependency on the assistance at the patient's end for equipment manipulations [4]. These limitations are being taken care of with time as the introduction of the robotic fourth arm and reducing cost factor

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(decrease equipment cost and increased turnaround time of robotic usage for patient management). The major advancements in robotic surgery for urology are the application of minimally invasive robotics in radical urologic cancer surgery and the addition of robotic arms for extra maneuverability. Anesthesia providers must modify their technique to suit the surgical requirements and at the same time not compromise with patient safety.

20.1.2 General Anesthetic Considerations for Robotic Urologic and Gynecologic Onco-surgery

The important and peculiar concerns should be known to anesthesiologists for uneventful perioperative care of patients undergoing robotic surgeries. These are primarily related to equipment and positioning for robotic surgery which mandates certain modifications of anesthetic and perioperative management. A thorough preoperative evaluation is crucial for a successful robotic surgery program outcome.

The da Vinci™ system is a commonly used robotic system and has three main components [5]. These components are:

- Surgical cart with robotic arms
- Three-dimensional vision tower
- Surgeon console

These robotic arms have seven degrees of freedom of mobility and have "endo-wrist" technology [6]. This has an advantage of hand tremor filtering and has the benefit of motion scaling. These robot systems are usually bulky and thus the spatial arrangement needs to be adequately made during infrastructural development for robotic surgery suits (Fig. 20.1). Also, after docking of the robot on to the patient, not only the access to the patient is reduced, but also at times, inadvertent injuries can occur to the patient from moving robot arms. These can lead to interference with ventilation, venous and arterial lines, and other monitoring equipment by causing displacement, kinking, etc. The monitoring devices,

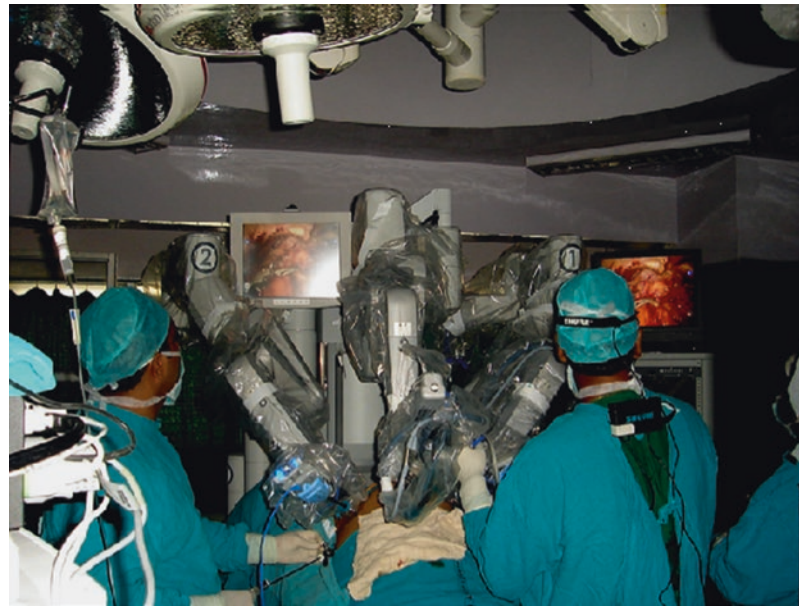

Fig. 20.1 Overview of spatial arrangements for robotic surgery

cables, airway gadgets, circuits, vascular access, and tubing should be properly secured before the robot is docked and rechecked before start of surgery. The same precautions should be followed when the robot is being de-docked. The positioning of the patient requires due diligence by proper padding and support (shoulder braces, slings, bandages) as the patient may skid due to steep Trendelenburg position or also injuries due to moving robotic arms.

The general dictum is to maintain normothermia, normotension, and normocarbia. Extubation must be cautiously done after excluding airway edema or residual neuromuscular weakness. Postoperatively, the patient must be monitored in a high dependency unit to detect and manage delayed complications. There are certain specific concerns related to robotic surgeries in the perioperative period, and they will be discussed in the subsequent section of this chapter.

20.1.3 Effects of Steep Trendelenburg Position

The majority of lower abdomen robotic surgical interventions require the Trendelenburg position which is at times very steep as well. This is required for better surgical visualization. The major effects of the Trendelenburg position are on the cardiovascular, central nervous, and respiratory systems, depending upon the degree of head-down position: mild (10–15°), moderate (20–30°), and severe (45°). A nautical inclinometer can be mounted to the operating room table to facilitate accurate positioning. The following are the available restraints to prevent the patient from sliding in the Trendelenburg position:

(a) The Bandito Position: The tapes and foams are crisscrossed across the chest of the patient. It may result in suboptimal respiration.
(b) Bean Bag Restraints: These are vacuum bags to take the shape of the structure being protected and are attached to the hand support and railings.
(c) Full-Length Gel Pads: These pads provide good contact between the patient and the operating table.
(d) Friction or Conforming Pad: It is a disposable pad strapped to the table rail and slipped the least.
(e) Egg Crate Foam: These restrain the patient's skidding.

Antacid premedication is suggested for all patients to reduce the risk of reflux of acid or gastric juices. Mild to moderate Trendelenburg position causes a fall in cardiac output by 10–30% and an increase in pulmonary capillary wedge pressure (PCWP) > 18 mmHg [7]. Extreme degrees of head-down position with pneumoperitoneum as required for robotic pelvic urologic surgery can cause doubling of central venous pressure (CVP), mean pulmonary artery pressure (MPAP), and PCWP [8]. This also causes an increase in blood pressure by 25% and a 65% increase in right ventricular and left ventricular stroke work. These are manifested as hyperdynamic circulation postoperatively. This may have an adverse impact on the patients with compromised systolic function and may lead to acute cardiac failure, and patients with obstructive coronary disease may manifest demand ischemia. The increase in CVP impairs venous drainage of the head. The elevation of hydrostatic forces can lead to an increase in extracellular water and perivascular edema in the brain. Venous stasis can also lead to swelling of the face, lips, tongue, and eyelids [9]. This leads to a rise in intracranial pressure (ICP) and cerebrovascular resistance along with reduced cerebral blood flow and cerebral edema. Steep Trendelenburg position can also cause an increase in intraocular pressure (IOP) which can be deleterious in patients with pre-existing ocular disorders [10]. This occurs due to a combination of increases in systemic blood pressure, CVP, ICP, and airway pressures. Another complication is the occurrence of airway edema and delayed extubation after the proce-

dure, which can increase patient morbidity and prolong hospital stay [11]. The pressure-controlled ventilation has been used to mitigate the respiratory effect of the steep Trendelenburg position.

20.1.4 Effects of Pneumoperitoneum

The robotic abdominal surgeries require an insufflating abdomen with gases to provide better surgical visualization of the intra-abdominal organs. A 12 mmHg pneumoperitoneum causes increase in the mean blood pressure by 25% and systemic vascular resistance (SVR) by 20% along with a reduction in mesenteric, hepatic, and renal blood flow [12]. CVP, PCWP, and cardiac output remain unchanged. A 15 mmHg pneumoperitoneum causes a 9 mmHg rise in intrathoracic pressure. The creation of pneumoperitoneum causes cephalad splinting of the diaphragm and thus reduces functional residual capacity (FRC) by >50%. These mechanical changes lead to lung atelectasis, increased shunt, and a fall in oxygen saturation [13]. Minute ventilation must be increased to offset hypercarbia. Pressure-controlled ventilation probably yields better lung compliance and lower airway pressures. Care must be taken while applying positive end-expiratory pressures (PEEP) (to prevent atelectasis) in Trendelenburg position as the combined effects of pneumoperitoneum with PEEP can abruptly decrease the cardiac output. On the other hand, increased intra-abdominal pressure causes blood to be squeezed out of the abdominal organs causing a sudden increase in preload. Reduction in blood flow through mesenteric arteries causes a rise in mucosal pH and gut ischemia. There is a reduction in renal and hepatic perfusion as well as decreased return through the IVC (inferior vena cava). It affects the neurohumoral regulation by increasing vasopressin and norepinephrine levels. It also leads to the activation of the renin-angiotensin system. The hypercarbia and head-down position can lead to increases in intracranial pressure. The additional factors for these changes are also due to decreased resorption of CSF due to impedance of lumbar venous drainage [14].

20.1.5 Effects of Prolonged Surgical Times and Positioning

Each surgical robotic intervention requires specific patient positioning for robot docking and placement of robotic arms to facilitate optimal surgical intervention (Table 20.1). The extreme positioning required for various robotic urologic surgeries can lead to perioperative sliding, falls, or neurovascular injuries. Prolonged compressions due to inappropriate positioning and padding can eve lead to rhabdomyolysis. The prolonged duration of robotic surgeries also taxes the scheduling of other operating room cases as well as the operating room staff. Prolonged general anesthesia with deep neuromuscular blockade required for these surgeries increases the incidence of anesthetic complications, more so with a steep Trendelenburg position [15]. Delayed awakening, prolonged ventilation, airway edema, vision loss, hypothermia, endotracheal tube displacement, and hemodynamic instabilities are the main complications cited. Ocular complications like cornea damage, eyelid injuries, and ischemic optic neuropathy can occur in otherwise uncomplicated robotic surgeries [16]. Greater attention to minute details of positioning is imperative to prevent pressure or crush injuries and neuropathies. Specialized cushions and gel pads are available for prevent-

Table 20.1 Positioning for different robotic surgical interventions

S. no.	Type of robotic surgery	Position
1.	Radical prostatectomy	30–40° Trendelenburg with lithotomy, arms tucked by the side
2.	Radical or partial nephrectomy	45° lateral decubitus with flank elevation and 15° Trendelenburg
3.	Adrenalectomy	Same as for nephrectomy
4.	Cystectomy	Same as for prostatectomy
5.	Radical hysterectomy	Steep Trendelenburg with lithotomy

ing pressure injuries. All bony prominences must be padded. Most robotic urologic procedures are performed in various degrees of lithotomy positions, which are also prone to cause postoperative neuropathies. Improper arm positioning can also cause stretch injuries to nerves. Greater attention needs to be given during the positioning of the patient with pre-existing deformities like rheumatoid arthritis [17] or osteoarthritis for robotic procedures. In a recent study of adult robotic urologic surgeries, the incidence of positioning injuries was documented to be 6.6% [18]. We should be aware of other complications of prolonged pneumoperitoneum like subcutaneous emphysema, pneumothorax, pneumomediastinum, air or gas embolism, which also need to be guarded against.

20.1.6 Monitoring

The intraoperative monitoring for these robotic surgeries includes an electrocardiogram (ECG), blood pressure, pulse oximetry, capnography, and temperature. In addition, urine output monitoring must be utilized (except in prostatectomy). The prolonged surgery in steep Trendelenburg position with pneumoperitoneum increases cardiac workload, and thus patients with compromised cardiovascular status not only require assessment, optimization, but also intensive monitoring in the perioperative period. Additional advanced monitoring may be required based on the patient assessment, the extent of surgery, and associated comorbidities [19]. Invasive monitoring in the form of arterial and central venous lines may be inserted (under ultrasound guidance) in indicated cases. Noninvasive and invasive cardiac output monitors [20] like the FloTrac™/Vigileo™ and transesophageal echocardiography (TEE) can be utilized for advanced patient care based on patient assessment and surgical need. Since intense neuromuscular blockade is required for robotic surgeries, peripheral neuromuscular monitor [21] is a mandatory requirement to guide neuromuscular blocking drugs infusion doses and reversal. Bispectral Index (BIS) monitor may also be used to monitor the depth of anesthesia which helps us titrate the inhalational agent use and intravenous anesthetic infusions [22]. Recently, intraoperative lung ultrasound scanning is being investigated as a monitor to guide fluid therapy and mechanical ventilation parameters. The fluid status by monitoring central venous pressure (CVP) is not commonly being done nowadays. Also, CVP may prove to be an unreliable measure of intravascular status in an extreme head-down position.

20.1.7 Fluid Balance

Fluid management is always challenging in robotic procedures due to concerns related to robotic use and its associated concerns as discussed earlier and also related to surgical intervention. Restrictive fluid administration remains the fluid management strategy in robotic surgeries to decrease surgical blood loss, airway edema, and head and neck swelling [23]. In urologic surgeries, it is beneficial in decreasing excessive urine flow which can obscure the surgical field. The average fluid requirements in most robotic urologic procedures are between 800 ml and 1500 ml. In most adult robotic surgeries, a basal infusion rate of 100 ml–200 ml of balanced crystalloids per hour is sufficient, unless complicated by hemorrhage. The use of noninvasive cardiac output monitors with the parameter of stroke volume variation (SVV) has been used for managing fluid management in such surgical interventions. Hence, advanced cardiac monitoring may be required in high-risk cases to monitor the fluid balance. Any balanced crystalloid solution can be utilized in measured amounts to reduce incidences of edema in soft tissues like the periorbital area, airway mucosa, tongue, lips, neck, and dependent regions. These areas are prone to accumulation of edema fluid in extremes of prolonged head-down positioning during robotic cancer surgery of the prostate, urinary bladder, uterus, cervix, and other pelvic areas. Advanced cardiac monitors like the pulmonary artery (PA) catheters and transesophageal echocardiography (TEE) can be utilized where expertise

and infrastructure exist. Other monitors of intravascular status, as mentioned previously, can be used in patients with cardiorespiratory or renal disease, to guide goal-directed therapy.

20.1.8 Pain Management

Robotic surgeries have a definite advantage of lesser postoperative pain as compared to conventional surgeries. Usually, common systemic analgesics are sufficient. Combining general anesthesia with epidural anesthesia [24] is an excellent modality especially in radical cancer surgeries involving both robotic and open procedures, not only for effective pain management but also for better lung and gut function. It was also found to decrease peak airway pressures and better oxygenation, leading to a decrease in blood lactate levels and requirements of neuromuscular blocking drugs. The epidural bolus of local anesthetics should be avoided in a head-down position. The use of intrathecal opioids including fentanyl and morphine has also emerged as one of the pain management modalities. Central neuraxial blocks are generally less preferred in robotic surgeries with planned early discharge from the hospital. In most instances, multimodal systemic pain management [25] is advocated in robotic surgeries, and epidural catheters are not required. Systemic analgesics like paracetamol, nonsteroidal anti-inflammatory agents (NSAIDs), and opioids can be administered. Patient-controlled analgesia (PCA) techniques [26], either epidural or intravenous, can be instituted for robotic radical cystectomies and retroperitoneal dissections. PCA pumps can be utilized in the first 24–48 h for improving patient well-being and better control of hemodynamics. With the advent of ultrasound (USG) in regional anesthesia, various local blocks and infiltration analgesia are increasingly being used. These techniques include transversus abdominis plane (TAP) block, rectus sheath block, quadratus lumborum, and pudendal block [27]. Continuous catheters can be threaded in the TAP plane for round-the-clock analgesia in select patients. Local anesthetic wound-site/port-site infiltration and intraperitoneal instillation of local anesthetics can also decrease postoperative opioid requirements.

20.1.9 Anesthesia for Robotic Radical Prostatectomy

Prostatectomy is largely being done using robots. The robot-assisted radical prostatectomy (RARP) was one of the initial surgeries being done by the robots [28, 29]. The outcome after RARP has been better as compared to open and laparoscopic prostate surgeries with regard to lower rates of positive surgical margins, lower perioperative blood loss, lesser need for blood transfusion, and lesser chance of anastomotic stricture.

The patent is positioned to allow the robot to dock between the legs and patient being in a steep Trendelenburg position. Also, the carbon dioxide (CO_2) pneumoperitoneum pressures are higher for this surgery as compared to other robotic surgeries for other organs. This causes cardiovascular and respiratory compromise. In the review article by Danic et al. regarding anesthesia for robotic prostatectomies, the incidence of complications reported were: corneal abrasion 3%; postoperative anemia 1.3%; postoperative transfusions 1%; reoperation 0.6%; pulmonary embolism 0.2%; da Vinci failure 0.2%; and delayed extubation 0.06% [30].

20.1.10 Anesthesia for Robotic Radical or Simple Nephrectomy

Nephrectomy has also been performed by robot-assisted techniques. The outcome of robot-assisted partial nephrectomy (RAPN) has been reported to be better than laparoscopic techniques in terms of blood loss, hospital stay, and associated surgical outcomes [31]. It also reduces the "warm ischemia time" which preserves the kidney function [32]. The positioning for RAPN is lateral with kidney bridge roll and mild Trendelenburg position (45° lateral decubitus

position with flank elevation). The perioperative care should aim to preserve the renal function by appropriate fluid resuscitations. Robotic nephrectomies or nephron-sparing surgeries (NSS) are being successfully performed in patients with concurrent comorbidities like cardiomyopathies [33].

20.1.11 Anesthesia for Robotic Radical Cystectomy

Bladder cancer surgeries are increasingly being done using robotics [34]. Robot-assisted radical cystectomy (RARC) has largely replaced open radical cystectomy (ORC) for urinary bladder cancer because of its advantages including lesser blood loss, lesser needs of blood transfusions, faster postoperative bowel function, and lesser pain to the patient. The oncological outcome has also been reported for RARC [35]. Neobladder reconstructions can also be done robotically instead of the standard open ileal conduit formation, in selected patients for better patient outcomes. These are prolonged procedures with attendant complications of greater anesthesia exposure time and positioning issues. Perioperative anesthetic concerns and management are like other robotic procedures. One main concern would be difficulty in monitoring urine and thus other surrogate markers may be used for fluid status.

20.1.12 Anesthesia for Robotic Adrenalectomy

Adrenal masses have also been surgically removed with robot assistance with the improved outcome as compared to laparoscopic and open interventions. The advantages of robotic adrenalectomy (RA) include lesser blood loss, decreased operative time, and improved surgical outcomes [36]. For RA, the patient is positioned in 60 degrees flank position, operating table flexed, and slight Trendelenburg. The robot is docked over the shoulder of the patient. The fluctuations in blood pressure may warrant a fine balance between inotropic and vasodilator infusions. Decreased perioperative blood loss and pain associated with robotic surgery is particularly beneficial in these patients, as it suppresses the already heightened hemodynamic responses in adrenal tumors. The hemodynamic changes during RA are related to adrenal and surrounding structures' manipulations. It needs to be remembered that steroid cover needs to be taken care of according to the standard anesthesia protocol in the perioperative period.

20.1.13 Anesthesia for Robotic RPLND (Retroperitoneal Lymph Node Dissection)

Robotic-assisted dissection of the retroperitoneal space [37] is a highly skillful procedure with advantages similar to laparoscopic dissection. There is greater absorption of CO_2 used for pneumoperitoneum. It is usually done for lymph node clearance in metastatic tumors like germ cell cancers. Special precautions should be taken during retroperitoneal dissection as it houses the major vessels (aorta, inferior vena cava), nerves, and lymph channels (*cisterna chyli*). Usually, nerve-sparing dissection is performed to preserve erectile functions. There have been case reports of chyle leaks following robotic retroperitoneal lymph node dissection [38]. Chyle leaks, if recognized intraoperatively, may be sutured to prevent future morbidity. Anesthetic considerations are the same for all robotic surgeries with special concern regarding positioning, accurate estimation of blood loss, maintaining adequate urine output, and normothermia.

20.2 Anesthesia for Robotic-Assisted Gynecologic Surgery

The first robotic gynecologic surgery was tubal reanastomosis [39]. The current gynecologic indications for robotic surgery include hysterectomy (total and radical), myomectomy, ovarian cystectomy, sacro-colpopexy, robotic-assisted vaginal hysterectomy, and pelvic floor repair. As

compared to laparoscopic surgery, robotic gynecologic surgeries allow greater maneuverability to perform complex procedures easily, like securing uterine vasculature or cardinal ligaments, greater accuracy in colpotomy, and oversewing the vaginal cuff [40]. In difficult cases with adhesions and scarring, fertility preservation has been made possible with robotic surgeries. The vital anesthetic concerns for robotic gynecology remain the same as highlighted previously for robotic urology. These considerations are related to the position (steep Trendelenburg), the creation of pneumoperitoneum, and associated cardiovascular and respiratory compromise. Also, limited access to the patient due to positioning and docking of the robot remains the concern for monitoring and any urgent intervention. As the patient becomes fixed in robotic gynecologic surgery, he/she should be prevented from sliding, which can have disastrous consequences. The potential complications of pneumoperitoneum are magnified in the steep Trendelenburg position. In a study [41] done by *Badaway* et al. in 133 patients undergoing robotic hysterectomy, the incidence of intraoperative hypercapnia ($ETCO_2 > 45$ mmHg) was 18% and that of significant intraoperative hypoxemia was less than 4%. Some of these patients required short-term postoperative ventilation due to hypercapnia, hypothermia, the inadequate reversal of neuromuscular blocking agents, and relative excessive narcotic administration.

Prolonged steep Trendelenburg position during robotic gynecologic surgery leads to facial edema, lid edema, tongue edema, and edema of supraglottic airway structures (epiglottis, arytenoids, and vocal cords) leading to delayed extubation, postoperative stridor, and difficult airway for re-intubation. The ophthalmic complications consist of an increase in intraocular pressure, posterior ischemic optic neuropathy (leading to permanent blindness), conjunctival edema, corneal abrasions, and eye injuries from passive aspiration of gastric contents into patients' eye [42]. The creation of pneumoperitoneum and steep Trendelenburg position leads to ventilation-perfusion mismatching, atelectasis, decreased oxygenation, and CO_2 retention.

Robotic video endoscopic inguinal lymphadenectomy (VEIL) is a recent type of minimally invasive surgery [43]. This procedure is for lymphadenectomy for various cancers of the penis, urethra, and vagina. The prolonged surgical time in bilateral VEIL has the propensity to cause deep vein thrombosis due to femoral vessel compression as well as compression neuropathy. In general, mechanical thromboprophylaxis is recommended in all robotic surgeries, especially robotic prostatectomy, hysterectomy, and VEIL.

20.2.1 Complications

The complications of robotic cancer surgeries can be divided into those due to operative positioning, prolonged pneumoperitoneum, surgical factors, and anesthesia-related issues (Table 20.2). Positioning concerns include pressure sores, neurovascular compression, peripheral neuropathy, organ injuries, sliding-off of shoulders or limbs, and dependent edema. Pneumoperitoneum can cause problems due to the increased intra-abdominal pressure, splinting of the diaphragm, hypercarbia, and pressure effects. Surgical factors could be due to the operative procedure per se or due to the robotic assembly. Anesthetic issues stem from increased anesthesia exposure times, ventilatory adjustments for pneumoperitoneum, cardiorespiratory stability maintenance during extremes of positioning, advanced monitoring requirements, adequate pain management, and continued postoperative care.

20.3 Future Prospects

Not only in urology and gynecology but robotics have also advanced into every other surgical field. One important consideration is the occurrence of da Vinci malfunctions [44], mainly related to instrument failures and malfunction of patient-side cart or surgeon console or the endoscope. Another consideration is the frequent training of the robotic operating room staff in quick de-docking of the robot in case of emergencies [45]. Patient safety is of paramount concern, and regular drills must be

Table 20.2 Perioperative complications in robotic onco-surgeries

S. no.	Complication	Probable etiology	Management
1.	Corneal abrasion	Manual compression, steep Trendelenburg position, mechanical	Proper eye cover, padding, prevention of secretions/cleaning solutions entering the eye, and avoid robotic equipment grazing the orbital area
2.	Brain edema	Steep Trendelenburg position	Avoid prolonged head-down position, fluid restriction, low-dose diuretics
3.	Airway edema and delayed extubation	Steep Trendelenburg position	Leak test before extubation, brief postoperative ventilation, adequate reversal under neuromuscular monitoring, reduce steep Trendelenburg time
4.	Patient or limb sliding	The position required for robotic docking and robotic intervention	Use of proper supports, shoulder straps, padding, body/head foam supports
5.	Hypercarbia	Creation of pneumoperitoneum	Ventilatory adjustments: increase in respiratory rate and/or tidal volume
6.	Peripheral neuropathy	Mechanical injury, compression, ischemia due to compression	Preoperative documentation of pre-existing deficits, padding of all pressure points, use of soft gel-based supports, avoiding perioperative hypotensive episodes, greater vigilance in lithotomy positions
7.	Organ injury	Robotic intervention per se	Ensuring complete muscle relaxation to prevent the slightest patient movement after docking of the robotic, use of neuromuscular monitoring and awareness monitor (BIS), avoid any external forces on robotic arms.

conducted to handle such crises. Adequate muscle relaxation, monitored by neuromuscular monitoring, is recommended to prevent patient movement during robotic surgery. In the future, most minimally invasive surgeries would be performed robotically resulting in better patient outcomes. The time would not be faraway when robotic surgery would be performed under robotic anesthesia, which is still in its infancy [41]. The cost of installation and maintenance of a robotic surgical system is a deterrent to its widespread use, especially among developing nations. There is also a learning curve [46] for performing robotic surgeries, and anesthesia personnel also need to be vigilant of the prolonged operative times in the formative years of robotic surgery. Even though robotic-assisted surgeries are advantageous for the patient, there should be a low threshold to open up the patient in the event of a complication or if the situation demands. Pediatric robotic surgery [47] is a challenging procedure with definite advantages, and several operations have been performed in pediatric urology like pyeloplasty, nephrectomy, and cystectomies. Special care must be taken during positioning, port introduction, and robotic instrument manipulation in pediatric patients.

20.4 Summary

Robotic surgery has revolutionized the minimal access to surgical interventions. Anesthesiologists should be aware of particular concerns and requirements for such types of surgical interventions and their perioperative management. The concerns for positioning, fluid balance, muscle relaxation, controlled ventilation, and pain management need to be taken care of and managed appropriately. Also, prevention of intraoperative patient awareness and positioning-related injuries, as well as postoperative nausea vomiting and DVT prophylaxis, is equally important. Urologic surgeries involve lithotomy and steep Trendelenburg positions with prolonged pneumoperitoneum. These have a significant effect on cardiovascular and respiratory function and thus need not only careful monitoring but also anesthetic management accordingly. Restricted access to the patient is another important consideration, especially in emergencies or crises. Anesthesia for complicated robotic radical uro-gynec surgeries can be quite challenging. Eternal vigilance and teamwork are the cornerstones of success in any robotic surgery program.

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Anesthesia for Cardiac Tumors

21

Mukul Chandra Kapoor

21.1 Introduction

Crafoord reported the first successful cardiac tumor resection surgery in 1954 [1]. In the beginning, surgical excision was not attempted in patients with cardiac tumor because of a lack of expertise and equipment required, and so the diagnosis of cardiac tumors was more for an academic purpose. With the improvement in cardiopulmonary bypass technology, tumor excision became a reality. The newer diagnostic modalities like echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI) have made it easier to diagnose cardiac tumors and its subsequent management.

Among all the tumors, cardiac tumors are comparatively rarer but the outcome prognosis is good for these tumors [2]. On average, one cardiac tumor is operated yearly in an average cardiac surgical practice [2]. Primary cardiac tumors constitute a very small segment of the overall cardiac masses reported. The most common cardiac masses are pseudo-tumors (abscesses, vegetations, thrombi, foreign bodies, echinococcal cysts, tuberculomas, saphenous venous grafts, and native coronary arteries aneurysms) [3, 4]. Patients of cardiac tumors perform well in the long term even if surgical resection is suboptimal [5, 6]. Cardiac masses can cause valve dysfunction; invade the heart wall and cause ventricular dysfunction; compromise coronary blood flow; limit cardiac output; and cause back pressure effects on the heart chambers and lung. Around 15% of the patients with left atrial myxoma have sudden death due to the embolization of lesion with mitral valve blood flow obstruction.

21.2 Epidemiology and Morphology

The primary cardiac tumor prevalence in autopsy outcome data has been reported to be 0.001–0.03% [7, 8]. Three-fourth of the primary cardiac tumors are benign [8]. Of these, 75% are myxomas in adults or rhabdomyomas in children (most common primary cardiac tumors in adults and children, respectively) [8]. Most of the prevalence data is based on postmortem findings as other advanced imaging modalities like CT, MRI, or cardiac echocardiography were not available while reports of those studies were published. With the improved imaging techniques, antemortem diagnosis is now common. In a recently reported study from Italy for primary cardiac tumors, the incidence was 1.38 per 100,000 inhabitants per year, and of these 90.5% were benign and 9.5% malignant [9].

Myxomas remain the commonest primary cardiac tumor in adults, 90% are solitary, and most

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originate from the left atrium (LA), near the fossa ovalis and a small number (2.5–4% of all cardiac myxoma cases) of myxoma arise from the left ventricle (LV) [10, 11]. Myxomas are more commonly seen in females and presents usually between 50 and 70 years of age. Myxoma presenting at an early age is usually familial and frequently presents with facial freckling and endocrine adenomas. Screening of close relatives should be undertaken in such cases.

Cardiac sarcomas are the most common malignant cardiac tumors, usually originate from the right atrium (RA), and are usually intramural in origin. Most cardiac sarcomas are angiosarcomas in adults, while in children rhabdomyosarcomas are most common. They tend to invade the pericardium and spread to the body cavities. The prognosis in patients with sarcomas is not good, and median survival is around 6 months and improves to around 12 months even after surgical resection. In patients who only undergo chemotherapy, the median survival is just 1 month [12, 13].

The benign cardiac myocardial tumors like cardiac rhabdomyoma are one of the commonest tumors seen in the fetus [14]. It is commonly seen in association with tuberous sclerosis and is usually diagnosed in utero or in infants [15]. The tumor originates usually from the left ventricle [16]. At times, rhabdomyomas may regress spontaneously. In infants with clinical symptoms of ventricular outlet obstruction and significant changes in electrocardiography, echocardiography requires surgical excision of the tumor. These infants may even have sudden death. Relatively less common cardiac tumors are cardiac secretory tumors (have systemic and local implications) and cardiac paraganglioma (neuroendocrine tumors with pheochromocytoma-like morphology).

Carney complex is a familial syndrome significantly associated with cardiac myxomas. This syndrome manifests a dominant pattern of inheritance. It is clinically manifested as multiple endocrine neoplasias [17]. A gene deletion at the 17q2 locus has been postulated as the cause of the Carney complex. Patients with these syndromes may pose anesthetic and surgical challenges, have a high rate of recurrence, and have associated comorbidities [18]. The primary pigmented nodular adrenocortical disease may be associated in 70% of cases resulting in Cushing syndrome. Carcinoid tumor is rare with systemic symptoms. When systemic symptoms are controlled, heart failure due to a carcinoid tumor can be treated by valve replacement [6].

The secondary cardiac tumors are more common than primary tumors by 20–100 times [19, 20]. Almost 15% of cancer patients have metastasis to the heart. The increased occurrence of these cardiac metastases in recent times is not only because of increased incidence but also because possibly due to an increase in the life span of cancer survivors [20]. In about 75% of the secondary tumors, pericardial involvement is found. Secondary cardiac tumors invade the heart by four routes: direct (from the mediastinum), hematogenous, lymphatics, and extension with the cavity lumen (from the inferior vena cava) [21]. The primaries of these tumors originate commonly from breast, lung, esophagus, kidneys, lymphomas, leukemias, and melanomas. 50% to 70% of patients with melanoma have cardiac metastases.

21.3 Tumor Classification Based on Location

Tumors affecting the heart are classified into five zones based on their anatomical location. Some tumors involve more than one zone. Most cardiac tumors are not true tumors and are not primarily sited in the heart but are an extension of tumors from other sites like the involvement of right atrium through inferior vena cavae extension of renal cell carcinoma. The zones defined are:

- Zone 1—Tumors with the invasion of the great arteries: These are the primary vessel tumors (sarcomas) or secondaries arising from the mediastinal or pulmonary tumors and invade the heart. They indicate very advanced disease and are rare. Great vessel primary

sarcomas are known. Pulmonary artery tumors are more common.

- Zone 2—Venous tumors: Both primary and secondary venous tumors are well known; however, secondary venous tumors are commoner. The commoner reported site for pulmonary tumors is superior vena cavae, while inferior vena cavae involvement is seen with renal cell carcinoma.
- Zone 3—Atrial tumors: The tumors arising primarily from the atria or breaching the atria from the other structures. Benign tumors are commoner than malignant tumors. Atrial myxomas are benign tumors, seen more commonly in the left atrium and usually arise from the intra-atrial septum but also seen from any site in the atria, on the valves, and the ventricles. These myxomas usually arise from the fossa ovalis of the left atrium but also observed from the atrial posterior wall, the anterior wall, or the appendage. These myxomas are round, oval, or polypoid in shape; have smooth or lobulated surface; and have gelatinous consistency. Myxomas are mobile, and mobility depends on its attachment to the interatrial septum and length of the stalk.
- Zone 4 (Ventricular tumors): Resection of ventricular tumors is difficult unless they have a stalk like that of a fibroelastoma. Extensive ventricular tissue resection can cause heart failure and even death. The best prognosis is associated with benign lesions (myxoma, fibroma, hamartoma, and fibroelastoma), where minimal margin resection is indicated and/or the growth can be eviscerated out. Unfortunately, most ventricular tumors are malignant with diffusely infiltrated margins, and less invasive ventricular tumors are uncommon. Cardiac transplantation may be performed in such non-resectable tumors, but recurrence is common.
- Zone 5 (Tumors of cardiac valves): Valve tumors are usually benign but need to be excised to reduce the risk of embolism. Most patients have a major liver tumor load which may require multiple surgical interventions. Anticoagulation required to maintain the mechanical valves becomes a burden during such interventions. The incidence of left-sided heart valve lesions is one-tenth that of right-sided valve lesions.

21.4 General Clinical Features

The cardiac tumors are clinically classified based on origin, location, and histology of the lesion [22]. The origin of the cardiac tumor may be primary or secondary; location can be intramural or intracavitary and histology of the lesion may be benign or malignant.

Cardiac tumors have a diverse clinical presentation that depends on the location of the tumor and whether these have benign or malignant histology. The cardiac tumors are usually asymptomatic and are diagnosed incidentally for workup of the cardiovascular system including echocardiography or magnetic resonance imaging (MRI). The systemic symptoms of atrial myxomas may mimic collagen vascular disease, malignancy, or infective endocarditis. Congestive heart failure is one of the presenting symptoms of cardiac tumors, and in such a case, they are usually of ventricular origin or they are intramural in location. The LV myxoma presents as syncope, angina, or embolism. The patient remains at risk of sudden death, primarily due to sudden embolization of the tumor. This mandates early surgical excision [23].

The symptoms of cardiac tumors may be broadly categorized as:

- Systemic symptoms: joint pains, fever, weight loss, malaise, and fatigue with features of anemia polycythemia, leukocytosis, and thrombocytosis on the investigation.
- Obstructive symptoms: the symptoms are related to cardiac obstructive symptoms like congestive heart failure, pulmonary edema, dizziness, chest pain, syncope, and sudden cardiac death.
- Other related symptoms: cough, hemoptysis, tachyarrhythmias (atrial/ventricular), dyspnea, orthopnea, electrical conduction

abnormalities, pericardial effusion, and cardiac tamponade.
- Symptoms due to systemic embolization of cardiac lesion: transient ischemic attack, stroke, myocardial infarction, and embolism (renal artery, lower/upper extremity, pulmonary).
- Symptoms due to metastasis of cardiac tumors: these symptoms are related to the site of systematic metastasis like the lungs, brain, or bones.

The salient features of various cardiac tumors are described in the following sections:

Congestive Heart Failure The patient presents with right-sided heart failure signs when the right-side heart chambers are involved and obstructed with a tumor. The patient presents with edema, ascites, hepatomegaly, and raised jugular venous pressure. Right heart failure progresses rapidly in sarcomas. If the inflow into the LV is obstructed, left heart failure occurs, and patients present with dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and evidence of pulmonary congestion in chest skiagram. A few series have reported dyspnea as the most common symptom in patients with myxomas [24]. Hypoxia may be secondary to a low pulmonary flow caused by mechanical obstruction due to tumor, thus increasing the work of breathing; shunting of blood flow can occur in the heart through the foramen ovale or due to pulmonary embolization.

The left atrial myxomas are pedunculated with its atrial wall attachment. So, these remain mobile and may pop-in and pop-out of the mitral valve and obstruct inflow into the LV as well as cause mitral valve incompetence. The symptomatology of LA myxoma thus mimics mitral valve disease [25]. Unlike in mitral valve disease, atrial fibrillation is not normally present because there is no LA enlargement. Paroxysmal heart failure or dyspnea may be present, which may present only in certain body positions.

Thromboembolism Myxomas may remain asymptomatic and may be diagnosed only their tissue embolization causes symptoms. Myxomas have a gelatinous structure, and thus tumor fragments tend to break off and embolize. Thrombi formed may also embolize from the tumor surface. Some myxomas are very friable and embolize frequently but other tumors may do so occasionally. The site of embolism depends on the site of the tumor in the heart. Pulmonary embolism is commoner in right-sided cardiac tumors, while left-sided tumors embolize into the arterial system causing strokes, peripheral/visceral infarcts/ischemia, and peripheral vascular aneurysms. Based on the site of embolism, the patient can manifest signs and symptoms of infarction or ischemia of organs [25, 26]. The embolic phenomenon depends on the tumor morphology and is observed more with polypoid tumors as compared to round tumors and may be seen in about 30–40% of patients [26].

A high index of suspicion must be kept for an intracardiac tumor in young patients presenting with sinus rhythm with an embolic stroke. Multiple small systemic emboli mimic infective endocarditis or vasculitis. Larger emboli commonly embolize to the cerebral arteries and occlude them. The other arteries commonly occluded are the renal artery and femoropopliteal artery [27]. The infra-renal aorta may be blocked by a large myxoma at the aortic bifurcation. The cardiac tumors may emboli and occlude the aorta or its branches including the celiac trunk branch to the renal artery and may result in ischemic injury to the kidney, spleen, ascending colon, and small intestine [28].

Heart Sounds Systolic or diastolic murmurs are heard, especially in intracavitary lesions, due to turbulence of flow caused by obstruction. In atrial myxoma, the first heart sound may be split and a tumor plop heard. The tumors may also make the valves incompetent causing mitral or tricuspid regurgitation. Auscultatory findings in patients of LA myxoma are like those in mitral valve disease. Signs of pulmonary congestion such as loud wide split S1 (heard because LA pressure is elevated); S4 sound; a pan-systolic murmur (loudest at apex) resembling the mitral regurgitation murmur; and a diastolic murmur resulting from flow obstruction

at the mitral valve may be present [29]. The movement of the myxoma lesion toward the left atrium in systole makes a "tumor plop" in early systole. This tumor plop is heard about 100 milliseconds after S2 due to tumor movement into the LV during diastole or due to the tumor striking the myocardium. The degenerative valvular changes can occur due to mechanical damage by moving tumor lesions [30].

Constitutional Symptoms Weight loss, anemia, fever, exhaustion, arthralgia, muscle pain, night sweats, coughing, leukocytosis, and raised acute phase reactants may be present. A cardiac tumor must be suspected if constitutional symptoms are present along with findings suggestive of valve lesion. Malignant tumors may have features of hemorrhagic pericardial effusion. Intramural tumors may present with symptoms of hypertrophic or restrictive cardiomyopathy.

Arrhythmia Intramural tumors may impede electrical impulse conduction by conduction tissue infiltration or by myocardial irritation. Tumors like angiomas and mesotheliomas which arise near the atrioventricular node may be associated with a complete heart block [22]. Atrial tumors may trigger supraventricular tachyarrhythmias like atrial fibrillation/flutter and ectopic atrial tachycardia. Ventricular myocardium cardiac lesions may trigger ventricular premature contractions, ventricular tachycardia, and ventricular fibrillation and even lead to sudden cardiac arrest.

Obstruction Large atrial tumors may obstruct the atrioventricular valve flow. In left atrium (LA) myxoma, a change in position may obstruct the mitral orifice completely causing cardiac arrest, and body manipulation may be required to relieve the obstruction [29]. Ventricular tumors may obstruct the ventricular outflow tract leading to chest pain, breathlessness, or syncope. Though rare, primary cardiac tumors can cause superior vena cava obstruction resulting in life-threatening cerebral/neck edema and airway obstruction [31]. Syncope is a rare but sinister symptom associated with LA myxoma that results from transient occlusion of the LV inflow by the prolapsing tumor. Approximately 20% of patients experience severe dizziness/syncope because of this left-sided obstruction [32].

Obstruction by the tumor may lead to various cardiovascular fluctuations including acute hypotension, venous congestion, hepatomegaly, ascites, and peripheral edema. Atrial myxomas create a fixed cardiac output state by restricting the mitral/tricuspid valve outflow, and thus hypotension occurs whenever systemic vascular resistance falls (Fig. 21.1 displays a transthoracic echocardiography image of left atrial myxoma crossing the mitral valve, while Fig. 21.2 displays a TEE image of a giant left atrial myxoma pop-

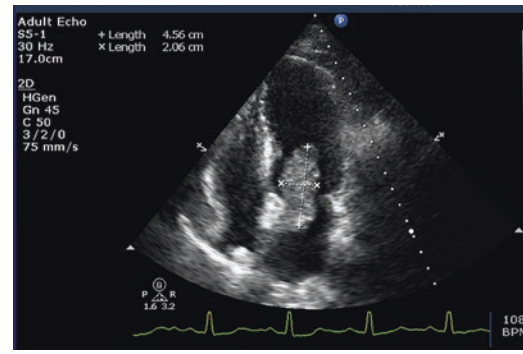

Fig. 21.1 A 2D transthoracic echocardiography image of left atrial myxoma crossing the mitral valve during diastole

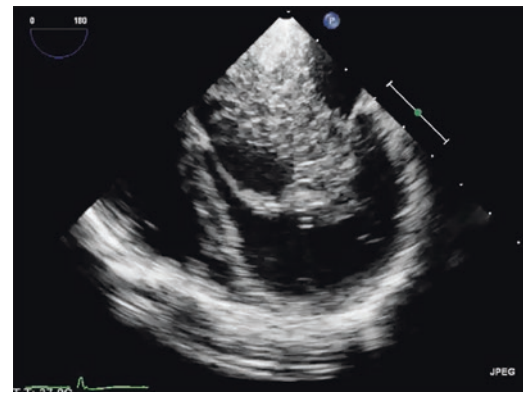

Fig. 21.2 A 2D transesophageal echocardiography image of a giant left atrial myxoma popping into the left ventricle and obstructing the mitral valve flow during diastole

ping into the left ventricle and obstructing the mitral valve flow during diastole). In case mitral orifice obstruction occurs with mitral regurgitation, then the patient may present with dyspnea on exertion which may progress to paroxysmal nocturnal dyspnea, orthopnea, and pulmonary edema [33].

21.5 Diagnosis

The diagnosis of cardiac tumors is usually made by echocardiography. The use of both modalities of thoracic and transesophageal echocardiography better delineates the location and extent of the cardiac lesions and thus is a better correlation with cardiovascular implications. Although the echocardiographic profile of a myxoma is distinct, it must be differentiated from valve vegetation and atrial thrombus (Fig. 21.3 shows a primary left ventricular apical tumor that could not be differentiated from an apical left ventricular thrombus on echocardiography).

Myxomas are heterogeneous and may have small lucent areas. Thrombi are usually homogenous in appearance and usually lie in the LA appendage [34]. Five percent of myxomas arise from the LA appendage, and these may present a diagnostic challenge on echocardiography [34]. The use of oral anticoagulation at times differentiates the diagnosis between myxomas and thrombus. Right atrial myxomas are commonly diagnosed as embolized or in situ thrombus. If echocardiography is inconclusive, magnetic resonance imaging (MRI) may help differentiate [34].

The surgical management of cardiac tumors requires detailed echocardiographic assessment for its tumor volume, its location, mobility, any obstruction to outflow, relation to adjacent structures, and valvular regurgitation. 3D TEE may further facilitate a detailed understanding of dynamic anatomy and accurately identify mitral valve pathology [35]. These findings help the operating surgeon for the site/size of the incision, siting of venous drainage cannulae, and cardiopulmonary bypass strategy.

Secondary tumors may be lesions extending into the heart (Fig. 21.4 depicts a transthoracic echocardiographic image of renal cell carcinoma extending in the right atrium from inferior vena cavae).

CT and MRI offer better fat identification and are excellent imaging modalities for the diagnosis of lipoma. MRI is useful to differentiate between thrombi, fibromas, myxomas, and fatty tissue [36]. CT helps in soft tissue discrimination and helps determine myocardial infiltration. However, these imaging modalities may not accurately distinguish a thrombus from a tumor [22].

The patient's clinical condition and the presence of metastatic spread must be gauged. Coronary angiography should be done to determine coronary obstructive disease, the dominant

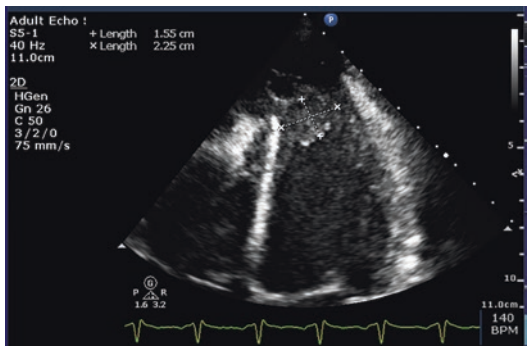

Fig. 21.3 A 2D transthoracic echocardiography image of a primary left ventricular apical tumor which could not be differentiated from an apical left ventricular thrombus on echocardiography

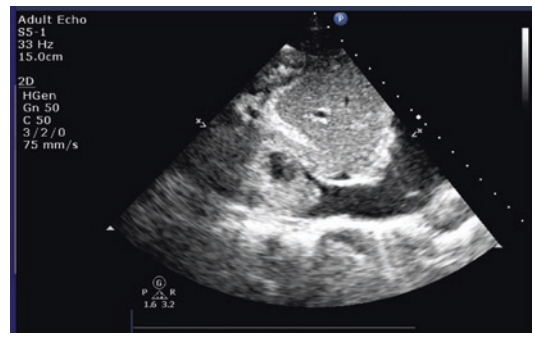

Fig. 21.4 A 2D transthoracic image of renal cell carcinoma extending from the inferior vena cava into the right atrium

coronary vessel, and coronary anatomy and to look for tumor feeding vessels or tumor blush. CT, MRI, positron emission tomography, echocardiography, cardiac catheterization, and coronary angiography are usually undertaken once the lesion is diagnosed [2].

21.6 Surgical Management

Early surgical resection on cardiopulmonary bypass remains the preferred modality for cardiac tumor management. In histologically benign tumors, resection is advised as patients may suffer effects of obstruction, systemic embolization, or arrhythmia. Minimum intraoperative manipulation of the heart is advised, especially during vena cava cannulation for cardiopulmonary bypass, to prevent dislodgement of tumor fragments. Although surgical survival following resection is good, meticulous follow-up is recommended to detect recurrence. The traditional approach in large tumors is resection of the tumor with extensive local reconstruction. Orthotopic heart transplantation [37] and autotransplantation (the heart is removed for back table resection, reconstructed, and re-implanted) [38, 39] have been performed for tumors with extensive cardiac involvement.

Delicate tumor handling during surgery is crucial. Suctioning of the tumor instead of excision, to avoid tumor fragmentation/migration, is advocated in patients with myxoma. The root of the pedicle is excised along with all layers of the adjoining interatrial septum. In cases of defect in the atrial septum, it needs to be closed with a pericardial patch. Residual lesions should be looked for after tumor excision. LV myxomas are excised by a transaortic approach or transvalvular approach after atriotomy to avoid the potential adverse hemodynamic effects of ventriculotomy.

21.7 Anesthetic Management

The anesthetic concerns in patients with right-sided tumors include acute right ventricular failure, hypoxemia, low cardiac output, tamponade, and pulmonary embolism [40]. Left-sided tumors are associated with systemic embolization, low cardiac output, paroxysmal dizziness/breathlessness with the change of position, and low cardiac output.

Preoperative evaluation should focus on accurate diagnosis, tumor size assessment, tumor location, valve involvement, tumor mobility, blood flow obstruction, cardiac function, and comorbidities. Preoperative hypovolemia should be avoided as it may promote obstruction of blood flow and precipitate low cardiac output. Intravenous fluid loading may be given preoperatively to prevent atrial wall prolapse, which can further restrict the already compromised atrial volume.

Preoperative sedation outside of the operation room should be avoided as it can worsen patient hemodynamics and can even result in cardiovascular collapse. Change in the patient position itself may precipitate hypoxemia and hypotension as tumor obstruction may reduce cardiac output and promote intracardiac shunting. An increase in pulmonary dead space may also occur due to decreased flow through the atrioventricular valves [41] and so oxygen supplementation must be provided. Air bubbles in the intravenous lines must be prevented as distal air embolism can occur due to the right to left shunt due to the involvement of the inter-atrial septum.

Emergency CPB Preparation for initiating emergency cardiopulmonary bypass is mandatory as preoperative sedation and induction of general anesthesia can cause hemodynamic collapse. Surgical part preparation and draping must be done before the induction of anesthesia. Preparation for femoro-femoral cannulation and bypass must be made in case the tumor is large, mobile, and likely to cause obstruction.

The induction of general anesthesia must be slow and smooth, with a titrated dose of the agent, to prevent hypotension due to vasodilatation and myocardial depression. Patients may present with fixed cardiac output due to mechanical obstruction. On induction of anesthesia, a fall in system vascular resistance and the resultant decrease in venous return may increase the

mechanical obstruction. Close patient monitoring, including invasive blood pressure, is recommended during the induction of anesthesia for early detection of hemodynamic compromise. The cardiac lesion can lead to a wrecking ball effect and may lead to valve incompetence [41].

Central venous cannulation, for monitoring central venous pressure, must be done after induction of anesthesia. Care should be taken during guidewire insertion and placement of the central catheter in patients being operated for the right atrial myxomas. The tip should be proximal to the superior vena cava-right atrium junction. In patients with right-sided mass, central venous pressure monitoring may not be an accurate measure of right ventricular filling.

Surgery is done by median sternotomy on cardiopulmonary bypass. Venous cannulation for initiating cardiopulmonary bypass can be difficult especially in patients with right atrial myxoma. Cannulations of the superior and inferior vena cavae must be done under TEE guidance to avoid tumor trauma. Complications such as hypotension, conduction defects, arrhythmias, and embolization can occur during the initiation of cardiopulmonary bypass [42].

Sudden dilatation of the right ventricle may cause acute right ventricular failure. Also, this may lead to shifting of the interventricular septum toward the left which in turn can severely reduce cardiac output by reducing the left ventricle volume.

Intraoperative Monitoring The modality of cardiac output measurement needs to be chosen cautiously as pulmonary artery catheter insertion is to be avoided. The non-thermodilution technique needs to be preferred which avoids insertion of pulmonary artery catheters. TEE monitoring offers multiple benefits such as diagnosis confirmation, tumor location/attachment to cardiac wall, cardiac chamber filling status, cardiac function, and comorbidities. TEE can also guide the surgical team during the surgical excision and thus prevent tumor dislodgement/embolization [43]. TEE monitoring helps detect intraoperative hemodynamic compromise and lethal events in patients undergoing giant cardiac tumor excision [40].

The use of inotropes must be judicious in these patients before the excision of the tumor. Inotropy may narrow the passage for intracardiac blood flow and worsen the mechanical obstruction [40]. So adequate fluid loading needs to be ensured when inotropes are used for increasing myocardial contractility to improve hemodynamics. Inotropic support may be required post-excision to help wean the patient off cardiopulmonary bypass.

21.8 Cardiac Transplantation and Artificial Heart

Tumors with extensive local spread but without metastasis can be treated by autologous heart transplantation or artificial heart as a last resort. However, the risk of recurrence needs to be ascertained due to micrometastasis which can further proliferate due to immunosuppression. The surgical technique needs to be toward radical resection with the addition of chemotherapy to improve the overall outcome [44].

With availability of better imaging techniques, cardiac tumors are being diagnosed more often. Apart from manifestations due to the cardiac lesion, the tumors have several systemic manifestations. Mechanical obstruction to cardiac output and the potential effects of embolization of tissue fragments and thrombi over them mandate early surgery to excise the tumor. Accurate preoperative assessment, avoidance of hypovolemia, timely use of cardiopulmonary bypass, and intensive hemodynamic monitoring are essential to managing these patients. The anesthetic technique needs to be appropriate for smooth induction. The prognosis is poor in malignant tumors.

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Anesthesia for Brain Tumors

22

Varun Jain and Girija Prasad Rath

22.1 Introduction

Tumors of the central nervous system (CNS) constitute about 2–4% of all malignancies [1]. CNS malignancies have the most varied presentation of all tumor types. Different anatomical locations in the CNS have a special predilection for specific tumor types. About 85% of the brain tumors are primary and 60% of them present in the supratentorial compartment (Fig. 22.1). The tumors may be intra-axial, i.e., they originate from the brain parenchyma or intraventricular tissue, or extra-axial. About one-sixth of cancer patients develop cerebral metastasis, which constitutes the remaining 15% of brain tumors.

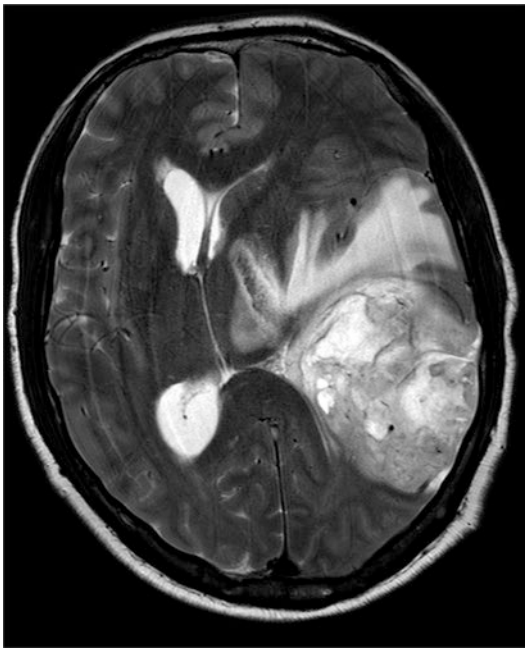

Fig. 22.1 Large well-defined supratentorial space-occupying lesion appearing heterogeneously hyperintense on T2-weighted axial images in the left parietotemporal region with significant perilesional edema, effacement of left ventricle causing midline shift toward the right side

22.1.1 Tumor Characteristics

The World Health Organization (WHO) in 2016 classified the tumors of CNS (Table 22.1) into a detailed list based on both histological and molecular parameters [2]. Most of the primary tumors arise from astrocytes, oligodendrocytes, or arachnoidal cap cells. Well-differentiated astrocytomas are the least aggressive but account for only about 3% of all brain tumors. Anaplastic astrocytomas account for 15–20% of primary brain tumors and usually disrupt the blood-brain barrier. Glioblastoma multiforme is the most common and most aggressive primary

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Table 22.1 Characteristic of brain tumors

Tumor type	Example	Characteristics
Diffuse astrocytic and oligodendroglial tumors	Anaplastic astrocytoma, Glioblastoma	Most common primary brain tumors and most malignant
Ependymal tumors	Ependymoma	Spreads via CSF – "seeding," in children common in the posterior fossa, in adults mostly intraspinal
Choroid plexus tumors	Choroid plexus papilloma	Infratentorial in adults and supratentorial in children
Neuronal tumors	Ganglioglioma, Dysembryoplastic neuroepithelial tumor (DNET)	Typically occurs in children. Location—temporal, frontal
Tumors of the pineal region	Pineoblastoma	Common in children, radiosensitive, CSF spread present
Embryonal tumors	Medulloblastoma	Most common pediatric brain malignancy, location—cerebellum with brainstem invasion
Tumors of cranial and paraspinal nerves	Schwannoma Neurofibromas	Associated with neurofibromatosis
Meningiomas	Meningioma	Slow-growing, extra-axial tumor, commonly located on the falx, convexity, or sphenoid bone. Complete excision possible in most cases
Mesenchymal, non-meningothelial tumors	Hemangioblastoma	Most common primary intra-axial tumor in the posterior fossa of adults. Highly vascular
Lymphomas	Diffuse B-cell lymphoma	Very responsive to steroids initially
Histiocytic tumors	Langerhans cell histiocytosis	Common in skull
Germ cell tumors	Germinoma	Occur in midline
Tumors of the sellar region	Craniopharyngioma	Develops from Rathke's pouch, common in children, risk of hypothalamic injury
Metastatic tumors		Mostly multiple in number

CSF - cerebrospinal fluid

brain tumor and constitutes 30% of all brain tumors. On radiological imaging, they are seen as irregular contrast-enhancing ring lesions with cerebral edema and mass effect. The median survival despite treatment with radiation, chemotherapy, and surgical decompression is only a few months. Pilocytic astrocytoma is a less common (1%) histologically benign tumor, mostly seen in children or young adults, and amenable to complete treatment by surgical resection. It usually arises in the cerebellum and has a contiguous cyst.

Oligodendrogliomas account for 6% of primary brain tumors. Seizures are the most common symptom and precede the diagnosis of a tumor by 5 to 10 years. These are calcified and radio-resistant. Meningiomas comprise the second largest group of tumors representing 15–20% of brain tumors. If location permits, these tumors can be completely resected. They have a high propensity for bleeding, and therefore, preoperative tumor embolization is advocated in very large tumors. Pituitary tumors, which are mainly adenomas, represent another 10–15% of all intracranial tumors. In children, both gliomas and medulloblastomas are common tumors.

Table 22.2 Syndromic association of brain tumors

Syndromes	Brain tumor
von Hippel- Lindau syndrome	Hemangioblastoma
Tuberous sclerosis	Subependymal astrocytoma
Neurofibromatosis type 1	Astrocytoma, optic glioma, neurofibroma
Neurofibromatosis type 2	Vestibular schwannoma, meningioma, astrocytoma
Turcot syndrome	Glioblastoma multiforme, medulloblastoma

CNS Central nervous system

Over 70% of brain metastasis arises from the lung, breast, or gastrointestinal tract. Appropriate treatment must be decided based on the number and location of metastasis, the overall general condition of the patient, and the present status of the primary tumor. Certain genetic diseases such as von Hippel-Lindau (VHL) syndrome, tuberous sclerosis, and neurofibromatosis type 1 (NF-1) may present with multiple intracranial tumors (Table 22.2).

22.1.2 Cerebral Autoregulation

Supratentorial tumors predictably change the intracranial hemodynamics. Normal intracranial pressure (ICP) is about 10–15 mmHg in adults. When the tumor is small, the increase in ICP is prevented by a shift of intracranial blood from veins and the displacement of cerebrospinal fluid (CSF). As these compensatory reserves are overwhelmed by increasing tumor mass, the increase in ICP is exponential with loss of cerebral autoregulation and risk of cerebral herniation syndrome [3]. This hypothesis is based on the Monro-Kellie doctrine, which suggests the brain as an incompressible structure surrounded by a rigid skull [4].

Clinical conditions where ICP can rise significantly despite a small tumor size are vasogenic edema, hemorrhagic conversion of a supratentorial tumor, or obstructive hydrocephalus due to posterior fossa tumor. Vasogenic edema occurs due to the leakiness of cerebral blood vessels induced by the release of protein products from malignant tumors [5]. This area of vasogenic edema is visible on T2- or fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI). It also represents the area of dysregulated autoregulation and may respond to steroid therapy. Hemorrhagic conversion happens when the center of the rapidly enlarging tumor tissue is outstripped of its blood supply. This may lead to sudden deterioration of the clinical status of the patient.

Cerebral perfusion pressure (CPP) is the difference in mean arterial pressure and ICP. Cerebral autoregulation aims to keep adequate blood flow to the brain during varying CPP. It does so by changing the diameter of cerebral arterioles in response to fluctuating blood pressure levels. Autoregulation is effective between a CPP of 50 and 150 mmHg and becomes pressure-dependent at either end. A critical increase in ICP decreases CPP, which compensates by vasodilating cerebral vessels to maintain constant cerebral blood flow (CBF). This in turn increases the cerebral blood volume (CBV), further decreasing intracranial compliance and increasing ICP, and creating a vicious circle.

22.1.3 Effect of Anesthetic Agents on Cerebral Blood Flow (CBF), Metabolism, and Autoregulation [6]

(a) *Intravenous agents* such as barbiturates (thiopentone), etomidate, and propofol cause dose-dependent reduction in CBF, the cerebral metabolic rate of oxygen ($CMRO_2$), and, hence, ICP. The decrease in CBF and $CMRO_2$ occurs until isoelectric EEG is achieved. The decrease in $CMRO_2$ is approximately 30–50%. All these agents are cerebral vasoconstrictors. Thiopentone and propofol have possible neuroprotective effects provided systemic blood pressure is maintained. Caution must be exercised when etomidate is used in patients with a history of seizures. Propofol infusion syndrome with metabolic acidosis and cardiac failure can occur if high doses of propofol are used for a prolonged period (more than 5 mg/kg/h for 48 h or more). Propofol is the preferred agent if neurophysiologic monitoring is planned because of its short duration of action and minimal interference with evoked potential recordings.

Ketamine increases CBF, $CMRO_2$, and, hence, ICP. Therefore, it should be used judiciously in patients with signs of raised ICP and compromised CPP. However, many recent studies have shown the neuroprotective role of ketamine with N-methyl-D-aspartate (NMDA) antagonism.

(b) *Other intravenous agents: Benzodiazepines* produce a decrease in $CMRO_2$ and CBF. *Opioids* decrease $CMRO_2$ and CBF and have a variable effect on ICP. Sufentanil and fentanyl bolus has been implicated in an increase in ICP, whereas remifentanil and alfentanil have minimal effect. Similarly, dexmedetomidine causes a decrease in CBF with minimal change or decrease in $CMRO_2$ and ICP. In general, all intravenous agents preserve cerebral autoregulation in standard doses.

(c) *Inhalational agents*: Nitrous oxide (N_2O) decreases brain metabolism. N_2O increases CBF, $CMRO_2$, and ICP. The ICP increase by N_2O can be obtunded by concomitant administration of propofol, barbiturates, or hyper-

ventilation. N_2O may increase the volume of intracranial air and increases the incidence of nausea and vomiting. The effect of volatile anesthetic agents on ICP is dose-dependent. At lower MAC (≤0.5 MAC) vasoconstriction caused by $CMRO_2$ suppression is predominant, but at higher MAC (≥1.5 MAC) the vasodilating property is predominant. The increase in CBF is in the order of halothane > desflurane > isoflurane > sevoflurane. All inhalational agents impair cerebral autoregulation when used in high concentrations. They cause an increase in ICP; desflurane is most potent followed by isoflurane and the least with sevoflurane.

(d) *Neuromuscular blocking agents: Depolarizing neuromuscular blocking agents* like succinylcholine causes an increase in ICP which can be prevented by maintaining an adequate depth of anesthesia, using a prior de-fasciculation dose of non-depolarizing muscle relaxant or lidocaine [7]. *Non-depolarizing neuromuscular blocking agents* do not have any effect on CBF and $CMRO_2$. An increase in ICP can occur if ventilation is not controlled and hypercapnia occurs. *Lidocaine* at lower doses is effective in decreasing $CMRO_2$ and CBF. It also prevents an increase in ICP. However, at higher doses, it has the potential of causing seizures.

22.2 Preoperative Evaluation

A preoperative visit helps the anesthesiologist to become familiar with the patient. Surgical positioning, any special intraoperative requirements such as neuromonitoring, blood conservation strategy, and hyperventilation are discussed beforehand.

22.2.1 History and Medical Examination

(a) *Neurological examination* includes evaluation of signs and symptoms of the patients, their onset, and severity. Mental status examination (e.g., by mini-mental status score) and a thorough neurological examination to assess all the deficits are essential. It helps the clinician to understand the intracranial compliance and the severity of raised ICP and find out whether the brain can tolerate any degree of intraoperative hemodynamic changes. Glasgow Coma Scale (GCS) score is routinely utilized for documentation of neurological status. Any new deficit on emergence is suggestive of injury to the normal brain parenchyma. Preoperative intracranial hypertension (ICH) may present are headache, nausea, vomiting, unilateral pupillary dilation, oculomotor or abducens nerve palsy, and diminished sensorium. Computed tomographic (CT) scan or MRI may show a midline shift (more than 5 mm) and obliteration of cisterns.

(b) *Cardiovascular examination* is important to assess the effort tolerance of the patient. Organ perfusion is dependent on the heart. If the cardiovascular function is compromised, there are important considerations during surgical positioning. The cardiac compromised state may occur because of the use of chemotherapeutic agents (e.g., cardiomyopathy caused by doxorubicin).

(c) *Respiratory system examination* should be done in two parts, upper airway assessment and lung parenchyma assessment, to decide on the adequacy of oxygenation. Airway assessment has been discussed in detail elsewhere in this book. Prolonged surgery and difficult positioning put a lot of stress on the cardiorespiratory system. Additionally, hyperventilation may be utilized intraoperatively to decrease brain bulge. Forty percent (40%) of brain metastasis arise from the lungs, and therefore the primary pathology may itself compromise the respiratory system [8].

(d) Glioblastoma multiforme is associated with iatrogenic bleeding as well as the risk of thrombosis due to the release of procoagulants [9]. Therefore, the coagulation profile must be assessed for these cases. *Kidney function* may be compromised because of

decreased oral intake as well as repeated use of diuretics like mannitol or furosemide or contrast agents. Besides, electrolyte imbalance is common due to decreased fluid intake, diuretics, or hypothalamo-pituitary disturbances leading to diabetes insipidus (DI), cerebral salt wasting syndrome (CSWS), or syndrome of inappropriate antidiuretic hormone secretion (SIADH). Hyperglycemia is frequently encountered due to the use of steroids. A pituitary adenoma may be associated with a variety of endocrine manifestations like Cushing's syndrome, acromegaly, hypothyroidism, etc. Primary brain tumors have little effect on the gastrointestinal system; however, nausea, vomiting, and stress ulcers in the stomach may occur due to increased ICP or the use of steroids.

(e) *Medications:* Prolonged usage of anticonvulsants such as phenytoin and valproate may lead to disturbances in the liver and coagulation system. These medications may alter the liver metabolism of other medications. Anticonvulsants, however, should be continued during the perioperative period. Steroids are used to reduce vasogenic cerebral edema. Perioperative steroid cover is provided to avoid withdrawal syndrome. These patients may also have a deranged blood sugar level. In most cases, anticoagulants and antithrombotic agents are discontinued before surgery because of the increased risk of bleeding and postoperative hematoma formation.

(f) *Diagnostic tests* such as complete blood count, renal function tests, liver function tests, coagulation profile, electrocardiogram (ECG), and chest x-ray (CXR) should be performed as indicated in any major surgery. Besides that, 2-D echocardiography (ECHO) and stress ECHO must be done in case of compromised cardiac function and expected major blood loss. It is a good practice for the anesthesiologists to understand the preoperative CT or MRI scans of the patients; to confirm tumor location, size, and type; and to check for signs of raised ICP and vasogenic edema.

22.3 Planning for the Anesthesia

The anesthesiologist should understand the following aspects before planning for anesthesia

- Tumor location and surgical approach: to decide positioning, degree of neck flexion, etc.
- Vascularity of tumor and expected blood loss: plan for central venous catheter, blood cell savage, use of tranexamic acid, and role of preoperative embolization to reduce vascularity.
- Does the patient have features of raised ICP? (e.g., vasogenic edema or large tumor): requirement of intraoperative ICP lowering measures.
- The requirement of neurophysiological monitoring during the intraoperative period.

22.4 Positions During Neurosurgery

Prolonged duration of procedures requires appropriate padding of the pressure points to prevent pressure sores and nerve injuries and application of lower limb compression stockings to prevent deep vein thrombosis (DVT). Head-up should be attempted in all positions to allow adequate venous drainage. The supine position is required for frontal, temporal, or parietal tumors. Extreme neck flexion should be avoided to prevent jugular venous compression. Semi-lateral (Jannetta) and lateral position is utilized for posterior parietal, occipital, or cerebellopontine angle tumors. An axillary roll helps prevent brachial plexus injury during such a position. Prone (Concorde) position is required for occipital lobe and posterior fossa tumors. The head is usually fixed on a three-pin (Mayfield's clamp) or four-pin (Sujita's clamp) head holder to prevent mobility. Flexion of the neck may be acute, thus necessitating the use of a flexometallic endotracheal tube (ETT), anti-sialagogue measures, and proper fixation of ETT. If horseshoe is used to rest the head in a prone position, care should be taken to avoid direct pressure on the eyeballs to prevent postop-

erative vision loss. Frames or bolster support should be such that the abdominal compression is not significant. The sitting position is used to access the midline structures in the posterior fossa. Knees should be at the level of the heart. Positioning must be gradual to prevent hemodynamic instability. A minimum of two-finger-width distance between the chin and sternum should be maintained during neck flexion to avoid jugular compression which may affect venous drainage. Macroglossia, quadriplegia, pneumocephalus, hemodynamic instability, and venous air embolism (VAE) are common complications encountered with this position.

22.5 Anesthetic Management

(a) Patients with a brain tumor may be unusually sensitive to the sedative premedicants, usually administered under supervision for extremely anxious patients. Short-acting benzodiazepines such as midazolam are given in titrated doses to allay anxiety. Antiepileptics, steroids, histamine receptor (H_2) blockers, and cardiac medications are usually continued during the preoperative period. ECG, pulse oximetry (SpO_2), noninvasive blood pressure (NIBP), temperature, end-tidal carbon dioxide ($EtCO_2$), and urine output monitoring should be done in all cases. The arterial line is preferred for beat-to-beat blood pressure recording; it also helps in the analysis of arterial blood gases, electrolytes, and osmolality. CVP catheter placement is preferred in patients at risk of massive intraoperative fluid shifts or VAE or in obtunded patients with the need for prolonged mechanical ventilation. If CVP is inserted to aspirate air in the case of VAE, its position at the SVC-RA junction must be confirmed with P-wave monitoring on ECG or by transesophageal echocardiography (TEE). Neuromuscular monitoring should be done in non-hemiparetic limbs when muscle relaxation is used. Because of upregulated acetylcholine receptors in the hemiplegic limb, neuromuscular monitoring in the affected limb might lead to inadvertent overdosing of muscle relaxants. Monitoring the coagulation parameters is essential. They may be deranged due to increased expression of tissue factor (TF) from astrocytic tumor or fibrinolysis [9], use of antiepileptic drugs leading to suppression of bone marrow [10], or co-existing paraneoplastic syndrome. These associations may promote a procoagulant state.

(b) Depth of anesthesia monitoring with processed electroencephalography (EEG)-based monitors like bispectral index (BIS) or entropy is useful when intravenous agents and lighter depth of anesthesia is needed intraoperatively like electrocorticography (ECoG) monitoring or evoked potential (EP) monitoring. Transthoracic Doppler or TEE should be considered in high-risk cases of VAE and blood loss. Placement of these probes is challenging while the patient is in a lateral or prone position. Placement of TEE should be avoided where extreme neck flexion is desired.

(c) The goal of induction of anesthesia is to prevent sudden and severe variations in hemodynamics which may increase ICP and compromise the CPP. Preloading of IV fluids may help prevent hypotension during induction of anesthesia in dehydrated patients. Induction may begin with the injection of an opioid analgesic such as fentanyl, sufentanil, or remifentanil followed by a bolus dose of thiopentone (4–6 mg/kg) or propofol (1–3 mg/kg) in titrated doses. Etomidate (0.2–0.4 mg/kg) may be preferred in frail, elderly, or in poor cardiac reserve patients who are at risk of hypotension. After confirmation of adequate ventilation, a non-depolarizing neuromuscular blocking agent such as rocuronium, vecuronium, atracurium, or cis-atracurium is given. An additional bolus of thiopentone, propofol, fentanyl, or lidocaine may be given before tracheal intubation to prevent hemodynamic responses due to laryngos-

copy and intubation. The ETT must be secured properly as accidental misplacement can be troublesome during the intraoperative period.

(d) Application of skull pin is one of the most painful steps which must be suppressed by infiltration of local anesthetics at the pin site or scalp block or by deepening the level of anesthesia with either additional boluses of propofol 1 mg/kg or increasing inspired concentration of inhalational anesthetics, analgesia with additional boluses of opioids, use of antihypertensive agents such as labetalol 0.5 mg/kg, esmolol 1 mg/kg, or a combination of these [11].

(e) The maintenance goal of anesthesia is to provide a lax brain to aid the neurosurgeon for adequate resection of the tumor. This requires the maintenance of adequate depth of anesthesia and ensuring that the metabolic demands of the brain are met. Inhalational agents (especially sevoflurane) are preferred as maintenance agents in patients with no signs of raised ICP because of easy titratability and predictable recovery. The vasodilatory effect of inhalational agents can be prevented by mild hyperventilation. Although controversial, nitrous oxide can be avoided as it increases $CMRO_2$ and CBF. Propofol at a dose of 3–8 mg/kg/hr is the preferred IV agent because it provides optimal operating conditions by decreasing ICP and preventing brain bulge [12]. It is recommended if the patient shows signs of raised ICP or develops intraoperative brain bulge.

(f) The practice is to maintain normotension, normovolemia, and normal to mild hyperosmolality (290–320 mOsmol/kg). Glucose-containing fluids and hypo-osmolar solutions should be avoided as they may cause brain edema. Normal saline and newer crystalloids like plasmalyte are commonly used. Hydroxyethyl starch (HES 130/0.4) is a useful volume expander till an adequate amount of blood is available in case of major bleeding. A hematocrit above 24% is desirable. A slow infusion of 20% mannitol (0.5–2 mg/kg) or 3% NaCl (3–4 ml/kg) helps in osmotic dehydration of the brain before dural opening.

(g) Intraoperative brain relaxation is necessary to help surgeons approach the tumor without unnecessary pressure exerted by retractors. Preventive measures include proper positioning without over-flexion of the neck, slight head-up position, osmotic agents, steroids if there is vasogenic edema, adequate ventilation targeting arterial partial pressure of carbon dioxide ($PaCO_2$) 32–36 mmHg without peak airway pressures (Paw) exceeding >30 cmH_2O, or use of propofol as maintenance agent with normotension. In case the brain is tight before dural opening, it is prudent to switch over to IV anesthetic agents like propofol, deepening the depth of anesthesia, liberal use of osmotic diuretics, hyperventilation to keep $PaCO_2$ between 28 and 32 mmHg, and keeping blood pressure slightly high (MAP 90–100 mmHg). CSF drainage by the ventricular catheter may be done if placed before surgery.

22.6 Emergence from Anesthesia

Sympathetic hyperactivity occurs during emergence and tracheal extubation along with cardiorespiratory changes. The hypertensive response may lead to intracranial hemorrhage [13]. Hyperemia with CBF velocity 60–80% above baseline has been demonstrated at emergence [14]. Therefore, the objective of recovery is to maintain stable blood pressure and avoid coughing, bucking, and shivering. Extubation should be performed once the patient is fully awake and has adequate breathing efforts. Beta-blockers, labetalol, lidocaine, and dexmedetomidine have been attempted in varied doses and methods to obtund the pressure responses. Nitroglycerine and sodium nitroprusside are cerebral vasodilators and therefore not preferred because of the risk of increased ICP. Close monitoring and blood pressure control are desirable during the postoperative period as the risk of neurological deterioration due to intracranial hemorrhage is high in the first 6 hours after surgery [15].

(a) *Early Emergence*: An awake patient is the best neurological monitoring available [15]. Therefore, all patients who are conscious and cooperative preoperatively with the uneventful intraoperative course should have a good recovery; the trachea is extubated once the criteria are met. Planning for early emergence should begin from the preoperative period, and care should be taken to maintain normothermia, normotension, normoglycemia, normocarbia, and adequate hemoglobin. The advantage of early emergence is that it happens in front of the team aware of the preoperative neurological status and can recognize any new-onset neurological deficit easily. On the other hand, it carries the risk of larger changes in hemodynamics and a greater risk of respiratory complications.

(b) *Late Emergence*: If the patient was drowsy during the preoperative period, had features of raised ICP, compromised autoregulation, and with a surgical course that was eventful with prolonged surgery (more than 6 hrs), major bleeding, and possible postoperative cerebral edema, it is advisable not to extubate the trachea. Late emergence allows for better hemostasis and improved intracranial autoregulation. However, a new-onset neurological deficit may be missed.

(c) *Delayed Emergence*: Anesthetic causes of delayed emergence should be readily identified and corrected. They could be hypothermia, anesthetic overdosage, electrolyte imbalance, seizures, etc. However, if the patient fails to awaken even after 20–30 minutes and common causes are ruled out or if the pupils are unequal or new-onset focal neurological deficit is present, a CT or MRI scan is advisable to rule out pneumocephalus, cerebral edema, intracranial hemorrhage, vessel occlusion, or ischemia.

22.7 Postoperative Care

Airway control and adequate respiratory effort are essential as both hypoxia and hypercarbia carry the risk of secondary brain injury. Hence, opioid analgesia has to be supplemented with other non-narcotic drugs to control pain with less probability of respiratory complications. Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are routinely used for the management of post-craniotomy pain. However, NSAIDs cause platelet aggregation, and therefore, should not be used in patients at risk of bleeding. Scalp block or incision site infiltration with longer-acting local anesthetics reduces opioid consumption and prolongs the postoperative pain-free period [16]. Nausea and vomiting after craniotomy may occur in up to 50% of cases in the first 24 hrs [17]. Therefore, prophylactic antiemetic should be administered before emergence and has to be continued for 24 hrs during the postoperative period. Routine anti-seizure prophylaxis for tumor resection surgery in the brain is not warranted and should be stopped, if initiated, within a week after surgery [18, 19]. Currently, levetiracetam is preferred over phenytoin because of fewer side effects with the former.

22.8 Specific Scenarios

22.8.1 Posterior Fossa Tumor

The posterior fossa contains the cerebellum, midbrain, pons, medulla, and multiple cranial nerves in a small rigid bony compartment (Fig. 22.2). Any space-occupying lesion in the posterior fossa can increase ICP; most commonly, it is due to CSF flow obstruction. About two-thirds of primary brain tumors in children occur in the posterior fossa. The posterior fossa tumors include medulloblastoma, cerebellar astrocytoma, brain stem glioma, and ependymoma. Hemangioblastoma is the most common adult primary cerebellar tumor. It can occur as part of the von Hippel-Lindau (VHL) syndrome. Acoustic schwannomas are benign tumors and commonly occur after the age of 60 years. Bilateral tumors can occur as part of neurofibromatosis type 2 (NF-2). A thorough preoperative examination with emphasis on the cardiorespiratory system and lower cranial nerve function

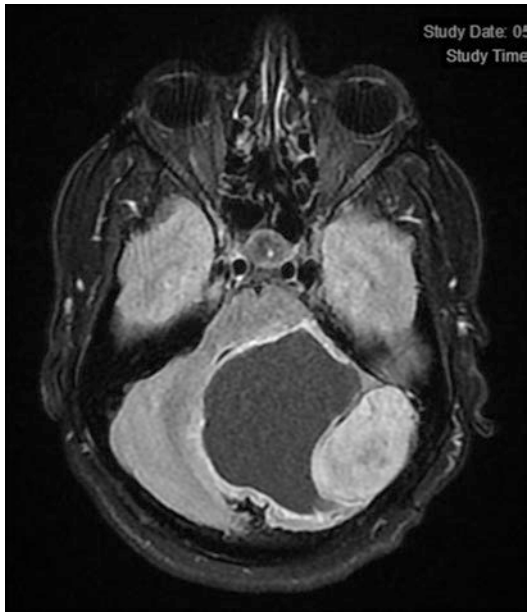

Fig. 22.2 Well-defined round homogenously enhancing extra-axial lesion in posterior fossa closely abutting the distal third of left transverse sinus with a large cystic component causing significant mass effect over the left cerebellar hemisphere compressing the fourth ventricle

is necessary. The cardiorespiratory assessment helps to analyze whether the patient will be able to tolerate varied positions under anesthesia. 2-D echocardiography may be done to rule out a patent foramen ovale (PFO), as it increases the risk of paradoxical air embolism (PAE). The presence of lower cranial nerve palsy indicates invasion or compression of the brainstem and helps plan tracheal extubation at end of surgery. Sitting, prone, lateral, and park-bench are some of the positions used to approach a posterior fossa tumor.

Intraoperative neurophysiologic monitoring requires a modified anesthetic plan with IV agents. Muscle relaxants may have to be omitted if motor evoked potential (MEP) or facial nerve monitoring is planned. The depth of anesthesia monitoring may be advantageous in such a scenario. IV agents are preferred over inhalational during maintenance of anesthesia because they have a lesser effect on cardiovascular structures and they reduce the severity of VAE by trapping microbubbles in the pulmonary circulation [20].

During emergence, a fully conscious patient obeying commands is suited for extubation provided there are no major intraoperative hemodynamic events due to brainstem handling and the risk of postoperative edema is less. As the posterior fossa is a small compartment, even a little volume change can lead to a significant increase in ICP. If postoperative mechanical ventilation is planned, then the flexometallic ETT has to be replaced with regular ETT.

Venous Air Embolism VAE occurs as a complication of posterior fossa surgery in a sitting position. It is due to the entrapment of air from open venous sinuses and diploic veins situated above the level of the heart. The incidence is up to 80% in sitting position, 15–25% in lateral and prone positions, and 10% in cervical laminectomy [21]. Entrapment of micro-air bubbles in pulmonary circulation leads to sympathetic vasoconstriction, pulmonary hypertension, ventilation-perfusion mismatch, and carbon dioxide (CO_2) retention. Sudden large-volume entrapment of air can lead to circulatory obstruction and cardiac arrest. VAE in children are more symptomatic and difficult to treat. Preventive measures include the liberal use of bone wax by the neurosurgeon. The anesthesiologist should maintain euvolemia and normotension and use lower limb stockings. The sensitivity of the pattern of monitors in detecting VAE is as below:

- TEE (0.02 ml/kg) > precordial Doppler (0.05 ml/kg) > pulmonary artery catheter > $EtCO_2$ = end-tidal nitrogen (ETN_2) > ECG changes.

A sudden fall in end-tidal carbon dioxide ($EtCO_2$) 2–4 mmHg is commonly observed, which helps in the diagnosis. Treatment of VAE aims at preventing further entrapment of air, removal of air bubbles, and management of complications. Informing the surgeon about VAE to flush the surgical field with saline application of bone wax and bilateral jugular compression prevents further air entrapment. Discontinuation of nitrous oxide (N_2O), and aspiration of blood from a central venous catheter (CVC) reduces the load

of VAE. Using 100% oxygen provides hemodynamic support to stabilize the patient. In extremes of cases, change of position to bring the operative site lower than the heart or left lateral position is indicated.

22.9 Pituitary Adenoma

A pituitary tumor is essentially an extradural tumor. A trans-sphenoidal approach (endoscopic or microscopic) is generally preferred over open craniotomy unless the tumor is very large and has intracranial extensions. The trans-sphenoidal approach carries a lesser risk of injury to optic chiasma and frontal lobes and lesser morbidity than an open craniotomy. Endoscopic technique is associated with a wider panoramic view, shorter resection time, lesser need for nasal packing, and shorter hospital stay [22]. Furthermore, the introduction of neuronavigation in surgical armamentarium has improved the accuracy of resection.

A pituitary adenoma may be functional due to hormone hypersecretion or non-functional which are usually large and with mass effect or pressure symptoms. Most adenomas arise from the anterior pituitary. Hormonal hypersecretion may be of prolactin, growth hormone, or adrenocorticotropic hormone (ACTH) leading to the presentation of galactorrhoea, acromegaly, or Cushing's disease, respectively. Larger tumors can compress optic chiasma producing bitemporal hemianopia or occasional hydrocephalus due to CSF flow obstruction. Rarely, bleeding inside the tumor can cause pituitary apoplexy and is a medical emergency.

All patients should undergo a thorough endocrinological evaluation during the preoperative period. The euthyroid state is essential for good postoperative outcome. Patients with acromegaly and Cushing's disease may have a difficult airway, diabetes, hypertension, cardiac dysfunction, and sleep apnea [23]. Preoperative electrolyte and blood glucose optimization should be done. Awake fiber-optic may be required in difficult airway situations.

Intraoperatively, ETT is fixed on the left side of the mouth as most of the surgeons prefer operating on the right side. Oropharyngeal packing is routinely carried out to prevent the trickling of the blood into the trachea and esophagus. Severe hypertension can occur due to nasal packing with adrenaline-soaked gauzes or pain due to nasal speculum insertion as a part of the procedure. Some neurosurgeons prefer lumbar drain preoperatively to push the tumor downward for better visualization. Surgical closure is abrupt; therefore, it is essential to follow the steps closely and titrate the depth of anesthesia accordingly [24]. Hyperventilation is normally avoided as it makes the tumor less approachable. Rarely, sudden massive bleeding may occur if the surgeon loses or alters the trajectory, leading to vascular injury of the carotid artery or cavernous sinus.

Postoperatively, complete awakening is essential before extubation. Blood in the oropharynx must be thoroughly cleaned. Bilateral nasal packing, associated sleep apnea, and residual anesthetic effects may threaten the airway. Serum sodium abnormality especially due to diabetes insipidus (DI) can occur and needs free water replacement and desmopressin. A lumbar drain may be needed if the procedure is complicated by CSF rhinorrhea.

22.10 Awake Craniotomy

Awake craniotomy is required when the tumor is located close to the eloquent cortex. Cerebral cortex topography is highly variable and may be altered because of radiotherapy or previous surgeries. Intraoperative neurological assessment by a conscious oriented patient helps in knowing the degree of tumor invasion in the vital cortex and thus, for optimal tumor resection with less morbidity avoiding over-resection. A cooperative patient and experienced neuro-operative team are the keys to the smooth and safe conduct of the procedure. The advantages of awake craniotomy are higher gross total resection of the lesion with lesser morbidity, avoidance of side effects of general anesthesia (GA), shorter intensive care unit

(ICU) stay, faster recovery, and lesser resource utilization, therefore decreasing procedural cost [25, 26]. Proper patient selection is the single most important task for the anesthesiologist. The steps of the procedure, possible side effects and complications, and necessary intraoperative tests should be explained and rehearsed with the patient to boost their confidence about the surgery. Patients with an anticipated difficult airway, morbid obesity, history of obstructive sleep apnea (OSA), anxiety disorder, claustrophobia, children less than 10 years, elderly, drug abusers, and low threshold to pain surgeries are some of the relative contraindications. A plan for emergency control of the airway must be ready and necessary gadgets should be available.

Preoperative antiepileptics and benzodiazepines may be omitted if intraoperative electrocorticography (ECoG) is planned during the intraoperative period. Inside the operating room (OR), the patient should be made as comfortable as possible; OR temperature should be kept at 22–24 °C, and the noise level should be kept to a minimum.

The anesthetic plan may vary from exclusive local anesthesia (LA) and conscious sedation (CS) to the asleep-awake-asleep (AAA) technique. Scalp block and infiltration with LA at the incision is given; it is followed for all types of anesthetic techniques to reduce the intraoperative opioid requirement. CS with propofol (50–150 μg/kg/min) or dexmedetomidine (0.2–1.0 μg/kg/hr) infusions help to allay the anxiety of the patient without compromising the airway or respiration. Remifentanil (0.03–0.09 μg/kg/min) is a commonly used opioid because of potent analgesic with a short half-life. However, it causes severe hypopnea in spontaneously breathing patients and has the risk of emergence of excitement and hyperalgesia. AAA technique involves GA during the first and last parts of the surgical procedure.

Various intraoperative complications may be encountered during awake craniotomy which includes pain, nausea/vomiting, loss of airway, brain bulge, seizures (2–20%), hemodynamic changes, and VAE. Nausea and vomiting may occur due to pain arising from temporalis muscle dissection or dural incision. Therefore, patients should be given adequate analgesia and antiemetics at these time points. The nasopharyngeal airway is very useful in maintaining the patency of the upper airway during sedation. Voluntary hyperventilation may not be possible, and anesthesiologists have to usually rely on osmotic agents to decrease ICP. Ice-cold saline should be available to calm the epileptogenic foci in case of seizure. Coughing is an otherwise stable patient is a symptom of VAE. Legs should be bent toward the abdomen in an attempt to increase the jugular venous pressure besides other usual steps. The postoperative course is short after awake craniotomy. Few patients may witness weakness in the postoperative period due to cerebral edema because of retraction and must be reassured that the episode might be transient.

22.11 Ommaya Reservoir Placement

Ommaya reservoir is a ventricular access device that has a catheter connecting the lateral ventricle to a subgaleal pouch. It is used for intrathecal administration of chemotherapeutic drugs in patients with CNS neoplasms such as carcinomatous meningitis, lymphoma, acute lymphoblastic leukemia, and Burkitt's lymphoma. It can also be used to administer intrathecal antibiotics in patients with meningitis or for CSF aspiration and analysis. The procedure is usually carried out under LA or GA. It carries risks similar to during the ventriculoperitoneal shunt insertion procedure.

22.12 Tumor Resection Under Intraoperative MRI (iMRI) Guidance

Repeated surgery carries increased morbidity due to tumor progression and recurrent anesthesia. Functional MRI (fMRI) is aiding neurosurgeons to check the extent of tumor excision with the eloquent cortex and therefore performing more complete tumor resection. Brain anatomy

changes with the use of ICP lowering drugs and after dural opening due to brain shift. Therefore, an iMRI and neuronavigation help in giving a more real-time picture of tumor location. Although anesthetic management does not change substantially, the real challenge is in providing a safe environment for the patient and operating room personnel [27].

All the equipment or instruments used for patient care must be either MR safe or MR compatible. A detailed preoperative checklist is used to confirm that the patient does not have any ferromagnetic implant in his/her body (like a cardiac pacemaker, aneurysmal clip, orthopedic implants, stents, large tattoos, etc.). Anesthesia machine, monitors, and infusion devices are checked for compatibility. The extension used for giving anesthesia increases the dead space and lag time in monitoring. Temperature is usually lower than regular OR and noise levels can reach up to 100 dB. Anesthesia duration is generally prolonged due to repeated imaging and re-registration of acquired images. Renal function must be normal if gadolinium contrast is used due to the high risk of nephrogenic systemic fibrosis.

22.13 Use of Tumor Dyes

Tumor dyes are now being increasingly used to improve the extent of resection, thereby improving the survival of patients with intracranial brain tumor patients. 5-Aminolevulinic acid (5-ALA), fluorescein sodium (FL), and indocyanine green (ICG) in combination with a dedicated surgical microscope filter are used for intraoperative visualization of tumor tissue such as low- and high-grade gliomas, meningiomas, metastasis, pituitary adenoma, etc. [28]. The disadvantage of 5-ALA dye is that it causes severe porphyria and skin reactions on exposure to light; hence, the patient has to be kept in a dark room for 24 hrs after administration. At times, it can hamper the clinical examination. Besides that, all types of dye carry inherent risks of allergic reactions for which anesthesiologist must be prepared.

22.14 Summary

The anesthetic concerns for brain tumor surgeries vary depending on the site of location in the cranial cavity and the clinical presentations thereof. The common anesthetic goals are maintenance of cerebral homeostasis with normovolemia, normoglycemia, normotension and preservation of CPP. Regulation of the systemic blood pressure as per the cerebral autoregulatory range is important to prevent ischemic injury or bleeding. Judicious use of osmotherapy, hyperventilation, and intravenous anesthetic agents is required to control CBF, cerebral blood volume, and ICP. Early awakening after elective neurosurgical procedures is desirable as it permits immediate neurological assessment. Adequate pain relief, blood pressure control, and treatment for nausea and vomiting are important aspects of postoperative care. Besides definitive excision, patients with CNS tumors may need various adjuvant procedures such as ventriculoperitoneal shunt, placement of Ommaya reservoir, or imaging techniques during the perioperative period. Appropriate knowledge of cerebrovascular physiology helps the anesthesiologists to provide optimal perioperative care in patients with brain tumors.

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Anesthesia for Spine Tumors

23

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23.1 Introduction

Anesthesia for spine surgeries has shown numerous advancements over the last two decades with a focus on making complex spine surgical interventions safe. Improvement in gadgets and equipment, anesthesia technique, neuromonitoring methods, and surgical skills has reduced patient morbidity even during the most complex scenario. Understanding the anatomy and physiology of the spine and spinal cord and the pathophysiology of spinal lesions is of paramount importance while managing these patients during the perioperative period.

Back pain, progressive spinal deformity, and emerging neurological deficit in a patient suggest a possible spinal pathology. Continuous pain may occur due to the mechanical effect of a lesion or radiculopathy. Spine deformity occurs due to bony destruction by the lesion, and further neural deficit may occur after tumor invasion or fracture and dislocation of the vertebral body. Spinal tumors form a subgroup of various pathologies that can affect the spine. Radiological imaging is necessary to confirm the size and extent of damage to the adjacent area.

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23.1.1 Tumor Characteristics

A simple classification divides all spinal tumors as extradural, intradural extramedullary (IDEM), or intramedullary types (Table 23.1). Metastasis can affect any part of the spine but is mainly extradural [1]. Metastasis to the spine is the third most common location after the lung and liver. Lung and prostate are sites of the primary tumor in males and breast in females. The thoracic region is the most common metastatic location of the spine with pain as the presenting symptom. Treatment of spinal extradural metastasis is primarily nonsurgical. Surgery is indicated only when the diagnostic biopsy is needed for a doubtful lesion, to decompress the tumor in case of progressive neurological deficit, spine stabilization, intractable back pain, and presence of the radio-resistant tumor. Other extradural tumors are mainly located in the bone

Table 23.1 Classification of the spine and spinal cord tumors

Tumor type	Example
Extradural	Metastatic
	Primary tumors: chordoma, osteoid osteoma, aneurysmal bone cyst, giant cell tumors
	Multiple myeloma, plasmacytoma, eosinophilic granuloma
Intradural extramedullary	Meningioma, neurofibroma, lipoma
Intramedullary	Astrocytoma, ependymoma, epidermoid, hemangioblastoma

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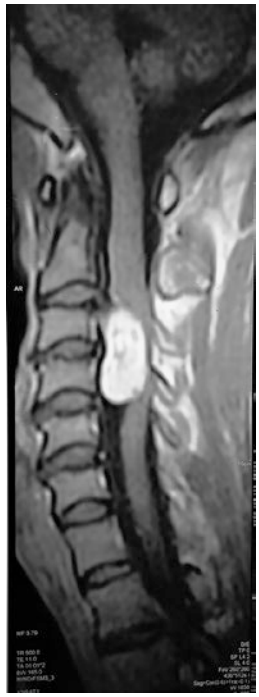

Fig. 23.1 MRI spine sagittal T1-weighted images showing a contrast-enhanced lesion at C2–C3 level compressing the spinal cord dorsally suggestive of an intradural extramedullary tumor

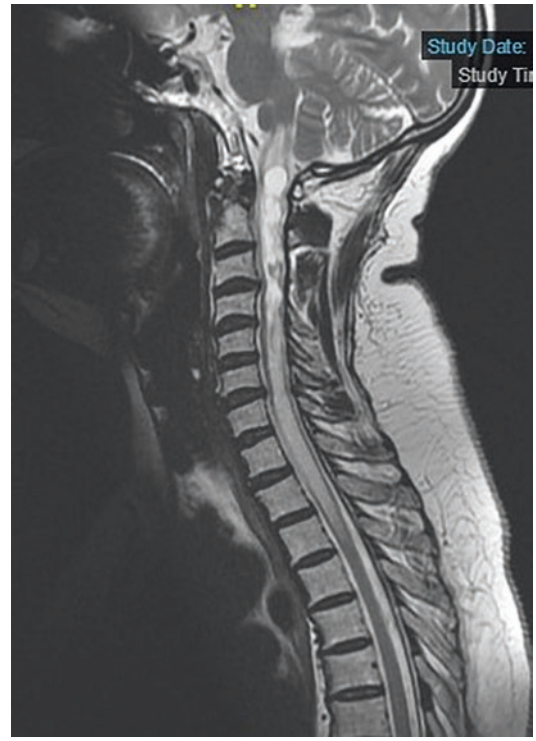

Fig. 23.2 MRI spine sagittal image showing an intramedullary lesion in the dorsal aspect of the cervical cord (at C3 level) associated with non-enhancing cyst extending from lower medulla till C4 level causing expansion of the cord

such as osteochondroma, osteoid osteoma, osteoblastoma, aneurysmal bone cyst, hemangioma, and Ewing's sarcoma.

IDEM tumors are located inside the dura mater but outside the spinal cord (Fig. 23.1). They arise from arachnoid tissue or nerve sheaths and are usually benign. Meningiomas, neurofibroma, schwannoma, and epidermoids are typical lesions. They present with radiculopathy or myelopathy; surgery is usually curative. Intramedullary tumors are located in the spinal cord (Fig. 23.2) and are usually astrocytomas and ependymomas. These lesions present with neurologic deficits due to the destruction of crucial neural elements. Destruction of conus medullaris can lead to cauda equina syndrome.

23.1.2 Spinal Cord Blood Flow

As compared to vast research on cerebral blood flow (CBF) and autoregulation, the literature on spinal cord blood flow (SCBF) is limited. The spinal cord is supplied by one anterior spinal artery (ASA) originating from the vertebral artery, two posterior spinal arteries (PSA) originating from the vertebral or posterior inferior cerebellar artery (PICA), and radicular arteries at each spinal segment. The artery of Adamkiewicz, major arterial collateral to ASA at D10 level, helps to perfuse the distal spinal cord. Therefore, occlusion of ASA below the D10 level may lead to paraplegia. Systemic hypotension and vasodilatation decrease the blood flow through the collateral radicular arteries, thereby compromising the spinal cord perfusion. Similar to CBF, SCBF is lower in white matter (10–20 mL/100 g/min) and higher in gray matter (41–63 mL/100 g/min). Besides that, there is regional variation in SCBF with a 40% higher flow at the cervical and lumbar regions than in the thoracic region. This is related to lesser gray matter in the thoracic region. SCBF increases with hypercarbia and decreases with hypocapnia. The limit of spinal cord autoregula-

tion is between 60 and 120 mmHg [2]. Like CBF, SCBF also decreases with increasing depth of anesthesia.

23.2 Preoperative Evaluation

Neurological examination should be done in cases of spinal cord injury to grade as per the American Spinal Injury Association (ASIA) scale [3]. This scale tests 10 groups of muscles for strength and 28 pairs of dermatomes for sensation. As per the location of the tumor and degree of weakness, the involvement can be of bilateral lower limbs, i.e., paraplegia when the lesion is below T1 or quadriplegia when all four limbs are involved due to cervical pathology. If the lesion is in between C3 to C5 spinal cord level, the diaphragmatic function may be impaired to a variable extent with possible need for prolonged mechanical ventilation during the postoperative period. If the lesion is further high up with the involvement of lower cranial nerves with a cervicomedullary lesion, it is known as pentaplegia. Bowel and bladder functions are to be carefully assessed as associated impairment may lead to long-term requirements of urinary catheterization.

The cardiovascular system should be examined as a part of routine evaluation especially when the spinal tumor is vascular or spine stabilization is planned with associated risks for bleeding. Effort tolerance is difficult to assess if the patient is bedridden. These patients may develop pulmonary hypertension from repeated chest infections. Stress echocardiography (ECHO) may be necessary to fully evaluate cardiac status. Spinal shock, hypotension, cardiac dysrhythmias, and autonomic dysfunction have been found associated with acute spinal cord injury. These complications may however occur in a patient of spinal tumor who suffers from sudden pathological fractures or instability of the spine.

Respiratory system: Diaphragm contributes to about 65% of vital capacity. A lesion above the C3 level paralyzes all respiratory muscles requiring life-long ventilatory support. If the lesion is between C3 and C5 spinal cord level, consequent partial diaphragmatic paralysis and complete accessory muscle paralysis lead to recurrent atelectasis and chest infections. Mechanical ventilation is usually prolonged. Lower cervical and higher thoracic lesions may present with impaired cough due to weakness of accessory muscles and therefore, need aggressive physiotherapy. Micro-aspirations occur due to ineffective clearance of pulmonary secretions leading to gradual hypoxemia and carbon dioxide (CO_2) retention. Pulmonary complications occur in as many as 75% of these patients. In the case of cervical intramedullary tumors, progressive ascending cord edema may occur during the first two postoperative days. Hence, repeated respiratory examination may be required during this period. Spirometry examination and air arterial blood gas (ABG) analysis should be performed if the patient has co-existing respiratory pathologies such as chronic obstructive pulmonary disease (COPD). Vital capacity of less than 30% of predicted suggests severe respiratory compromise and increased risk of major respiratory complications [4]. All reversible respiratory problems must be corrected or optimized preoperatively, e.g., antibiotics to treat pneumonia, abstinence from smoking, bronchodilators to improve asthma, and deep breathing exercises.

The coagulation profile may be deranged if the patient is on nonsteroidal anti-inflammatory drugs (NSAIDs) for prolonged periods. The incidence of deep vein thrombosis (DVT) is high if the patients have paraplegia (40–60%). Such patients may be on DVT chemoprophylaxis.

If bladder emptying is compromised, the patient is at high risk of developing repeated urinary tract infection (UTI), pyelonephritis, and renal insufficiency. Pressure ulcers can develop in patients if mobility is compromised. Regular dressing, padding, and skincare and alpha beds are necessary to prevent these ulcers.

Some of the spinal tumors may need combined chemotherapy and radiation along with surgery to treat the disease. In such cases, the anesthesiologist must be aware of the potential side effects of these chemotherapeutic agents. For example, cisplatin is associated with nephrotoxicity and electrolyte disturbance, and sirolimus is associated with thrombocytopenia. Postoperative radiation therapy is frequently employed for the treatment of chordomas. The patients may be on high-dose opioid treatment such as oral morphine or fen-

tanyl patch which needs to be converted to an equivalent intravenous (IV) dose during the perioperative period to control the pain.

Cervical spine tumors are considered as the second most common cause of difficult direct laryngoscopy in patients with cervical spine pathologies; next only to rheumatoid arthritis [5] with 24% of patients presenting with Cormack-Lehane (CL) grade 3 or 4 on direct laryngoscopy. Patients with disease pathology involving the occipito-atlantoaxial complex will have a higher prevalence of difficult airway than when it involves C3-C7. The best objective predictor of difficult laryngoscopy is reduced separation of C1 and C2 posterior elements on lateral x-ray, whereas Mallampati classification is the best clinical predictor [5]. Radiotherapy to head and neck with resulting fibrosis can pose difficulty in laryngoscopy and intubation.

Laboratory tests such as complete blood count, coagulation profile, renal function test along with urine analysis, serum electrolytes, chest x-ray, electrocardiography (ECG), 2-D echocardiography, spirometry, ABG analysis, and lower limb venous Doppler are done as per the clinical indication.

Initial examination of any spinal pathology is through a plain radiograph to see for the presence of a fractured, dislocated, and non-aligned vertebra. However, a computed tomographic (CT) scan now provides a more detailed spatial resolution of spinal canal compression or spinal instability. Magnetic resonance imaging (MRI) is most useful to delineate any spinal cord tumor. It helps to correctly identify the tumor location to the dura mater and spinal cord and therefore helps to plan out the surgical procedure and extent of neuromonitoring needed.

23.3 Plan for the Spine Surgical Procedure

The perioperative care for spine intervention needs to be planed for various aspects. The following are the questions to be asked while planning for surgical procedures on the spine.

- Tumor location and pathology? Does it involve the cervical spine? Is spinal stability compromised?
- What is the surgical approach? – to decide on a position.
- Vascularity of tumor and expected blood loss? – to suggest the need for central venous catheterization, use of cell saver.
- Neurophysiological monitoring planned?

23.4 Surgical Positioning

Three basic surgical positions in which spinal tumor cases may be operated are supine, lateral, or prone. The supine position is used when instrumentation is needed in the cervical spine. Lateral position may be required along with one-lung ventilation for upper thoracic spinal surgery. The prone position is most commonly employed for lesions in the lower thoracic and lumbosacral region and when posterior fixation is required for spinal stabilization. Surgical prone positioning is offered with patients on various frames with different advantages such as the Wilson frame, Relton-Hall frame, and Allen's table. The primary goal of using all these frames is to make the abdomen free to prevent vertebral venous engorgement while providing better surgical exposure. Airway pressures should be rechecked after positioning to rule out inadvertent kinking of the endotracheal tube or abnormal increase in thoracoabdominal pressures affecting ventilation. The head should be supported on a padded headrest or three-pin head holder to prevent pressure on eyeballs. The eyes should be checked two-hourly during the intraoperative period to make sure the headrest is not displaced, causing undue ocular pressure. Mirrors, with newer headrest, facilitate easier intraoperative checking of head position. It is also important to move the spine together keeping the head and body in alignment using a log-roll and Philadelphia neck collar. The extremities should not be overextended and must be thoroughly padded to prevent pressure ulcers or peripheral nerve injury.

23.5 Anesthetic Management

Sedatives premedication may be given to allay the anxiety. Glycopyrrolate is usually given if fiber-optic intubation or prone position is planned. If multimodal pain management is planned, gabapentin (300–600 mg) or pregabalin (75–150 mg) may be given preoperatively.

Standard monitoring including 5-lead electrocardiogram (ECG), pulse oximeter, and blood pressure monitoring should be applied in all the patients. An arterial cannula is usually inserted for multilevel fusion surgery or when severe blood loss is expected. Central venous catheterization may be done in high cervical lesions and when prolonged ventilatory support or vasopressors is anticipated.

The incidence of severe postoperative neurological deficit ranges from 23.8 to 65.4% after spine surgeries, and this incidence reduces to 0.5% with the use of intraoperative neurophysiological monitoring (IONM) [6]. Stagnara wake-up test has many disadvantages like the risk of accidental extubation and assessment of neurological function when the damage has already been done. Moreover, it cannot be done frequently and hence, does not give a real-time picture. Therefore, IONM is currently the standard of care, which helps in the early detection of perturbation in spinal cord function.

Combined somatosensory evoked potential (SSEP) and motor evoked potential (MEP) monitoring has been shown to be a safe, reliable, and sensitive modality to detect and reduce intraoperative injury to the spinal cord and promote aggressive spinal tumor excision (evidence level A) [7, 8]. *SSEP monitoring* checks the integrity of the dorsomedial spinal tract supplied by the posterior spinal artery. Peripheral nerves (usually posterior tibial, peroneal) are stimulated distal to or at the level of surgery with skin electrodes with 25–40 mAmp electrical stimulation in the square wave pattern at 3–7 Hz. Recording electrodes are kept over the cervical spinous process or over the somatosensory cortical region. Due to anatomical proximity, it has been assumed that any damage to the motor tract would translate into changes in SSEP. However, due to the distinct blood supply of the anterolateral corticospinal tract, patients with normal intraoperative SSEP can wake-up with paraplegia, warranting the need for combined SSEP and MEP monitoring [9]. *MEP monitoring* checks the integrity of corticospinal tracts supplied by the anterior spinal artery. It involves stimulation of the motor cortex by magnetic or electrical stimuli and recording the neurogenic responses (D wave) from the epidural space over the spinous process or the myogenic responses as summed up electromyographic potentials (EMG) by electrodes in muscles in the distal part, e.g., tibialis anterior, lateral or medial gastrocnemius, anterior hallucis, or adductor pollicis brevis. A significant response is a drop-in amplitude by 50% or an increase in latency by 10%. EMG responses of MEP are affected by muscle relaxants, and both SSEP and MEP are affected more by inhalational anesthetics. Inhalational agents reduce MEP potentials in a dose-dependent manner. D waves recording over the epidural space are minimally affected by anesthetics as there are no synapses involved in its production. Intravenous anesthetics suppress the MEP responses much less compared to the inhalational agents and therefore, propofol-opioid infusion-based anesthetic regime is preferred to provide a constant depth of anesthesia for neurophysiologic monitoring. Processed EEG helps guiding the depth of anesthesia.

23.5.1 Induction of Anesthesia

The stability of the cervical spine and the possibility of neurological deterioration guide the plan about the induction of anesthesia. If stability is a concern, then awake fiber-optic intubation is preferred. If there is no concern related to the stability of the cervical spine, IV induction may be done. Hemodynamic stability must be ensured during the induction of anesthesia. The use of succinylcholine in patients with muscular dystrophies and paraparesis/paraplegia has been implicated in causing cardiac arrest due to severe hyperkalemia and should therefore be avoided

after 24–48 h of acute weakness [10]. It occurs due to the proliferation of extra-junctional acetylcholine receptors in the denervated muscle groups. Short-acting muscle relaxants should be used at induction to allow subsequent MEP monitoring.

When cervical spine stability is a concern, the patients usually have one of the cervical immobilization devices such as the soft collar, Philadelphia collar, Halo brace, or axial traction placed in the neck [11]. Among them, the Halo brace is the most rigid and restricts neck movement most effectively. However, these immobilizing techniques make direct laryngoscopy difficult. Awake fiber-optic intubation is a useful aid in such a situation. The use of manual in-line stabilization (MILS) along with direct laryngoscopy is effective in limiting cervical spine movement. The maximum movement occurs at the atlantoaxial joint, and injury at this level is most likely to worsen with laryngoscopy. In one study, the movement of the cervical spine below C4 during direct laryngoscopy was found to be minimal, indicating the highest precaution to be taken while intubating patients with high cervical spine instability [12].

The use of video laryngoscopes (e.g., Glidescope) has been shown to reduce the movement at the cervical spine by about 50% as compared to direct laryngoscopy [13] and improvement of the laryngeal view by one grade in patients wearing a cervical collar. Mask ventilation along with chin lift or jaw thrust has been shown to cause more cervical spine movement than most other methods of ventilation. Nasal airway and laryngeal mask airway are useful adjuvants to assist in ventilation without causing undue cervical movement. Evoked potential monitoring is useful to guide that no significant spinal injury has occurred due to intubation or positioning.

23.5.2 Maintenance of Anesthesia

The goal of maintenance is to provide stable anesthetic depth and hemodynamics so that evoked potential recordings are considered reliable [14]. Inhalational agents at more than 0.5 MAC dampen the evoked potential recordings. Propofol too dampens the MEP at higher doses, but to a lesser extent. Therefore, a propofol-opioid-based anesthetic regimen is preferred when IONM is carried out. Muscle relaxants are usually avoided when monitoring MEP although a train-of-four (TOF) count of 1 or 2 has been shown to provide reliable readings. Besides the anesthetic agents, it is equally important to keep the intraoperative physiological milieu constant. Therefore, changes in blood pressure, the partial pressure of carbon dioxide ($PaCO_2$), and temperature must also be avoided. To prevent secondary injury to the spinal cord, a higher mean blood pressure (MBP at or above 85 mmHg) and adequate cardiac output are advised [15].

The use of methylprednisolone in acute traumatic spine injury within 8 hrs of injury is no longer recommended because of associated side effects including increased risk of infection [16].

Balanced isotonic crystalloids are preferred IV fluids. Goal-directed fluid therapy (GDFT) has an advantage in improving respiratory function, preventing acute kidney injury and ileus, and decreasing the length of hospital stay after high-risk surgical cases involving large blood loss like anteroposterior spine fixation and large vascular tumors [17]. Strategies to reduce intraoperative blood loss like preoperative embolization in highly vascular tumors, omitting NSAIDS, and avoiding raised intra-abdominal pressures should be considered. Increased blood loss is associated with increased operative time, higher incidence of wound infections, delayed healing, and allogeneic blood transfusion with its associated risks [18]. Blood transfusion should be considered when hemoglobin is less than 7–8 gm/dl. Antifibrinolytic agents like tranexamic acid are useful in decreasing intraoperative blood loss in spinal instrumentation surgery [19]. Intraoperative cell salvage technique is effective when instrumentation is done for spine stabilization but is not advocated when tumor resection is being carried out owing to the risk of the spread of tumor tissue.

23.5.3 Emergence from Anesthesia

Early awakening is desirable in all cases of spine surgery to allow neurologic assessment. Immediate extubation may not be possible in high cervicothoracic lesions associated with preoperative impaired respiratory function. These cases should be electively ventilated till they meet standard extubation criteria or otherwise should be tracheostomized. Cases performed in the prone position, for a long duration (>6 h), and with large blood loss (>30 ml/kg) and major fluid shifts may have risks for facial and laryngeal edema and are better left intubated till leak test suggests no significant edema. Hoarseness due to recurrent laryngeal nerve injury and airway edema leading to obstruction and hypoxia are concerned after cervical spine surgery. Reintubation due to airway compromise has been reported to be as high as 1.9% after anterior cervical spine surgery [20].

23.6 Postoperative Care

The provision of adequate postoperative analgesia is challenging due to significant pain as a result of large skin incision and bone manipulations. Good pain control helps in effective physiotherapy, reduces pulmonary complications, and decreases the length of hospital stay. In general, pain after cervical spine procedures are less as compared to spinal fusion and instrumentation procedures of the thoracic or lumbar spine, which are associated with severe pain. Oncological patients may already be on regular opioids or other analgesics translating into increased demand intra- and postoperatively. Multimodal pain management strategies involving opioids, NSAIDs, acetaminophen, and regional analgesia should be considered in the early postoperative period. Patient-controlled analgesia via IV, intrathecal, or epidural route provides better pain control and satisfaction than continuous infusion [21]. The use of NSAIDs in the postoperative period is restricted because of concern about hematoma formation causing spinal cord injury and dose-dependent and duration-dependent effect on fusion rates. However, low-dose short course (<2 weeks) of NSAIDS use can be considered because of their improved pain control and opioid-sparing effect [22]. Paravertebral or intercostal nerve blocks provide good pain relief from thoracotomy.

The incidence of postoperative vision loss (POVL) is 0.2% after spine surgery, and it is a devastating complication [23]. Ischemic optic neuropathy (ION) is the most common cause of POVL after spine surgeries. The risk of ION is increased in patients who have undergone prolonged spine procedures (>6 h) in the prone position and/or have substantial blood loss (average loss, 44.7% of blood volume) [24]. Therefore, whenever feasible, complex surgical procedures needing longer operative duration and blood loss should be planned for staged correction.

The risk of deep vein thrombosis (DVT) after spine surgery varies from 2 to 15.5% [25]. It can be particularly high in malignancy, prolonged surgery, and paraparesis. Other risk factors are deliberate hypotension, hypothermia, combined anterior-posterior surgical procedure, and delayed mobility. Therefore, mechanical prophylaxis with intermittent pneumatic compression stockings or pneumatic boots should be applied as early as possible. Pharmacologic prophylaxis with low-dose unfractionated heparin or low-molecular-weight heparin should be considered as soon as hemostasis is assured, generally within 48–72 h after surgery.

Inadequate (non-watertight) closure of the dura mater can lead to CSF leak, causing headache, postoperative collection, and risk of meningitis. Redo dural closure or CSF shunt procedure may be needed for such cases.

23.7 Summary

Surgery for spine tumors presents a wide range of challenges to the surgeon as well as the anesthesiologists. A detailed preanesthetic evaluation and optimization of pre-existing conditions especially the cardiorespiratory system help in preparing and prognosticating these patients. Assessment of radiological imaging and surgical plans and

approach guide in preparing the intraoperative anesthetic regimen. The perioperative morbidity has been reduced with advancements in IONM and surgical skills. Airway management is an important aspect of any anesthesia-related procedure and is particularly tested while managing unstable cervical spine pathologies. Early emergence to facilitate neurological assessment is desirable. Good postoperative care includes adequate pain control, DVT prophylaxis, and a vigilant watch on the possible complications.

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Anesthesia for Pediatric Cancers

24

Nandini Malay Dave

24.1 Introduction

Cancer in children is increasingly being reported and remains an important concern of morbidity and mortality. The perioperative care of these children needs a thorough understanding of childhood cancers and their impact on the various body systems. Also, the treatment modalities and their related toxicities should be well known for appropriate assessment and management. The management of cancer remains multidisciplinary and anesthesiologist involvement is integral to many aspects of cancer management including sedation and anesthesia for diagnostic and therapeutic interventions. These procedures are not limited to operating room interventions but also outside the operating room management modalities. Children and their caregivers undergo considerable psychological stress due to the illness, and appropriate support needs to be provided to the patient and family members.

The incidence of various cancers differs from adults, and across different childhood age groups. The most common malignancy in children is leukemia. Intracranial tumors are the most frequent non-hematological malignancies followed by lymphoma and embryonal tumors. The other common tumors in children include sarcomas (bone and soft tissues), germ cell tumors, and gonadal tumors [1].

24.2 Role of the Anesthesiologist

Anesthesiologists, being part of the multidisciplinary team, often interact with patient and family members at various times during the disease process. These children require sedation and anesthesia for short procedural interventions (biopsies, bone marrow aspirates, venous access including central venous catheter), diagnostic modalities, radiotherapy, and surgical interventions. These children may also require postprocedural, postsurgical, or cancer-associated pain management.

24.3 Preprocedural Evaluation

Children with cancer often have multiple comorbidities, due to the primary disease and because of cancer treatment. Cancer and its treatment e.g. chemotherapy and radiotherapy can have an impact on various body systems. This mandates a thorough evaluation (clinical history, examination, and review of relevant investigations) before the intended procedure or surgical intervention to individualize the perioperative care. Chemotherapy and radiotherapy can have sev-

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eral adverse effects, and these are discussed in detail later.

Preprocedural investigations should be individualized according to the patients' history, physical findings, and the planned procedure. The various blood investigations and radiological imaging need to be individualized as per patient clinical assessment including the type of cancer, its treatment, and impact on body systems. This helps in optimization of the patient's preoperative status, planning of perioperative care, and risk stratification as well. The complete hemogram is desirable in patients with hematological malignancies, a history of chemotherapy and radiotherapy, or clinical signs of bleeding manifestations. Anemia is commonly seen. Thrombocytopenia can occur due to myelosuppression, infiltration, disseminated intravascular coagulation (DIC), and sequestration as in splenomegaly. Generally, a platelet count >50,000/μl is preferable, although platelet transfusion may be required during surgery to ensure adequate levels [2, 3]. Placement of ports or vascular access lines is often performed at a much lower platelet count. Leukopenia and neutropenia are common with radiotherapy and chemotherapy. Coagulation abnormalities can occur due to chemotherapy, consumptive coagulopathy due to septicemia, hepatic tumors, vitamin K deficiency, or malnutrition. Coagulation testing including prothrombin time (PT), partial thromboplastin time (aPTT), international normalized ratio (INR) is required in patients who have a clinical suspicion of bleeding disorder due to cancer, its treatment-related adverse events or other conditions and in the child requiring surgery with a risk of major hemorrhage.

Hyperleukocytosis [defined as white cell count (WBC)>100,000/μL] is one of the manifestations of the child with a diagnosis of leukemia [4]. Leukocytosis is associated with an increased occurrence of cerebrovascular and pulmonary manifestations due to either blood sledding or bleeding. Before surgery, an oncology consultation should be sought, regarding leukapheresis or partial exchange transfusion in infants to reduce the white cell count [5].

Renal function may be impaired due to the nephrotoxicity of chemotherapeutic agents. Obstructive uropathy can be caused due to a large tumor. In such scenarios, the renal function needs to be assessed by blood urea nitrogen, serum creatinine, and electrolytes. Electrolyte abnormalities in cancer patients may also occur in conditions like tumor lysis syndrome (TLS), excessive vomiting (due to chemotherapeutic agents), dehydration, malnutrition, repeated/massive blood transfusions, parenteral nutrition, etc. Bone tumors and neuroblastomas are associated with hypercalcemia. Liver function may be affected due to chemotherapy and radiotherapy. Because of repeated cycles of chemotherapeutic agents, the derangement may be seen at various stages of the diseases and their treatment. So, the investigations need to be reviewed before the scheduled surgical intervention.

A chest radiograph remains an important screening tool for assessing respiratory symptoms like cough, or dyspnea. The anterior mediastinal mass needs further evaluation and is discussed later in the chapter.

Pulmonary fibrosis has been observed after exposure to radiotherapy to the thoracic region or as a side effect of chemotherapeutic agents like bleomycin. Pulmonary function tests (PFTs), whenever feasible, remains a good tool to look for respiratory compromise and may reveal features suggestive of a restrictive pattern. A reduction in carbon monoxide (CO) diffusing capacity may also be seen in these patients.

Children receiving cardiotoxic chemotherapy undergo serial echocardiography, beginning with baseline and then at regular intervals during treatment, at completion, and sometimes during remission. The subclinical nature of cardiac toxicity may be missed on clinical assessment and hence the echocardiography reports should be reviewed before anesthesia [6, 7].

24.4 The Psychological Impact of the Disease

The presence of cancer causes a psychological impact not only on the child but also the family. The response of the child depends upon the age and the initial experience with diagnostic and treatment modalities. Preschool children experience separation anxiety, while school-age children may have fears of disfigurement and anticipation of pain during treatment. Adolescents may fear the loss of control and can suffer from depression and anxiety. The anesthesiologist should be sensitive to the emotional needs of the patient. Parental presence at induction and gentle mask induction can be used whenever appropriate. A frank discussion with older children detailing what to expect is often helpful. The older child should be involved in the planning for the perioperative care and explained the contents of consent (assent) as well for a sense of control and encouraged to be active participants in their treatment.

Sedative premedication should be individualized based on age, understanding, the temperament of the child, the presence of an indwelling vascular access device, and the preference of the child and the family.

Pain remains the most distressing physical symptom of the child receiving cancer treatment. Hence, pain assessment and its optimal management are very important to gain the confidence of the child as certain procedures are repeatedly done. A majority of children report that the most distressing experience of their treatment was moderate to severe pain (procedures, e.g., bone marrow biopsy or surgery). The administration of balanced general anesthesia is effective for reduced pain scores [8]. Hence, whenever deemed fit and safe, general anesthesia must be offered for all painful procedures. Providing a calm, nonthreatening environment preoperatively, providing adequate pain relief, and managing complications like nausea and vomiting help in reducing perioperative stress. A multimodal approach to managing pain, including the use of regional blocks must be considered. The presence of bleeding abnormalities needs to be considered when using regional analgesic techniques.

24.5 General Considerations in the Cancer Patient

24.5.1 Infection Control Measures

Cancer and its treatment have an impact on immunity leading to an increased risk of infections. Certain malignancies viz. leukemia, lymphoma are associated with immune compromise, chemotherapy, and radiotherapy cause immune suppression, immune incompetence after bone marrow transplant due to graft versus host disease, malnutrition can further compromise the immune system, and splenectomy further predisposes to infections. Also, mucositis, invasive lines, and frequent procedures all make the patient vulnerable to infections [9].

Meticulous asepsis must always be employed by personnel caring for these patients. Strict hand hygiene and use of personal protective gear, e.g., mask, gloves must be adhered to. Patient contact with other sources of infection, e.g., other patients or staff members with respiratory tract infection must be avoided. Intramuscular injections are avoided, especially so in those with coagulation defects for the risk of abscess formation. Mucosal injury during airway management needs to be avoided. Rectal medications and the use of rectal temperature probes are best avoided.

Many patients have indwelling vascular access catheters, and these are very prone to infection. The patient should be educated on general care and precautions related to indwelling catheters. The physicians and nursing staff should follow all aseptic precautions during its insertion and maintenance, its use for administering drugs and fluids [10]. The dressings should be changed timely, but not on an everyday basis unless is soiled. When using the access site for administer-

ing sedation/anesthesia, the port must be cleaned with chlorhexidine and flushed with normal saline after use to remove any residual drug. Sterility must be adhered to while preparing and drawing up drugs.

24.5.2 Tumor Lysis Syndrome

Tumor lysis syndrome is manifested due to sudden malignant cell lysis releasing the intracellular components into the circulation manifested spontaneously or in response to chemotherapeutic agents, steroids, or radiotherapy. This is frequently seen in cancers with large tumor load, and commonly with acute leukemias and high-grade lymphomas [11]. Such high-risk patients may be initiated with preventive interventions before a stressful event like the administration of chemotherapeutic agents or surgical interventions [12]. These preventive measures include appropriate hydration, use of drugs like allopurinol, and alkalinization of the urine. Certain drugs like recombinant urate oxidase enzyme rasburicase have been found useful to prevent tumor lysis syndrome manifestation.

Biochemical changes include rapidly rising potassium due to cell lysis and progressive renal impairment due to hyperuricemia following purine breakdown. Malignant cells contain high phosphate levels. Hyperphosphatemia and precipitation of calcium phosphate in tissues may result in hypocalcemic convulsions. Also, in some cases and if timely management is not initiated, this may progress with acute renal failure, cardiac arrhythmias, metabolic acidosis, and even sudden death.

The manifested tumor lysis syndrome is an emergency and needs to be managed with correction of hyperkalemia, hypocalcemia, and hydration. Hydration to induce kidney flushing is important but such hyperhydration may be a concern in a patient with compromised cardiac function and may also lead to pulmonary edema [13]. Steroids can precipitate tumor lysis syndrome and its use (for its antiemetic properties) may be avoided during the administration of sedation or anesthesia [14].

24.5.3 Management of Cancer Pain

One of the most distressing symptoms in a child with cancer is pain. This may be related to cancer per se or due to cancer-related treatment effects like mucositis, infections, etc. Also, in cases of advanced cancers, a child may require chronic cancer pain management. It is imperative to plan for analgesia and provide as much comfort to the patient as possible, while maintaining patient safety.

The pain management strategy usually follows the World Health Organization's analgesic step ladder. However, the use of step 2 may be avoided in the child because of the unpredictable effects of tramadol. A multimodal approach combining opioids and non-opioids including adjuvants appropriately provides optimal analgesia to these patients [15]. The analgesic regime should be individualized, kept simple, and with minimum side effects in this younger population. The intravenous route is the only option intraoperatively and may be switched over to the oral route postoperatively whenever feasible. The intramuscular and rectal route needs to be avoided in major cancer surgeries. A child of over 6 years of age accepts patient-controlled analgesia (PCA) well and this modality can be used successfully for optimal analgesia.

Major cancer surgeries require the use of opioids as part of a multimodal regimen and this remains an important modality. At times, patients may be receiving opioids preoperatively because of cancer pain. The dose of opioids needs to be recorded and continued in addition to opioids used for surgical pain. Morphine remains the most common analgesic in cancer patients. Alternatively, fentanyl may also be used wherein morphine is contraindicated or a shorter-acting agent is required. Opioids may have side effects like nausea, vomiting, urinary retention, constipation, pruritis, etc. and needs to be managed accordingly.

Non-opioid analgesics include paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs). Paracetamol remains a routine acceptable drug as part of a multimodal regimen and its intravenous preparation is well accepted to be used perioperatively. NSAIDs may have con-

cerns in cancer patients due to chemotherapy-induced platelet dysfunction and hence needs to be avoided routinely.

The adjuvant analgesics like antidepressants, anticonvulsants, local anesthetics, and corticosteroids may also be considered as part of a multimodal analgesic regimen. Non-pharmacological techniques like behavioral, cognitive therapies, may also be integrated into the analgesic regimen wherever feasible.

24.6 Hematological Malignancies

The management of various hematological malignancies like leukemias requires the involvement of anesthesiologists at various stages. Such malignancies require certain invasive interventions during diagnosis and treatment such as lumbar puncture, bone marrow aspirate, and biopsy, etc. At times, central venous access is required for the administration of chemotherapeutic agents. These patients may also require radiation in cases of brain lesions [16, 17]. These interventions require sedation, analgesia, and at times, anesthesia as well. During such a scenario, anesthesiologists should be aware of the systemic impact of these malignancies, the adverse effect of chemotherapeutic agents, and thus appropriate planning.

24.7 Anesthesia for Short Procedures

A child with cancer requires various interventions for diagnosis and treatment. Such intervention is usually of short duration and associated with intense acute pain. The interventions required for diagnostic purpose includes lumbar puncture, bone marrow aspiration, bone marrow biopsy/trephine biopsy, etc.; at times, intrathecal injection of chemotherapeutic agents is also required. These procedures may be repeatedly required. So, proper planning of optimal analgesia, sedation, and anesthetic technique is important to not only improve the success of intervention but also to keep the confidence of the child for repeated procedures. Also, the side effects related to repeated administration of drugs needs to be considered. These procedures are usually done outside a well-structured operating room setting. Hence, anesthesiologists should be well acquainted with nonoperating room anesthesia and analgesia techniques for these cancer interventions. The associated staff members should be well trained and adequate infrastructure with regards to the anesthesia machine, monitors should be made available [20]. The propofol-based anesthesia or sedation for such short procedures are well accepted [18, 19].

24.7.1 Lumbar Puncture/Bone Marrow Biopsy

Chemotherapy regimens for leukemia are often administered intrathecally via lumbar puncture. Lumbar puncture is also required for sampling to look for tumor cells in cases of brain involvement. Bone marrow aspirates and biopsies are required to make a diagnosis and to observe the response to treatment. Bone marrow is also harvested as a part of treatment modalities for bone marrow transplant procedures. Bone marrow biopsies or aspirates is relatively a short procedure as compared to bone marrow harvesting. The common site is the posterior superior iliac crest and the child is placed either in lateral or prone position. Irrespective of the duration, these procedures elicit acute pain. So, these procedures need not only analgesia but also sedation or anesthesia for child cooperation. These drugs should be rapid and short acting. Usually, propofol and short-acting opioids like remifentanil or fentanyl are the choice of drugs for such interventions because of their favorable characteristics. Ketamine is also well known for its anesthetic and analgesic properties. The combination of propofol and ketamine has been well used for such procedures [21]. In the absence of a vascular access line, inhalational anesthesia via mask is sufficient for short procedures viz. lum-

bar puncture and biopsy. The use of the Entonox is also an acceptable method for pain management, with many patients reporting no recollection of undergoing the procedure [22]. Use of EMLA cream before procedures like insertion of central venous access puncture, lumbar puncture is also an acceptable option and decreases the need or depth of sedation. Bone marrow harvest can result in anemia and hypovolemia. Fluid resuscitation may be required. Cross-matched blood should be available; however, transfusion is withheld until after the procedure to prevent transfused cells from contaminating the harvested marrow.

24.7.2 Long-Term Venous Access

Central venous access is placed in cancer patients for repeated administration of chemotherapeutic agents. This may be used for various other purposes like fluid administration, blood sampling, administration of analgesic, and sedative drugs during various cancer-related interventions. These long-term catheters may be either tunneled subcutaneously or remain externally. An implantable access device or port for venous access is also used in some patients [23]. Common sites are the internal jugular and subclavian veins. Ultrasound imaging has made the procedure safe and is the standard of care. Known complications of indwelling catheters are infection, thrombosis, leakage, and displacement [24].

The catheter requires proper maintenance for avoiding any complications like accidental dislodgement or infections. Care should be taken by anesthesiologists while using these catheters for drug and fluid administration. Induction can be inhalational or intravenous depending on the preference of the child. Maintenance is with TIVA or inhalational anesthesia via facemask. Laryngeal mask airways (LMA) have been used, but the bulge of the LMA cuff may distort neck anatomy. Endotracheal intubation is preferred by some in small infants due to the proximity of the airway to the procedure site.

24.7.3 Radiotherapy

Radiotherapy is used for treatment as well as palliation in cancer management. The radiotherapy procedures require the patient to remain immobile. Older children may tolerate radiotherapy without sedation or anesthesia. However, a younger child may not remain immobile and thus requires sedation and/or anesthesia depending upon the type of radiotherapy procedure. In such situations, propofol remains the drug of choice to achieve sedation for the immobility of the patient [25]. The drug has the benefit of its short duration of action, titrable as per desired sedation, and rapid recovery. More recently, dexmedetomidine is emerging as an alternate drug for sedation in such procedures. Dexmedetomidine has been used in pediatric radiotherapy and has the advantages of producing sedation without respiratory depression [26]. Opioids are not required as such procedures are usually painless, though opioids may be required due to side effects of radiotherapy like mucositis which may cause pain [27].

LMA is an option for airway management; it is preferred over endotracheal intubation to avoid the trauma associated with repeated intubations.

To reduce radiation exposure, the anesthesiologist is away from the radiation suit, and monitoring can be challenging. Minimum monitoring includes a pulse oximeter and respiratory monitoring with camera surveillance. The child receiving radiation to the head or cervical spine is often required to wear a face mould; limitation of airway access should be borne in mind.

24.7.4 Imaging: Magnetic Resonance Imaging (MRI), Ultrasonography (USG), and Computerized tomography (CT)

The cancer patient requires imaging for diagnosis, planning for surgical management, to assess the response to treatment and follow-up. The

imaging modality depends on the type of cancer, site, and purpose for which it is being done. The imaging modalities are painless; however, they require the patient to be immobile for image acquisition. Also, the duration of imaging maybe for 30–60 minutes in MRI requiring patient cooperation. The child may be afraid and uncomfortable when in the imaging suite especially during the MRI due to the place and the noise that it generates. These all mandate the use of sedation and anesthesia during the imaging process.

The anesthetic considerations of MRI includes the availability of MRI-compatible anesthesia equipment and monitoring devices. Also, the patient assessment should exclude any contraindications to MRI because of MRI noncompatible implants in the body. Since the patient is being monitored from a distance, all these equipment sensor wires should have extra length. Also, the anesthesia equipment like breathing circuits should be extra long.

The anesthetic technique depends on the nature of imaging, patient age, presence of intravenous access, and airway management need. The strategy may range from oral/nasal sedation to general anesthesia. For airway management, the use of a laryngeal mask airway remains the preferred modality. Spontaneous ventilation can be maintained with monitoring including pulse oximetry and capnography. The use of propofol infusion or sevoflurane has been used in such situations. Dexmedetomidine has been used as the sole sedative in pediatric MRI [28, 29].

Cancer patients require biopsies. Presently, the image guided biopsy is always preferred. The use of USG, CT, and fluoroscopy-guided biopsies provides better sampling with minimal complications. The choice of imaging depends on the site of the tumor to be biopsied. This requires not only analgesia but also at times immobility by patient cooperation to avoid the needle hitting the wrong or vital structures. Good patient counseling (older child) along with analgesia by intravenous agents and local infiltration is acceptable. The younger child requires general anesthesia for such biopsy procedures [30].

The CT is a small duration procedure but requires patient immobility including breath holding at times for better images. Positron emission tomography (PET)-computed tomography (CT) is another modality being used for cancer patients [31].

24.8 Anesthesia for Major Surgery

This section outlines the key challenges and principles of anesthesia management of some common pediatric malignancies.

24.8.1 Abdominal Tumors

24.8.1.1 Nephroblastoma

Nephroblastoma (Wilms' tumor) is the commonest cancer of the kidney in children, representing 6% of all childhood cancers and presents at a younger age (<3.5 years) [32].

Clinical Presentation

The usual presentation of nephroblastoma is usually an asymptomatic abdominal lump. Few of these children may have pain, nausea, vomiting, and anorexia. Ten percent of patients have a syndromic association, and associated features—WAGR (Wilms' tumor, aniridia, genitourinary malformations, mental retardation), Beckwith–Wiedeman syndrome (macroglossia), Denys–Drash syndrome (pseudohermaphroditism) may be present [33]. Hypertension is present in >50% of patients. Depending on the extent of the tumor, patients may require preoperative chemotherapy.

Anesthesia Challenges

These are related to major abdominal surgery, raised abdominal pressure with risk of impaired ventilation and gastric aspiration, the potential for massive hemorrhage, and intraoperative hypotension. Other issues include associated hypertension, coagulopathy, vascular involvement of the tumor (inferior vena cava or right atrium), and side effects of preoperative chemotherapy.

Preoperative Evaluation

The majority of children are asymptomatic. A focused preoperative evaluation should look for syndromic associations (macroglossia, hypotonia, hyperinsulinemia with Beckwith–Wiedemann, and Simpson–Golabi–Behmel syndromes; congenital heart disease and hypotonia with Soto's syndrome; micrognathia with Trisomy 18). Congenital association-related difficult airway needs assessment and planning accordingly. Baseline blood pressure measurements must be performed to detect hypertension.

Complete hemogram and renal function tests including electrolytes must be ordered. Renal functions are usually normal. Anemia may be present due to hematuria or tumor lysis. Tumor lysis can also cause hyperkalemia. Some patients (<10%) may have associated coagulopathy and this needs assessment for the presence of associated acquired von Willebrand's disease [34]. Coagulation profile and cross-matched blood should be available. Cryoprecipitate may be required preoperatively to correct coagulation defects. Imaging studies should be reviewed to note the presence and extent of inferior vena cava (IVC) thrombus.

Some children may have received preoperative chemotherapy. Side effects relevant to anesthesia (hepatic and hematopoietic impairment with actinomycin D, syndrome of inappropriate antidiuretic hormone secretion (*SIADH*) with vincristine, cardiac dysrhythmias, and cardiomyopathy with doxorubicin) should be assessed. The cardiac assessment includes echocardiography for cardiac function and the presence of thrombus due to tumor extension.

Perioperative Management

An individualized planning and management strategy is required for such surgical intervention [35]. Surgical access is via a large transverse supraumbilical incision. Routine monitoring and wide bore access are mandatory. A low thoracic epidural, in the absence of any contraindication, is ideal for perioperative analgesia and general anesthesia with endotracheal intubation is the suggested option. The author prefers maintenance with air/oxygen and desflurane with low flow and fentanyl for intraoperative analgesia. Apart from routine monitoring, invasive blood pressure monitoring may be required in patients with renal hypertension. Intraoperative handling of the kidney can cause hypotension due to IVC kinking or major hemorrhage. Third space losses can also be significant.

Intravascular extension of the tumor can sometimes occur. Associated complications include pulmonary embolization, IVC obstruction, and atrial extension with tricuspid valve obstruction. Preoperative ultrasound or MRI can detect the extent of tumor invasion. Echocardiography will determine chamber involvement and myocardial function.

Intravascular tumor extension has additional implications for anesthesia [36]. Patients with abnormal liver drainage may have congestive hepatomegaly and ascites. Pleural effusion can result because of outflow obstruction due to atrial thrombus. IVC clamping may be required intraoperatively, and the risk of major hemorrhage is increased. The surgical plan and the need for cardiopulmonary bypass (CPB) should be discussed with the surgeons. IVC obstruction leads to engorgement of the epidural venous plexus, so there is a risk of bleeding during the epidural block. The possibility of CPB and heparinization must be borne in mind while planning for epidural. TEE facilitates monitoring for emboli during IVC handling in the non-CPB approach.

24.8.1.2 Hepatoblastoma

Hepatoblastoma manifests in younger children (<3 years) and remains the most common primary liver tumor. Most cases are sporadic, but there is an association with genetic abnormalities viz. Beckwith–Wiedeman syndrome and familial adenomatous polyposis.

Clinical Presentation

The child presents with an abdominal lump, distension (lump, ascites) and some may manifest other symptoms like discomfort, fatigue, decreased appetite, weight loss, and gastrointestinal bleeding. Jaundice and pruritus can be seen in case the lesion obstructs the biliary drainage.

Preoperative Evaluation

Serum alpha-fetoprotein is a key marker in diagnosis, response to treatment, and relapse. An abdominal ultrasound will reveal the liver mass and presence of satellite lesions in the liver or areas of hemorrhage. The imaging modalities like CT and MRI reveals the tumor site, extent, and its relation to the hepatic vasculature. In certain patients, preoperative chemotherapy is part of a therapeutic strategy depending on the risk stratification and thus needs assessment for any chemotherapy-related systemic effects. The hemogram, liver, and renal function tests need to be reviewed.

Anesthesia Challenges

The anesthesia challenges are due to long-duration surgery, the potential for massive hemorrhage, the risk of air embolism, and post-resection liver insufficiency. The surgery is performed through a large transverse abdominal incision and oncological clearance is attempted to preserve the residual healthy liver.

Perioperative Management

An individualized approach is required for optimal anesthetic management [37, 38]. Liver resection is conducted under general anesthesia with tracheal intubation and mechanical ventilation. The patient should have wide bore venous access and routine monitoring is used. Additional monitoring like central venous pressure, invasive blood pressure may also be required depending upon the patient's status and the extent of the surgery. In the presence of abdominal distension, a rapid sequence induction and intubation technique is adopted. The neuromuscular blocking agent of choice is cisatracurium or atracurium on account of its metabolism being not dependent on the liver. Maintenance is with oxygen, air, and a halogenated inhalational agent. Isoflurane has been found to maintain the hepatic blood flow. Desflurane has the advantage of being minimally metabolized by the liver. Sevoflurane has an ischemic preconditioning effect. Significant hemodynamic fluctuations can happen during the surgical procedure due to bleeding, during liver mobilization, and vessel clamping [39].

Monitoring has to be stepped up to diagnose and manage these complications. Central venous pressure monitoring is not the standard of care for fluid management because of its limited value. Cardiac output monitoring by TEE, and arterial waveform-based techniques have been used. Thromboelastography (TEG) is useful as coagulopathy can ensue, and appropriate correction can be administered. Hypoglycemia can occur, especially during periods of vascular clamping and post-resection; regular monitoring of blood sugar is essential.

Several vascular occlusive techniques are employed to reduce blood loss during dissection [40]. Hepatic pedicle occlusion (Pringle maneuver) controls both the hepatic artery and portal vein flow and provides inflow occlusion. Maintaining a low CVP during this phase minimizes bleeding. This must be balanced against the risk of organ hypoperfusion and the risk of air embolism. Vascular clamping during surgical resection leads to hemodynamic fluctuations with a decrease in cardiac output. It is prudent to maintain optimal fluid status before clamping of IVC and portal vein. Patients who have significant hemodynamic instability during test clamping and those where the total occlusion time exceeds 60 minutes will need a venovenous bypass. Renal injury can occur due to perfusion deficit or sympathetic activation related to decreased renal flow. Newer devices and techniques like ultrasonic cutting and coagulation devices, pressurized jets of water, the LigaSure™ Vessel Sealing System dissecting sealer, and endoscopic staplers with reduced blood loss during liver resection are being increasingly used [41]. Intraoperative blood salvage and use of tranexamic acid is useful in major resections [42].

Epidural analgesia using local anesthetics with or without opioids provides excellent pain relief. The risk of epidural hematoma in a coagulopathic patient must be borne in mind, and the plan for epidural must be individualized depending on the coagulation profile and the expected perioperative course.

Intraoperative complications like venous air embolism (VAE) can occur during liver resections. Risk factors include large tumors in the right lobe, proximity to the IVC, and low CVP. TEE and Doppler ultrasonography are sensitive monitors to detect VAE. Management includes supportive therapy with fluids and vasopressors. The central catheter may be used for air aspiration.

The patient may have increased liver dysfunction due to damage during surgical manipulation leading to metabolic acidosis, hypoglycemia, and coagulopathy. These need to be monitored and corrected accordingly.

24.8.1.3 Pheochromocytoma

Pheochromocytomas are tumors of the adrenal medulla mostly but extrarenal tumors are also reported [43, 44]. In contrast to adults, these tumors are frequently extra-adrenal, bilateral, and multifocal in children. They are commonly familial, associated with inheritable conditions such as multiple endocrine neoplasias, neurofibromatosis, tuberous sclerosis, and von Hippel–Lindau syndromes.

Clinical Presentation

The most characteristic feature is hypertension, which in children, is usually sustained. The classic triad of paroxysmal sweating, palpitations, and headaches is less common. Other less specific symptoms include sweating, visual problems, fatigue, weight loss, and nausea.

Wide fluctuations in blood pressure are common, and marked increases may be followed by hypotension and syncope. Intense peripheral vasoconstriction due to alpha-adrenergic receptor-mediated action leads to pallor. The resultant reduction in heat loss causes hyperthermia and flushing. Hypermetabolism leads to reflex sweating, poor weight gain, and cachexia despite a good appetite. Alpha-receptor mediated inhibition of insulin release causes glucose intolerance and hyperglycemia with resultant polyuria and polydipsia. Severe uncontrolled hypertension can cause acute neurological injury or cardiac compromise. Rarely the child can present with acute pulmonary edema and shock.

Diagnosis and Treatment

Diagnosis is confirmed by measurement of catecholamine breakdown products—metanephrine and normetanephrine in plasma and urine. Location of the tumor (or tumors) is by radiological investigations, MRI being the modality of choice in adrenal neoplasms. Radioisotope studies with I^{131}-labeled metaiodobenzylguanidine (MIBG) are useful in localizing abnormal medullary tissue in extra-adrenal sites.

Surgery is curative; preoperative medical preparation using α-adrenergic blockade-phenoxybenzamine 0.2–1 mg/kg/day, phentolamine 1–2 mg/kg/day is mandatory to block the effects of catecholamines and control hypertension, tachycardia, arrhythmias and optimize the blood volume. Theassessment should include a 12-lead electrocardiogram to detect the presence and/or extent of left ventricular strain, hypertrophy, bundle branch blocks, and ischemia. Preoperative echocardiography is essential to assess global systolic function and detect diastolic dysfunction. Cardiomyopathy can result from long-standing tumors due to the release of catecholamines.

Serial monitoring of hematocrit provides an idea of the adequacy of volume expansion following α-adrenergic blockade. Serum electrolytes, blood urea, and serum creatinine provide information on the metabolic and renal function status. Hypercalcemia is consistent with MEN Type II syndrome. Hyperglycemia can be present; blood sugar should be assessed preoperatively.

Anesthesia Challenges

Pheochromocytoma surgery presents the anesthesiologist with the challenge of maintaining stable hemodynamics in the face of catecholamine surges (especially at laryngoscopy, surgical stimulation, and tumor handling). Not only hypertensive crisis during tumor manipulation but also hypotension may occur after removal of the functional tumor.

Perioperative Management

Surgery is performed via laparoscopy in many centers, the open approach is reserved for very

large tumors and extra-adrenal tumors with limited access. Multiple techniques and adjuncts have been described for the anesthetic management of children with pheochromocytoma [45]. The maintenance of a good depth of anesthesia is crucial, rather than the agents or techniques used to achieve this. Combined general and epidural anesthesia is a preferred technique. Apart from routine monitoring, invasive blood pressure monitoring is required for these surgical procedures.

Premedication to achieve parental separation and reduce anxiety is warranted. The use of drugs like clonidine for anxiolysis has an added advantage of attenuating hemodynamic response during airway management [46]. The agents for inducing anesthesia includes thiopentone and propofol. Fentanyl is used for analgesia and obtunding laryngoscopy and tracheal intubation response. Intravenous lignocaine, esmolol, magnesium sulfate, and high-dose opioids have been used to blunt the intubation response [45]. Sevoflurane and isoflurane are commonly used for maintenance. Desflurane is avoided due to its ability to cause significant sympathetic stimulation. Nitrous oxide is generally avoided during laparoscopic resection. Vecuronium is the preferred muscle relaxant due to its stable cardiovascular profile. Atracurium and rocuronium have also been used safely. Epidural analgesia blunts the surgical response. Intraoperative hemodynamic fluctuations need to be controlled using various pharmacological agents like nitroglycerin, esmolol, sodium nitroprusside that needs to be used appropriately [47]. More recently, dexmedetomidine has been effectively used as adjuvant analgesic and to reduce anesthetic requirements [48, 49]. Post tumor excision, hypotension may ensue and needs to be managed using optimal fluid resuscitation. Fluid refractory hypotension will necessitate phenylephrine, adrenaline, or noradrenaline infusions. An increase in insulin levels post-resection can cause hypoglycemia. Postoperatively, close monitoring of vital parameters is necessary to detect complications related to hemodynamic fluctuations.

24.8.2 Thoracic Tumors

Tumors in the anterior and superior mediastinum pose several life-threatening challenges and have been discussed elsewhere in this book. In children, hematological malignancies are common thoracic lesions. Others include teratoma, neuroblastoma, germ cell tumors, and bronchogenic and enteric cysts.

The definitive treatment is antitumor therapy; however, a biopsy is essential for precise histological diagnosis and to guide treatment regimens. Anesthesia in such patients is fraught with several dangers, and a discussion with the surgical team is mandatory to plan what is best and safe for the patient.

Biopsy of a lymph node under local anesthesia (LA) or bone marrow biopsy may be an option to establish a diagnosis. Pleural effusions are common; pleural aspirate may provide material for diagnosis. CT guided needle biopsy of the mass provides reliable material for establishing the diagnosis. Patient cooperation is paramount during these biopsy procedures because of the vicinity of vital structures. This mandates the need for sedation and general anesthesia depending on the patient's age, cooperation, and site to be biopsied.

24.8.2.1 Preoperative Evaluation

A thorough assessment including a detailed history and clinical examination can often detect patients at risk of cardiorespiratory compromise. Stridor and orthopnea signify tracheal, bronchial, or carinal compression. Wheeze can be present due to pleural effusion, pulmonary outflow tract obstruction, or ventricular dysfunction. A chest radiograph is performed as an initial investigation. The presence of mediastinal widening should then prompt further tests viz. CT scan gives information on anatomic location, size of the tumor, and relation to surrounding structures. Spirometry and flow-volume loops can help assess the degree of airway compression; however, accurate results are difficult in young children. Echocardiography is useful to assess myocardial function and the presence of pleural and pericardial effusion.

24.8.2.2 Anesthesia Challenges

The impact of thoracic mass on airway and vascular structures are more prominent due to higher compliance in children. Patients at risk of cardiorespiratory collapse at induction are those with tracheal diameter <70% normal and/ carinal or bronchial compression, presence of superior venae cavae (SVC) obstruction, pericardial effusion, pulmonary outflow tract obstruction, and ventricular dysfunction [50]. Complete airway collapse can occur in patients with tracheal compression and in those with supine PEFR <50% of the predicted value [50].

Patients may require preoperative chemotherapy, steroids, and/or radiotherapy for shrinkage of the mass followed by a surgical attempt to remove the residual mass. Concerns exist about the accuracy of histological diagnosis following pretreatment but remain a safer option in the child with a high risk of cardiovascular compromise.

24.8.2.3 Perioperative Management

Anesthesia should be administered in a well-equipped facility by experienced pediatric anesthesiologists [51–54]. General anesthesia and neuromuscular blockade cause a reduction in the tone of major vascular structures and the airway. Tracheal compression can result in complete airway obstruction. Cardiovascular collapse can ensue because of the compression of great vessels by the lesion.

A safe approach is to preserve spontaneous ventilation until securing a definitive airway. Awake fibreoptic intubation is an option in the older, cooperative child. In other patients, inhalational induction with sevoflurane is commonly used; titrated infusion of propofol, combined with ketamine or fentanyl or remifentanil is an alternative technique. Reverse Trendelenberg position reduces the cephalad movement of the diaphragm and consequent reduction in FRC. Lateral decubitus position may be beneficial with regards to airway maintenance and preventing any cardiovascular compromise. Careful positioning is essential as a change in position may lead to vascular or distal airway compression. Cardiovascular collapse is treated by positioning the patient lateral/prone and with fluid boluses and vasopressors.

24.8.3 Medulloblastoma

Medulloblastoma is the most common malignant brain cancer in pediatric age group, and its management includes surgical resection and adjuvant chemo-radiotherapy. The clinical presentation varies with the age of the child and includes irritability, vomiting, etc. Focal neurological deficits may be manifested like hemiparesis, quadriparesis, cranial nerve palsies, etc. At times, increased intracranial pressures (ICP) may lead to life-threatening events.

24.8.3.1 Anesthetic Challenges

These include elevated ICP, cerebral edema, intraoperative blood loss, coagulopathy, the potential for venous air embolism, and fluid and electrolyte imbalance. The main goals for perioperative management include the maintenance of cerebral perfusion with rapid and full recovery after the reversal of anesthesia.

24.8.3.2 Perioperative Management

The perioperative management including the anesthetic strategy is based on individual patient assessment [55]. Preoperative sedation, commonly oral midazolam, will ease parental separation and reduce anxiety and crying, which can increase ICP. Inhalational induction is performed in children without an intravenous line; however, all volatile anesthetics increase CBF and ICP. Mild hyperventilation can offset this increase. In patients with an intravenous line, propofol or thiopentone, both of which lower ICP can be used. Anesthesia maintenance is best managed using a balanced technique using opioids, inhalational agents, and neuromuscular blocking drugs. Inhalational agents blunt cerebral autoregulation in a dose-dependent manner, by increasing CBF and ICP and affect evoked potentials used in neurologic monitoring. Hence, their use is limited to concentrations <1 MAC. Normal saline is preferred as the perioperative fluid, as it is slightly hyperosmolar, and may reduce cerebral edema formation. In patients with raised ICP, hyperosmolar drugs such as mannitol, hypertonic saline, and diuretics are commonly used. Careful assessment of the volume status of

the patient is essential to prevent dehydration and maintain organ perfusion.

24.8.3.3 Positioning

Proper positioning of the neurosurgical patient is important to ensure surgical access and patient safety [56]. Posterior fossa tumors can be operated on with the patient in lateral, prone, or sitting positions. Neck flexion can result in endobronchial intubation and obstruction of venous drainage with a resultant rise in ICP. The prone position increases the risk of eye injury due to hypoperfusion and direct pressure on the globe. Appropriate padding and care of pressure points are necessary to prevent injury. The sitting position poses a significant risk for venous air embolism, and a high vigilance along with the use of appropriate monitoring (Doppler, transesophageal echocardiography) is important.

24.8.4 Sacrococcygeal Teratoma

The germ cell tumor with its origin of the coccyx is labeled as sacrococcygeal teratoma (SCT) and is one of the common congenital tumors seen in children. 10% of SCTs are malignant during the neonatal period, and by 1 year of age, these become malignant in 50% of cases. Surgical excision including complete resection of the lesion along with coccyx is usually planned at the earliest. Perinatal mortality is high and is related to polyhydramnios-related preterm delivery, anemia due to blood loss from tumor, the rich blood supply of tumor-related high output cardiac failure, and tumor rupture. The vascular steal phenomenon may occur, with a large part of the fetal cardiac output going to the tumor, rather than the fetus. Fetal surgery has been performed in fetuses that are at risk of significant secondary morbidity [57]. For large tumors, planned cesarean delivery is necessary.

24.8.4.1 Anesthesia Challenges

Anesthesia concerns include the potential for massive hemorrhage, coagulopathy, cardiovascular instability, hypothermia, long-duration surgery, and prone positioning [58, 59]. Due to these concerns and in large tumors, the presence of wide-bore venous access and invasive monitoring (arterial line, central venous line) is desirable. Perioperative morbidity is related to massive blood loss and coagulation dysfunction [60, 61]. Long-term complications include urologic problems and incontinence.

24.9 Anticancer Therapy and Its Anesthetic Implications

The anesthesiologist caring for children needs to be aware of the tumor biology, its treatment modalities, and related side effects. Cancer management remains multidisciplinary and involves a multimodal approach including surgery, radiation therapy, and chemotherapy. Classification and listing of major chemotherapeutic drugs are presented in Table 24.1. Children undergoing cancer therapy are often quite ill and susceptible to several complications. Treatment protocols also include stem cell transplantation. Consequently, the toxicities of these individual therapies can overlap, and virtually every organ system is at risk. Systemic toxicity of common chemotherapeutic agents occurs and requires not only monitoring but also timely management (Table 24.2).

Radiation therapy damages cellular Deoxyribo Nucleic Acid (DNA) causing the death of tumor cells while also affecting healthy tissue (Table 24.3). To limit the damage to healthy tissue, radiation therapy is delivered in fractions over days. The concurrent administration of chemotherapy can also add to adverse effects.

System-wise toxicity of chemotherapy and radiotherapy and the implications for anesthesia is presented below [62]:

24.9.1 Oral Cavity and the Airway

One of the common adverse events of chemotherapy, and radiotherapy to the head and neck region is oral mucositis which usually occurs

Table 24.1 Classification of major chemotherapeutic drugs [89]

Drug class	Drug
Alkylating agents	• Nitrogen mustards—Mechlorethamine, Cyclophosphamide, Ifosfamide, Melphalan, Chlorambucil • Ethylenemines—Thiotepa • Alkylsulphonates—Busulphan • Nitrosoureas—Carmustine, Lomustine, Streptozotocin • Platinum complexes—Cisplatin, Carboplatin, Oxaliplatin • Triazenes—Dacarbazine
Antimetabolites	• Folic acid analogs—Methotrexate • Pyrimidine analogs—Fluorouracil, Cytarabine • Purine analogs—6-Mercaptopurine, 6-Thioguanine, Pentostatin, Cladribine, Fludarabine, Clofarabine
Natural products	• Vinca alkaloids—Vinblastine, Vincristine, Vinorelbine, Vindesine • Epipodophyllotoxins—Etoposide, Teniposide • Enzymes—L-Asparaginase • Camptothecin analogs—Topetecan, Irinotecan • Taxanes—Paclitaxel, Docetaxel
Antibiotics	Actinomycin D, Daunorubicin, Dactinomycin, Doxorubicin Idarubicin, Bleomycin, Mitomycin, Plicamycin
Hormones	Estrogens, Progesterone, GRH analogs, Hormone antagonists—Tamoxifen
Miscellaneous	Anthracenedione • Mitoxantrone Hydroxyurea Adrenocortical suppressants Methylhydrallazine derivative • Procarbazine Estradiol-Mustard ester Estramustine
Molecularly targeted therapy	• Antiangiogenic therapy • Gene therapy • Immunomodulators • Monoclonal antibodies—Rituximab, cetuximab

Table 24.2 Systemic toxicity of common chemotherapeutic agents [89]

System	Chemotherapeutic agents
Heart	Anthracyclines, Busulphan, cisplatin, cyclophosphamide, 5-fluorouracil
Lungs	Methotrexate, bleomycin, busulphan, cyclophosphamide, cytarabine, carmustine
Kidney	Methotrexate, L-asparaginase, carboplatin, ifosfamide, mitomycin-C
Liver	Actinomycin D, methotrexate, androgens, L-asparaginase, busulphan, cisplatinum, azathioprine
Nervous system	Methotrexate, cisplatin, interferon, hydroxyurea, procarbazine, vincristine

Table 24.3 Adverse effects of radiation therapy [89]

Radiation field	Adverse effects
Head and neck	• Neurocognitive defects • Leukoencephalopathy • Panhypopituitarism • Growth hormone deficiency • Hypo-/Hyperthyroidism • Thyroid cancer • Dental damage • Cataract • Ototoxicity
Chest	• Pericardial effusion • Conduction defects • Endocardial fibrosis • Cardiomyopathy • Valvular heart disease • Coronary artery disease • Pneumonitis • Pulmonary fibrosis • Restrictive lung disease
Abdomen/pelvis	• Chronic enteritis, fibrosis, bowel obstruction • Hepatic fibrosis, cirrhosis • Nephritis, renal insufficiency • Cystitis, fibrosis, bladder Ca • Gonadal dysfunction
Miscellaneous	• Skin cancer • Affection of bone growth • Pathologic fractures • Bone marrow hypoplasia
Airway	• Fibrosis resulting in limited mouth opening and neck extension • Supra and subglottic stenosis • Xerostomia • Jaw hypoplasia • Chondronecrosis of airway cartilages

around a week of chemotherapy, 2–4 weeks after radiotherapy, and persists for 1–2 weeks [62–64]. Severe mucositis can cause difficulty in airway management due to edema, bleeding, and aspiration risk. These patients are prone to infections and hence utmost care is required during airway management. Radiation to the head and neck can cause several chronic changes (Table 24.3). Fibrosis of soft tissues of the oral cavity and neck can limit mouth opening and neck extension with resultant airway difficulty.

24.9.2 Cardiac Toxicity

The chemotherapeutic agents associated with cardiotoxicity include anthracycline antibiotics group like doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone [65]. Cardiotoxicity can occur acutely (within days to a week) or may present late (months to years of receiving chemotherapy). Acute toxicity manifests as cardiomyopathy and is usually reversible. Late toxicity relates to the cumulative dose of the chemotherapeutic agents received. Other chemotherapeutic agents may also manifest cardiac toxicity symptoms like cardiac failure, arrhythmias, myocarditis, pericarditis, myocardial ischemia, and cardiomyopathy [66]. Young children are more susceptible. Cumulative dose risk for anthracyclines is <1% for doses <300 mg/m^2, 5–10% for doses 350–450 mg/m^2; 30% for doses>550 mg/m^2 [16].

Radiation therapy, especially to the thoracic region can lead to cardiac toxicity and manifests as pericarditis, pericardial effusion, endocardial fibrosis and related conduction disturbances, cardiomyopathy, coronary artery disease, and valvular fibrosis [67].

Concomitant radiotherapy and chemotherapy have cumulative toxicity and thus need vigilance. Children should be monitored for any of these toxicities using appropriate monitoring tools including an echocardiogram (baseline and follow-up). Also, where the child requires surgical intervention, care should be taken as subclinical toxicity may be manifested overtly due to perioperative surgical stress [68].

24.9.3 Pulmonary Toxicity

Chemotherapeutic agents like bleomycin, busulfan, lomustine, carmustine, cyclophosphamide, methotrexate, mitomycin, vinca alkaloids have an impact not only acutely but also have their late manifestations. The toxicity profile includes interstitial pneumonitis, hypersensitivity pneumonitis, pulmonary fibrosis, or noncardiogenic pulmonary edema [69–71]. Radiation therapy also causes pulmonary toxicity and ranges from pneumonitis to fibrosis.

Patients should be evaluated for pulmonary toxicity and its severity before the surgical intervention. Diagnostic modalities include chest X-ray, computed tomography, spirometry, oxygen saturation, or arterial blood gas measurement. The anesthetic management needs to be initialized based on the existing pulmonary limitations and its severity. Airway management, mechanical ventilation, and perioperative stress can exacerbate pulmonary manifestations. The fraction of inspired oxygen needs to be kept minimal in perioperative care along with minimizing peak airway pressures during mechanical ventilation and optimal administration of positive end-expiratory pressure (PEEP). Judicious perioperative volume administration is crucial to prevent overhydration and pulmonary edema [62].

24.9.4 Renal Toxicity

Chemotherapeutic agents like cisplatin, carboplatin, and ifosfamide are associated with renal toxicity. Acute renal failure (ARF) can be caused by drugs like lomustine, carmustine, cyclophosphamide, and high-dose methotrexate [72]. Cisplatin causes hypomagnesemia and impairment of glomerular function. Fanconi syndrome, tubular nephropathy can present several months after discontinuation of treatment. Hemorrhagic cystitis is associated with cyclophosphamide therapy. Prolonged therapy with nitrosoureas (lomustine, carmustine) can cause Fanconi syndrome and renal failure. Ifosfamide is associated with glomerular and tubular toxicity which can progress to renal failure.

Radiation therapy can cause nephritis and renal impairment progressing to renal insufficiency. Severe sepsis with hemodynamic compromise and tumor lysis syndrome can impair renal function.

Renal function must be assessed before surgery, especially when patients have received nephrotoxic therapy. Meticulous attention to the maintenance of preload and renal perfusion, and avoiding drugs with nephrotoxic potential, e.g., NSAID, is essential [62].

24.9.5 Hepatic Function

Chemotherapeutic agents like methotrexate, actinomycin D, 6-mercaptopurine, and 6-thioguanine can lead to hepatotoxicity. However, the effects are reversible and progression to chronic liver failure is rare [73].

Acute radiation toxicity can manifest as sinusoidal obstruction syndrome, which can occur weeks to months after therapy. This can progress to portal hypertension and liver failure. High-dose radiation can rarely cause hepatic fibrosis [74].

Impaired hepatic function can impact the synthesis of coagulation factors, proteins, and the elimination of anesthetic agents. Attention to maintenance of hepatic blood flow and titration of anesthetic agents dependent on hepatic biotransformation is required [62].

24.9.6 Gastrointestinal Effects

Mucositis, stomatitis, nausea, vomiting, and diarrhea are common with many chemotherapeutic agents. Diarrhea occurs with the administration of melphalan, fluorouracil, etoposide, topotecan, and irinotecan [75]. Radiation can cause acute bowel mucosal edema. Chronic effects include chronic enteritis, fibrosis, and bowel obstruction [76].

Mucositis, vomiting, and diarrhea can result in dehydration. The risk of regurgitation and aspiration must be considered in patients with acute cytotoxicity and bowel obstruction. Opioid therapy for pain relief further delays gastric emptying. Malnutrition with subsequent hypoproteinemia and electrolyte imbalance can impact drug requirements and recovery from anesthesia.

24.9.7 Nervous System

Chemotherapy regimes that include platinum agents (cisplatin, carboplatin, oxaliplatin), L-asparaginase, ifosfamide, methotrexate, cytarabine, etoposide, vincristine, and cyclosporin A have been found to have neurotoxic potential of various types and severity [77]. The usual acute manifestations include seizures, infarct, encephalopathy, altered mental status, and peripheral neuropathy. Chronic toxicities may also occur, especially with repeated doses, and manifests as leukoencephalopathy, focal necrosis, vision loss, ototoxicity, and cognitive deficits.

Transient or permanent chemotherapy-induced peripheral neuropathy can occur. Symptoms include tingling, weakness, difficulty in maintaining balance, and neuropathic pain. Common agents include plant alkaloids vincristine and vinblastine, and platinum derivative cisplatin. Treatment includes opioids, non-opioid analgesics, tricyclic antidepressants, and gabapentin.

Careful positioning and padding of pressure points is a must during surgery. Opioid requirements may be higher for patients on opioid therapy. If a peripheral nerve block is planned as part of the anesthetic regimen, a neurologic examination with documentation of the preexisting neuropathy and reduction in LA dose is recommended [62].

24.9.8 Neuroendocrine System

Glucocorticoids, which are a common part of chemotherapeutic regimens, suppress the hypothalamic–pituitary–adrenal (HPA) axis [78]. Adrenal suppression is noted with steroid administration of more than 3 weeks in the doses of >20 mg/day of prednisone or equivalent. The

period of HPA axis suppression is extremely variable from weeks to months. So, steroid replacement therapy is usually required for these patients with 1–2 mg/kg of hydrocortisone or dexamethasone (0.05–0.1 mg/kg) intravenously [62].

Hypothalamic–pituitary dysfunction may be seen with radiation therapy to the head and neck region and may occur even years after therapy. Thyroid dysfunction may be seen after radiation to the head, neck, and chest [79, 80].

24.9.9 Hematologic System

Myelosuppression is the most common side effect of chemotherapy. Typically, the reduction in cell count starts at around 1 week of initiation of therapy, reaches the nadir at 15 days with recovery at 28–30 days. Rarely marrow suppression can persist chronically with chemotherapy, and also with high-dose radiotherapy. Neutropenia leads to significant morbidity and mortality from sepsis. Anemia is common and results from many factors: direct infiltration of marrow by the tumor, myelosuppression due to therapy, malnutrition, hemolysis, and repeated blood sampling [81]. Thrombocytopenia is very common as a result of myelosuppression due to therapy. Other causes include marrow infiltration, consumption due to infection or DIC, platelet sequestration in splenomegaly, and dilutional thrombocytopenia due to blood transfusion.

When administering anesthesia to a neutropenic patient, standard precautions to prevent infection must be taken [82].

The decision to transfuse red cells perioperatively must be made judiciously based on patient assessment. Blood transfusion has an immunomodulatory effect and can lead to cancer recurrence, in addition to the risk of infection. Transfusion with leuko-reduced blood products to reduce risk of infection, and irradiated red cells and other components to reduce transfusion-related graft versus host disease is recommended [83, 84]. Platelet counts of 40,000–50,000/mL is acceptable for invasive procedures, but for neurological and ocular interventions, counts should be more than 100,000/mL [85, 86].

Coagulation defects can occur due to cancer therapy, hepatic dysfunction, vitamin K deficiency due to malnutrition, and following infection and sepsis. Thrombophilia, with thrombosis and thromboembolism, can occur with pediatric cancers, with a high incidence in sarcomas and hematological malignancies.

Administration of fresh frozen plasma (FFP), cryoprecipitate, and other components should be based on testing or if surgical bleeding is ongoing despite adequate platelet function and number. Children at risk of thrombosis will be on prophylactic heparin or warfarin. The risk of intraoperative bleeding should be balanced against the risk of thrombosis.

24.10 Summary

The anesthesiologist caring for children with cancer should possess a basic understanding of chemotherapeutic drugs, radiation therapy, and its toxicities to formulate a safe anesthetic plan. Anesthesiologists must address the psychological aspects of the diagnosis of disease and treatment, and its impact on the child and the family. Moderate to severe pain is a significant symptom caused by a tumor, metastasis, post-surgery, or antineoplastic therapy. A multimodal approach to the management of pain must be given the highest priority. Preoperative testing and evaluation must be individualized, depending on the type of cancer, its effects on end-organ systems, and the adverse effects of concurrent chemotherapy and radiation therapy regimens.

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Anaesthesia for Video- and Robot-Assisted Onco-surgery

25

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25.1 Introduction

Since the establishment of laparoscopic gynaecological surgery in the 1980s, minimal-access video-assisted surgical techniques have risen dramatically in popularity, such that for many cancer operations they now represent the default approach. The aims of video-assisted surgery, to minimise tissue trauma without compromising surgical view and technical performance, align closely with modern anaesthesia goals of enhancing postoperative recovery. The advent of robotic assistance for the operator has brought additional benefits in terms of improved surgical view and enhanced tissue manipulation, and can further reduce tissue trauma and operating time [1]. Patients are increasingly seeking out minimal access and robot-assisted surgery where this is available [2].

Laparoscopic techniques have evolved for most gynaecological and general surgical cancer operations [3], while video-assisted thoracoscopy has become established in thoracic cancer surgery and other fields such as head and neck surgery are developing their video-assisted approaches to operations that have traditionally been carried out as open procedures.

Video- and robot-assisted surgery has several significant implications for anaesthesia. Benefits for the patient relate mainly to the postoperative period. With reduced tissue damage, the surgical stress response is less pronounced, which has an immediate bearing on the speed of patient recovery and may have a long-term benefit in terms of immune modulation and reduced cancer recurrence [4, 5]. There is also less postoperative pain, which reduces the need for analgesia and associated side effects.

However, the intraoperative conditions required for successful minimal access surgery, namely extreme degrees of operating table tilt and pressurised gas insufflation into a body cavity, place demands on a patient's physiology that can prove difficult or even impossible to manage. As a result, some patients' pre-existing comorbidities make them unsuitable for a video-assisted approach to cancer surgery, even if this option appears possible from the surgeon's technical perspective.

In this chapter, we explain the physiological consequences of video-assisted minimal access surgery in the abdomen and pelvis (laparoscopy) and summarise current evidence concerning the risks and benefits of this approach, and strategies for preoperative, intraoperative and postoperative care of patients having these operations. We do not discuss in detail the implications for anaesthetists of video-assisted surgery in the chest or

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minimal access surgery in other areas of the body, such as head and neck surgery.

We also discuss the implications of robotic assistance for minimal access surgery and summarise the literature regarding perioperative care for patients undergoing robot-assisted operations.

25.2 Minimal Access Surgery Techniques and the Surgical Stress Response

Video-assisted minimal-access surgery entails the insertion of a camera into a body cavity to allow the operator a view of the surgical field. For laparoscopic surgery, this is achieved by making a small incision in the abdominal wall, usually at the umbilicus. The peritoneal cavity is then insufflated with gas, now almost always carbon dioxide, to allow the operator space to see and operate. This initial stage can, rarely, be complicated by inadvertent puncture of a solid or hollow viscus, major haemorrhage and even gas embolism.

The operation is carried out using one or more surgical instruments, controlled directly by the operator, that enter the body cavity via separate access incisions. Manipulation of these instruments is not intuitive and there is a steep learning curve for any new operator, compounded by the lack of tactile sensation at the operation site.

To operate laparoscopically, the surgeon needs to be able to visualise and access the surgical site. This can demand extreme degrees of operating table tilt, while obesity and adhesions from previous surgery can make the surgery more difficult, or even impossible.

The arrangement of the operating room is dictated by the additional equipment required for this type of surgery. The operator must stand near the patient to manipulate the instruments, and an assistant must stand close enough to handle the camera. Video screens must be placed so that the operator, assistant and any others involved in the operation can see.

Use of a robot brings additional considerations to laparoscopy. At the time of writing, the commercially available surgical robot is the Da Vinci® system (Intuitive Surgery Inc, Mountain View, California). The robotic system allows the operator to control the camera and surgical instruments remotely from a console equipped with magnified binocular stereoscopic vision. Also, and in contrast to laparoscopic instruments, those utilised with the robot are wristed and can rotate and bend to a greater extent than the human hand. A scrubbed assistant stands next to the patient to perform tasks such as providing suction, swapping instruments and introducing swabs (Please see Figs. 25.1, 25.2 and 25.3 for a schematic operating room layout and illustrations of the robot in use). Communication between the remotely placed surgeon, the assistant and the rest of the theatre team is achieved via a microphone and loudspeaker built into the console. Once the robot arms are in place, they are locked and do not move with the patient. Undocking the robot takes 1–2 min with a practised team but must be done before the table position is changed. The use of a robot can facilitate surgical progress and may demand different patient positioning, but from a perioperative medicine perspective, the principles are broadly similar to traditional minimal-access video-assisted surgery.

Minimal access techniques have been shown to produce a less pronounced neuro-humoural stress response to tissue trauma than open surgery. In particular, laparoscopic cancer surgery is associated with a less marked deterioration in postoperative immune function than open surgery, with a reduced peak in interleukin (IL)-6 production and better preservation of human leucocyte antigen DR (HLA-DR) expression [4, 5]. The reduced tissue trauma also helps reduce postoperative pain and consequently promotes earlier mobility and faster recovery (Table 25.1 for a summary of evidence for this). Initial concerns that carbon dioxide-related impairment of peritoneal immunity would lead to local seeding have not materialised in large clinical trials. In general, laparoscopic interventions are associated with less postoperative morbidity and faster recovery, although the evidence is stronger for some operations than for others. Similarly, robotic assistance for laparo-

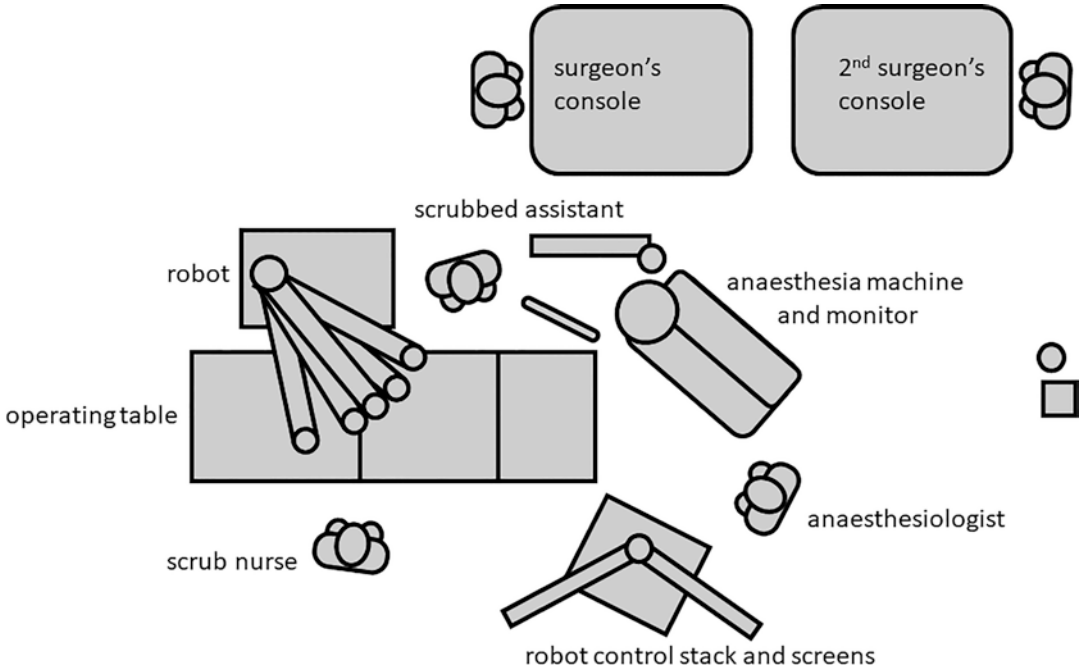

Fig. 25.1 An example theatre layout for robotic surgery (robot-assisted laparoscopic prostatectomy). Image provided by the authors

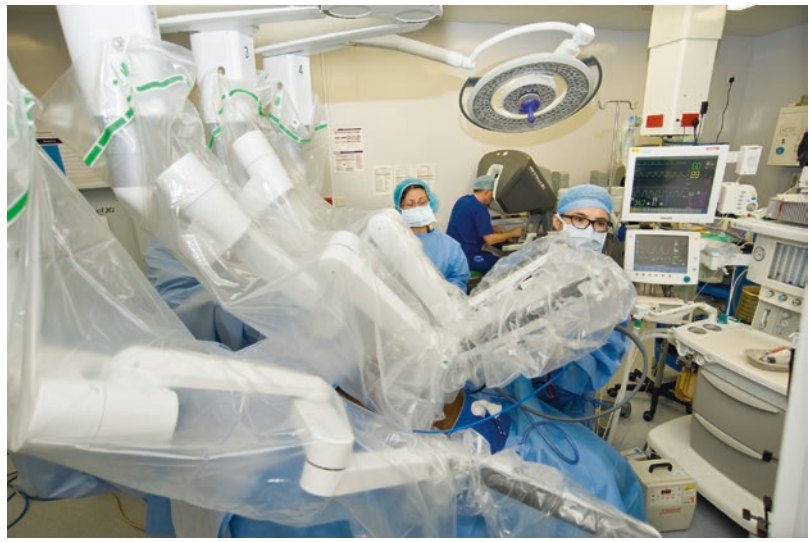

Fig. 25.2 A robot-assisted laparoscopic prostatectomy demonstrating a typical theatre layout. Note the diffculty of patient access for the anaesthesia team once docking is complete. Images supplied by the Royal Marsden Hospital medical photography service

scopic surgery has been shown in some settings to lead to reduced operating time, reduced tissue damage and faster recovery time for some operations, although the evidence is often anecdotal and the technology is still at a relatively early stage of adoption.

25.3 Physiological Considerations for Laparoscopic Surgery

The establishment of capnoperitoneum and the effects of steep table positioning present the main physiological concerns during anaesthesia for

Fig. 25.3 A robot-assisted laparoscopic prostatectomy in Trendelenburg position. Images supplied by the Royal Marsden Hospital medical photography service

Table 25.1 Operations commonly carried out wholly or partially laparoscopically/robotically and a summary of the evidence for benefit with this approach

System	Surgical interventions	Benefits
Urology	Robotic/laparoscopic prostatectomy	Reduced length of stay and reduced blood transfusions [6]
	Cystectomy	Reduced blood loss, length of stay [7], fewer postoperative complications
Lower gastrointestinal (GI)	Colorectal cancer excision	Reduced length of stay, fewer postoperative complications [8]
Hepatobiliary	Hepatic resection	Reduced length of stay, reduced blood loss, fewer postoperative complication [9]
Upper GI	Oesophagectomy	Faster recovery [10]
	Gastrectomy	Reduced blood loss, faster recovery and fewer postoperative complications [11]
Gynaecology	Hysterectomy	Fewer postoperative complications and reduced length of stay [12, 13]

video- and robot-assisted cancer surgery. In most cases, these factors can be managed using appropriate anaesthetic techniques. However, some patients will have comorbidities that make them unsuitable for this type of surgery, regardless of the technical surgical considerations.

Gas insufflation into the peritoneal cavity can produce profound cardiovascular instability in a manner that can be hard to predict from a patient's known comorbidities. Insufflation of 4–6 L/min to a pressure of 8–12 mmHg usually establishes an adequate capnoperitoneum for the surgeon, although in obese patients the surgeon may need higher pressure to produce a suitable working space. The initial peritoneal stretch can trigger a vagal reflex leading to profound bradycardia. After the first few seconds, increased intra-abdominal pressure leads to reduced cardiac filling and a stroke volume-mediated fall in cardiac output that can be quite marked in a hypovolaemic patient. Systemic vascular resistance rises, partly due to direct pressure, mainly affecting the splanchnic vessels, and partly due to increased sympathetic nervous system activity. As a result, the mean arterial pressure may rise after initial hypotension, although with higher afterload stroke volume and cardiac output are usually reduced. Peritoneal gas insufflation and the tissue trauma of the specific operation, as well as the systemic effects of hypercarbia, all contribute to

this increased sympathetic tone, which can also lead to a tachycardia [14–16].

Increased intra-abdominal pressure also affects individual organ perfusion. In particular, renal perfusion falls and urine output is decreased during capnoperitoneum [17]. Clinical evidence suggests that the laparoscopic approach is not associated with an increased risk of perioperative kidney injury [18], although this risk should be considered for patients with significant existing renal disease or for whom a long duration of capnoperitoneum is expected. Pneumoperitoneum can also reduce splanchnic and portal blood flow [19].

In the respiratory system, capnoperitoneum reduces diaphragmatic excursion and lung functional residual capacity (FRC). Inflation pressures rise, dynamic lung compliance falls, as the reduced FRC starts to encroach on the closing capacity of the lung, patients develop intra-tidal recruitment/de-recruitment and basal atelectasis, although the latter issues can be ameliorated using positive end-expiratory pressure (PEEP) [20]. As a result, patients are at risk of increased V/Q mismatching and consequent arterial hypoxia. Also, carbon dioxide (CO_2) absorption from the peritoneal cavity increases the minute ventilation required to maintain normocapnia, usually necessitating shorter inspiratory times and consequently high peak inspiratory pressures.

The insufflation of CO_2 itself is cooling and dries the peritoneum. There is some evidence that immediate postoperative pain and intraoperative hypothermia can both be reduced by warming and humidifying the insufflating gas [21].

Extreme table tilt is often required to optimise the surgeon's view during laparoscopic surgery. Steep head-down (sometimes as much as 45°, although 20–35° is more common) is used to demonstrate the pelvic organs for gynaecological, rectal, prostate and bladder surgery, while head-up tilt is used for surgery on the liver, stomach and other upper abdominal organs. The main physiological consideration for head-up tilt is the reduction in venous return due to gravitational pooling in the lower limbs. This is reversed in head-down tilt, helping to maintain cardiac output but at the cost of higher venous pressure in the head and neck, which contributes to raised intracranial pressure (ICP) and intraocular pressure (IOP) pressure. Central venous pressure (CVP) can rise nearly threefold in 45° steep Trendelenburg position, while pulmonary artery pressure and pulmonary capillary wedge pressure can double [22].

During laparoscopy in the 30° Trendelenburg position, optic nerve sheath diameter rises to values indicating raised intracranial pressure (>20 mmHg) after 2 h of surgery [23, 24]. ICP has been shown to raise more quickly in the 45° Trendelenburg position [25]. Cerebral autoregulation is also progressively impaired [26]. Cerebral oxygenation does not seem to be affected, at least where normocapnia is maintained in patients without pre-existing intracranial hypertension or other central nervous system diseases [27]. Nonetheless, head-down positioning and capnoperitoneum for prolonged operations have been implicated as a potential contributing factor to neurological complications such as cerebral oedema, stroke and intracranial haemorrhage [28].

Intraocular pressure has been shown to rise from normal awake values of just under 20 mmHg to more than 30 mmHg when using the extreme 45° steep Trendelenburg position for robot-assisted laparoscopic prostatectomy [25]. Higher peak inspiratory pressures and higher MAP were associated with IOP increase.

Trendelenburg positioning also adds to the adverse effects of capnoperitoneum on lung compliance, recruitment and functional residual capacity. In this context, it is important to note that capnoperitoneum and Trendelenburg position, as with obesity, increase the pressure required to distend the thoracic wall and so higher inspiratory pressures measured on the ventilator will not be fully reflective of the transpulmonary pressure (which determines the propensity to barotrauma), which will be less [13].

Steep head-down positions can also promote upper and lower airway oedema formation. Steep Trendelenburg position for robot-assisted laparoscopic prostatectomy increases upper airway resistance in patients with and without the pre-existing and chronic obstructive pulmonary

Table 25.2 Physiological changes during capnoperitoneum and steep Trendelenburg position [22, 25, 31]

Systemic variables	Change during capnoperitoneum and steep Trendelenburg position from baseline
Stroke volume (SV)	15% increase
Mean arterial pressure (MAP)	25% increase
Mean pulmonary artery pressure	80% increase
Pulmonary capillary wedge pressure (PCWP)	80% increase
Central venous pressure (CVP)	100% increase
Pulmonary compliance	53% reduction
Intraocular pressure (IOP)	50% increase
Intracerebral pressure (ICP)	Rises over 20 mmHg or more

disease (COPD) for up to 24 h. Forced expiratory volume in 1 s (FEV1) and vital capacity is reduced for up to 5 days in patients without COPD and for longer in patients with COPD [29].

Steep head-down positions also place the legs significantly higher than the heart, reducing perfusion pressure to the legs by as much as a 30-mmHg drop in hydrostatic pressure from the horizontal. This is not of concern in patients with a normal cardiovascular system but can lead to critical ischaemia when combined with peripheral vascular disease or intraoperative hypotension [30]. The various physiological changes during capnoperitoneum and steep Trendelenburg position are thus important to understand and plan the intraoperative management accordingly (Table 25.2) [22, 25, 31].

25.4 Preoperative Assessment and Suitability for the Laparoscopic Approach

There are arguably no absolute contraindications to laparoscopic surgery. Despite initial concerns based on the physiological changes associated with laparoscopy and steep degrees table tilt, clinical experience over the last two decades has demonstrated that video- and robot-assisted surgery is safe and well-tolerated by most patients, even those with comorbidities. Elderly patients, who were once thought unsuitable for laparoscopic surgery, are now recognised to be a group for whom this approach is most appropriate [32]. Nonetheless, for some patients, an open approach may be more suitable for reasons related to the technical aspects of the surgery. In other cases, it may be appropriate to attempt a laparoscopic approach but plan to convert to an open technique if the procedure is poorly tolerated.

Laparoscopy does not seem to reduce cardiac risk compared to open approaches but appears to be safe in patients with heart failure and coronary artery disease [33]. Patients planning to have video- or robotic-assisted surgery should have the same preoperative cardiac assessment and treatment optimisation as if they were undergoing an open procedure [34].

Mild valvular regurgitation can become moderate or severe with the combination of head-down positioning and capnoperitoneum, and pulmonary hypertension and right to left shunts will be exaggerated. Some specialist centres achieve laparoscopic surgery even in preload-dependent patients such as those with a single ventricle, albeit with a low threshold for conversion to an open procedure.

Maintenance of normocapnia may prove impossible in patients with severe restrictive or obstructive lung disease, and those with obstructive sleep apnoea or other upper airway obstruction will be at risk of worsened symptoms after steep Trendelenburg positioning.

Morbid obesity presents numerous problems for both the anaesthetist and surgeon during laparoscopic surgery. Nonetheless, experience from bariatric centres shows that laparoscopy in some positions can be reasonably well tolerated in this population and has become the approach of choice for weight-reducing gastric bypass or banding operations, which use the head-up position. As with significant pulmonary disease, the combination of morbid obesity and steep Trendelenburg position may reduce lung compliance to a degree where laparoscopy has to be

temporarily halted or abandoned in favour of an open approach. Body mass index (BMI) is often used to categorise obesity, but it is a blunt tool for preoperative assessment since it masks widely differing body shapes. For any given BMI, patients with predominantly central obesity, indicated by a waist to height ratio greater than 0.55, are more likely to have impaired spirometry at rest [35]. These patients will be much more likely to require high inflation pressures and to develop intraoperative ventilation-perfusion (V/Q) mismatching from intra-tidal recruitment/de-recruitment. In our institution, we do not regard very high BMI as a contraindication to laparoscopic and robot-assisted surgery, and we believe that these patients have the most to gain from a minimal access approach, if possible. We routinely perform long robotic gynaecological operations in the steep head-down position for patients with BMI over 40 and up to 60 kg/m^2. However, we discuss with the patient and surgeon the possibility that the minimal access approach may have to be abandoned intraoperatively if the patient does not tolerate the position and capnoperitoneum.

Perioperative acute kidney injury has rarely been attributed to capnoperitoneum, but physiological evidence predicts that diseased kidneys may be more vulnerable to intraoperative ischaemia and that discussion with a renal physician may be appropriate for patients with stage 4–5 chronic kidney disease when a prolonged laparoscopic operation is being planned [36]. Angiotensin converting enzyme (ACE) inhibitors and Angiotensin 2 receptor blockers should probably be stopped in these patients to protect the autoregulation of renal blood supply.

Although there is little evidence for a strong association between raised IOP and ICP and postoperative blindness and intracranial bleeding, these complications can occur and should be taken into account when discussing risk and treatment options with patients preparing for cancer surgery. Patients with intracranial hypertension should probably not have a prolonged laparoscopic operation in Trendelenburg position. Patients with ventricular shunts can probably have laparoscopic procedures but it is important to establish the type of shunt valve and whether it is functioning properly, especially for shunts emptying into the peritoneum [37]. Patients with a recent stroke should have preoperative carotid Doppler studies as for any other surgery [38] and those with significant stenoses may need intervention before robotic surgery. Patients with glaucoma should have their intraocular pressures measured and optimised before surgery. We try to avoid steep head-down procedures for patients with IOP greater than 30 mmHg.

Table 25.3 Items to highlight in the preoperative discussion, in addition to the important features of routine general anaesthesia and the planned analgesia strategy

Concerns	Occurrence
Pressure sores and neuropraxia as a result of prolonged immobility	Rare
Postoperative visual loss	Very rare
Postoperative neurological deficit	Very rare
Acid reflux and facial burns	Very rare
Postoperative somnolence and ventilatory compromise	Rare

Patients with peripheral vascular disease and significant claudication may not be suitable for prolonged head-down positioning, particularly those with night pain associated with relative ischaemia when the legs are level with the heart. There is little evidence to guide patient selection in this regard, but vascular doppler studies and the opinion of a vascular surgeon would be advisable in these cases.

Laparoscopic surgery is seldom considered appropriate for emergency cancer operations and should not be undertaken in a hypovolaemic or critically ill patient.

Table 25.3 shows items to highlight in the preoperative discussion, in addition to the important features of routine general anaesthesia and the planned analgesia strategy.

25.5 Anaesthetic Strategies for Laparoscopic Cancer Surgery

There is little evidence to suggest that any one style of induction or maintenance of anaesthesia is preferable to others. Tracheal intubation will

probably be required for almost all cases given the need for controlled ventilation with reduced lung compliance. Advanced monitoring may be indicated by the patient's comorbidities or the particular operation, but video- or robotic-assisted surgery does not by itself require more than standard monitoring. Since the operations are often long, a urinary catheter may be indicated.

An inflated stomach can make it harder for the surgeon to see it may be helpful to insert a nasogastric tube for decompression at the start of the case. This should probably be removed after decompression, however, as it may otherwise facilitate gastro-oesophageal reflux. Patients with symptomatic gastro-oesophageal reflux can experience acid burns to the face and eyes, so acidity-reducing premedication may be advised, and the eyes should be carefully protected with liquid-resistant dressings.

Patients need to have an adequate circulating volume to be able to generate adequate cardiac output during the physiological derangements of capnoperitoneum. However, administration of large volumes of intravenous fluid will promote airway and cerebral oedema, and should be avoided, in the absence of bleeding.

Mechanical ventilation needs to be set to target maintenance of normocapnia to avoid cerebral hyperaemia. Pressure or volume control can be used to achieve this. Pressure control modes usually achieve high dynamic compliance, but are more difficult practically as changes in intra-abdominal pressure during laparoscopy can lead to large changes in tidal volume. A pressure-controlled, volume guarantee mode may be the most suitable choice, if available [39]. If ventilation is difficult, the inspiratory time may need to be increased, and even with this intervention, peak inspiratory pressures may still climb above 30 cm H_2O. It is difficult to set a specific peak airway pressure as a universal limit, but in our institution, we have found that patients tolerate pressures up to 35 cm H_2O and occasionally exceeding this for 2–3 h, as in the context of obesity and elevated intra-abdominal pressure transpulmonary pressure remains in the normal range. Positive end-expiratory pressure (PEEP) should be set high enough to prevent intra-tidal recruitment/de-recruitment, usually somewhere between 6 and 10 cm H_2O and may need to be even higher [40], although in very obese patients a balance will need to be struck between the idea PEEP for lung recruitment and the deleterious effects of high PEEP on the cerebral circulation [41]. Recruitment manoeuvres and continuous muscle relaxation may also be required to facilitate ventilation.

If the operation requires steep head-down or head-up positions, then the patient must be positioned in such a way so as not to slide off the table. In our institution, we place a large gel mat between the operating table and the patient's skin. Other institutions use corrugated or "memory" foam mats, or deflatable beanbags for this purpose, although the latter can be quite hard and additional padding may be required. Some institutions use shoulder bolsters for steep head-down positions. If these are employed, they should be carefully placed to avoid pressure over the path of the brachial plexus in the operating position, to reduce the risk of neural injury. Some modern operating tables display the degree of tilt applied, but if not, it is worth using alternative methods to measure this (such as smartphone apps) to ensure consistency. Once the table is tilted, the anaesthetist should check that the patient has not slipped and that the neck has not become hyperextended, impairing venous flow.

The combination of Trendelenburg positioning and capnoperitoneum can also lead to the cranial displacement of the carina and inadvertent bronchial intubation, so endotracheal tube position should be reconfirmed at appropriate intervals [42].

Video- and robot-assisted cancer surgery are often very lengthy and pressure area care needs to be meticulous. We make liberal use of padding, separating any hard bony areas and wires or intravenous infusion lines from the adjacent skin.

Intraoperative sympathetic stimulation can be treated with a combination of long- and short-acting intravenous opioids, and with regional or neuraxial techniques. For major laparoscopic surgery, our institution and others have found that spinal diamorphine with propofol/remifentanil total intravenous anaesthesia (TIVA) provides

excellent intraoperative conditions and postoperative pain relief, but there is no great evidence to date for the superiority of any one technique over another.

Where steep Trendelenburg positions are employed, the tilt at the head end of the table can be reduced to allow better venous drainage and blunt the rise in IOP [43], with a likely similar benefit for ICP. Dexamethasone is sometimes used as a treatment for cerebral oedema, although there is no real evidence for it in this setting.

In our centre, when conducting anaesthesia for very prolonged surgery (>4 h), we consider undocking the robot for mid-procedure flattening of the patient to allow resolution of elevated ICP and IOP and to normal perfusion of the legs where there is peripheral vascular disease. Patients who develop conjunctival chemosis during surgery are much more likely to have developed cerebral oedema and/or airway oedema. Sitting these patients in a head-up position for up to 30 min before extubation has been described as a strategy to promote venous drainage and resolution of these changes.

25.6 Additional Considerations for Robotic Surgery

Once the robot arms are docked in place, the patient must remain completely immobile or risk damage to the abdominal wall or viscera. This requires a controlled ventilation technique and either the use of muscle relaxants or a remifentanil infusion to provide good surgical conditions and to prevent coughing, bucking and spontaneous breathing activity.

Access to the patient will be limited even more than with traditional laparoscopic surgery, and so the anaesthetist must meticulously ensure the patency of intravenous access and adequacy of monitoring connections and padding of pressure points. Positioning needs to be to the satisfaction of the operating surgeon and so the operator must be present at this time.

The addition of a robot to minimal-access surgery brings a new degree of complexity to the operating theatre environment and this goes some way to explain the number of adverse events associated with robot-assisted techniques. A study of United States (US) Food and Drug Administration reports noted that although the total number of adverse events associated with robot-assisted surgery has risen over the last decade, as would be expected given the increasing adoption of surgical robots, the rate of events per procedure has remained relatively steady [44]. Reassuringly, the number of events was noted to be lower with high-volume specialities such as urology and gynaecology, implying a learning curve that can be acknowledged and planned for by centres aiming to introduce robot-assisted surgery. Overall reports of robot malfunction appeared to fall with time in this study, but issues with broken instruments and electrical arcing appeared to occur at a more constant rate. Unintended operation of the instruments or spontaneous powering off and on accounted for about a tenth of the reported adverse events. A more detailed treatment of the risks of robot-associated harm is beyond the scope of this chapter, but institutions introducing robot-assisted surgery should ensure they review up to date literature ahead of adoption.

An intuitive finding from the FDA data study is that reports of catastrophic events during robot-assisted surgery were associated with lack of team preparedness for emergencies. If the surgeon needs to convert quickly to an open approach, or if airway intervention is needed, the robot will be in the way and the theatre team will need to be familiar with a sequence for rapid, safe undocking. The best way to ensure this is with regular practice and simulated drills. In our experience a practised team can undock the robot from a patient in around 30 s, allowing the surgeon to open and control bleeding and other complications.

As noted above, robotic surgery introduces a learning curve for the perioperative team. A study evaluating the implementation of robotic colorectal surgery noted that whole-team training supported the integration of the robot into operating theatre practice, as would be expected. Another finding was that team communication strategies need to take account of the relatively remote position of the surgeon in the operating booth [45].

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Anesthesia for Palliative Surgery

26

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26.1 Introduction

Due to recent advances in medicine, the mortality from chronic diseases is decreasing. More and more patients are presenting with complex chronic progressive diseases where only symptomatic cure is possible. Such interventions are considered palliative and are based on the patient's symptoms and disease status. World Health Organization (WHO) defines "palliative care as an approach that improves the quality of life of patients and their families facing the problem associated with a life-threatening illness, through the prevention and relief of suffering through early identification, impeccable assessment, and treatment of pain and other problems, physical, psychosocial and spiritual" [1, 2]. In oncology setup, up to 10–15% patients may present for palliative surgery [3, 4]. Other nonmalignant conditions like Human Immunodeficiency Virus infection and *Acquired Immune Deficiency Syndrome* (HIV/*AIDS*), organ transplant recipients, chronic systemic diseases (cardiac, respiratory, renal, and hepatic systems) also present for palliative surgery [5]. Most of these patients suffer from severe pain, nausea, vomiting, dyspnea, and fatigue. Optimal relief of symptoms, pain control, and minimal hospitalization is the most desired priority for patients requiring palliative surgical interventions [6]. In advanced diseases, palliative surgery is done to relieve the intractable symptoms which improve the quality of life. It ranges from minor intervention to maximal surgical invasiveness. Since these patients are at high risk, they have a high degree of morbidity and mortality [7, 8]. Appropriate patient selection and degree of invasiveness helps in the improvement of surgical outcome [9].

As a member of the surgical team, the anesthesiologist plays an important role in relieving the suffering and distress of such patients in the perioperative period [1]. The perioperative management is difficult in such patients due to frail physical condition because of malnutrition and cachexia, multiple organ toxicities due to prior chemotherapy/radiotherapy. The choice of surgical approach depends on the patient's current health status, past medical and surgical history, prognosis, and goals of care (Table 26.1).

Perioperative anesthetic management of advanced cancer patients for various palliative surgical interventions is challenging and has many unique concerns. Some of these concerns include:

1. **Malnutrition**: Often these patients are malnourished and cachectic [13]. These patients have poor skin integrity and skin may be fragile. One should take care during the positioning of the patient on the operating room table.

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Table 26.1 Common palliative surgical interventions [10–12]

S. no.	Indication	Surgical interventions
1	Dyspnea	• Tracheostomy • Rigid bronchoscopy guided stenting • Drainage of pleural effusion
2	Abdominal and urogenital Emergencies	• Relieve obstruction: Bowel resection/stenting, Esophageal dilatation, colostomy, ileostomy • Feeding: jejunostomy, gastrostomy, • Ascites drainage • Nephrostomy/ureteric stenting • Gastrointestinal bleeding management
3	Pain control	• Tumor debulking • Fixation of pathologic fracture • Relieve obstruction • Craniotomy/subdural hematoma evacuation
4	Neurological symptom	• Ventriculoperitoneal shunting • Spinal decompression
5.	Amputation	• Limb amputation
6.	Fungating mass in the breast	• Simple/toilet mastectomy

The padding of bony points as is done routinely should be taken care of. They have hypoalbuminemia, anemia, and dyselectrolytemia. This leads to altered protein binding, the volume of distribution, and elimination of drugs so the dosage needs to be altered accordingly. The severely anemic patient may need to be transfused preoperatively depending upon the patient's comorbidities and extent of surgical dissection [14].

2. **Performance status**: They have poor energy reserves and sarcopenia due to cancer and associated systemic effects of treatment as well. This leads to poor exercise tolerance. Poor performance status is correlated with poor quality of life and poor patient survival. This aids in the surgical decision as a poor performance score in the preoperative period have a higher risk of perioperative complications and morbidity [15–17].
3. **Psychosocial distress**: Cancer patients also have psychosocial distress. Common causes of psychosocial distress are fatigue, pain, anxiety, and depression. Various factors related to distress are female sex, older age, rural background, low socioeconomic status, low education, and prior treatment within 1 month. So, early detection of psychological distress and appropriate interventions among these groups of patients is of utmost importance [18, 19].
4. **Immunosuppression**: Patient receiving radiotherapy, chemotherapy, stem cell transplant for malignancy develops immunosuppression. They are susceptible to systemic infection. Proper hand hygiene and aseptic precaution should be taken during the perioperative period. Broad-spectrum antibiotic coverage should be instituted early in case of infection. They should be nursed in high dependency units/isolation to avoid infection [20].
5. **Chemotherapy**: The patient may have received chemotherapy before presenting for surgery. Patients are prone to develop multiple organ toxicities depending upon the agent received (Table 26.2) [27]. Anesthesiologists should take precautions during the perioperative period. The anesthesiologist has to understand these complexities and manage the patient accordingly. For example, the patient having pulmonary fibrosis due to bleomycin may benefit from a lower fraction of inspired oxygen (fiO_2) during surgery [21–24]. Most of the chemotherapy drugs are irritant, their infusion leads to sclerosis, inflammation, and fibrosis of veins. This leads to thrombophlebitis leading to loss of veins. This causes difficult venous access. So, these patients require a central/peripherally inserted central catheter for venous access [25].
6. **Radiotherapy**: Radiotherapy is frequently used in combination with chemotherapy. Radiotherapy causes tissue damage through the production of oxygen-free radicals. As a consequence, they may lead to poor wound healing, induration of overlying skin, tissue fibrosis, vascular stenosis, myocarditis, pneumonitis, and pulmonary fibrosis depending

Table 26.2 Representative chemotherapy agents and perioperative concerns [27]

	System involved	Chemotherapy drug	Manifestations	Perioperative consideration
1	Cardiac	Doxorubicin, daunorubicin, busulphan, cyclophosphamide, 5-fluorouracil	Arrhythmia, cardiomyopathy, and ventricular dysfunction	The symptomatic patient should have a proper cardiac evaluation, transthoracic echocardiography in the preoperative period, and intraoperative transesophageal echocardiography
2	Pulmonary	Bleomycin, busulphan, methotrexate, cyclophosphamide, cytarabine	Pulmonary edema, pulmonary fibrosis	Room air ABG, PFT should be done Intraoperative FiO_2 should be <40%. PEEP may be used to reduce FiO2
3	Renal	Methotrexate, L-asparaginase, carboplatin, ifosfamide, mitomycin-C	Acute tubular necrosis, acute renal failure	Proper hydration and diuresis should be maintained during chemotherapy administration. Potentially nephrotoxic drugs should be avoided
4	Liver	Actinomycin D, methotrexate, androgens, L-asparaginase, busulphan, cisplatinum, azathioprine	Raised serum enzymes, fatty infiltration, and cholestasis occurs	Halothane and other anesthetic drugs causing liver dysfunction should be avoided
5	Central nervous system	Methotrexate, Vincristine Cisplatin, Hydroxyurea, Procarbazine	Peripheral neuropathy, motor and gait disturbance	The preoperative neurological deficit should be documented. Regional anesthesia should be avoided if possible
6	Electrolytes	Cyclophosphamide, vincristine	SIADH, Electrolyte disturbance and fluid imbalance	Electrolytes and fluid balance should be corrected before taking for surgery

upon the organ which received radiotherapy. Radiotherapy to the head and neck area may cause limited neck extension and rigidity of the oropharyngeal tissues. This may lead to difficult mask ventilation and tracheal intubation [26].

Chemotherapy and radiotherapy have a broad range of complications and toxicity. Therefore, preoperative assessment to identify any side effects of treatment, as well as structured intraoperative and postoperative management plans, is required for all patients with a history of cancer. The interval between the end of neoadjuvant chemotherapy and surgery depends on the type of cancer. Surgery should be delayed until the resolution of acute side effects of chemotherapy and/or radiotherapy if possible. These side effects may include myelosuppression, coagulation disorders, and renal or hepatic function derangements.

7. **Do not attempt resuscitation (DNAR):** If a patient suffers from cardiac arrest usually cardiopulmonary resuscitation is attempted to revive him. If it has to be withheld, an explicit physician's order is required. DNAR is an order of the patient's intent to avoid resuscitation in case he/she suffers from cardiorespiratory arrest. Patients may refuse medical care including resuscitation as per the ethical principle of patient autonomy. This right to refuse is legitimate and known as a negative right. But patients cannot demand a medical treatment which is considered futile by their physician [28, 29].

Anesthesiologists are in dilemma in the perioperative period for DNAR patients presenting for palliative surgery due to the following reasons:

(a) Anesthesia may cause exaggerated cardiovascular instability in patients with advanced disease. Anesthesiologists are trained in resuscitation and minimize hemodynamic instability. So, resuscitation is a part of standard anesthesia practice.
(b) Tracheal intubation and vasopressor use may be considered as resuscitation in the general ward while in the operation room this may be standard and necessary during anesthesia.

(c) Anesthesiologists may not give appropriate anesthetic care to minimize the risk of cardiac arrest in patients having a DNR order in place. Under these circumstances, the patient may not receive optimal care.

If a DNAR patient is intubated and given vasopressors during anesthesia without suspension of the DNAR order, this would be considered as a violation of his/her autonomy. To avoid such a situation, a detailed discussion about the patient's goals and values in the context of the proposed surgery is mandatory by both the surgeon and the anesthesiologist [30].

American Society of Anesthesiologists (ASA) guidelines recommend three possible options for the management of DNAR orders in the perioperative period:

(a) Full resuscitation wherein the DNAR order was suspended throughout the perioperative period.
(b) Limited resuscitation is based upon specific procedures.
(c) Limited resuscitation is based upon specific goals and values.

The patient, his family, and the anesthesiologist should discuss which procedures to be done or not in case of cardiac arrest. This should be based on the patient's goals and values and it should be documented and family member/surrogate decision-maker should be made aware of this decision [31–33].

DNAR is not legal in India. In 2006, the court recommends the formation of an expert panel to take health care decisions like consent to a DNR order or withholding/withdrawal of life-sustaining treatment [34].

8. **Patients receiving opioids for chronic pain:** Perioperative management of patients taking opioid therapy for chronic pain is very challenging for anesthesiologists. The number of opioid-tolerant patients requiring acute pain treatment is increasing. This population is at risk of suffering severe postoperative pain [35]. These patients consistently report higher pain scores. The effective pain management of opioid-tolerant patients requires a comprehensive multimodal analgesic approach that encompasses local anesthetics, regional blocks in addition to pharmacological therapy according to the World Health Organization (WHO) analgesic ladder [36–38]. The aim is to control pain while avoiding opioid withdrawal and overdose. A few suggestions for the management of perioperative analgesia are as follows:

(a) The patient will require supplemental opioids in response to surgical trauma in addition to his usual opioid consumption. This additional opioid dose should be carefully titrated to the pain score.
(b) Opioid-sparing techniques:
    I Adjuvant pain medications like paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), cycloxygenase-2 (COX-2) inhibitors should be continued in the perioperative period unless contraindicated. They have a synergistic effect on analgesia.
    II Local anesthetic techniques like wound infiltration, regional or neuraxial block should be used wherever possible. This will decrease opioid requirements and improve perioperative analgesia.
    III Ketamine has been shown to reduce the opioid requirement.
    IV Intravenous lignocaine infusion during surgery also reduces pain.
(c) Do not restrict opioid treatment in these patients. Weaning or tapering of opioids should not be done in the perioperative period.
(d) If the patient is having neuropathic pain and receiving tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and selective noradrenaline reuptake inhibitors, then they should be continued in the perioperative period. One should be aware of the potential for serotonin syndrome.
(e) Anticonvulsants drugs like carbamazepine should be continued perioperatively.
(f) If a patient has a spinal cord stimulator, it should be turned off during surgery as the

use of diathermy or electrocautery may cause damage to the device and/or injury to the underlying tissues.

(g) If the patient has an intrathecal drug delivery system, it should be continued perioperatively and supplement the patient with additional analgesia for the acute event. Abrupt cessation of intrathecal medications may lead to severe pain and withdrawal.

26.2 Preoperative Evaluation

Preoperative evaluation helps in the assessment of comorbidities and risk factors of surgical patients which is helpful in the optimization of patients. Prehabilitation of patients improves the surgical outcome. It should be tried if feasible by the improvement of nutritional status, incentive spirometry, deep breathing exercise, use of hematinics, cessation of smoking, and enrolment in an exercise program. The value of preoperative optimization of cardiac and pulmonary status has been shown to benefit in some high-risk surgical cases [39–41].

Routine laboratory investigations like complete hemogram, renal and liver function, random blood sugar, electrocardiogram, and chest X-ray should be ordered in all patients. Further studies are needed based on preexisting comorbid illnesses and surgical procedures. Patients who had received cardiotoxic chemotherapy may need cardiac evaluation by echocardiography and/or thallium scanning. While ordering investigations one should bear in mind that these surgical procedures are of palliative intent, specialized investigation should be done only if it alters the anesthetic and perioperative management.

26.3 Specific Palliative Surgical Interventions

No anesthesiology technique is the gold standard and it needs to be individualized depending upon the coexisting factors and the surgical procedure. Some of the commonly done palliative surgical interventions include:

Tracheostomy It can be an elective or emergency procedure. Usually done for impending airway obstruction especially in head and neck cancer patients. It is usually done under local anesthesia and/or sedation. Difficult airway cart which includes different size endotracheal tubes, tracheostomy tube, laryngoscopes, video laryngoscope, fiberoptic bronchoscopes, gum elastic bougies, stylet, laryngeal mask airway, and if available THRIVE (transnasal humidified rapid insufflation ventilatory exchange) should be kept ready. If the patient is already tracheal intubated and on sedation, then it may be supplemented for inducing general anesthesia. If a difficult airway is anticipated, then the airway should be secured with awake fiberoptic intubation or tracheostomy should be done under local anesthesia.

Airway Stenting Airway stenting is required in central airway obstruction with significant airway compromise. The patient presents with obvious stridor. Placement of stent in the airway requires rigid bronchoscopy under general anesthesia. This procedure is usually of 30–45 min duration. Total intravenous anesthesia is given with ventilation through the side port of a rigid bronchoscope. This is an open system and a leak occurs from the circuit. This leads to carbon dioxide retention. To compensate for a leak from the bronchoscope, the high fresh gas flow is utilized and hyperventilation is done to wash off carbon dioxide. At the end of the procedure, the residual neuromuscular block is reversed and the trachea is extubated depending on the recovery [42].

Feeding Gastrostomy/Jejunostomy This is indicated in the case of carcinoma esophagus and carcinoma base of the tongue causing complete dysphagia. This procedure is usually performed under general anesthesia but the use of local anesthesia and monitored anesthesia care (MAC) has also been reported in the literature [43]. The various blocks like transverses abdominis plane block, rectus sheath block along with sedation using propofol, dexmedetomidine infusion has been reported in literature [44]. Percutaneous endoscopic gastrostomy is usually done in the radiology suite. This is particularly useful in

high-risk patients and can be done under local anesthesia along with sedation using opioids and drugs like propofol and dexmedetomidine with minimal morbidity.

Bowel Diversion Surgery (Ileostomy/Colostomy) Terminal stage cancer patients (e.g., gall bladder cancer, gut cancer, and ovary cancer) usually have metastasis to mesentery or omental deposits. This may lead to bowel obstruction. Bowel diversion in the form of ileostomy or colostomy is done depending on the level of obstruction. These patients should be considered as a full stomach. The suction of the nasogastric tube should be done followed by preoxygenation and rapid sequence induction and cuffed orotracheal intubation. Transversus abdominis plane block may be given for postoperative analgesia.

Percutaneous Nephrostomy (PCN) The patient with carcinoma cervix usually develops hydronephrosis due to obstruction of the ureter. PCN is usually done under local anesthesia with sedation.

Fixation of Pathologic Fracture The patient may develop pain and pathological fracture due to bone tumors or metastasis. Treatment consists of radiotherapy and/or surgical management (plate fixation, intramedullary nails, and endoprosthesis). The choice of modality depends on the localization, extent of bone involvement, and life expectancy. Also, vertebroplasty and kyphoplasty are usually done for vertebral fracture. Lower limb fracture fixation can be under regional anesthesia while upper limb fracture usually requires general anesthesia. Vertebroplasty and kyphoplasty are done under local anesthesia and sedation.

Amputation Patients having soft tissue sarcoma or gangrene are posted for amputation. These patients usually have severe pain preoperatively and are usually receiving opioids for analgesia.

Lower limb amputation is usually done under regional anesthesia while upper limb amputation requires general anesthesia. Epidural anesthesia helps in postoperative analgesia. General anesthesia is standard induction and maintenance. Moderate blood loss may be expected in above-knee amputation so a tourniquet should be used during the procedure. A large-bore intravenous cannula should be secured. Standard monitoring is sufficient. Invasive blood pressure and CVP monitoring should be done depending upon the comorbidities. In the postoperative period, epidural opiates should be used for analgesia. The incidence of PLP postamputation varies from 49 to 88% [45–48]. The preoperative analgesic should be continued and gabapentinoids have been found to reduce the intensity of phantom pain.

Toilet Mastectomy Toilet mastectomy is done for patients having locally advanced breast cancer involving the chest wall with fungating mass. It is usually done under general anesthesia [49]. A standard anesthesia technique is used. Since this is a short duration procedure, the airway may be secured with a supraglottic device.

Ascitic Tapping Patients presenting with malignant ascites have abdominal distension and dyspnea due to diaphragmatic splinting. Ascitic tapping is done under local anesthesia. The patient's vital should be monitored including pulse rate, blood pressure, and oxygenation (SpO_2). An intravenous line with ringer lactate/balanced salt solution should be started. The volume of fluid to be removed depends on the patient's general condition and hemodynamic status.

Thoracocentesis Malignant pleural effusion (MPE) usually presents in the advanced stage of malignancy. These patients present with severe debilitating dyspnea necessitating urgent palliative management. Single time aspiration or insertion of a chest tube/pigtail catheter will depend on the patient's expected survival and quality of life. This can be done under local anesthesia.

When Not to Operate The aim of palliative surgery is a relief of distressing symptoms. The quality of life of the patient is very important for

the decision of surgery. If the quality of life improves after surgery, then only surgery should be done; otherwise, the patient should be managed conservatively. For example, for a patient having bowel obstruction and short life expectancy, it is better to manage him conservatively (with nil per orally, nasogastric aspiration steroid, and analgesic) instead of doing permanent colostomy. If the patient is in the terminal/end-stage of illness, then end-of-life care should be initiated. Patients and relatives should be explained about the disease process and only symptomatic care should be provided.

26.4 Conclusion

Palliative surgery is done in advanced chronic illness and metastatic cancer. It may range from minor intervention to major surgical dissection depending on the procedure, patient's symptom, and life expectancy. Anesthesia for palliative surgery is challenging. These patients are usually nutritionally depleted and have a functional limitation due to disease and its progression. Moreover, as a part of definitive treatment, they may have received prior chemotherapy and/or radiotherapy in addition to surgery. Due to this, they have multiple organ toxicities and drug interactions. Anesthetic management requires a thorough understanding of preoperative status and cautions during the perioperative period to avoid complications. When done appropriately, palliative surgery relieves the distressing symptom and improves the quality of life of such patients [9].

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Part IV

Analgesia for Onco-Surgery

Perioperative Pain Management for Onco-surgery

27

P. N. Jain and Sumitra G. Bakshi

27.1 Introduction

With advances in anesthesia and surgical techniques, the need for perioperative services is on the rise and is expected to continue [1]. The understanding of pain mechanisms, adverse effects of uncontrolled perioperative pain, concerns of persistent postsurgical pain, and increasing numbers of major onco-surgeries mandates the provision of optimal analgesia to the patients [1, 2]. The onco-surgical interventions are usually extensive and thus more prone to increased pain in the perioperative period. The impact of inadequate pain relief can result in delayed mobilization, increase in respiratory, cardiovascular, and thromboembolic morbidity and mortality due to such complications, prolonged hospital stays psychological stress, and anxiety [1]. These factors are further potentiated by the presence of underlying cancer. Acute pain can cause a change in the pathophysiology of the body, which starts with activation of the nociceptors after tissue injury causing local inflammation, behavioral, and neuroendocrine activation. Ongoing inflammation or injury to peripheral nerves may lead to chronic persistent postsurgical pain. Certain factors are related to the increased occurrence of postoperative pain with more severity. These include redo surgical intervention, preoperative pain, patients on preoperative analgesic drugs, long-duration surgeries, preoperative cancer therapy like radiotherapy/chemotherapy, and psychological dysfunction. Perioperative pain management includes steps taken before, during, and after a procedure to reduce or eliminate postoperative pain [2]. With the current focus on enhanced recovery, the choice of analgesics is gaining utmost importance concerning preventing avoidable side effects of pain management along with effective management of postoperative pain [3]. This chapter focuses on various aspects of perioperative pain management in patients undergoing onco-surgeries.

27.2 Preoperative Education

Evidence suggests that pain perception is influenced by demographic, personality, genetic, and psychological factors. The preoperative risk factors for increased occurrence of postoperative pain should be modified by pharmacological or non-pharmacological methods to reduce the quantum of postoperative pain and its sequelae [4]. The independent predictors for postoperative pain severity include preoperative pain intensity and pain catastrophizing [4].

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Preoperative education of the patient by providing information about the surgical procedures, postoperative recovery, and adequate pain management allays anxiety, psychological preparation for the patients and improves patient satisfaction [5]. Patients are also taught about scoring the pain severity by busing various scoring scales or numbers. The pain assessment is usually done using conventional scales like the visual analog scale (VAS), numerical rating scale (NRS), behavioral scale, etc.

27.3 Preemptive Analgesia

Preemptive analgesia in which there is the administration of one or more analgesic drugs in response to a noxious event to avoid central sensitization due to incision and inflammation [6]. Preemptive analgesia may be affected by multiple factors like choice of analgesic, type, and degree of tissue damage, surgical time, route of drug administration, and period of central sensitization [2]. Though the existing literature is not mainly confined to cancer patients, the benefits of most interventions are opioid-sparing strategies and appear to be beneficial for cancer patients [7, 8] and hence must be incorporated whenever feasible. Preoperative gabapentin has been found to reduce opioids consumption on the first postoperative day. Gabapentin has been found beneficial following mastectomy, spinal, abdominal, and thyroid surgeries [9]. In women undergoing hysterectomies preemptively administered nonnarcotic medications including paracetamol, bupivacaine, gabapentin, and phenothiazine resulted in less cumulative use of narcotics when compared with placebo [6]. Women receiving gabapentin and paracetamol used lesser narcotics than those receiving gabapentin alone [6]. Regional analgesia has a promising role in preemptive analgesia. Local anesthetic plain and with combination with steroids have shown to be beneficial in various orthopedic procedures [10, 11].

27.4 Multimodal Analgesia

Multimodal analgesia involves combining two or more analgesics and techniques (pharmacological vs non-pharmacological, opioids vs non-opioids, regional blocks) to alleviate pain and augment analgesia. The choice of drugs is from different classes with a different mechanism of action and thus reduced drug-related side effects. Multimodal analgesia in the form of paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, central neuraxial block, peripheral nerve blocks, fascial plane blocks is effective [12–14]. The administration of drugs using patient-controlled modes has further improved the quality of pain control. The selection of drugs and their dosages should be adjusted appropriately for optimal analgesia. Thus, for optimal analgesia, medication choice, dosage, route, and duration of therapy are specific for the type of surgery, patient's existing comorbidities.

27.5 Regional Analgesia Techniques

Regional analgesia techniques have become an integral part of multimodal analgesia. With the addition of various newer blocks and the use of tools like ultrasound, nerve stimulator has increased the success of these blocks leading to better analgesia and lesser complications. The various modalities of regional analgesia include central neuraxial blocks (spinal, epidural), nerve plexus blocks, peripheral nerve blocks, fascial plane blocks, wound infiltration with either single-time drug administration or continuous infusion of local anesthetic and other adjuvants like opioids. The use of patient-controlled analgesia (PCA) has also been used with catheter placement for these regional blocks. Each of these techniques has its own set of advantages and limitations. The limitation of wound infiltration was the short duration of its effect; however, the use of liposomal bupivacaine analgesia lasts for 72 h

[15]. These regional blocks have been found to have an opioid-sparing effect as well which appears to be beneficial for cancer patients [16].

Regional anesthesia may reduce the stress associated with surgery, reduce pain, and lead to improved neuroendocrine function and cytokine-mediated stress response [17]. Most of the earlier procedure-specific guidelines favored epidural analgesia for colonic onco-surgeries [18]. With the growing evidence of the effectiveness of truncal blocks, safety profile and significant opioid-sparing nature, usage of regional catheters for onco-surgeries is growing steadily [19–21]. The interest in regional analgesia extends beyond pain control. The preliminary reports have highlighted the potential usefulness of regional analgesia as part of perioperative multimodal analgesia in cancer patients with possible improvement in long-term oncological outcomes [22]. Though strong evidence is lacking at the moment, regional analgesia techniques like paravertebral, pecs block have been proposed as a part of balanced anesthesia for breast surgeries [22–24].

Epidural analgesia using local anesthetics combined with an opioid can provide better analgesia than many of the other techniques. Epidural analgesia has been found to have better perioperative pain control as compared to systemic opioids [2]. Studies have also shown that epidurals may have decreased the risk of myocardial infarction and beneficial effects on cardiopulmonary outcomes. Also, analgesia using thoracic epidurals have been found to have an earlier return of gastrointestinal activity after surgery and decreases postoperative pulmonary complications [2]. The nurses need to be educated about the incidence of side effects, to recognize and treat them since the patients would be treated in wards.

Safety Issues: A recent 1-year audit for perioperative complications due to central neuraxial block revealed that the occurrence of major adverse events have decreased as compared to earlier reports and were more related to epidural analgesia administration in adults [2]. Peripheral nerve catheters have increased in popularity in the past decade. It results in early mobilization and some centers allow use in the outpatient facility for an early discharge and recovery. The probable reason for such decreased incidence of complication and increased success rate regarding analgesia is related to a better understanding of regional blocks and the use of visualized techniques like ultrasound-guided blocks rather than conventional blind blocks [2].

27.6 Pharmacotherapy

Paracetamol has been widely accepted as an effective, better tolerated, and safer analgesic [2]. It is one of the important components of multimodal analgesia for all severity of pain and has an opioid-sparing effect. The intravenous preparation provides faster onset and predictable analgesia effect after surgical intervention [25, 26].

NSAIDs, including cyclo-oxygenase inhibitors (aspirin, diclofenac, and ibuprofen) and new COX-2 selective inhibitors are often used as postoperative analgesics. They have been used as part of multimodal analgesia but NSAIDs' regular use is limited by associated adverse and their contraindications in certain patients like underlying renal diseases, pulmonary function impairment, bleeding tendencies, etc. The NSAIDs can lead to platelet dysfunction, ulcers (gastric, duodenal), and risk of bronchospasm in asthmatics [2]. So, the use of NSAIDs should be for selected patients and preferably for a shorter duration. NSAIDs being peripherally acting analgesics alleviate pain significantly, reduce hyperalgesia at the incision site, have the opioid-sparing effect, lesser sedation, and decreased occurrence of nausea and vomiting.

Patient-Controlled Analgesia (PCA): The use of opioid-based intravenous PCA is better accepted with good pain control as compared to conventional administration of intramuscular (IM) or subcutaneous (SC) opioid regimes as they maintain the minimally therapeutic serum opioid concentrations better [27]. PCA improves patient satisfaction, reduces morbidity, and hastens recovery. It allows the patient to independently titrate their analgesic requirements allowing them greater control over their treatment. It is important to remember that PCA is

essentially a maintenance therapy; therefore, before starting the PCA (individually titrated doses), the patient's pain should be initially controlled by giving analgesic boluses [2]. Other routes for PCA are oral, transdermal, regional infusions, intranasal, subcutaneous, epidural, and intravenous routes [2].

Intravenous PCA has become popular as an opioid delivery system to patients because of its better pain control and thus increased patient satisfaction. PCA has additional benefits of lesser pulmonary complications, better safety profile, less time-consuming for nursing staff as compared to the other modalities of administration of analgesics. PCA has shown favorable results in both young and elderly patients who have good cognition ability.

Although PCA is a relatively simple concept, its dosing is controlled by the patient with safety features under the control of the doctors to prevent overdosing. The patients require to be sensitized preoperatively for the appropriate use of the PCA and its safe use requires a balanced and controlled dynamic interaction between the patient and the PCA pump. The patient must be counseled about its correct use, and he/she must be comfortable to use it independently without fear of overdose and addiction. Preoperatively pain-related counseling must be done by the anesthetist responsible for the patient. Subsequently, the ward and recovery nurses should reinforce education. Errors may include faulty equipment and programming errors. Well trained staff and standardized systems, including monitoring equipment, is essential [2].

Opioid-based regimens for perioperative pain management are associated with side effects and nausea and vomiting remains one of them. It is important to have communication, careful attention and education to reduce side effects. Considering a change to another opioid, due to persistent side effects in a patient, is also important [2].

27.7 Opioid-Sparing Strategies

With the recent concerns for opioids for cancer recurrence, associated side effects and concerns for its misuse, opioid-sparing strategies are increasingly being used. Many agents have been added to the multimodal regime including gabapentinoids, ketamine, dexmedetomidine, and many other newer agents.

***Gabapentinoids** like* pregabalin and gabapentin have been used clinically not only for chronic neuropathic pain but also for perioperative surgical pain. The use of these adjunct drugs has been found to reduce not only pain scores but also have an opioid-sparing effect. The mechanism of action is by inhibiting calcium influx by binding to the subunit of voltage-gated calcium channels and thus prevents the release of the excitatory neurotransmitters [2]. These drugs may have certain side effects like dizziness, lightheadedness and the increased tendency of sedation but decreased vomiting and pruritus.

Dexmedetomidine, an alpha-1 agonist, used for sedation and analgesia in the intensive care setting has also been found to be an analgesic effect as well. Its usage has been found to have decreased the requirement of other analgesics [2].

Ketamine is one of the older anesthetic agents and has been remerged for its usage in the perioperative period for its analgesic action as well. It is an *N*-methyl-D-aspartic acid (NMDA) receptor blocker, prevents central sensitization, pain sensitivity, attenuates hyperalgesia due to opioid administration, and hence may improve the efficacy of opioids. Its usage in sub-anesthetic doses has been used in the perioperative period for analgesia and has been found to have an opioid-sparing effect with lesser pain intensity and side effects [2]. The associated psychotomimetic effects such as hallucinations with intravenous ketamine in low doses for analgesia have not been reported [2].

27.8 Newer Drugs

Targinact is a recently launched modified-release combination of strong opioid (oxycodone hydrochloride) and opioid antagonist (naloxone hydrochloride). The opioid antagonist prevents the side effect of opioid-induced constipation by preventing its action on opioid receptors in the gastrointestinal system. However, it does not reduce the analgesic efficacy of the opioid as it has extensive first-pass hepatic metabolism.

Methylnaltrexone bromide and **alvimopan** are the opioid antagonists that act on peripheral μ receptors. This action reverses certain opioid-related side effects like bowel ileus while maintaining opioid analgesic action [28, 29].

27.9 Pain Management in Special Population

A certain specific group of patients like the geriatric population requires modification of perioperative analgesic regime due to various physiological body changes.

Elderly Patient: The elderly population may require various onco-surgical interventions and perioperative pain management is not only essential but challenging as well. These patients have various physiological changes in the body, have associated concomitant diseases and receiving drug therapy for the same. These all warrant appropriate selection of analgesic regime considering the interaction of the drug therapy, age-related change in the metabolism of the analgesic drugs (altered pharmacokinetics and pharmacodynamics) and risk of analgesic drugs-related side effects. Cognitive impairment may prevent elderly patients from using a PCA, but the staff often assumes that the elderly are unable to cope with a PCA. Elderly patients should be counseled and well acquainted with simple pain assessment tool preoperatively. These patients require careful titration of opioids, dose adjustments of other analgesics and regular repeated assessment of pain and any side effects.

27.10 Opioid-Dependent Patient

Cancer patients may be receiving analgesics including opioids in the preoperative period primarily because of a cancerous lesion. These patients require a thorough assessment of the need, opioids, and dosage along with a team approach to provide holistic care in the perioperative period. Patients should be counseled and assured about the optimal analgesia provision in the perioperative period. The appropriate management includes the use of a multimodal approach with a focus on local anesthetics via regional blocks and appropriate doses of opioids to prevent withdrawal. The doses of opioids need to be appropriately titrated to match the baseline requirement (as per preoperative usage) and additional doses to manage the surgical pain.

27.11 The Multidisciplinary Role for Perioperative Pain Management

A multidisciplinary approach in the perioperative period improves pain management and ensures effective analgesia. The patient-centered approach and involvement of a perioperative operative team inclusive of nurses, physiotherapists, counselors, etc. remain the preferred approach. The role of surgeons and anesthesiologists as the core person remains important as the pain due to surgical intervention and related complications are better understood. Patient education and counseling help the patient to accept the various analgesics modalities effectively. The regular pain assessment by nurses helps to titrate analgesics, understand the patient requirement, and thus improves overall patient satisfaction. The pain services team inclusive of anesthesiologists should play active leadership to provide optimal analgesia in the perioperative period.

27.12 Summary

The patients undergoing cancer surgeries should be offered optimal analgesia using a multimodal approach [30]. It includes patient education, regular pain assessment, pharmacological/non-pharmacological analgesic interventions. The emerging use of opioid-sparing techniques and regional blocks needs to be ascertained as per patient needs and the type of surgical intervention.

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Part V

Anaesthesia for Outside the Operating Room Procedures

Anesthesia for Radiation Therapy Procedures

28

Nishkarsh Gupta, Vinod Kumar, and Sachidanand Jee Bharati

28.1 Introduction

Radiation therapy (RT) has been used as one of the important multidisciplinary modalities for the management of cancers for a long [1]. With time, RT has made much advancement with regards to the safety of its delivery and effectiveness on cancer management. It remains an integral part of surgery and chemotherapy (CT) for various cancers. RT may be the sole management option in various cases, it may be given concurrently with CT, or along with surgery. RT is also considered for symptomatic management in patients with advanced cancers. The duration, technique, dose, and related toxicities are variable and depend upon the primary diagnosis including the site and extent of cancer and treatment plan.

In modern radiation oncology, anesthesia plays an increasingly important role in facilitating RT. Anesthesiologists are often required to manage sedation for RT in children, provide anesthesia for intraoperative radiotherapy and brachytherapy. Sophisticated techniques of RT reduce tumor to a minimum without affecting normal tissue margins but these may not be effective if the patient moves during the whole procedure [2]. This may be required for techniques like brachytherapy, intraoperative irradiation, and external beam treatment of children or mentally challenged persons.

RT is often required in children for various cancers. Mostly, it requires multiple sessions and the child should stay immobile during the RT sessions. This mandates the need for the provision of sedation and/or anesthesia. Traditionally external beam radiotherapy (EBRT) is given following surgery to eliminate the micro-metastasis and reducing the chances of local recurrence. Intraoperative radiation therapy (IORT) is one the modalities wherein radiation therapy is administered during the surgical intervention itself, focused at the surgical bed with an indent to manage any residual tumor. In recent times, IORT has become popular due to the availability of advanced radiation therapy delivery devices like mobile linear accelerators and self-shielding devices Providing anesthesia in these cases is particularly challenging due to remote monitoring and debilitating condition of cancer patients.

Also nowadays in the era of organ preservation, there is the constant endeavor of the physicians to place the radioactive source as close to the tumor with the help of brachytherapy catheters [3]. Such placemen allow delivery of higher doses of radiations to the tumor cells with sparing of surrounding normal tissues [4]. The availability of newer artificial high activity isotopes, afterloading systems together with improved imaging and sophisticated dose planning techniques has led to the increasing role of brachytherapy [5].

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RT is generally given in well-shielded rooms to prevent unwanted exposure to other personnel and avoid radiation hazards. Due to this, they are often away from routine operation theaters and the challenges of providing anesthesia in a remote location are present. Also, the anesthesia equipment needs to be modified to go well with the RT suite and during the actual radiation exposure, the patient needs to monitor remotely through the camera using slave monitors and screens.

This chapter provides a comprehensive discussion on the anesthetic challenges faced during RT procedures like EBRT, brachytherapy, and IORT.

28.2 Basic Principles

The main principle of the RT remains to kill the tumor cells with minimal impact on the surrounding normal cells by the delivery of sufficient radiation doses. The tumoricidal effect of radiation on cells is dependent on cell activity, its phase of multiplication, nutrient status, and oxygen delivery to it [5, 6]. The normal cells affected by radiation exposure tend to get repaired with time and thus the resolution of adverse effects related to it. However, sufficient time needs to be provided for such repair before cells are exposed again to these cells. The total radiation doses are usually divided into fractions delivered at intervals to prevent the adverse impact on normal tissues. Such fractionation also is desirable as rapid dividing tumor cells may be in the radioresistant cell cycle phase during a fraction but maybe in the radiosensitive phase during subsequent sessions of RT.

28.3 Anesthetic Challenges

Providing anesthesia or sedation for RT procedures has concerns like other Non-operating room anesthesia (NORA) procedures [7]. The challenges for providing anesthesia for RT procedures include [5]:

(a) The unfamiliar environment of the RT suite.
(b) RT suite may be inadequately equipped.
(c) Difficulty in airway management due to physical distancing and physical difficulty due to the positioning of the patient in the RT suite table.
(d) The room layout of the room with bulky RT machines restricts access to the patient and makes it difficult to provide anesthetic services.
(e) Inadequate electrical points for anesthetic apparatus and absence of piped medical gas, scavenging, or suction.
(f) These RT areas are generally away from the main theater and with limited assistance available in case of emergency.
(g) Also, inadequate staffing may pose additional challenges. This suboptimal assistance adds to the complexity in cases with difficult lines, difficult airways, and emergencies [8].
(h) Many times, these patients may be inadequately assessed in the preoperative period and may pose additional challenges due to unoptimized comorbidities.
(i) Requires different modality of monitoring from distant and its physical, electrical interference due to positioning devices and frames and their electro-magnetic effect.
(j) Risk of hypothermia to the patient due to the need for lower ambient temperature for RT equipment.
(k) Risk of radiation exposure to health care workers.

28.4 Choice of Anesthesia or Sedation

RT is the main modality of treatment for several tumors like central nervous system (CNS) tumors, retinoblastoma, neuroblastoma, Wilms' tumor, rhabdomyosarcoma, etc. [9]. It involves an initial setup to plan for treatment and mark the anatomical site to be treated. This is followed by RT which is usually short duration but requires a motionless child for effective therapy for multiple sittings which may extend up to a few weeks in the desired position. Also, the child needs to be left alone in a small dark room for therapy, which may lead to anxiety and claustrophobia. So, good anxiolysis and sedation to ensure a calm and

Table 28.1 Goals of EBRT in children

Patient immobility Smooth and fast onset of action Short duration with prompt recovery Safe on repeated administration	Minimal cardio-respiratory side effects Low risk of tolerance Cheap

motionless child during the RT. The goals of outpatient EBRT in children are related to the optimal outcome of the procedure (Table 28.1) [8].

28.5 Concerns During Simulation and Planning for RT

The process of RT involves planning and then actual delivery of desired doses of radiations. The delivery of RT requires a precise anatomical location, total dose, and fractionations [10]. The radiation oncologists also plans for patient position, the direction of exposure, appropriate size plaster immobilization casts for safe and effective delivery of RT [11]. Patient needs immobility during the process so that not apply appropriate planning is made but subsequently RT is delivered to the target area only without affecting the normal tissues [12]. This is more of the concern in children to keep them immobile as the process of planning may take a longer time. Mostly the patients are treated in the supine position; but RT to the brain and spinal cord may require a prone position throughout therapy, which adds complexity to already challenging scenarios [10]. The radiation oncologists also determine if any shield or blocks are required to protect radiosensitive organs from the effects of RT.

The RT is a short and painless procedure and hence older children and adults will not require anesthesia or even sedation in most cases. Smaller children may not understand or accept to be immobile during the procedure primarily due to a new environment, absence of parental vicinity, and thus mandates the need for sedation and/or anesthesia. Such patients along with anxious patients, complex cases (like prone position), uncooperative patients, and patients with the previous failure of planning may require sedation or anesthesia.

Table 28.2 Common drugs used in present-day practice for pediatric sedation

Drug	Route	Dosage
Midazolam	Oral	0.5 mg/kg (max 20 mg , 30 min beforehand)
	Intranasal	0.2–0.4 mg/kg
	Rectal	0.3–1.0 mg/kg
	Intravenous	0.05–0.2 mg/kg (sedation), >0.5 mg/kg (deep sleep)
Ketamine	Intranasal	3–9 mg/kg
	Intramuscular	2–5 mg/kg
	Intravenous	0.5–2.0 mg/kg
Dexmedetomidine	Intranasal	1.5–3.0 μg/kg
	Intravenous	0.5–1.0 μg/kg bolus over 10 min followed by 0.2–0.5 μg/kg infusion
Propofol	Intravenous	Initial bolus of 2.0 mg/kg and repeated boluses titrating to immobility

Various drugs have been used in isolation or combination for sedation during the radiation therapy procedures (Table 28.2). The choice of anesthetic (general anesthesia/ sedation under monitoring) will depend on patient cooperation and complexity of the case (disease site/extent/positioning or patients at risk of airway compromise). This treatment planning may take longer than actual RT treatment so sometimes general anesthesia (GA) may be preferred especially in posterior fossa tumors where prone positioning is required to develop immobilization casts.

The anesthetic drugs may be given throughout the procedure depending upon the anxiety and movement of the patient. Most patients can be managed with minimal to moderate sedation. (Table 28.3). In some cases like children with retinoblastoma, the complete immobility of the patient is required and one may need a higher degree of sedation [13]. For patients requiring GA, modifications, and arrangements are required for the appropriate usage of the anesthe-

Table 28.3 Clinical states of sedation [14]

Level of sedation	Airway patency	Responsiveness	Cardiac function	Respiratory function
Minimal	Patent	Verbal commands	Maintained	Maintained
Moderate	Patent	Verbal command/light tactile stimulation	Maintained	Maintained
Deep	May require assistance	Repeated painful stimulus	Maintained	Impaired
GA	Assistance required always	Not arousable to the painful stimulus	May be impaired	Impaired

sia delivery equipment. The anesthesia workstation needs to be stationed at a distance to prevent its interference with the RT equipment and thus need for extended hoses and circuits. After the RT planning, the patients need to be observed in the recovery suite. The need for anesthesia during the planning phase can guide the anesthesiologist for further management during actual RT sessions.

28.5.1 Pre-procedural Concerns

(a) The child planned for RT should be nil per oral as per standard guidelines for children [15].
(b) A comprehensive preoperative assessment of the patient's history, associated congenital anomalies, effect of malignancy, relevant treatment history, and airway assessment should be performed. Some tumors like Wilms' tumor may be associated with cardiac congenital anomalies and thus needs their assessment [16]. These children are prone to develop fever, upper respiratory tract infections, and productive cough during treatment which may cause airway hyperreactivity. A rational decision balancing the risk of delaying the RT procedure or get the radiation treatment under increased risk should be taken in consultation with radiation oncologists. Brain tumors may have neurological deficits affecting protective airway reflexes increasing the risk of aspiration peri procedurally.
(c) A written informed consent /assent needs to be taken with an appropriate explanation of the procedure and associated risk.
(d) The Intravenous (IV) route is the preferred way of delivering drugs. The intramuscular (IM) route is not preferred because of repeated trauma associated with painful IM injection daily for several days. Securing an IV line is often difficult because many children would have received multiple CTs or surgery. Also considering multiple treatment sessions an IV line may be required to be changed many times during radiotherapy. Generally, a peripheral IV access is obtained on Monday morning of the week and used throughout the week before removing it Friday [17]. The cannula should be properly fixed and an immobilizer or splint may be applied. The cannula should be adequately flushed after its usage. Many of these patients may be receiving concurrent chemotherapy and have a central venous catheter in situ which can be utilized for procedural sedation.

28.5.2 Intra-procedural Concerns

1. The children requiring RT are usually anxious, especially younger children, due to unaccustomed new environment, usage of monitoring devices, immobilization frames, and casts, etc. (Figs. 28.1 and 28.2). Due to previous exposures and distress related to it, may make the child more anxious and uncooperative [18]. RT therapy is painless so anxiolysis and hypnosis without respiratory depression are required.
2. The immobilization cast may restrict access to the airway for the anesthetist in case an urgent airway intervention is required.

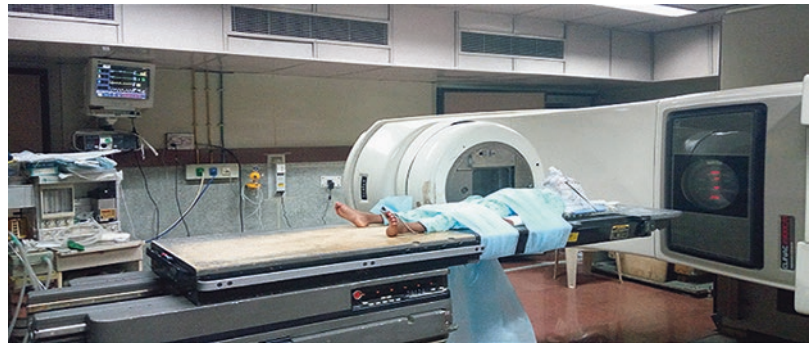

Fig. 28.1 A child after being positioned for radiotherapy with an oxygen mask and monitors in place

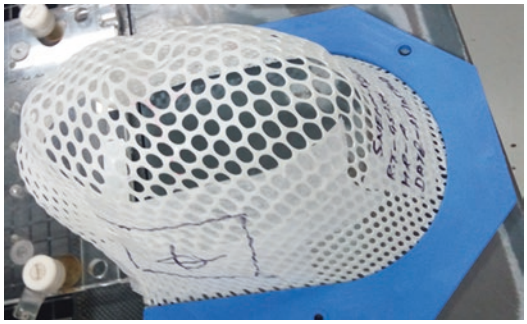

Fig. 28.2 A regular head immobilization cast used in children

3. Anesthesiologists should be familiar with the surroundings and ensure adequate anesthesia drugs, appropriate size pediatric airways, endotracheal tubes, laryngoscopes, and supraglottic devices. A functional AMBU™ bag and suction equipment should always be present and checked every day before starting any case. A simple pneumonic "SOAPME" can be used to remember all the essential requirements before providing sedation for RT. These include "Suction (yankauer), Oxygen, Airway (nasopharyngeal, oropharyngeal, laryngoscopes (checked and functional), endotracheal tubes, supraglottic airway devices, face mask, and resuscitation bag), Pharmacy (lifesaving drugs and antagonists of all sedative medication), M- monitors and special equipment (defibrillators)." [19]
4. Apart from pharmacological measures, non-pharmacological measures may also be considered to ally anxiety among the children receiving RT. Appropriate counseling, making rapport with the child, use of games, music, designing the room with a child-friendly environment may help in allaying anxiety and keep them calm [20–22]. These non-pharmacological strategies may not replace the need for drugs completely but may reduce the need for sedation. Also in busy RT areas, it may be difficult to create this kind of atmosphere for all the children.
5. The ideal anesthetic agent should have a fast onset and offset of effect and ensure complete immobility while maintaining respiration. Various agents have been used through oral, intravenous, intramuscular, and rectal routes for providing sedation (Table 28.2). Some of the commonly used drugs include:
   (a) IV midazolam provides good anxiolysis and amnesia and is found to be safe even in inexperienced hands [23]. It may be the only drug required for the entire series of painless RT procedures.
   (b) In cases where midazolam alone is not adequate, the addition of another agent like propofol has been found to provide optimal sedation for the RT procedure [19]. the properties of faster acting, short duration with titratable doses have made propofol a safe and appropriate sedative drug [24, 25]. An initial propofol bolus of 0.5–0.8 mg/kg is usually administered during RT without affecting respiration and airway control [26]. Initially there were some concerns about tachyphylaxis with repeated doses of propofol but these have been unfounded in recent studies [27–29].
   (c) Ketamine can be used for RT sedation but tachyphylaxis is commonly witnessed

with ketamine. It may not be an ideal agent especially in orbital and intracranial tumors because of increase intracranial pressure and intraocular pressure with its use [30].

(d) Recently, α-2 agonist dexmedetomidine is available and has been described for sedation for RT. However, it is not widely used because it is not approved for pediatric sedation and the initial bolus needs to be given slowly which may outlast the duration of the procedure itself.

6. Monitoring during radiotherapy sedation requires two cameras with one focusing on the patient (with anesthesia machine and monitor) showing breathing movements and one facing the monitor within the procedure room which can be viewed in the console room. There can be slave monitors that transmit the information from the main monitor in the procedure room (Fig. 28.3). The patients should have an electrocardiogram (ECG), pulse oximeter (SpO2), non-invasive blood pressure (NIBP), and capnography (end-tidal carbon dioxide, especially for procedures under reduced ambient light) monitored throughout the procedure [19].
7. Post-Procedural concerns: After the procedure patient must be shifted to a recovery room for observation until the child is fit for discharge. The recovery room should be equipped with equipment for resuscitation if necessary, like oxygen, emergency drugs, and rescue airway devices.

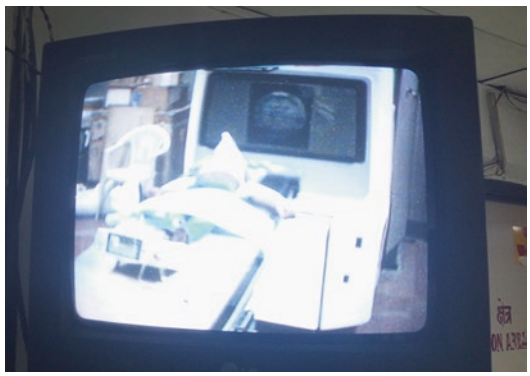

Fig. 28.3 Closed-loop monitoring with portable pulse oximeter in place which can be viewed in the observation/console room

28.6 Intraoperative Radiotherapy (IORT)

Nowadays RT is not limited to EBRT but efforts are made to give RT immediately after surgical debulking. This IORT was first used in the 1960s by Abe *et al* for various intraabdominal tumors but since then its efficacy has been proven in locally advanced and recurrent cancers of breast, rectum, pancreas, gynecologic, and other genitourinary malignancies [31, 32].

The advantages of IORT are:

(a) Precise localization of the malignancy and focused delivery of RT to ensure a better tumoricidal effect.
(b) Minimum damage to healthy tissues by shielding them.
(c) Immediate delivery of radiation following surgery reduces the chance of repopulation of the tumor and the risk of the seedling.
(d) Patient compliance is better due to shortened overall treatment course and high therapeutic ratio.
(e) The single high dose is another radiobiological advantage.
(f) Provides opportunities for dose escalation and re-radiation in case of recurrent tumors.

28.7 Techniques of IORT

The various modalities of delivery of IORT include intraoperative electron radiation therapy (IOERT), high-dose rate brachytherapy (HDR-IORT), and electronic brachytherapy/low-kilovoltage X-rays (KV-IORT). Low energy X-ray IORT is provided by Intrabeam (Carl Zeiss, Oberkochen, Germany). IOERT can be delivered by three mobile linear accelerators—Novac 7, Liac, and Mobetron.

28.8 Unique Anesthetic Considerations of IORT (Fig. 28.4)

1. IORT Operating Room: The place of IORT could be either a dedicated IORT suite for anesthesia, surgery, and radiation therapy, or an operating room facility is created in the radiation oncology area. In a dedicated IORT OT, a radiotherapy system is used to provide radiation. This room should comply with all the standards for a surgical suite like proper air circulation, operating room lights, suction apparatus, emergency drugs, anesthesia machine, anesthetic equipment, suitable operating table as per need of its suitability to RT equipment, patient monitoring equipment with remote monitoring and slave monitors, and scavenging system [33].It should also have facilities like laser lights detecting coronal, sagittal, and transverse patient motion, slave monitoring devices with remote control, dosimetry cable channels, and adequate space for RT equipment movement to 360° with appropriate shielding. The setup should have a preoperative holding area and post-anesthesia care unit fully equipped to deal with any eventualities that must be available [34].
2. Risk of Radiation Exposure: All safety measures to protect the operation room personnel from radiation hazards must be strictly followed [35].
   (a) Safety boards should be placed at the most visible site outside the IORT OT. This signboard should have additional red light illuminated during the irradiation phase to prevent accidental entry.
   (b) The main limitation of IORT is the absence of all personals inside the place where RT is being delivered. Hence, there is a risk of the patient being unattended during this period, in case the patient needs immediate corrective measures and management for some event. The provision of a slave monitor is to be placed at the console region to continuously monitor the patient. Provision of the emergency switch to stop the RT delivery and instant access to the patient should be prominently placed. Newer brachytherapy systems like Axxent Electronic deliver brachytherapy uses an X-ray source of 50-kVp. Exposure during IORT may be up to 200 mR/h, 30 cm from a treated area, and movable lead shields have been found to reduce it by >95%. These can be used in regular OT without shielding if protective lead aprons/lead shield is used by the operator [35].
   (c) This remote patient monitoring of vitals can be challenging for the anesthesiologist. This requires arrangements like the use of slave monitoring devices, use of cameras, or use of lead reinforced glass

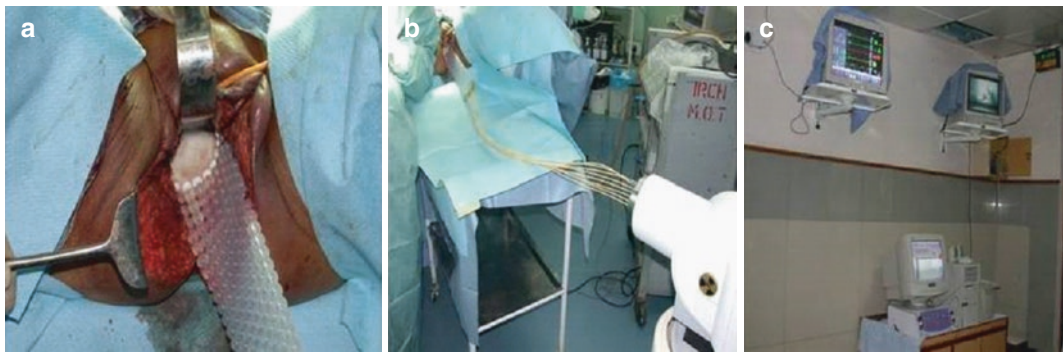

Fig. 28.4 IORT set up in a patient with rectal cancer. (**a**) The exposed field with Freiburg's applicator in situ; (**b**) IORT being delivered with HDR brachytherapy machine; (**c**) slave monitor for monitoring the patients from outside and (**d**) monitoring the radiation dose being delivered

partition to observe the patient while RT is being delivered [34]. An audio-visual communication facility can provide easy communication and also helps in observing patients' status or monitoring of heart sounds as well. Wall-mounted cameras connected to the television in the treatment room can assist in observing not only patients but other monitoring devices as well [36].

3. Movement of Patient/ Linear Accelerator: Following induction of anesthesia, surgery is done followed by a repositioning of the operating room table to target the radiation beam to provide IORT.
   (a) Previously, anesthetized patients had to be transported from the operating room with an open wound to the location of the linear accelerator and back to the operating room. But with the availability of mobile accelerators, the therapy can now be delivered in the operating room itself. A mobile accelerator delivers radiation to the tumor bed in the form of an electron beam.
4. When the patient is being positioned for radiation therapy, the linear accelerator rather than the operating table should be moved preferably because it moves with more finesse, and moving the operating table with an intubated patient under anesthesia may be riskier. Also, the table cannot be moved as precisely and this may affect the overall alignment of the accelerator and the delivery cone. Moreover, as the patient slides towards the head of the table, the fulcrum of the table is close to the patient's feet and can lead to the tipping of the operating room table towards the head.
5. The main concern during IORT is that patients must remain immobile for precise delivery of radiation. It also delivers the maximum dose of radiation to the tumor lesion without much affecting the surrounding normal tissues [9, 10]. Hence, the anesthetic technique must be planned accordingly. General anesthesia with an endotracheal tube (GETA) and muscle relaxation is a preferred technique. Nowadays supraglottic devices are available freely and can be used. But the patient should be paralyzed in most of the cases because large fluctuation in tidal volume in spontaneously breathing patients may reduce the preciseness of focused electron beams and affect the overall results.
6. Some surgeries like breast conservative surgeries require sentinel lymph node biopsy. Muscle relaxation may make sentinel biopsy difficult because surgeons may not be able to identify nerves during sentinel node biopsy and lead to postoperative complications. So, a single dose of a muscle relaxant may be given at the time of induction and a repeat dose should be avoided at a later stage when the sentinel lymph node biopsy is being done.
7. There is a risk of inadvertent hypothermia in the accelerator unit as low temperature is to be maintained for the proper functioning of radiotherapy machines. Hence, core temperature monitoring and measures to combat hypothermia like warming blankets, fluid warmers, and humidified gases must be used.
8. Challenges faced during anesthesia in a remote location as highlighted earlier are present and need to understand to plan safe anesthesia for IORT.
9. Patient-related
   (a) Debilitated patients either due to cancer or due to cancer therapy. These patients might also have anemia, protein malnutrition, electrolyte disturbances, deranged liver, and renal function which can prolong the anesthetic drug effects, causes cardiovascular compromise, and thus affect the overall perioperative outcome. Hence, drugs must be carefully titrated.
   (b) These patients might have received chemotherapy and must be evaluated for the presence of chemotherapy-related side effects like anemia, thrombocytopenia, deranged coagulation, cardiotoxicity, hepatic and renal dysfunction, and pulmonary toxicity.
   (c) Patient-related other symptom management like pain, nausea, and vomiting also needs to be managed.

28.9 Intraoperative Monitoring

The monitoring of patients requiring IORT needs to be monitored using standard monitors like 5 lead electrocardiogram, blood pressure, pulse oximetry, capnography, and temperature. Other specific advanced and invasive monitoring like invasive blood pressure, cardiac output, urine output, etc. depends on the extent of surgical intervention and associated comorbidities. All pressure points must be padded and protected carefully. Good communication between anesthesiologists, surgeons, radiation oncologists, physicists, and nursing staff is imperative for a successful procedure.

The choice of anesthetic technique needs to be individualized based on patient status, and type of proposed surgical intervention. GA with endotracheal intubation is the preferred technique. The choice of induction drugs, opioids, muscle relaxants, and inhalational agents will vary based on the anesthesiologist's preference, drug availability, patient requirement, and the surgical intervention planned. Monitored anesthesia care may not be sufficient in most cases because of the extent of surgical resection. Other techniques of anesthesia like total intravenous anesthesia and regional anesthesia may also be used. The extubation plan depends on the patient's status at the end of surgery and if the patient is stable, on-table extubation may be planned, or otherwise, it may be delayed [37].

28.10 Anesthesia for Brachytherapy

Brachytherapy is one of the RT technique in which the high dose of radiation is delivered in the tumor lesion or just in its vicinity to deliver the radiation dose without having much adverse effect on the surrounding normal cells [4]. Newer artificial high activity isotopes, after-loading systems together with improved imaging and sophisticated dose planning techniques has led to the increasing role of brachytherapy [5]. various types of brachytherapy are in clinical use (Table 28.4). Brachytherapy has its own set of advantages and disadvantages over other modalities of radiation therapy (Table 28.5).

Table 28.4 Types of brachytherapy [3]

Based on the technique		
Intracavitary & endoluminal brachytherapy	Interstitial brachytherapy	Surface brachytherapy (Plesiotherapy)
Applicators loaded with sealed radioactive sources are introduced into the body cavities such as the vagina or uterine cavity or the lumen of the esophagus or bronchus	These needles or catheters are placed within the tumor and surrounding tissues which are then loaded with radioactive wires or seeds It is used in urogenital, intestinal, breast, tongue, oropharynx, skin, and soft tissue malignancies. Also used in brain tumors	The radioactive source usually in the form of molds or plaques is placed on the tumor surface. This technique is used in sites such as the vagina, nasopharynx, conjunctiva, intraocular melanoma, retinoblastoma, etc.
Based on the dose rate of sources used		
Low dose rate (LDR)	Medium dose rate (MDR)	High dose rate (HDR)
0.4–2 Gray/h	2–12 Gray/h	Over 12 Gray/h

Table 28.5 Advantages and disadvantages of brachytherapy [3]

Advantages	Disadvantages
• Administration of high doses to small volume with an acceptable risk of complications • Spares the surrounding normal tissues • Shorter treatment time • Better patient compliance	• High risk of radiation exposure to the involved medical personnel (can be reduced by after-loading system) • Increase complication due to non-homogeneous dose distribution • Risk of late radiation damage if HDR brachytherapy is given in inadequate fractionation • Technically difficult

28.11 Clinical Suitability for Brachytherapy

Tumors with clinically and radiologically well-defined margins, easily accessible are suitable for brachytherapy [5]. Brachytherpy can be used along with other RT modalities like external beam radiotherapy (EBRT) for providing a highly localized boost. Brachytherapy is helpful for areas of gross residual disease or to achieve palliation of obstructive symptoms in lung and oesophageal cancers.

28.12 Role of Anaesthesiologist During Brachytherapy

Both interstitial and intracavitary brachytherapy procedures are painful during the placement of the catheters. Also after the placement, the applicators are in situ, analgesia and immobilization may be required since the source should not be moved during application [38]. Occurrence of pain during the procedure can affect the precise positioning of the applicator and reduce patient satisfaction leading to discontinuation of session and poor compliance. Recent studies have shown that patients experience pain and anxiety during brachytherapy, particularly in gynecological and prostate cancer [39]. Hence, adequate anesthesia is essential for the successful application and delivery of brachytherapy.

28.13 Specific Anesthetic Concerns for Patients Undergoing Brachytherapy

1. **Patient-related**
   (a) Brachytherapy could be an alternative therapeutic modality for patients unfit for major surgery due to the extent of malignancy or have high perioperative risk. Such patients can present different challenges than a normal surgical patient [40].
   (b) Some patients undergoing brachytherapy (especially palliative brachytherapy) are often elderly and may present with multiple comorbidities, poor performance status, poor nutritional status, and metabolic derangements [41].
   (c) These patients might also have received external beam radiotherapy (EBRT) and chemotherapy. Chemotherapy drugs like anthracyclines, taxanes, and 5FU may cause cardiac dysfunction. Radiation therapy to the thorax can also lead to cardiac dysfunction. Other anesthetic concerns post radiation and chemotherapy are enumerated in the previous chapter.
   (d) Primary tumors involving the oropharynx, buccal mucosa, and tongue may complicate airway patency. Cancer-related therapy may lead to mucositis and airway management in these patients remain challenging due to the risk of bleeding and distorted airway.
   (e) During the placement of brachytherapy catheters and actual brachytherapy complete immobility is required. So, the selection of anesthesia including analgesia should be selected accordingly.
   (f) Positioning related complications may occur especially during ICRT where a lithotomy position may be required.
2. **Procedure-related**
   (a) The duration of anesthesia is variable because it involves the procedure for applying the brachytherapy catheters, imaging to confirm the correct placement applicator, computer-based calculation of dose for brachytherapy, and subsequent brachytherapy sessions [8]. All these leads to a long duration of applicator remaining in situ.
   (b) Brachytherapy sessions can take place in specially designed rooms that may be located at a distant place from the operation theatre. After placement of the brachytherapy catheters, we may need to transport the patients between the radiation room, computed tomography, magnetic resonance imaging. This could be challenging and also increases the risk of dislodgement of catheters during transport.

(c) During all these steps good analgesia ensures patient cooperation and is important for a successful outcome. Also, multiple sessions might be planned for the treatment requiring repeated analgesia.
(d) The operating room for brachytherapy and the actual radiation therapy room may be located at a distant place outside the main operation complex due to radiation hazards. So, unique challenges faced during anesthesia in remote locations like the unfamiliar environment, bulky equipment, and non-availability of immediate assistance are additional concerns for providing anesthesia services for brachytherapy.
(e) Most of these procedures are done on a day care basis. So, the anesthetic technique chosen should have a rapid onset and recovery, early return of cognition, minimal postoperative nausea vomiting, dizziness and provide maximum comfort with minimal residual effects [42].

28.14 Pre-anesthetic Evaluation

Pre-anesthetic evaluation should look for associated comorbidities, nutritional status, side effects of chemotherapy, and radiotherapy. Patients with an oral malignancy might present with difficult intubation. Further, these patients could have received external beam radiation to the neck area which causes anatomical alterations in the upper and lower airway leading to difficult mask ventilation, laryngoscopy, and intubation. Hence, a thorough airway examination and planning is essential. A difficult airway cart should always be kept ready. Tracheostomy may be required in case of impending airway obstruction.

28.15 Monitoring

The routine monitors include five lead electrocardiograms, pulse oximetry, non-invasive blood pressure, capnometry, and temperature. Other advanced monitoring is dependent on need as per patient assessment, and associated comorbidities.

28.16 Anesthetic Techniques

The choice of anesthesia depends on the site of brachytherapy, associated comorbidities, choice of anaesthesiologist, and duration of the procedure, LDR versus HDR brachytherapy, local infrastructure, and preference of the patient.

General anesthesia (GA) is preferred for brachytherapy of the oropharynx, bronchial, liver, and breast. While for brachytherapy to genitourinary areas a regional anesthetic technique may be preferred. Some radiation oncologists mainly used local or topical anesthetics when anaesthesiologists are unavailable to provide the services.

28.17 Anesthesia for Cervical Brachytherapy

Intracavitary and interstitial brachytherapy are important modalities of treatment of gynecological cancer. The patients undergoing brachytherapy for cancer cervix can vary from younger women to elderly patients with multiple comorbidities. It has been noted these patients have a high degree of anxiety and distress due to underlying medical conditions more so in younger patients [43]. In Also most of these patients are from low socioeconomic status, may have poor nutrition status, and are frequently anemic. Brachytherapy unlike other radiation modalities has minimal effect on bone marrow.

Pain and discomfort during brachytherapy are multifactorial. The presence of applicators along with vaginal packing, catheters, presence of a template, etc causes discomfort [44]. Also, supervision in the ward is limited to reduce radiation exposure to staff which also adds to patient anxiety. Adequate pain management can make this ordeal to slightly unpleasant treatment. Various anesthetic techniques have been used during pel-

vic brachytherapy. Every technique has its advantages and disadvantages.

Various anesthetic and analgesic technique has been used for cervical brachytherapy [45–50]. These include general anesthesia, central neuraxial blocks (subarachnoid block, epidural block, or combination of both), regional blocks (paracervical block), conscious sedation with local anesthesia with either advantages and limitations. The caudal block has been used for this type of brachytherapy but was reported to have patient discomfort due to the presence of applicators placed in the uterus [51, 52]. Further research is required for the best-preferred technique for such type of procedures [53].

28.18 Anesthesia for Prostate Brachytherapy

Various modalities for prostate cancer management are available. Transperineal brachytherapy is one of the accepted alternative to surgery (radical retropubic prostatectomy) along with postoperative RT (Fig. 28.5). The HDR brachytherapy requires a shorter duration of intervention but the insertion of brachytherapy catheters (around 20) is extremely painful which obligates the need for general anesthesia, spinal anesthesia, or local anesthesia [54–57].

Various anesthetic techniques have been reported for its use for prostate brachytherapy (Table 28.6) [55–60]. The use of the local anesthetic technique is limited due to a lack of optimal anesthesia and analgesia. This technique should be used judiciously and cautiously only n selected populations where general anesthesia and subarachnoid block are contraindicated. The subarachnoid block has been safely and successfully using for prostate brachytherapy [59]. General anesthesia has been used and technique based on TIVA allows early recovery [60].

28.19 Head and Neck Brachytherapy

Head and neck cancers require multidisciplinary management. The selection of treatment modality depends on ton the type, extent, and site of the tumor. Brachytherapy has been found useful in selected head and neck cancers (Fig. 28.6). It found its role in the lip, oral cavity, nasopharynx, oropharynx cancers, wherein the involvement is of cosmetic relevance or functional

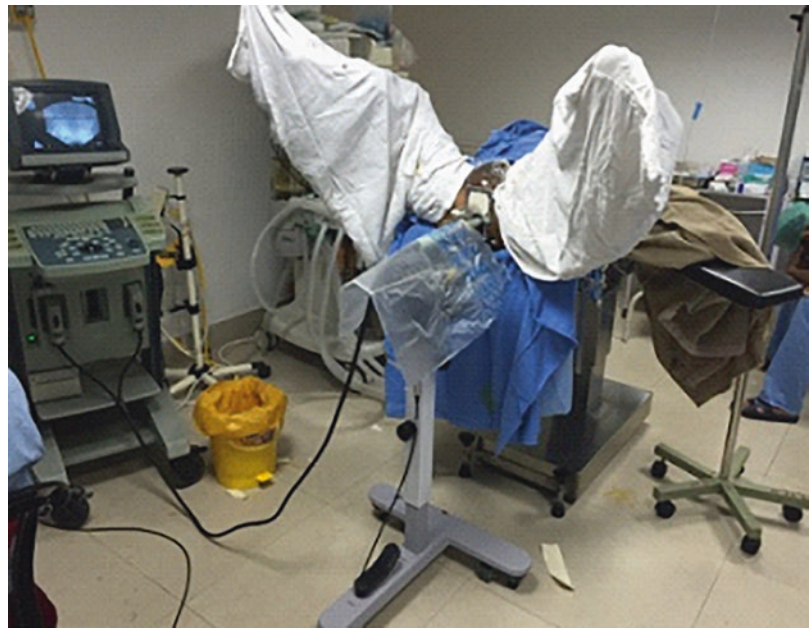

Fig. 28.5 Prostate brachytherapy

importance. It is also used in conjunction with surgery and ERT [61, 62].

Patients with oropharyngeal cancers often present with a difficult airway. Associated mucositis may lead to friable mucosa which bleeds particularly during instrumentation. Previous EBRT to the head and neck region might lead to distortion of the airway along with edema of the tissues resulting in difficult mask ventilation and laryngoscopy [32]. It can obliterate the lymphatics and increase the risk of postoperative edema. A thorough airway examination is essential.

Benrath et al found that half of their patients with oropharyngeal cancers required fiberoptic intubation of the trachea [40]. Hence, it is imperative to have a pre-planned strategy for managing the airway. A difficult airway cart should be available. General anesthesia with nasotracheal intubation is the preferred technique. A throat pack should be inserted after intubation. For the base of tongue implants, the patient should be prepared to have tracheostomy which can be reversed once the post-implant edema subsides. Facilities for postoperative ventilation must be available as extubation might have to be delayed due to the risk of post-procedural edema. Adequate analgesia must be provided both during and following the procedure.

Table 28.6 Common sites of brachytherapy with preferred anesthetic techniques

Site of brachytherapy	Anesthetic techniques
1. Ca Cervix, vagina, endometrium, rectum, penis	LA, GA (TIVA, inhalational), CS, Caudal epidural, SAB, saddle block
2. Ca breast	LA, GA, CS, Thoracic Paravertebral, SAP block
3. Ca prostate	LA, SAB, lumbar epidural, CSE, GA, sedation
4. Ca tongue	LA, GA

LA local anesthesia, *GA* general anesthesia, *CS* conscious sedation, *SAB* subarachnoid block, *CSE* combined spinal and epidural, *SAP* serratus anterior plane

28.20 Anesthesia for Accelerated Partial Breast Irradiation (APBI)

A selected group of breast cancer patients can be treated by APBI [63]. It has emerged a suitable and acceptable alternative with whole breast irradiation with comparable outcomes and lesser adverse events (Fig. 28.7). The literature on anesthesia on breast brachytherapy is limited. GA is the preferred technique. Anesthesia is required for a shorter duration during the insertion of the applicator. Analgesia is needed when the applicator is in situ. Ultrasound-guided TAP block or thoracic Paravertebral blocks could be attempted.

28.21 Post-procedural Care

A dedicated post-procedural recovery area with the availability of oxygen delivery devices, emergency drugs, and equipment including airway

Fig. 28.6 Head and neck brachytherapy

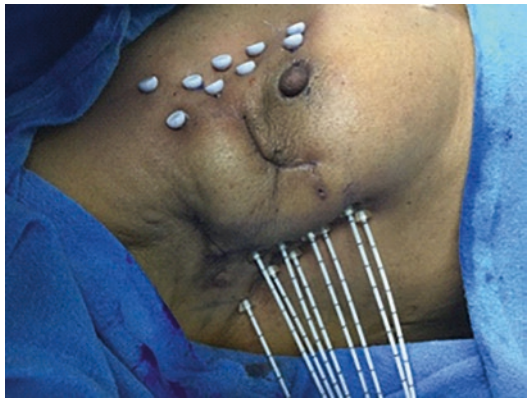

Fig. 28.7 Anesthesia for APBI

equipment is preferable. The patient is monitored after the completion of brachytherapy until fit to be discharged. Modified Aldrete score or post-anesthesia discharge score can be used as a criterion for discharge.

28.22 Summary

Anesthesia for radiation therapy is challenging. There are unique considerations in providing anesthesia for these procedures and these should be thought of before planning anesthesia. A careful pre-procedural assessment, meticulous planning, and good intra-procedural and post-procedural care help to provide safe anesthesia. Good communication with radiation oncologists is also required for a successful outcome.

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29 Anaesthesia and Sedation for Radiological Imaging

J. S. Dali and Anju Gupta

29.1 Introduction

Cancer has emerged as one of the leading causes of mortality all over the world and its incidence continues to rise. Researchers across the globe are putting in diligent efforts to develop new weapons to combat it. Imaging modalities form the backbone of the management of cancer patients as a means to diagnose tumor and metastasis, decide treatment plans, prognosticate, and do image-guided procedures. Historically, computed tomography (CT) has dominated the scene of oncology imaging because of its easy availability, was less time consuming, and radiologists were more accustomed to it. However, magnetic resonance imaging (MRI) has become the cornerstone of contemporary onco-imaging because of advancements in its technology and concerns about radiation with CT. MRI has several advantages over CT scan with regards to scanning patients with cancer: superior contrast resolution, tissue characterization (e.g., cystic versus solid), ability to perform dynamic post-contrast imaging, and lack of ionizing radiation [1]. MRI has improved sensitivity for many lesions (e.g., metastatic lymph nodes, bone lesions, liver lesions) and allows better assessment of vasculature, e.g., vascular invasion. Furthermore, emerging techniques will keep MRI at the forefront of onco-imaging—whole-body MRI, qualitative diffusion, Positron emission technology (PET) MRI, MRI guided biopsy.

Since CT/MRI is a painless procedure, most imaging studies in adults can be performed without the use of anesthesia or sedation. However, young children are unable to lie still during the study and form the vast majority of those needing anesthesia services for imaging procedures. Anesthesia may be indicated for patients with young age, claustrophobia, severe anxiety, inability to lie still (e.g., parkinsonism), prolonged procedures in the prone position, mental retardation, psychiatric illness, and a history of the need for sedation in past. However, anesthesia in such remote locations has many risks inherent to the location, facilities, monitoring, and patient population (Table 29.1) [2, 3].

The high risk of anesthesia at these locations is reflected in a study by Vander Griend, et al. where out of 101,885 anesthetics for imaging procedures in children, ten anesthesia-related deaths were reported [4]. This incidence is much higher than that reported for operating room anesthesia (1:100,000). In all these cases, pre-existing medical conditions were the major contributory factor to the deaths. The utilization rate

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Table 29.1 Anesthetic challenges in CT/MRI suite

Challenges of anesthesia in CT/MRI suite [2, 3]
(I) Pediatric population with its own set of concerns
(II) It is usually difficult and time consuming to acquire personnel support, extra drugs, or equipment in case a need arises due to the unfamiliar and remote location
(III) Need to maintain physical distance from the patients during the scan
(IV) Restrictions in entry to the suite and access to the patient during the procedure making any assistance for difficult intravenous lines/ airways, or in case of anesthetic emergencies unavailable or delayed

of off-site anesthesia serves has shown tremendous growth in a short span of 28.3% in 2010 to 35.9% in 2014 and it is expected to steadily grow in the future [5]. Hence, anesthesiologists need to be abreast of the challenges and safety concerns of non operating room anaesthesia (NORA).

29.2 General Considerations

29.2.1 Computed Tomography (CT)

CT is a commonly used modality for diagnostic and interventional procedures. The scan quality can be improved by using contrast agents. Personal protective equipment, e.g., lead apron, thyroid shields, and dosimeters should be worn by all staff involved in patient care at the CT scan suite. Movable leaded glass screens separate the patient from the caregivers during the scan. Video monitoring provides remote mirroring of monitor data. The minimum sizing recommendation for a CT scan room is an area of 250 ft^2 with a clear dimension of 3 ft on three sides of the procedure table. The maximal permissible dose of occupational radiation exposure is a cumulative annual dose of 50 millisieverts (mSv) and a lifetime total dose of 10 mSv times the age of the worker [6, 7].

Anaesthesiologists—Anesthesia care providers are also exposed to ionizing radiation during a CT procedure. Radiation dose is determined by:

- Time—Anaesthesiologists may be exposed to longer durations and higher doses of radiation than radiologists during CT scans because the CT team can perform their duties within the shielded control room, while the anesthesiologist may need to remain by the patient's side, particularly for sedated patients with a potentially difficult airway and those undergoing general anesthesia [3].
- Distance—The amount of radiation to the anaesthesiologist decreases in proportion to the square of his distance from the scanning tube.
- Shielding—Lead aprons and thyroid collars should always be worn while maintaining a reasonable distance from the patient [7]. Portable shields and eye protection mitigate risk. Dosimeter badges should be worn by anesthesiologists and staff routinely exposed to ionizing radiation so that cumulative radiation exposure can be monitored regularly over some time [3, 8].

29.2.2 Magnetic Resonance Imaging (MRI)

The property of paramagnetic elements to act as magnetic dipoles and their ample presence in bodily tissues with high water content is the basis of MRI. The magnetic field strength is measured in tesla units and one tesla (T) equals 10,000 gauss. Clinical MRI examinations use field strengths between 0.05 and 3.0 T.MRI suite should be spacious (at least 150 ft^2 control room and cryogen storage of 50 ft^2) [9].

MRI is a time-consuming procedure. The extremely powerful static and gradient magnetic field and radiofrequency electromagnetic waves pose potential hazards to patients and workers [9]. Limitations and hazards for patients and anesthesia providers during MRI [3, 9–11]:

1. Switching the radiofrequency generators on and off produces loud noises (>90 dB).
2. Even physiologic motion (e.g., breathing) can produce image artifacts.
3. Restricted access and patient visibility during the examination for caregivers and during an emergency for emergency personnel.

4. Magnetic field interferes with equipment for patient monitoring and stray radiofrequency currents from the monitoring equipment can in turn potentially degrade the MRI images.
5. The anesthetic equipment cannot be moved when the scan has started as their rapid movement can impair magnetic field homogeneity.
6. Ferromagnetic materials (scissors, pens, keys, mobiles, cylinders, etc.) may turn into dangerous projectiles and must be eradicated from the MRI suite.
7. Implanted biological devices (vascular clips and shunts, wire-reinforced endotracheal tubes, pacemakers, mechanical heart valves) or intraocular ferromagnetic foreign body may get dislodged/ migrate or malfunction.
8. Transdermal patches may consist of aluminum or other metals (e.g., fentanyl, buprenorphine, scopolamine being received by many cancer patients) or tattoo ink (contains iron oxide) that carry the risk of causing skin burns.

MRI suite is functionally divided into four different zones [10]:

- Zone I: freely accessible to everyone.
- Zone II: buffer area between free access of zone one and restrictive access of zone three.
- Zone III: only approved MR personnel and patients that have undergone a thorough screening are allowed inside zone Three. The MR control room is located in this zone.
- Zone IV: actual scanner room, also called the magnet room. People can enter only through zone three.

29.2.2.1 Anesthetic Concerns Specific to MRI Suite

According to the American Society of Anaesthesiologists (ASA) task force advisory on anesthetic care for MRI [10], all the anesthetic care, monitoring and resuscitation equipment, and drug supplies at this off-site facility should be parallel to the recommendation followed for standard operative settings. This includes (but is not limited to) basic amenities, e.g., adequate electrical outlets and lighting, storage areas for equipment and drugs, suction, and standard anesthesia equipment, e.g., an anesthesia machine with integrated medical gases and gas scavenging. MRI safe/conditional anesthesia machines are safer for use in an MRI suite than anesthesia delivered via an elongated circuit through a waveguide using a traditional anesthesia machine kept inside zone III [9, 10]. Age appropriate airway and resuscitation is a must. Alternatively, total intravenous anesthesia (TIVA) can be used by either of the following methods: (1) MRI safe/conditional pumps in zone IV, (2) traditional (i.e., MRI unsafe) pumps in zone III with intravenous tubing passed through a waveguide, or (3) periodic bolus injections in either zone III or IV [3, 9, 10]. At all times, equipment for the administration of positive pressure ventilation with oxygen should be immediately available [9, 11].

29.3 Anesthetic Management of Cancer Patients for CT/ MRI

Anesthetic management of patients undergoing CT/MRI examination presents unique challenges to anaesthesiologists although the scans are usually very short and do not entail any fluid shifts/ blood loss. Anesthetic concern for these procedures is linked mainly to the remote anesthesia location, patient population (cancer patient, pediatric age group), and the procedure (CT: radiation, MRI: ferromagnetic field) [2, 3, 11].

29.3.1 Preoperative Assessment and Investigations

Before anesthetizing the patients, it is mandatory to carry out a thorough pre-anesthetic evaluation of the patient and obtain relevant consent for the procedure. PAC visits should be considered as an opportunity to evaluate the patient based on physical as well as psychosocial aspects. Also, modality-specific concerns should be kept in mind [3]. Any congenital anomalies, previous personal or family history of complications during anesthesia and surgery, history of allergies to

any drug, medical illnesses, recent respiratory illness, current or past intake of any general or chemotherapeutic medications, and history of systemic toxicity due to chemo/radiotherapy should be specifically elicited [2, 3, 12]. Chemotherapy and radiotherapy can lead to various systemic manifestations. (Table 29.2) [13–18] and (Table 29.3) [19, 20].

The presence of an anaesthesiologist is mandatory for sedation in case of a neonate, history of obstructive sleep apnoea, respiratory failure, hemodynamic instability, cardiac disease, anomaly involving head and neck, e.g., Apert's or Crouzon's syndrome, severe gastroesophageal reflux disease, or in a child with myopathies, mitochondrial, or metabolic disease [3, 9, 21, 22]. Oncologic patients requiring high dose medications for their baseline pain control need careful evaluation of treatment regimen to achieve safe and adequate sedation and analgesia [18].

Table 29.2 Effect of chemotherapy drugs on various organ systems [13–18]

Organ system	Drugs	Implication
Pulmonary	Cytotoxic antibiotics Nitrosoureas Alkylating agents Anti-metabolite Plant alkaloids Biological response modifiers Others: taxol	Interstitial pneumonitis; acute non-cardiogenic pulmonary edema; Bronchospasm; Pleural effusion
Cardiac	Anthracyclines Cytotoxic antibiotics Alkylating agents Others, e.g., 5-fluorouracil	Myocardial ischemia and depression, hypo/hypertension, myocarditis, endomyocardial fibrosis, and conduction defects
Hepatotoxicity	Nitrosoureas Cytotoxic antibiotics Anti-metabolites Others: vincristine,5-FU, cisplatin	
Nephrotoxicity	Nitrosoureas Others, e.g., bleomycin, cisplatin, cyclophosphamide, vincristine, methotrexate, mitomycin C	Renal tubular; and glomerular impairment, haematuria, urate nephropathy, hemorrhagic cystitis
Hematological toxicity	Alkylating agents Natural alkaloids Antibiotics	Anemia, neutropaenia, thrombocytopaenia and thrombosis
Neurotoxicity	Cisplatin Carboplatin Methotrexate Vincristine Cyclosporine	Peripheral neuropathy, encephalopathy, autonomic neuropathy cerebellar ataxia
Gastrointestinal toxicity	Almost all chemotherapeutic agents	nausea and vomiting, diarrhea, mucositis, enterocolitis, stomatitis delayed gastric emptying, and aspiration

Table 29.3 Systemic effects of radiotherapy [19, 20]

System	Effects	Remarks
Airway	Fibrosis of soft tissue of mouth, neck, and airway mucosa, Subglottic edema or stenosis, Hypoplasia of the jaw, xerostomia, Mucositis	Limited mouth opening and neck extension, poor submandibular compliance, difficult mask ventilation, and intubation
Respiratory system	Radiation-induced pneumonitis, Restrictive lung disease	Higher risk of intra and postoperative pulmonary complications
Cardiovascular system	Pericarditis and pericardial effusion, Endocardial and valvular fibrosis, Conduction system defects, ischemic heart disease	Risk is increased with simultaneous chemotherapy with vincristine or doxorubicin

Some pediatric malignancies have a higher association with other medical conditions (e.g., Down's syndrome with lymphoma) which increase the likelihood of cardiac anomalies, such as endocardial cushion defects [18, 19]. Standard ASA fasting guidelines are followed for the child(solid food up to 6 h, breast milk up to 4 h, and clear liquids are permitted up to 2 h before the procedure [23]. If the tumor or medical condition is impairing gastric emptying, stricter guidelines may need to be enforced.

A suggested scheme for the pre-anesthetic evaluation of a child with malignancy has been summarized in Table 29.4 [19, 24].

Table 29.4 Pre-anesthetic evaluation concerns for a pediatric oncology patient [19, 24]

Toxicity	Risk factors	Evaluation	Anesthetic consideration
Cardiac	Anthracycline Radiation	Obtain echocardiogram if: • Cumulative drug dose>240 mg/m^2 • Any dose in infants • Chest radiation>40 gy	New-onset hypotension and arrhythmia during anesthesia
Airway, Circulatory	Anterior mediastinal mass/ SVC syndrome	CXR, CT, ECHO, and Flow-Volume loop	The plan will depend on symptoms and status of the tumor, may be done under local anesthesia alone, postponing procedure after local irradiation, or general anesthesia with all precautions
Pulmonary	Pneumonia, BOOP, pulmonary fibrosis from chemotherapy, RT, and HSCT.	CXR, ABG, and pulmonary function tests depending on the severity	The obstructive and restrictive disease may interfere with ventilation. Keeping FiO_2 lowest possible after CT with bleomycin.
Renal and Hepatic	Chemotherapy, radiotherapy, and HSCT	RFT and LFT	Modify drugs and their doses
Hematopoietic	Anemia, leukopenia, hyperleukocytosis, thrombocytopenia	CBC, coagulation profile.	Preoperative transfusion of blood products may be considered in case of severe pathology and anticipated prolonged procedure or image-guided interventions. Consider the use of irradiated and leuco-depleted products.
Neurological	Central and peripheral nerve dysfunction	Establish baseline values	Document
Radiation airway changes	Mucositis, airway fibrosis, and edema	Airway assessment: mandibular mobility, neck movements, MMP class, etc.	Anticipate airway to be difficult even with/ without the use of muscle relaxants
Oncological emergencies	Elevated ICP, SC compression, tumor lysis syndrome, hypercalcemia	Assessment as per particular abnormality	Treatment is based on a particular abnormality present.
Gastrointestinal	Diarrhea, vomiting, ulceration, obstruction, perforation, malnutrition, etc.	Assess aspiration risk, electrolytes, metabolic derangements, and glucose levels as appropriate	Consider hydration and nutrition supplementation. Consider a higher risk of aspiration
Endocrine	Thyroid and growth hormone dysfunction, adrenal suppression	Assessment as appropriate, any exogenous supplementation required.	Consider corticosteroid stress dose as appropriate
Congenital anomalies	Apert's/Crouzon's/Pierre Robin syndrome, etc.	Airway assessment	Anaesthesiologist presence mandatory for off-site anesthesia, DA cart ready

BOOP, bronchiolitis obliterans organizing pneumonia; CXR, chest X-ray; MMP, modified mallampatti class; ICP, intracranial pressure; SC, spinal cord; RFT, renal function test; LFT, liver function test; CBC, complete blood count

29.3.2 Staffing Requirements

Imaging procedures have routinely been conducted using several sedation models and sedation has been administered by the radiology staff or pediatricians at the point of care apart from anaesthesiologists [12, 25–29]. Midazolam is frequently administered by non-anaesthesiologists [26]. For propofol sedation by non-anaesthesiologists (e.g., pediatricians in the pediatrician-delivered model), propofol credentialing is a prerequisite. This encompasses a 3-h didactic session followed by 10 days of OR training under an anaesthesiologist inclusive of 25 supervised propofol sedation administered by the trainee [30]. Even after initial credentialing, to maintain certification to deliver propofol, a minimum administration of 50 propofol sedations per year (with the backup provision of an anesthesiologist) is mandatory by the pediatrician [30].

However, in the recent past, there is increasing awareness about the risks of such practice and now it is commonly recommended that a dedicated trained anesthesia team should provide the service in all pediatric cases [9, 10, 12, 21, 31]. The most dreaded and frequent complication of inducing sedation or general anesthesia at these locations is cardio-respiratory depression, which includes upper airway obstruction, hypoxia, hypotension, and in rare cases even cardiac arrest [9, 10, 12, 24]. Other rarer adverse effects purportedly are nausea, vomiting, disorientation, sleep disturbance, and nightmares.

AAP guidelines for off-site sedation provision recommend the constant presence of at least one dedicated individual trained and competent in providing airway management skills and pediatric advanced life support [12]. Anesthesia technicians (assistants who transport and restock all equipment and supplies) should be available during the preparation of equipment as well as during the scanning procedure. All assistants working in the MRI suite should receive specialized training in patient and personal safety in this environment, as well as the types of special equipment and supplies that may be needed [10, 12].

29.3.3 Safety Requirements for Imaging Facilities with the Provision of Off-Site Anesthesia

A facility for NORA should be fully equipped with a reliable oxygen source, resuscitation equipment, emergency drugs, defibrillator, and provision for recovery care along with staff trained in BLS skills. Safety requirements for NORA services are provided as described by ASA have been mentioned in Table 29.5 [32]. All anesthesiologists providing such care should be familiar with the setup and its limitations to plan accordingly.

29.3.4 Goals of Anesthesia

The goals of providing sedation/anesthesia in imaging suites are mainly to ensure safety and comfort while providing anxiolysis, analgesia, and immobility pain control and control of excessive movement. The AAP has defined the goals of sedation as mentioned in Table 29.6 [33].

29.3.5 Indications of Anesthesia/Sedation

Parental reassurance (along with some reward as an incentive), swaddling, feeding, warmth, quiet atmosphere, and giving sucrose can be sufficient

Table 29.5 Safety requirements for the imaging facilities [32]

ASA guidelines for non-operating room anesthesia
• Full compliance with safety and building codes • Sufficient space for the anesthesia care team • A means of reliable two-way communication to request assistance Constant supply of oxygen with a reliable backup source and gas scavenging • Safe electrical outlets and suction • Adequate monitoring equipment and self-inflating resuscitator bag • Adequate illumination with battery-powered backup • Emergency cart (with a defibrillator, Emergency drugs, and other emergency equipment)

Table 29.6 Goals of sedation as defined by AAP for children undergoing diagnostic/ therapeutic procedures [33]

Goals of sedation:
• To minimize any physical discomfort and psychological trauma
• Anxiolysis, amnesia, and analgesia
• Maximize patient safety
• To restrain abnormal behavior and/or any motion and allow safe procedural completion
• To ensure complete recovery of the patient and allow safe discharge is possible

to allow short, painless procedures to be performed in young infants and children without any sedation [34]. Moderate sedation would suffice for CT scanning with the latest multi-slice scanners which allow rapid image acquisition. However, MRI is very noisy and involves lying still in an enclosed space for a prolonged time, and can be frightening for children. Hence, the majority of infants and toddlers and some older anxious children undergoing complex or prolonged examinations would require to be anesthetized [12, 33]. General anesthesia (GA) is increasingly gaining favor among radiologists because it ensures optimal conditions and reduces failure rates for imaging in children. A large prospective study on compared children undergoing MRI or CT scan receiving either sedation or general anesthesia, found sedation to be incomplete in as high as 16% of cases and it failed in 7% patients whereas while all scans under GA could be completed [3]. It has been observed that the failure rates are drastically low when experienced anaesthesiologists provide sedation, clear protocols are in place and a team dedicated to the facility provides sedation [25]. Lighter plane of anesthesia generally needed for these procedures may have higher airway complications (e.g., laryngospasm, coughing, etc.) that may require urgent treatment and alteration of anesthetic depth [10, 12, 26].

29.3.6 Monitoring

Standardized ASA monitoring guidelines apply when providing anesthesia for NORA (pulse oximetry, capnography, electrocardiogram, non-invasive blood pressure, and the constant presence of a trained person) [33, 34]. All deeply sedated patients and those moderately sedated patients whose visibility or access is hampered, e.g., during an MRI should be monitored using exhaled carbon dioxide ($EtCO_2$) [10]. Body temperature alterations may be seen in young children during prolonged MRI examination and monitoring is indicated in them [35]. Recent advances in NORA monitoring have made closed-circuit monitoring of the patient possible and improved safety to a large extent as compared to the previously done remote monitoring of the patient from the control room through a transparent window [36]. This consists of two cameras (controlled by switches next to the television screens which allow individual control of zoom and focus)to provide visual monitoring. In this setting, one of the cameras is focused on the patient for monitoring respiratory efforts and the absence of unwanted movements. Another camera is directed upon the monitors which are relayed to a screen outside the scan room. In a patient who is receiving GA, the patient camera can be zoomed out to include the anesthesia machine and ventilator in the field of vision. Remote audio monitoring of an oesophageal stethoscope has been reported but not widely practiced [37]. Documentation of the consent and monitoring data and post-anesthesia care instructions are as important for sedation procures as for GA.

29.3.7 Monitoring and Equipment Concern Specific to MRI

Any electromagnetic equipment producing radio frequencies will interfere with image acquisition by MRI and similarly, RF produced by MRI scanners can interfere and make it difficult to monitor the patient [2, 3, 9, 10]. All monitoring and other anesthetic equipment including the anesthesia machine should therefore be MRI [10, 29, 37]. All oxygen or IV tubing, monitoring wires, and equipment cables should be padded and direct contact with the patient's skin is carefully avoided [38]. recently, several manufactur-

ers are making MRI-compatible anesthesia machines as denoted by the equipment label of MRI safe/conditional(e.g., BleaseGenius MRI anesthesia workstation which is safe with MRI strength up to the 1000-Gauss) [10, 37]. The MRI suite setup configuration should allow the anesthesiologist to maintain an unobstructed view of the patient, anesthesia machine, and monitors from a control room, either by direct observation or a video monitor [10, 21, 31]. Radiofrequency currents induced by blood flow through the arch of the aorta may produce ECG artifacts mimicking hyperkalemia [39]. Hence, MR-compatible electrodes should be applied to the patient's chest in a narrow triangle, leads should be braided and short [21, 31, 40]. Newer MRI safe ECG and pulse oximeter use either wireless transmitters or fiberoptic cables to eliminate the use of long conductors that are transmitted to a remote display unit [10, 21, 29, 37, 39]. Capnography signal may be delayed up to 20s due to the longer length of the sampling tubing [10, 29]. Monitoring cables can be passed through the waveguide ports to facilitate remote patient monitoring with MR incompatible equipmenmt [10]. Noise made by the MR scanner may obstruct audio alarms and therefore, all alarms should be visual. Hearing impairment can occur to the staff chronically exposed to loud noise from the MR machine and should use earplugs.

29.3.8 Anesthetic Management of the Patient During CT/MRI

The greatest source of concern is the considerable distance between the anesthesiologist and the patients. When possible, the anesthesiologist should remain at least 0.5–1 m from the bore of the scanner and should move slowly when it is necessary to be near the bore [2, 9, 39]. Neonates can develop increased episodes of hemodynamic instability and decrease in oxygen saturation levels during MRI [41]. Rapid motion in the strong magnetic field near the MRI scanner produces an electrical current within the body, which may cause symptoms such as nausea, vertigo, headache, light flashes, loss of proprioception, or a metallic taste in both patients as well as the anesthesiologist [9, 10]. Open communication is essential between care teams in these procedures. CT suite poses a radiation hazard to the caregivers while in the MRI suite staff needs to be careful about excluding any ferromagnetic objects before entering zone IV of the suite as mentioned earlier [42]. The imaging study may need to be terminated at any time to allow safe entry of caregivers in case of emergency and initiation of resuscitative efforts by the staff in the vicinity [2, 3, 43]. The patient should be immediately shifted to an MR safe location for subsequent treatment.

29.3.9 Equipment Check

One can follow the "SOAPME" acronym [33] -S (suction): suction catheters of apposite size and a functional suction machine, O(Oxygen): dependable oxygen source along with backup emergency oxygen supply, A(Airway): appropriate size airway equipment, P(Pharmacy): emergency anesthesia drugs, M(monitors) and E(Equipment). Apart from these, MRI compatibility of all anesthesia delivery and monitoring equipment should be carefully checked for MRI scans [10, 38].

29.3.10 Airway Management Concerns for CT/MRI Anesthesia

Airway management during an imaging study under anesthesia is unique due to the restricted approachability of the patient's airway and difficulty in visual and auditory assessment (due to the darkroom, physical distance) [2, 3, 10, 29]. The anaesthesiologist should have a backup plan to manage the airway related issues (e.g., apnoea, obstruction, hypoventilation, secretions, laryngospasm) during the MRI [10, 33]. One should avoid deeper levels of sedation in patients with an anticipated difficult airway (Table 29.7) [2, 3, 29, 33, 42].

ASA task force cautions that in patients with risk of airway compromise, a more definitive airway should be established (e.g., intubation or

Table 29.7 Causes of difficult airway management during sedation in imaging suite [2, 3, 29, 33, 42]

Condition	Examples
1. Airway abnormality	Enlarged tonsils, anomalies of the upper or lower airway, history suggestive of obstructive sleep apnoea (OSA), nasal obstruction, etc.
2. High risk of respiratory failure	Neuromuscular disease, Drowsy patient, severe respiratory illness, heart failure, severe pulmonary hypertension, etc.
3. Risk of pulmonary aspiration	Cases with increased intracranial pressure, comatose patient, obstructed bowel, pneumoperitoneum, ascites

supraglottic airway insertion) before the patient's airway becomes less accessible during the scan [10]. If the patient's airway is to be managed near the scanner, it is also necessary to use MRI safe laryngoscope(lithium batteries and plastic laryngoscopes), stylets, and stethoscopes. Airway management using complex equipment like a fiberoptic bronchoscope should preferably be done in a controlled setting outside zone IV.

29.3.11 Anesthesia Techniques and Drugs

Regardless of the type of anesthesia selected, the patient must remain immobile for the procedure since even very small movements cause image artifacts. Maintenance of anesthetic depth sufficient to prevent movement may be challenging. The majority of patients who require anesthetic intervention for CT scans can tolerate the procedure with only monitored anesthesia care (MAC) due to the brief duration and lack of any painful stimulus. A patient's inability to cooperate due to young age, delirium, agitation, or extreme claustrophobia may necessitate relatively deep sedation. Deep sedation is not advisable and may result in hypoxemia, hypercarbia, or airway compromise, especially in obese patients or those with OSA [10, 33, 44]. ASA has defined various levels of sedation ranging from minimal sedation (anxiolysis) to deep sedation depending on the maintenance of the patient's responsiveness, airway patency, respiratory, and cardiovascular functions [26]. The quality of sedation may be differentiated into anxiolysis, hypnosis (from sleepy to unconscious), and amnesia. To each of these components, analgesia may be added during painful procedures.

29.3.12 Medications for Sedation and General Anesthesia

When oral drugs are used (e.g., benzodiazepines, chloral hydrate), one should wait adequate time for its action before considering supplementation. Midazolam is effective orally in doses of 0.25–0.5 mg/kg [45, 46]. Its combination with ketamine (2–3 mg/kg) and atropine (and 0.2 mg/kg) is an effective regimen for oral sedation and may be sufficient for very short non-stimulating procedures like CT scan in some children. However, in most cases, intravenous sedatives are required to provide reliable hypnosis and immobility. Anaesthesiologist may prefer the various combination of midazolam, propofol, ketamine, fentanyl [25, 30, 47–49]. Prophylactic antiemetic therapy with ondansetron (0.1 mg/kg) should be given because of the increased risk of emesis due to concomitant chemotherapy and stress [20]. The various routes and doses of commonly used sedatives/anesthetic drugs have been mentioned in Table 29.8.

Doses should be carefully titrated. Antagonists (naloxone and flumazenil) should be available [53]. Intravenous access secured and maintained throughout. IM route for the administration of drugs is not desirable due to the trauma and associated pain. A large majority of these patients would be receiving chemotherapy and have a chemo port in place which can be accessed using a Huber needle [19, 36]. Strict aseptic technique is critical while handling the chemo port or placing an IV line because the children may be immunosuppressed due to RT/CT or their primary disease [19]. EMLA cream can be applied to the site one hour before the procedure to reduce the pain [24, 36]. Various commonly used sedative agents have been described below:

Midazolam: IV midazolam has been the foundation for pediatric sedation since its introduc-

Table 29.8 Pharmacologic agents for sedation and anesthesia outside the operating room

Drug	Dose (various routes)	Mechanism of action	Anesthetic effect
Midazolam [29, 45, 46, 50–52]	PO: 0.5–1.0 mg/kg IV: 0.05–0.15 mg/kg IM: 0.1–0.2 mg/kg IN: 0.1–0.2 mg/kg	GABA receptor agonist	Anxiolysis, Sedation
Chloral hydrate [36, 46]	PO: 25–50 mg/kg	Unknown	Sedation
Fentanyl [29, 36, 46, 51, 52]	IV: 0.5–2.0 μg/kg IN: 0.5–2.0 μg/kg IM: 50–100 μg/kg	Opioid receptor agonist	Sedation and analgesia
Ketamine [46, 53]	PO: 3–6 mg/kg IV: 0.5–2 mg/kg IM: 2–6 mg/kg Rectal: 5–10 mg/kg	NMDA receptor blocker	Analgesia, sedation, dissociative amnesia & anesthesia
Dexmedetomidine [50, 54, 55]	Bolus: 0.5–1.0 μg/kg over 10 min; Maintenance: 0.3–0.7 μg/kg/h	Central α-2 receptor agonist	Sedation, analgesia, anxiolysis, sympatholytic effect
Remifentanyl [53]	Bolus: 0.5–2 μg/kg Infusion: 0.025–0.1 μg/kg/min	Opioids receptor agonist	Sedation/ analgesia
Etomidate [46, 56]	IV: 0.2–0.4 mg/kg	GABA-A receptor agonist	Sedation/general anesthesia
Propofol [46, 53, 57]	IV: 1.5–2.5 mg/kg Infusion: 6–12 mg/kg/h	GABA-A receptor facilitator	Sedation/general anesthesia
Fospropofol [50, 58]	IV: 6.5 mg/kg Repeat dose: 1.5–2 mg/kg	Propofol prodrug	Sedation

GABA, gamma-aminobutyric acid; PO, oral; IN, intranasal; IM, intramuscular; IV, intravenous; NMDA, *N*-methyl-D-aspartate

tion due to its excellent safety profile along with good anxiolytic and amnesia properties. Therefore, in controlled settings with adequate monitoring, even non-anaesthesiologists can use it to provide sedation. Midazolam is a very useful anxiolytic premedication before the procedure and allows easier parenteral separation from the parents in the case of children [50, 51]. A small initial dose of 0.05 mg/kg IV may calm the child to allow the placement of monitors. Later, more potent sedatives, e.g., ketamine/propofol may be added to allow completion of the procedure, or midazolam can be re-administered (total dose of 0.2 mg/kg) [59]. It also decreases the incidence of post-procedure delirium due to ketamine [47]. Benzodiazepine antidote flumazenil should be available to promptly reverse its overdose [45].

Propofol: Propofol is the mainstay of pediatric procedural sedation [50, 53, 57]. Propofol either alone or combined with other agents like midazolam/fentanyl provides excellent scanning conditions. After a midazolam premedication to calm the child, a small propofol bolus (0.5–1 mg/kg) provides adequate sedation for safe positioning and application of restraining devices to the child while maintaining airway patency. Continuous infusion of propofol (6–10 mg/kg/h) is then begun for the rest of the procedure [50–53]. Subsequently, anesthesia depth can be regulated by stepping up or down by increments or decrements of 0.5–1 mg/kg/h [59]. Rapid recovery is the norm with spontaneous eye opening usually seen within 4 min of stoppage of the infusion [53, 57]. Onco-patients on chemotherapy usually have a chemo port in place and pain on injection with this central access port is not a concern.

Ketamine: Ketamine is another popular drug in pediatric sedation practice. It is usually administered after midazolam premedication. It is usually given in the dose of 0.5–0.75 mg/kg initially followed by further small increments of 0.25 mg/kg as required. It is rarely administered as an infusion in the dose of 25 mg/kg/h [50, 51, 53].

29.3.12.1 Newer Anesthetic/ Sedative Agents

Dexmedetomidine: It is the newer more specific α-2 receptor agonist which is now increasingly being preferred for use in the MRI suite due to its beneficial properties of anxiolysis, analgesia, sedation while avoiding respiratory depression thus improving safety [50, 51, 54, 55]. The main disadvantage of its use is that its administration to pediatric patients is still considered an off-label usage and that the initial bolus administration requires 10–15 min [53].

Fospropofol: It is a progenitor of propofol that has recently been FDA approved for procedural sedation by trained practitioners [50, 58]. Fospropofol is broken down to propofol, formaldehyde, and phosphate in vivo. The recommended dose is an initial bolus 6.5 mg/kg, followed by repeat doses of 1.5–2 mg/kg as needed every four minutes. It is very safe with only minor side effects in clinical studies [50, 58]. Only consistent side effect is a tingling or burning sensation in the genital and perianal area while pain on injection is not a concern, unlike propofol. However, its use in children is also considered off-label currently [58].

29.3.13 Target-Controlled Infusion (TCI)

This system for drug administration uses weight-based simple mathematical calculations to automatically administer a bolus dose and infusion rates using a computerized infusion pump [60].

Propofol TCI A computerized pump can be programmed to administer propofol automatically to achieve a target (plasma) concentration (or plasma concentration) and effect site (brain) concentration of 2.5–3 μg/mL (corresponding to infusion rates of 6 mg/kg/h) [60, 61]. If a greater anesthetic depth is desired, the target level can be increased in small increments (e.g., to 3 μg/mL) [60]. If a shallower depth of anesthesia is desired and the target concentration is reduced (e.g., to 2 μg/mL), the computer automatically stops the infusion briefly and then starts it again at a lower target concentration. A major limitation with TCI is that there is a delay in equilibrium between plasma and brain concentrations [61]. Because the anesthetic drug effect is in the central nervous system, TCI with effect site models is better. With these models, an overshoot in plasma concentration occurs initially (to account for the quicker equilibration to effect site in the brain) and with every increase in target concentration, to create a stronger drug gradient from plasma to brain, and thereby a more rapid effect can be achieved. Multiple models are in use for propofol, of these Paedfusor and Kataria are most commonly used [61]. TCI models are not yet available for infants [61, 62]. The Paedfusor model has been prospectively tested in TCI mode [63].

Remifentanil TCI In the case of remifentanil, only the Minto model of TCI that considers patients' weight, height, and age for plasma concentration modelling are used. For maintenance of analgesia during surgery, a remifentanil infusion of 0.1 μg/kg/min will correspond to a target concentration of about 2.5 ng/mL [64]. When remifentanil is used as an infusion in doses of less than 0.1 μg/kg/min, spontaneous respiration often can be retained, as during endoscopic procedures. However, during surgery, usually, a dose of 0.2–0.5 μg/kg/min (equivalent to ES concentration of 5–12 ng/mL) is needed [64]. To tolerate a laryngeal mask insertion, a rule of thumb is to ensure a dose of 2 μg/kg (≈ effect concentration of 6–8 ng/mL) is administered over 2–3 min, whereas for intubation without muscle relaxant, a dose of 3–4 μg/kg (equivalent toES concentration of 10–12 ng/mL) is needed. When using these doses, however, the ventilation needs to be controlled, because hypopnea and apnea are common. Propofol and remifentanil can be mixed in the same syringe (concentrations of 2.5–10 μg of remifentanil per milliliter of propofol) for ease of delivery depending on the clinical situation [61]. The combination of agents is not recommended for patients under 10 kg or when individual agent titration is required [61].

29.3.14 Patient-Controlled Sedation

Patient-Controlled Sedation (PCS) has a concept similar to that of patient-controlled analgesia. An infusion pump attached to a reservoir delivers an infusion of a sedative drug to the patient. A predetermined bolus is injected when the patient presses a button. This is followed by a lockout period. The endpoint is when the patient is comfortable enough to tolerate the procedure. Most PCS systems involve the delivery of a mixture of propofol and other short-acting drugs, e.g., remifentanil//fentanyl/midazolam. The natural advantage and in-built safety in the system are that over-sedation is avoided and thereby the risk for respiratory obstruction has been prevented [65]. This method of sedation delivery has not been popular in the pediatric population probably due to lack of cooperation in young children and supporting literature.

29.3.15 General Anesthesia (GA)

Indications: Patients requiring deeper levels of anesthesia should receive GA with airway control especially if the patients are not fasting are neurologically impaired, have anticipated difficult airway, developmental delay, behavioral disturbances, cardiac or respiratory instability, or certain procedures where immobility is desired, e.g., eye scan or lung scan [59, 66].

When GA is required, the induction agent should be selected depending on the duration of the procedure. A neuromuscular blocking agent (NMBA) may be unnecessary. A supraglottic device such as the LMA is favored for these procedures [66, 67]. MRI-compatible ETT/ LMA is mandatory for MRI scans [10]. If a general anesthetic is necessary, induction may be accomplished inside the CT suite. For MRI procedures, induction of general anesthesia and establishment of airway access is typically completed in a holding area near the MRI suite, with subsequent transportation of the unconscious patient into the MRI suite [10, 22]. The patient must remain immobile throughout the scan since even small movements cause artifacts in the image [3]. Typically, a relatively light anesthetic depth may be maintained since there are no painful stimuli. If necessary, the scan can be interrupted to allow the anesthesiologist to enter the scan area to assure airway patency and/or administer an NMBA to maintain immobility.

Either an inhalation anesthetic technique, total intravenous anesthesia (TIVA), or a combination of the two may be employed to maintain general anesthesia [22, 59, 68].

Inhalational Technique If an inhalation anesthetic technique is employed during MRI scanning, the use of an MRI safe/conditional anesthesia machine with sevoflurane vaporizer is ideal [10, 59]. Sevoflurane is the usual choice since there are no MRI safe/conditional desflurane vaporizers [22, 68, 69]. In neonates up to 4% Sevoflurane in oxygen whereas in older children up to 8% increased gradually is used [46]. In absence of an MRI-compatible anesthesia machine, a normal machine placed in Zone III with an elongated breathing circuit through a "wave guide" (copper-lined conduit that maintains radiofrequency isolation) may be used [2, 10, 22, 59].

TIVA Technique A TIVA technique propofol using oxygen with nasal cannula is a reasonable alternative to an inhalational anesthetic and preferred choice for many anesthesiologists [59]. This technique is reliable, titratable, and preserves spontaneous ventilation. During MRI scanning, MRI safe/conditional infusion pumps are used to administer the anesthesia and an MRI safe/conditional ventilator or other equipment to provide positive pressure ventilation should be available [10]. If these are not available, multiple lengths of IV tubing are used to connect the patient in the MRI suite to MRI unsafe infusion pumps that are located in the control room. However, awakening and movement are a possibility, if occlusion of the IV tubing or catheter occurs as the pressure occlusion alarm may be delayed due to the length of the tubing.

29.3.16 Management of Emergencies in Radiation Suite

The initial response to any medical (contrast reaction, cardiac arrest) or environmental (fire, quench) emergency is often delayed due to the remote location of the facility and restricted availability of additional personnel or equipment during an emergency.

29.3.16.1 Management of Cardiopulmonary Collapse/ Arrest in MRI Suite

In case of a serious medical emergency, the anesthesiologist should immediately call for help, relocate the patient from zone IV while simultaneously initiating CPR as per standard AHA algorithms [10, 42]. A delay in the institution of life-saving measures may occur due to the need for removal of the patient from the scanner and relocation to a nearby environment. The resuscitation zone should be close to zone IV and have fully stocked with resuscitation equipment defibrillator, monitors, and a crash cart that includes resuscitation drugs, airway equipment, oxygen, and suction [2, 10, 21, 31]. For pediatric cases, responding personnel subspecialized in pediatric resuscitation should be immediately available [21, 59].

29.3.16.2 Adverse Reactions to Iodinated Contrast Media

Up to 3% of patients who receive non-ionic, low osmolarity contrast medium develop some form of reaction to it, though life-threatening reaction occurs only in 0.04% [70, 71]. Reaction to ionized contrast media can range from mild to immediately life-threatening. It is more common in patients at extremes of age, previous history of bronchospasm, allergy, cardiac disease, and those on treatment with beta-blockers and nonsteroidal anti-inflammatory agents [72]. Symptomatic patients need to be treated with corticosteroids and antihistamines. Patients with a previous history of contrast reactions may be administered prophylactic corticosteroid (prednisolone 50 mg or equivalent steroid 12 and 2 h before the contrast procedure along with diphenhydramine 50 mg just before the procedure.

29.3.16.3 Fire Emergency

Radiofrequency energy from the magnet can cause tissue or device heating and can also induce currents in conductors such as (ECG) leads, equipment cables, or fluid-filled tubing [21, 31, 39]. This may lead to skin or other tissue burns, and in rare cases, even fire may result. Therefore, MRI-compatible ECG leads should be used, and equipment cables and IV tubing are not positioned directly on the patient's skin [39]. MRI staff should have-designated fire management roles that have been assigned and practiced beforehand and in case of any such fire emergency, everyone should perform as a team as described in the ASA practice advisory for the prevention and management of OR fires [73]. Every such off-site facility should have a preformulated and documented plan to deal with such a mishap.

29.3.16.4 Projectile Emergencies

All MRI suites should have a preformulated plan to tackle projectile emergencies which should be followed at this occurrence [2, 31, 74]. The scan should be discontinued, and the patient should be immediately removed from the magnet room. A controlled quench is performed to remove the patient from the bore [10]. All precautions for entering the zone IV still apply even after quench as strong static magnetic fields may persist after a quench [31]. Any medical emergency should be managed as indicated in the individual patient [74].

29.3.16.5 Unintentional Quench

A quench is defined as loss of magnet superconductivity with sudden boil-off of cryogenic [–269 °C] liquid helium. Quench is generally intentionally performed in case of any indicated as The most common reason for quench is an intentional magnet shutdown in case of any life-threatening emergency [10, 21, 31]. In an event of the quench, all of the stored energy of the mag-

net is released as heat, which boils off its stored cryogens which are released as gas. In such an event, the magnet's quench duct should vent above the MRI facility into the atmosphere [2, 31]. If improperly vented, the released gas can result in hypoxia to the patient and staff [10, 31]. Although the patient and all staff are evacuated from the scanner room as quickly as possible during a quench, entrance or exit from the suite may not be possible for several seconds due to high pressure against the doors generated by escaping gases. The patient should be immediately administered oxygen after prompt removal from the magnet tube [10].

29.3.17 Recovery Care

The standards of post-anesthesia recovery care after an imaging procedure under sedation/GA should match those in the OR [10, 21, 31]. Provision of oxygen delivery, monitoring, and resuscitation equipment should be there in the recovery area and while on the transport cart. Parental presence should be ensured to calm the child. In the post-procedural phase, all the vital parameters should be continually assessed and properly documented. Immediate availability of personnel trained in basic and advanced life support skills is mandatory [2, 21, 31]. Suitability of discharge should be assessed using modified Aldrete's recovery criteria and post-anesthesia discharge score (stable vital signs, return to a baseline level of consciousness, age-appropriate ambulation, and minimal nausea/vomiting/pain) [75] have been adequately managed. Children should be escorted by a responsible adult and avoid motor activities. Written discharge instructions and contact details in case of any emergency should be provided.

29.4 Summary

Imaging procedures requiring anesthetist-led NORA continue to grow in magnitude and complexity. Safe provision of anesthetic care in radiation suites can be extremely challenging especially in the setting of pediatric malignancy. Awareness of the systemic implications of the malignancy and its therapeutic regimens is mandatory for the safe provision of anesthesia to these patients. One should follow appropriate guidelines for the maintenance of a safe environment for the patient and staff, keeping modality-specific concerns in mind, providing intra and post-procedural monitoring and quality recovery care. All clinicians providing sedation/GA to children should be competent in airway management and resuscitation skills.

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Anesthesia for Endoscopic Gastrointestinal Procedures

30

Anjan Trikha and Preet Mohinder Singh

30.1 Introduction

The endoscopic procedure is being increasingly used for various diagnostic and therapeutic purposes. These procedures not only require an experienced endoscopist but also need monitoring and some form of anesthesia or sedation. There has been an increasing demand for anesthesia services in the gastroenterology suites that range from simple sedation to general anesthesia. The number of endoscopic procedures is increasingly been done at various centers and it was reported that in the USA nearly 6.9 million upper, 11.5 million lower, and 228,000 biliary endoscopies are being performed every year [1]. Another unique fact that underlines the healthcare burden of these numbers is the rate of the requirement of anesthesia or sedation that has gone up for these procedures. A simple literate search yields interesting insight into the change in the practice of sedation for these procedures [2]. Even in the developing world (where anesthesiologists: patient ratios continue to remain suboptimal) more and more facilities are striving to initiate and use regular sedation practices for gastrointestinal endoscopy (GIE) suite.

30.2 Gastrointestinal Procedures an Overview

The complexity of gastrointestinal (GI) procedures has evolved significantly over the last two decades. Most procedures earlier used to be limited to only diagnostic interventions like gastric ulcer detection, esophageal stricture evaluation, etc., however, the present inclination is to perform more and more therapeutic procedures that vary from simple upper and lower GI endoscopy, to complex endoscopic retrograde cholangiopancreatography (ERCP), peroral endoscopic myotomy (POEM).

Further, even the same type of procedure within the domain of endoscopy varies drastically in terms of complexity. In any given scenario the complexity of ERCP demonstrates so many variations that even the American Society of Gastrointestinal Endoscopy has come forward and proposed different levels of clinical complexity [3]. Based on the type of endoscopic intervention and underlying pathology, various anesthetic concerns, and different type of anesthetic management is desirable. This makes the GIE sedation field a unique work field for anesthesiologists.

For the sake of simplicity, major GIE procedures can be divided into:

1. *Upper GI Endoscopic Procedures*

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As already discussed they can be diagnostic or therapeutic or even combined in nature. The general principle remains to visualize the oropharynx, esophagus, stomach, and proximal duodenum. The endoscopist does this in real-time assessment and interprets the findings seen. The salient points relevant to the anesthesiologist for upper GIE include-

(a) *Shared Airway*
As the scope is introduced from the oral cavity the airway proximity to the anesthesiologist is often challenging to maintain. The scope negotiation needs manipulations that may further hamper the anesthesiologist's access to the airway and delay any intervention that may be warranted. Intuitively, airway complications continue to remain the number one cause of mortality or morbidity of patients undergoing upper GIE [4].

(b) *High Probability of Aspiration*
As a part of the procedure to improve the visualization of upper GI the endoscopist may often need to insufflate the upper gut using carbon dioxide (CO_2). This leads to an increase in the intragastrical procedure and thus predispose to gastric regurgitation [5]. Further, many gastrointestinal ailments themselves are associated with a very high incidence of aspiration risk related to poor lower esophageal sphincter tone. One such procedure that has recently gained popularity amongst gastroenterologists globally and in India is POEM [6]. These patients often have high residual stomach content volume and have a chronic history of reflux.

(c) *Technical Difficulties in Monitoring—Breathing*
The insufflation of CO_2 during the procedures limits the use of non-invasive devices using capnography to ensure breathing, and monitoring remains challenging during these procedures. As most often patients are under sedation and not tracheally intubated, any insufflated CO_2 escaping orally can lead to false assurance of breathing when the patient may be apneic. Many trials evaluating the efficacy of various conventional breathing monitors like capnography, plethysmography, etc. have shown that these monitoring modalities are inadequate for effective monitoring [7]. This mandates a high level of concentration and vigilance by the anesthesiologist.

(d) *Radiation Exposure*
Certain procedures under the subset of upper GIE often require the use of radiations. These may include fluoroscopy during the ERCP or high strength of electromagnetic radiations during the Magnetic Resonance Cholangiopancreatography (MRCP). Although, efforts are often taken to minimize the radiation exposure to both patients and the anesthesiologist the complexity of the procedure can often prolong the duration and lead to inevitable very high radiation exposure [8].

(e) *Post-Procedure Nausea and Vomiting*
Although during the procedure most of the gastric contents are sucked out retching after the procedure is a common complaint. This is related to gastric distension that occurs due to continuous insufflation of CO_2 or air during the upper GI. Stretch is known to induce reflex gastric contraction that generates this unpleasant sensation of distension and possible nausea.

2. *Lower GI Endoscopy*
Lower GIE includes preventive, diagnostic, or therapeutic procedures. To prevent and treat the high incidence of carcinoma colon in the western population, the preventive task force recommends screening colonoscopy every 10 years or a sigmoidoscopy every 5 years starting at age of 50 years. This means that implementation of these recommendations would have population-based screening colonoscopies performed at fixed intervals making it one of the most routine procedures. Although lower GIE avoids the airway-related complications associated with upper GIE, It has its share of intricacies-

(a) *Bower Preparation*
Visualization of the lower bowel relies on a well prepared lower gut that needs to be free of stools. Patients often need extensive bowel preparation that can lead to hypovolemia and electrolyte abnormalities (like hypokalemia) [9]. These changes may be further of consequence in patients with ailments related to altered bowel motility like patients with prolonging diabetes with autonomic neuropathy.

(b) *Post-Procedure Abdominal Distension*
Analogous to the gastric distention reported in the upper GIE, the lower bowel remains distended post-procedure. The insufflated gas takes time to clear, till this gas is either passed or absorbed patient's complaints of distension and discomfort. This sensation can be annoying can mask any complication like (perforation or bleeding) that might have occurred because of the procedure or scope negotiation.

(c) *Bradycardia*
Refractory bradycardia has been reported during colonoscopy, this is especially true during the negotiation of scope across the anal sphincter [10]. Adequate patient perperation and good sedation depth before the initiation of the procedure can help avoid this complication.

30.3 Pre-procedure Patient Valuation and Risk Stratification

Pre-procedure evaluation of patients remains one of the most critical preventive steps in predicting and alleviating complications. In general, the same standard evaluation should be in a place that is done for general anesthesia. One must strictly adhere to the American Society of Anesthesiologist's (ASA) guidelines while evaluating these patients.

(a) *Risk Stratification—ASA Physical Status and Interpretation*
Evidence specific to upper GIE suggests that pre-procedure ASA status remains one of the strongest predictors of patient outcomes. Enestvedt et al. in their large retrospective review evaluating outcomes in patients undergoing ERCP reported that the number of complications (or the complication rate) had a direct correlation with the preoperative patient state that was categorized using the ASA physical status. Interestingly, the same study authors suggest that other well-known factors like age failed to attain a statistical significance in a multivariate risk prediction model [11]. This further highlights that ASA status takes precedence over other factors and remains highly reliable.

Having said that, it is important to keep in mind the limitation of ASA physical status classification. The task force states that the abnormalities that can be directly attributed to the cause-related to surgery or procedure should not lead to a step-up of the ASA physical status. In terms of patients undergoing ERCP, the raised bilirubin should not lead to increased ASA physical status—this might seem a bit counter-intuitive. As a result, most therapeutic procedures planed in GIE would underpredict the risks. Patients with higher ASA physical status still takes a significant proportion as compared to lower ASA physical status. This just underlines the fact that one might continue to find sicker patients in higher proportions when compared to patients undergoing general anesthesia.

(b) *Cardiovascular Risk Assessment*
The crux of evaluation again is to follow the standard protocols as for any patient requiring administration of various anesthetic drugs and general anesthesia. Such periprocedural assessment and care have its limitations and caveats. The commonest evaluating tool used is the "Revised cardiac risk index" (RCRI). RCRI uses a six-point scale to grade the cardia risk associated with a procedure. RCRI often predicts the risks in these patients. In the recent ASA cardiac evaluation protocol, the term "Major adverse cardiac events" (MACE) was recently introduced

[12]. One of the predictors used in MACE is the nature of the procedure. As a possible fallacy (or lack of evidence) all endoscopy procedures continue to be classified as low risk. This is underprediction in most cases. Given the increasing number of therapeutic procedures like complex ERCPs, grouping them into low risk is more or less under stating the associated risks.

(c) *Airway Evaluation*
A standardized evaluation of the airway in patients undergoing GIE should history related to airway and airway assessment tools and scoring systems. The conventional use of tools like mouth opening, upper lip bite test, Modified Mallampati (MMP) score, neck movement (flexion, extension), a short neck, or any airway-related abnormalities. Unfortunately, again this standard airway evaluation under-classifies the patients. Most endoscopy procedures are performed under sedation and do not warrant routine endotracheal intubation. Thus in case of airway-related complications during the procedure, one might have to intubate these patients at a short notice or in an emergency. Certain GIE intervention requires the patient to be placed laterally or even prone or semi-prone. Such scenarios remain challenging for airway management and at times emergent tracheal intubation in patients undergoing endoscopy in prone poses challenge. It would be impractical to lose time in positioning the patient supine or ideal position for intubation when the patient is hypoxic. Thus, the MMP grade used for predicting the difficulty of the airway might be an underprediction given the practical needs.

30.4 Drugs Used for Sedation in Gastroenterology Suite

Over the years many drugs have been used for providing sedation for patients undergoing GIE. Discussing all such drugs is beyond the scope of the present text, thus we will be limiting ourselves to popular and well-established choices.

(a) *Propofol—Is it the ideal drug?*
Propofol is a phenol derivative with hypnotic and anesthetic properties. It is by far the most commonly used drug during endoscopy. Many desired properties make it the present drug of choice for endoscopy anesthesia. The key advantages of propofol include

(i) *Rapid Onset*—The peak action of propofol can be achieved within around 90 s. This means that the onset is almost instantaneous. In a busy GIE suite, waiting for patients to get under optimal levels of sedation with other drugs is impractical.

(ii) *Clear-Headed Recovery*—The GIE procedures most often are short procedures residual effects of sedation would always be un-warranted. Patients when woken up after a short duration of propofol-based sedation have a very clear-headed recovery and can meet the discharge criterion rapidly [13]. This again enhances the efficiency of the GIE suite significantly. A common comparison that can be made is with midazolam or even ketamine where post-sedation effects can be a major limitation for patient ambulation.

(iii) *Minimal Effect on Airway Secretions*—Agents like ketamine increase the airway tone and secretions. Such drug-related effects make endoscopic interventions difficult and also possess the risk of airway-related complications. Thus, making propofol a clear choice over these agents. Translated clinically, this would also mean a lower incidence of aspiration and laryngospasms during the procedure—thus enhancing the possible safety and minimizing procedural interruptions.

(iv) *Rapid Recovery*—In modern-day anesthesia, propofol is a nearly ideal "switch on and switch off" drug. Not only do the patients wake up clear-headed but they do so rapidly as well. Within a couple of minutes of discontinuation of the infusion, the patients wake up rapidly.

Studies have shown minimal prolongation in propofol effects especially after short procedures; the context-sensitive half-life is not significantly altered with short infusion durations [14].

(v) *Additional Antiemetic Properties*—As already discussed that the GIE predisposes the patients to increased retching or gaseous distention. Propofol by its antiemetic properties helps alleviate these symptoms.

(vi) *High Extrahepatic Metabolism Ability*—A significant proportion of patients undergoing GIE are likely to have a hepatic compromise. These can present in form of primary hepatic injury (in patients with cirrhosis) or with patients with obstruction in enterohepatic circulation (obstructive lesions of the biliary system). Nevertheless, propofol is known to undergo significant extrahepatic metabolism in the lungs and kidney. This can amount to nearly 30% of the total metabolism in normal subjects. Owing to this unique property the expected rates of adverse events in patients with hepatic injury are significantly lowered.

Although there are many advantages of propofol, there are several disadvantages associated with it. These are-

(i) *Dose-Response Variations*—Propofol is known to show marked pharmacokinetic variations. Reports have documented nearly 10-fold concentration variations across populations with similar doses. A high volume of distribution and differences in metabolism rates are likely to account for these variations seen. Clinically, the predictability of sedation depth thus shows marked variations.

(ii) *Loss of Airway Tone*—Propofol is known to decrease the tone of the upper airway even when used in the doses required for sedation. This would clinically imply that chances of airway obstruction increase in such instances which could have fatal consequences if timely measures are not instituted [15].

(iii) *Apnea*—Propofol is a high ceiling sedative or hypnotic. This means that the dose-response curve is not only steep but also capable of converting sedation to actual general anesthesia rapidly. As a result of these pharmacological variations, patients can become apneic and hypoxic rapidly. Airway and hypoxia-related complications are the number one cause of mortality or morbidity during GIE [16].

(iv) *No Analgesic Potential*—Propofol is a good hypnotic but is devoid of any analgesic potential. Many GIE procedures are associated with pain (sphincterotomy, etc.) thus additional analgesics may be needed during these procedures. This requirement of additional analgesics (usually fentanyl) would increase the sedation potential and could further pose safety challenges.

Other sedatives that have been used for GIE sedation include:

1. *Midazolam*—It is a short-acting benzodiazepine. The primary advantage is the preservation of airway tone and also a high threshold for induction of apnea. Midazolam however fails to match the advantages of propofol as it has very poor dose-response predictability, residual effects, slower onset. Further many studies evaluating midazolam in comparison to propofol have demonstrated poor acceptability by the gastroenterologists as—the number of procedure interruptions is more; patient acceptability is lower and hypoxia rates are not significantly lower [17]. The use of midazolam sedation may be associated with longer recovery duration and thus lowers the turnover in busy GIE suits.
2. *Ketamine*—Many pediatric and adult studies have evaluated the use of ketamine during GIE. The only advantage being the preservation of airway tone and high apnea threshold. However, ketamine falls significantly short when compared with propofol. The major limitations reported include a prolonged post-

procedure residual effect, poor endoscopy conditions, increased airway secretions, and incidence of laryngospasms [18].

3. *Dexmedetomidine*—It is an alpha-2 agonist that has many desirable properties for sedation. Many trials have evaluated dexmedetomidine for GIE sedations and the main advantages reported are—maintenance of airway tone and reflexes, no effect on the secretion volume, and the analgesic effect that is enough for most GIE procedures. The incidence of apnea with its use is almost non-existent. Further, the quality of sedation is comparable to propofol in terms of the post-sedation clear-headed recovery. However, there are many demerits associated with the use of dexmedetomidine that includes—slow onset and offset, more pronounced cardiovascular side-effects (bradycardia and prolonged hypotension) [19].
4. *Fentanyl*—It is a strong mu-opioid agonist that can only achieve desired sedation levels in combination with other (any above agents) rather than when used alone. Thus its use should be restricted to an adjuvant rather than the primary sedative during GI.
5. *Remifentanil*—Remifentanil has also attracted the attention of many clinicians in the GIE world. Most studies have evaluated remifentanil in combination with propofol for GIE and have reported satisfactory analgesia along with rapid wake up times [20]. Trials have reported the ability to provide neuromuscular blocker free sedation when remifentanil even for procedures requiring akinesia [21]. However, like fentanyl, it cannot be used as the sole agent and has been associated with significant bradycardia on the initiation of the infusion [22].

30.5 Drugs for the Future

1. *Remimazolam*
   Remimazolam is a new drug recently introduced to the anesthesia practice and is undergoing Phase II trials. It has useful properties of two of the available and commonly used drugs—remifentanil and midazolam. It has its action on GABA receptors (similar to midazolam) and owing to its ester-based chemical composition (similar to remifentanil), it has organ-independent metabolism. Although it is not presently available in the market for regular use, many recent trials have demonstrated that it has minimal residual effects on prolonged infusions. These desired properties make it a preferred drug for the future for procedural sedation. The other advantageous properties include its rapid onset characteristic and other properties that have been reported are rapid onset and offset with minimal risk for apnoea. The availability of a specific antagonist (flumazenil) adds to its safety even in cases of overdose [23].
2. *Methoxycarbonyl Etomidate (MOC etomidate)*
   This molecule is derived from etomidate that has organ-independent metabolism owing to its ester nature. It is metabolized by plasma esterases and the half-life is not prolonged even in multiorgan damage patients. The concerns with the etomidate of adrenal suppression have not been reported with it owing to its rapid metabolism. However, it possesses the most desired property of etomidate being its cardiovascular stability. This allows it to be used even in sickest patients with hemodynamic compromise (patients in sepsis due to cholangitis) which may not be the case with propofol [24].

30.6 Airway Devices Unique to Endoscopy

As the field of endoscopy has evolved so has the technology associated with it. As most patients often do not need endotracheal intubation many airway devices have been designed to not only enhance the procedural ease but to allow simultaneous airway safety and monitoring. Some of the specific devices include

(a) *Simple Face Mask*
   This is a commonly available mask that derives oxygen supply from the wall mounts and is capable of providing 40–50% fraction of inspired oxygen (FiO_2). It can be used

especially during the colonoscopy. During upper GIE—the access to the mouth may be limited and thus is not a preferred device.

(b) *Endoscopy Mask*
It is a modification of the facemask that provides an airway seal using a cushioned cuff that fits around the facial contours. It has a special port through which the endoscope can be introduced. Endoscopy mask also has side hooks and can be used with a harness thus no additional hands may be needed during its use. Since it provides an airway seal—it can help give positive pressure or continuous positive airway pressure (CPAP) if needed. Further, the ability to introduce an endoscope through the mask makes it a useful device during the upper GI [25].

(c) *DEAS Mask*
It is similar to the endoscopy mask but has an additional port to measure end-tidal carbon dioxide ($EtCO_2$). This adds a vital safety feature with the ability to measure patient breathing during the procedure. Further, it has another port that can help anesthesiologists measure the positive inspiratory pressure as well. All these vital monitoring capabilities make it a unique device for upper GI [25].

(d) *Gastrolaryngeal Tube*
This is a specialized tube designed for complex GI procedures in adults. The tube is designed to have two cuffs. The proximal cuff seals the nasopharynx and allows for ventilation and the distal cuff lies in the esophagus. Once both the cuffs are inflated the system works similarly to a combitube. The tube not only allows for ventilation but also prevents the chances of aspiration via the inflation of the oesophageal cuff. One of the disadvantages reported with this tube is the decrease in the ability to maneuver the endoscope after the introduction [25].

(e) *Hague Airway*
This airway can be applied to the patients' mouth, secured using a strapped and has modification that allows connecting port for measurement of the end-tidal carbon dioxide. These modifications allow the scope introduction easy and prevent the tongue from falling back and causing airway obstruction [25].

(f) *The LMA® Airway for Endoscopic Procedures*
This is one of the recent additions to the armamentarium of airway devices for endoscopy. It has contours similar to the conventional laryngeal mask airway (LMA) but has a much larger port for the introduction of the endoscope. Reports suggest simultaneous ability to ventilate the patient and continuous $EtCO_2$ monitoring with a good trace.

(g) *Nasopharyngeal Airway*
It is one of the simplest yet very effective devices for sedation during endoscopy. Once properly inserted it prevents airway obstruction and allows full oral access to the gastroenterologist. Further, one can connect a Mapleson C circuit to it using an endotracheal tube connector to monitor breathing and provide positive pressure or continuous positive airway pressure therapy (CPAP) whenever needed.

(h) *Endotracheal Tube*
This is the conventional endotracheal tube and is occasionally used in the GI suite. Most patients do not need routine endotracheal intubation. One must consider intubation in situations of the difficult airway or the level of expertise available if intubation may be needed to perform during the emergency. It is prudent to remember that most procedures are carried in odd patient positions (prone, lateral, or semi-prone), if the anesthesiologist is not comfortable in maintaining the airway in these positions pre-procedure endotracheal intubation must be considered. Further, the patient profile may also dictate this decision-when faced with moribund, morbidly obese a low threshold for intubation needs to be set. Certain procedures are associated with a high risk of aspiration (like cystogastrostomy or POEM) these patients need endotracheal intubation as a standard practice. In the end, patient safety must take precedence over all factors and one must not feel obligated not to intubate as a routine. Situational assessments are more critical in such scenarios and no blanket recommendations can be made.

30.6.1 Patient Monitoring

It is recommended that ASA guidelines for minimum monitoring standards must be followed. This includes continuous pulse oximetry, electrocardiogram (with heart rate), blood pressure, and $EtCO_2$. In the practical scenario, $EtCO_2$ does face some limitations in a non-intubated patient. The situation becomes trickier when the gastroenterologists use CO_2 as the gas for insufflation. CO_2 escaping orally may give false assurance that the patient is breathing, thus utmost vigilance is advised especially while monitoring these patients for apnea. Plethysmography can be used as an alternative to assist in the monitoring of chest excursions for continuously monitoring the breathing. Neuro-depth monitoring using sedation approved monitors like SEDLine (Masimo Inc) can help to titrate sedative/Propofol infusion and thus enhance patient safety [26].

30.6.2 Positioning the Patient

Most of the procedures in the GIE suite are performed in positions other than supine. This has both direct and indirect implications for the anesthesiologist. As already stated, the comfort level of sedation providers would vary in managing patients in lateral, prone, or semi-prone positions. Securing the airway in emergencies often would be challenging in these odd positions. Further, it is not uncommon to have post-procedure nerve injuries resulting from nerve compression or stretch during positioning these patients. Thus standard safety principles followed while positioning patients in general anesthesia must be followed in patients undergoing GIE.

30.7 Sedation for Gastroenterology: Time for a Specialized Field

Available literature demonstrates that anesthesiologists who regularly work only in the GIE sedation field perform better. Goudra et al. showed that anesthesiologists specializing in GIE sedation have higher safety rates with lower hypoxic complications [27]. Further, the same authors also went on to demonstrate that more experienced anesthesiologists in GIE have a better turnover rate thus saving valuable operating room time with increased safety [28]. The field of GIE sedation is very unique as patients often are sick yet the procedure is mandatory and cannot be often postponed—thus one has to learn specifically to deal with this unique situation. As an analogy, endoscopy within the domain of gastroenterology now is offered as a separate course and similar should be the case for anesthesiology as well. Frequently the availability of resources outside the operating room is limited yet the patients' complexity is even more thus specialized skill sets can help deliver safer, comfortable, and effective sedation.

30.8 Summary

The endoscopic gastrointestinal interventions are increasingly been done. These procedures require anesthesia services for sedation or general anesthesia. These procedures have peculiar concerns and are not related to underlying disease but also related to airway protection. The anesthesia strategy should be safe with rapid onset and recovery.

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Anesthesia for Onco-Radiosurgery

31

Karuna Puttur Rajkumar, Jon Livelsberger, and Ashish C. Sinha

31.1 Introduction

Cancer management is a multidisciplinary approach. With the advancement in various fields of medical sciences, more safe and effective treatment modalities have emerged over time. Stereotactic radiosurgery (SRS) is one such modality that has found its way into an important management strategy for cancer patients. A large radiation dose is targeted to tumor lesions accurately for optimal destruction of the tumor cells using the minimally invasive technique. It has found its role as a suitable acceptable option for onco-surgeries or conventional administration of standardized fractioned doses of radiation therapy. This technique has been used effectively and safely for a biopsy of the lesions from the brain and the technique is labeled as frame-based stereotactic biopsy (STX). For delivery radiation therapy to body tumors, this technique finds its effective role and is labeled as stereotactic body radiotherapy (SBRT). These procedures can be performed on an outpatient basis. Mortality and morbidity associated with these procedures are known to be very low and postoperative neurological deficits are rare [1].

Although some of these procedures have been performed under local anesthesia by neurosurgeons for brain tumors, anesthetic management of these patients can be very challenging in terms of the bulkiness of the frame placed on the head, transport to multiple locations within the hospital at least three to four times and duration of the procedure itself, which can last 4–6 h. An additional challenge of the head frame is the concern of respiratory compromise during sedation and the need to assist ventilation or intubate. Beyond a jaw thrust, access to the airway is almost impossible.

Radiosurgery has been advocated for various brain lesions including both benign and malignant. The mechanism of action of SRS is via radiation-induced damage to the DNA of tumor cells. This impact leads to the prevention of further division of cells, which in turn leads to tumor lesion shrinkage. Various tumors that have been managed with radiosurgery like gamma knife are gliomas, astrocytomas, chordomas, meningiomas, chondrosarcomas, etc. SRS has also been used for metastatic brain tumors. Many such interventions are offered for patients who do not have other modality of definitive management. They may be meant as a treatment or can be purely palliative [1].

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31.2 Stereotactic Radiosurgery Procedures

The SRS can be done using various available modalities. Some of these commonly used includes Gamma Knife, and linear accelerators-based systems—LINAC (e.g., cyberKnife).

Gamma Knife: The process of Gamma Knife based SRS includes four phases. These are the placement of the head frame, locating tumor by imaging, computerized planning of radiation dose, and finally delivery of the planned calculated dose to the tumor lesion. This procedure obtains the portion to be radiated by imaging from magnetic resonance imaging (MRI) (before frame placement) and Computed tomographic scan (CT) (after frame placement) and static delivery of the radiation is done [1] (Fig. 31.1).

LINAC: The linear accelerator-based SRS is procedurally like Gamma Knife and the steps of its final delivery as described for Gamma Knife. This modality has become more popular and is being used clinically for many tumor managements. For this procedure, the focused delivery of radiation beams from different angles to predetermined brain lesions is done by rotatory gantry around the patient.

Proton beam (charged particle radiosurgery): The proton beam radiosurgery is a newer addition of SRS in the armamentarium to cancer management. It has found its role in the management of brain cancers and is used as a single-session modality of SRS or fractionated multiple session stereotactic radiotherapy [1].

31.2.1 Perioperative Considerations

Many parameters may affect the overall outcome of SRS. The age of the patient is such an important parameter (pediatric versus adult for anesthetic management). These patients may be on long-term chemotherapy which, expectedly, has significant adverse effects on various organ systems and there is a potential for adverse reactions being exaggerated by certain drugs employed in anesthetic care, especially volatile anesthetics and high oxygen concentrations [2]. The effect of various chemotherapeutic agents on different system of the body has been discussed elsewhere in this book.

Previous radiotherapy or surgery can cause limited neck extension and rigidity of the oropharyngeal tissues which could lead to difficult face mask ventilation and airway intubation.

Fig. 31.1 Imaging for correct frame placement

31.2.2 Choice of Anesthesia

The choice of anesthesia for radio-oncosurgery needs to be individualized based on patient assessment and type of intervention being done on the patient.

31.2.3 Local Anesthesia

In adults and older children with a high level of understanding, the frames can be placed after local infiltration of the site with local anaesthetic drugs (lidocaine or bupivacaine), and thereafter the patients are transported to MRI to confirm placement and targeted radiation is delivered. The procedure can last from 4 to 8 h. The patients can receive mild to moderate sedation for the procedure to ease discomfort. However prone position and brain stem lesions can be contraindications for local anesthesia due to the inability to access the airway and increased discomfort to the patient [3]. Local anesthesia is has been considered advantageous over general anesthesia because of its inherent benefit related to the monitoring of neurological status during the intervention. This allows early detection of any neurological insult and thus affects the overall outcome of the patient [4].

31.2.4 General Anesthesia

General Anesthesia is the preferred technique in pediatric populations and also in most adults. The anesthesiologist must always be able to monitor the patient from outside the room. There are several intra- and postoperative complications to be considered with these procedures and include difficult intubation, bronchospasm, increased intracranial pressure, seizures, failure to extubate, and fresh neurological deficits. Studies show an increased incidence of pulmonary complications with general anesthesia and increased incidence of bleeding secondary to increased mean arterial pressure (MAP) with local anesthesia [5].

31.2.5 Anesthetic Management and Technical Challenges

One of the main determinants of successful procedural delivery is an immobile patient. So the decision between general anesthesia versus local anesthesia with optimal sedation is paramount. General anesthesia has been favored over sedation and local anesthesia as it provides an immobile patient while in a stereotactic frame (Fig. 31.2). Previous radiotherapy to the brain also makes the cranial bone osteopenic with a risk of fracture and its consequences if patients move with frame in situ. Also, pin displacement or its puncture through the cranium may lead to neurological injury and also the risk of bleeding leading to an epidural or subdural hematoma [6]. Sedation also carries other risks which include loss of airway integrity, partial or complete airway obstruction, oxygen desaturation, and aspiration requiring emergency tracheal intubation, with all its attendant challenges.

These procedures are initially started in the operating room with the induction of anesthesia, tracheal intubation, and the then placement of the head frame. After induction, maintenance of anesthesia is usually with total intravenous anesthetic agents, usually propofol, since these procedures involve transport to multiple locations within the hospital several times. Also, the use of other agents for sedation and analgesia needs to be added for patient comfort [5]. However, once the frame is in place there is very little stimulation or pain experienced by the patient.

When the MRI/scan is performed, the anesthesiologist is forced to deal with the typical things experienced in remote locations such as limited supplies/additional staff support, etc. The availability of adequate extension tubing and fully charged infusion pumps with backup batteries and chargers is essential for the conduction of a safe anesthetic.

The anesthesiologist must be able to monitor the patient during the procedure and patient transport. The routine monitoring including electrocardiogram, blood pressure, oxygen saturation,

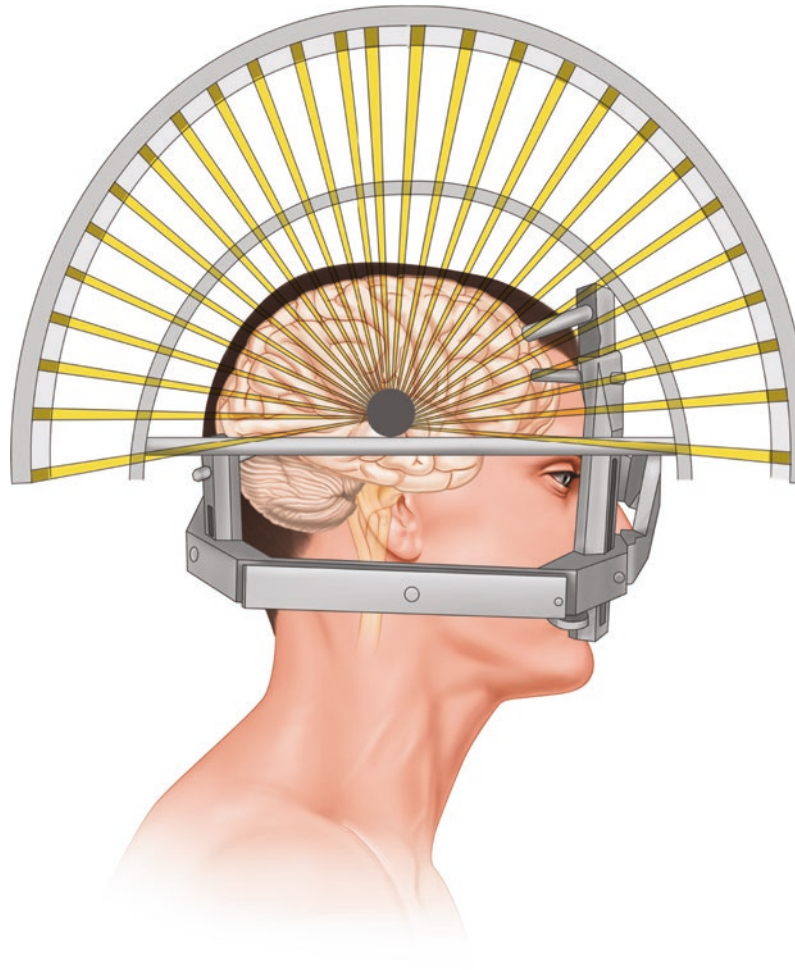

Fig. 31.2 Patient in Leksell frame

temperature, and capnography remains important. The need for invasive monitoring needs to be individualized based on patient assessment. Routine use of invasive blood pressure or intracranial pressure monitoring is no suggested. The most important challenge is limited access to the patient. Limited access to their arms to assess IV patency and when they are in the scanner limited access to the patient's airway. Also, the breathing circuit is often longer than what would be required in the operating room leading to increased dead space ventilation as well as issues estimating end-tidal carbon dioxide ($EtCO_2$) which in a patient with potentially elevated intracranial pressure (ICP) could be deleterious.

31.3 Summary

The SRS is one of the emerging modalities of the management of brain tumors. Peculiar concerns are primarily related to a preexisting neurological condition and early detection of any neurological deterioration during the procedure. The choice of anesthetic technique needs to be individualized with monitoring.

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Part VI

Onco-Critical Care

Onco-Critical Care

32

J. V. Divatia and Jacob George Pulinilkunnathil

32.1 Introduction

Over recent years, there have been several advancements in the early diagnosis and management of cancer. With a better understanding of disease pathologies and better chemotherapy, the overall five-year survival has improved significantly [1]. The intensive care unit (ICU) survival rates in both solid tumor and hematologic malignancies also have significantly improved from 15% to 50% over the recent years despite admitting sicker patients [2–5]. Oncology intensive care has contributed significantly to vital organ support among patients with cancer and treatment-related complications. Earlier considered as a futile attempt, now oncology critical care can be rewarding, with reduced mortality rates and substantial 5-year survival rates, especially if the intensivist can recognize the potentially curable critical illness among cancer patients [6].

32.2 Patient Admission into Oncology Critical Care

The common indications for ICU admission in oncology are outlined in Table 32.1 [7]. All critically ill patients with a reasonable prospect of recovery from their current illness or ailments should be offered critical care support abiding by the basic ethical principles, namely, beneficence, nonmaleficence, autonomy, and social justice [8]. Patients with aggressive malignancies resistant to treatment or in advanced stages of malignancy where the only option remains palliation of symptoms should not be admitted to ICU [9, 10]. Similarly, patients with aggressive graft-versus-host-disease (GVHD), reduced cancer-related life-expectancy (<1 year), and patients with poor performance score within the last 3 months before the precipitating event should not receive aggressive ICU therapies [11].

For those patients in whom the disease control is modest but has a probable control of disease, ICU admission may be considered on a case-by-case basis [12, 13]. Unduly delayed ICU admission may be associated with increased mortality in critically ill cancer patients [14, 15]. Existing screening tools have poor sensitivity and specificity to identify critically ill cancer patients who may benefit from early admission to critical care units [16, 17]. The development of a rapid response team combined with the use of predictive scoring systems and biomarkers such as lactate has proven to be effective in enhancing prompt admission to the ICU but needs further validation [18]. In the absence of accurate prediction systems, the current strategy of ICU admission for the majority of patients is that of a time-limited ICU trial admission. The various

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Table 32.1 Common indications for ICU admission in cancer patients

Medical emergencies unrelated to malignancy	Sepsis and septic shock, diabetic ketoacidosis, dyselectrolytemia, acute respiratory failure, acute myocardial infarction, pulmonary embolism, stroke
Exacerbations of pre-existing comorbid conditions	Chronic obstructive pulmonary disease (COPD) exacerbations, glycemic emergencies, hypertensive emergencies
Malignancy related	Oncologic emergency—tumor lysis syndrome, hyperviscosity, hypercalcemia, airway compromise, disseminated intravascular coagulation (DIC), seizures, and intracranial hypertension
Treatment-related	Chemotherapy-induced toxicities Radiation-induced toxicities Postoperative, after high-risk surgery Postoperative complications such as anastomotic dehiscence, and secondary hemorrhage. Anaphylaxis Cytokine storm Drug-induced coronary spasm or congestive cardiac failure Febrile neutropenia Tumor lysis syndrome (TLS) Differentiation syndrome
Infection related	Neutropenic sepsis Invasive fungal infections Septic shock
Miscellaneous	Transfusion-related circulatory overload Transfusion-related acute lung injury Drug-induced polymyositis

policies practiced for admitting oncology patients into critical care units are as follows [17]:

- Full code—patients are admitted for aggressive life support care anticipating complete recovery and good ICU free survival, for example, newly diagnosed malignancy, cured malignancy, and postoperative patients.
- ICU trial—patients are admitted for aggressive life support with periodic reevaluation, for example, in cases where cure is probable or the therapeutic response to treatment is uncertain. In cases of no improvement after 3–5 days, treatment escalation is withheld.
- Limited ICU Trial—ICU admission for patients with clear advance directives, only for partial life support with no escalation, for example, for procedures as a part of palliative care, not provided in the ward (e.g., noninvasive ventilation).
- Exceptional ICU admission—even in cases that would have been otherwise rejected, ICU admission may be considered at times for the management of acute and reversible causes, for example, dyselectrolytemia, diabetic ketoacidosis and for observation after high-risk interventions.
- Prophylactic admission—for expected tumor lysis syndrome (TLS) or early in course of acute renal failure or in case of anticipated tumor bleeding in high-risk cases.
- Miscellaneous—not fitting in the above criteria, especially when there is a conflict regarding the intention of treatment and treatment goals among intensivist/primary physician/relatives.
- NO admission—the intensivist at times denies admission to patients who are unlikely to benefit from ICU admission, for example, patients with advanced malignancy, who have failed on all possible treatment regimes, and moribund patients.

32.2.1 Trends in Onco-Critical Care

- As the uncertainty surrounding the benefit of critical care in oncology reduced over years, oncologic admissions to critical care units have significantly increased. Current data sug-

gest that oncology patients occupy almost 15–20% of total ICU beds in developed countries and approximately 6% among Indian ICU beds [17, 19, 20]. Over years, there has been a better understanding of disease processes, better preventive strategies, evidence-based management of organ dysfunction, increased use and familiarity with noninvasive modalities for diagnosis and management of acute respiratory failures such as noninvasive ventilation (NIV) and high-flow oxygen by nasal cannula (HFNC), newer antimicrobial agents to combat infections, clear transfusion policies, and early recognition of rare conditions like macrophage activation syndrome and cytokine storm and complications such as drug toxicities [4, 17]. Due to increased familiarity with the common chemotherapeutic agents, the ICU staff are currently capable of administering chemotherapy in patients admitted to the ICU with life-threatening oncologic emergencies such as hyperleukocytosis, TLS, and hemophagocytic lymphohistiocytosis. All these together have reduced the time lag to treatment and has led to a significant reduction in mortality. Currently, ICU survival of oncology patients is at par with any other critically ill patients having comorbidities such as heart failure and liver cirrhosis [21]. More importantly, the patients who survive ICU have been shown to have an excellent quality of life comparable to non-ICU patients [17].

32.2.2 Challenges in Onco-Critical Care

- Cancer patients form a vulnerable group because of their primary disease, chemotherapy/radiotherapy related toxicities and organ dysfunction, immunocompromised status, and in case of cancers of the head-neck region—a physiologically and anatomically challenging airway [1, 7]. At times, they present with oncologic emergencies such as TLS, airway emergencies such as mediastinal masses causing airway compression and airway compromise, obstruction of superior vena cava, metabolic emergencies such as hypercalcemia and hyponatremia, and circulatory complications related to the hyperviscosity states. They are prone to fulminant sepsis due to neutropenic states and otherwise rare complications such as macrophage activation syndrome. Drastic elevations of cytokines like interferon-gamma, interleukin (IL)-10, IL-6 (cytokine storm), and resultant life-threatening complications including capillary leakage, hypotension, and acute respiratory distress are seen in patients receiving chimeric antigen receptor-modified T cells (CART) [22]. Oncological postoperative patients often have a severe inflammatory response due to extensive tissue handling, prolonged surgeries, massive blood loss, and increased blood transfusion requirements. Certain surgeries like pancreaticoduodenectomy and esophageal surgeries are often associated with a stormy ICU course due to surgical complications and medical complications including postoperative respiratory failure [8].

32.3 Critical Care Issues in Oncology

Oncologic emergencies (metabolic or nonmetabolic) are a common cause of ICU admission in oncologic critical care. A brief introduction to the diagnosis and management of these are mentioned below.

32.3.1 Tumor Lysis Syndrome (TLS)

Acute TLS is a serious and life-threatening emergency among patients with aggressive tumors such as Burkitt's lymphoma and leukemias, and some solid tumors [23]. Chemotherapy induces massive cell destruction and release of large amounts of intracellular nucleic acids, phosphorous, and potassium into the circulation. In aggressive and rapidly proliferating tumors, tumor lysis can also occur spontaneously. The nucleic acids are broken down by xanthine oxidase into uric acid, which being water-insoluble,

crystallizes causing acute urate nephropathy, cardiac conduction defects, and gout. Phosphorous binds with calcium, (reducing serum calcium levels dangerously) and form calcium phosphate crystals which in turn can worsen renal failure and urate nephropathy. Dangerously high levels of serum potassium and low calcium together can lead to cardiac conduction defects and death. The kidneys try to handle elevated phosphorous and potassium levels by increased elimination. In cases of acute renal failure, or in cases where the electrolyte levels rise above the kidney's capacity to excrete them, life-threatening arrhythmias can occur. Early identification and adequate hydration (200 ml/kg/day or 2–3 L/m^2—targeting a urine output of 100 ml/m^2) in high-risk cases reduces the severity of tumor lysis. Other medical management includes reduction of uric acid production by allopurinol (xanthine oxidase inhibitors) or urate oxidase inhibitors like rasburicase administration (if not contraindicated) along with potassium-binding resins and phosphorous-binding resins (Sevelamer). Renal replacement therapy might be required in cases of signs of fluid overload or severe life-threatening hyperkalemia. A calcium phosphorous ratio of more than 60 in the setting of tumor lysis syndrome along with worsening renal failure and oliguria also predicts the possible requirement for renal replacement therapy [24–26]. Management of tumor lysis syndrome is outlined in Fig. 32.1.

32.3.2 Hypercalcemia

Approximately 10–20% of cancer patients develop hypercalcemia sometime in course of their malignancy. Hypercalcemia is commonly associated with multiple myeloma, cancers of lung, breast, head and neck region, T-cell lymphomas, renal carcinoma, etc. The clinical presentation is nonspecific with presenting symptoms like confusion, nausea, constipation, polyuria, lethargy, which if uncorrected can progress to coma and death. An increased circulating parathyroid hormone-related peptide (PTHrP), parathyroid hormone (PTH) over secretion, vitamin D overproduction by lymphoma cells, or direct osteolytic destruction of bone by tumor are the major causes for hypercalcemia. Management includes aggressive rehydration, calcitonin for the initial period, followed by intravenous bisphosphonates. Steroids can be tried if the etiology is suspected to be of the granulomatous

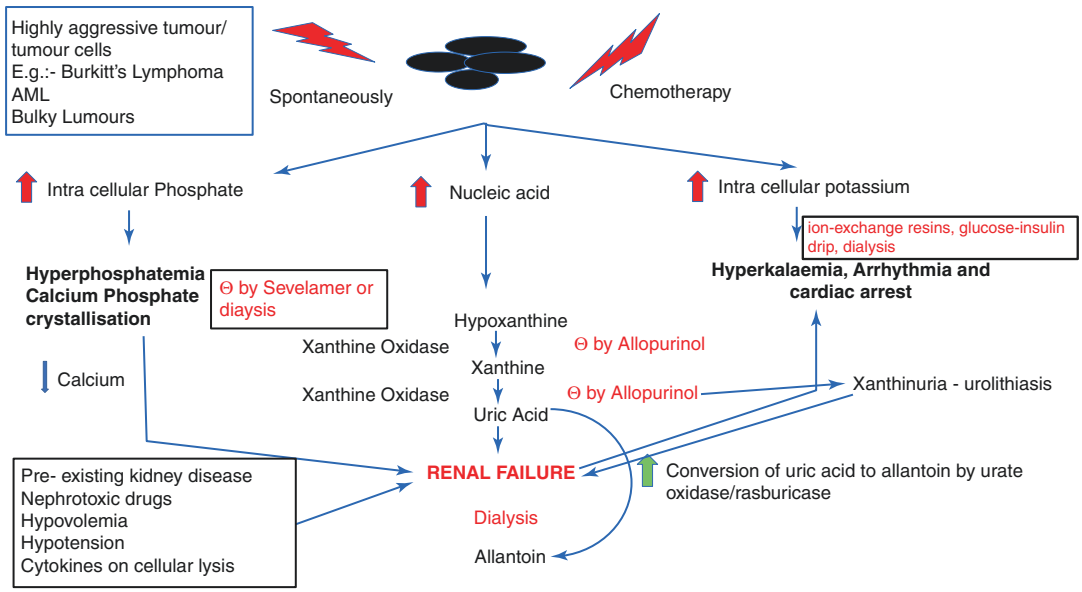

Fig. 32.1 Management of tumor lysis syndrome

origin or if associated with lymphomas. As with tumor lysis, dialysis may be required for metabolic correction if hypercalcemia is resistant to ongoing medical treatment, presence of comorbidities that contraindicate aggressive hydration, or in cases of acute renal failure [23, 24].

32.3.3 Hyponatremia

Hyponatremia is a common occurrence in malignancy and can be either directly related to the disease or therapy. The pathophysiology may be related to the underlying syndrome of inadequate ADH secretion (SIADH) or hypovolemia. At times patients present with acute onset of hyponatremia (of duration less than 48 h) commonly seen among patients with psychogenic polydipsia, after chemotherapy with intravenous (iv) cyclophosphamide, in postoperative patients (due to intraoperative or postoperative administration of hypotonic fluids) or following therapy with laxatives for colonoscopy preparation [27]. The threshold of 48 h is because the brain requires 48 h to adapt to a hypotonic state of hyponatremia by resetting the osmotic equilibrium. After 48 h, the brain is vulnerable to the adverse effects of the acute rise in serum sodium, such as pontine and extra pontine osmotic demyelination syndrome. Cancer patients are at increased risk of demyelination because of associated malnutrition and hypokalemia. Common causes of SIADH in cancer patients include drugs, cancer per se, infections, and other associated causes (Table 32.2) [27, 28]. In ICU, the evaluation of hyponatremia includes acquiring necessary information from histories such as symptoms and duration, clinical assessment of volume status, and laboratory evaluation such as urine osmolality and urine spot sodium, serum osmolality (to distinguish between true and pseudo hyponatremia), and fractional excretion of sodium and urea. A practical algorithm toward the approach to hyponatremia can be adapted from reference [27]. As cerebral edema is a potential killer, for patients presenting with symptoms of raised cerebral edema such as headache, vomiting, confusion, seizures, or altered level of consciousness—irrespective of duration and degree of hyponatremia, treatment should be initiated with 2–4 ml/kg of 3% saline as a bolus over 20 min with repeated dosing, if the patient is still symptomatic and acute rise is less than 10 mmol/day [27].

Table 32.2 Common etiologies of SIADH

Drugs	Cyclophosphamide, cisplatin, vinca alkaloids, methotrexate, cyclophosphamide Valproic acid, carbamazepine, and oxcarbazepine Morphine, NSAIDs Proton pump inhibitors
Infections	Infections like TB and pneumonia, meningitis, encephalitis
Primary malignancy itself	Small-cell carcinoma of the lung, head and neck region, upper gi malignancies (stomach, pancreas, and duodenum), endometrium, bladder, and prostate
Miscellaneous	Pain, nausea, cerebrovascular accidents, general anesthesia, positive pressure mechanical ventilation

32.3.4 Acute Respiratory Failure

Acute respiratory failure (ARF) is the leading cause of ICU admission among patients with malignancy [29]. ARF has an incidence of 5–50% in patients with hematologic and solid malignancies and an increased incidence of 42% up to 88% among hematopoietic stem cell transplant recipients [30, 31]. The etiological diagnosis of ARF are varied and include infections, pulmonary edema, treatment-induced lung injury, diffuse alveolar hemorrhage [DAH]), pulmonary embolism, airway obstruction secondary to disease progression. In postoperative patients, type III respiratory failure may also occur [32].

Pulmonary infections are the commonest cause of ARF in patients with cancer. The majority of the infections are caused by common bacterial agents [33]. Opportunistic infections of the lung such as invasive pulmonary aspergillosis, *Pneumocystis jirovecii* pneumonia, mucormycosis, cytomegalovirus, and other respiratory viral infection are also important etiologies for respi-

Table 32.3 Etiology of ARDS among cancer patients

Pulmonary infection	Secondary causes	Disease/treatment-related	Miscellaneous
Gram-negative and gram-positive bacterial infections Fungal infections including invasive pulmonary aspergillosis *Pneumocystis jirovecii* Viral diseases like influenza Tuberculosis	Secondary ARDS (extrapulmonary ARDS) Secondary to sepsis	Drug-induced and radiation-induced Transfusion-associated acute lung injury (TRALI) Autoimmune Lymphangitis carcinomatosis Pulmonary alveolar proteinosis Bronchiolitis obliterans and organizing pneumonia Hemophagocytic Lymphohistiocytosis Pulmonary leukostasis/leukemic infiltration Postengraftment syndrome	Unclear etiology

ratory failure. Prolonged neutropenia, administration of corticosteroids, broad-spectrum antibiotics, and hematologic malignancies are risk factors for invasive fungal infections. Infections are also the major cause of acute respiratory distress syndrome (ARDS) in these patients although secondary ARDS can also occur following septic shock. The common etiologies for ARDS among cancer patients are shown in Table 32.3.

It is often challenging to come to an etiological diagnosis and the inability to identify an etiology is an independent predictor of mortality [34]. Recently, the practice has changed from invasive investigations like bronchoscopy, bronchoalveolar lavage (BAL), and surgical lung biopsy to noninvasive investigations like high-resolution computed tomography (CT), biomarkers, and molecular tests [35]. The majority of these patients will be at risk of invasive fungal infection due to prolonged neutropenia and multiple antibiotics. Signs such as lobar pneumonia, bronchopneumonia, cavitating pneumonia, feeding vessels, halo sign, and ground glassing with the tree in bud appearance on CT scans aid in supporting the etiological diagnosis of bacterial pneumonia, atypical pneumonia, or fungal pneumonia, tuberculosis, etc. (Table 32.4). None of these radiologic signs (air bronchogram, halo sign, ground glassing tree in bud appearance) are specific or sensitive and need to be correlated with microbiological investigations such as galactomannan and polymerase chain reaction (PCR) of a directed or nondirected BAL [36]. Galactomannan detected in different body fluids with a cut-off of 0.5 is sensitive and specific enough to diagnose invasive pulmonary aspergillosis. As nonneutropenic patients' clear galacto-

Table 32.4 Common radiologic patterns in ARF on CT scan

Radiological signs	Probable etiological diagnosis
Lobar consolidation with air bronchogram	Typical bacterial pneumonia, viral pneumonia
Cavitation	Staphylococcus, Klebsiella, tuberculosis, cavitating malignancy, etc.
Patchy consolidation	Focal atelectasis, organizing pneumonia, atypical pneumonia
Ground glass opacities (GGO)	Pulmonary edema, vasculitis, interstitial lung disease, atypical bacterial pneumonia, viral pneumonia
Miliary pattern	Tuberculosis
Air fluid level	Lung abscess, hydropneumothorax
Air crescent sign	Aspergilloma/fungal ball
Halo sign	Aspergillosis
Reverse halo	Aspergillosis, mucormycosis, cryptogenic organizing pneumonia
Crazy paving	Pneumocystis pneumonia, viral pneumonia
Feeding vessel sign	Septic embolism

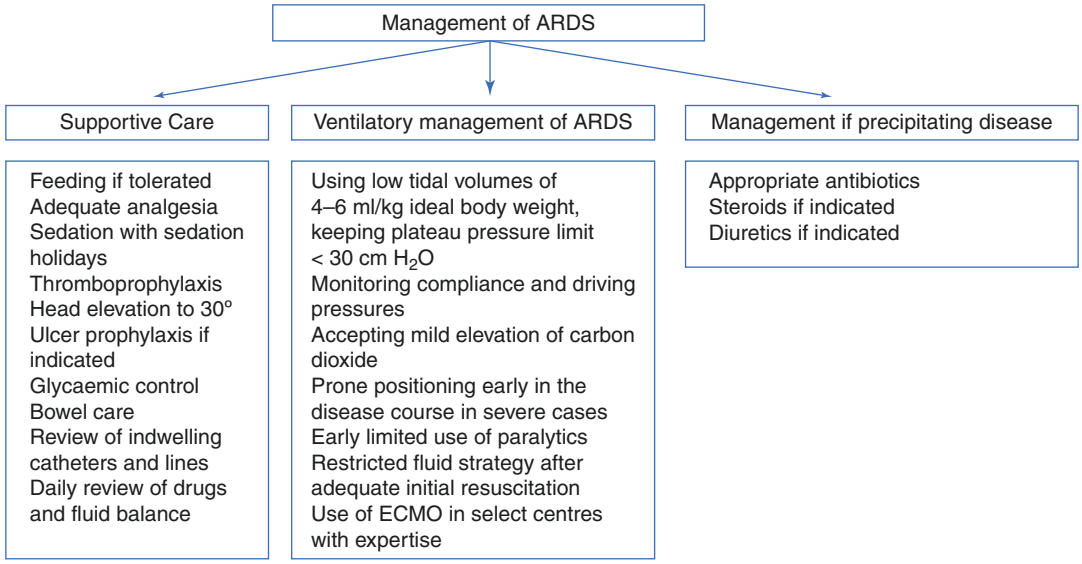

Fig. 32.2 General principles of ARDS management

mannan rapidly from their body, this test cannot be recommended in them [37].

32.3.5 Management of Acute respiratory distress syndrome (ARDS) in ICU

In cancer patients with acute respiratory failure, increased mortality has been observed to be associated with oxygen requirement and the risk exponentially increases if ventilatory support is required. Historically, ARDS among oncology patients had a dismal prognosis and high mortality. With an evolving understanding of disease pathophysiology and the current practice of lung-protective mechanical ventilation strategies, there has been a remarkable drop in the in-hospital mortality of cancer patients with ARDS. With a multimodality approach, including low tidal volumes, limiting plateau pressure to less than 30 cm of water, prone positioning in severe ARDS early in the disease course for prolonged periods, permissive hypercapnia, early but limited use of muscle relaxants, the mortality of ARDS has reduced from 89% to 59%, 63%, and 68.5%, respectively, in mild, moderate, and severe ARDS groups [33, 38]. The general principles of ARDS management are outlined in Fig. 32.2.

32.3.5.1 Role of Noninvasive Ventilation (NIV) in ARDS Management

As mentioned earlier, the initial treatment outcome for ARDS patients requiring intubation and mechanical ventilation was very high and up to the ranges of 80% or more mortality [39]. It was then hypothesized that if respiratory support was provided without intubation, the mortality might fall. Initial small studies hinted at the same [39–41], and NIV was advocated as an initial option to manage ARDS in immunosuppressed patients [42]. This was debated as further trials failed to replicate similar beneficial findings [43]. A multicentric trial from France failed to demonstrate any difference in mortality among early NIV versus oxygen therapy [44]. Similarly, the recently concluded EFRAIM study also could not find any association between NIV and mortality benefits [45]. A gradual but significant reduction in the ARDS mortality over years due to a general improvement in critical care and better ventilation strategies together with the potential harms of high tidal volume and swings in pleural pres-

sure in NIV are the reasons postulated for the discrepant trials [17]. The initial enthusiasm for NIV against intubation has currently plateaued, and current literature suggests overall NIV failure rates of 70%, particularly in severely ill patients [34]. It is currently clear that early NIV does not improve mortality rates nor does it fare better than high-flow oxygen therapy. As NIV failure is a proven risk factor for increased mortality [33], till further studies are available, NIV should be judiciously used in these patients and preferably avoided among patients with moderate to severe ARDS [17, 45].

32.3.5.2 Role of High-Flow Oxygen Therapy in ARDS Management

High-flow nasal cannula (HFNC) delivers 100% humidified oxygen with flow rates up to 60 l/min. These high flows generate a flow-dependent positive end-expiratory pressure (up to 7 cm of water), maintain alveolar recruitment, improve oxygenation, and reduce the work of breathing [46]. Hence, it seems probable that HFNC might significantly reduce intubation rate and mortality in patients with hypoxemic respiratory failure. The FLORALI trial showed a trend toward reduced 90-day mortality in hypoxemic respiratory failure patients (which also included immunosuppressed patients) treated with HFNC compared to those treated by NIV [47]. A retrospective study among cancer patients also suggested a survival benefit with HFNC compared to NIV [48]. Similar results (reduced intubation rates and mortality rates) were also seen in an observational cohort study with HFNC faring better than NIV [49]. A recent meta-analysis of trials looking into HFNC in immunocompromised patients suggests that the use of HFNC improves the outcomes of acute respiratory failure in immunocompromised patients significantly. However, good quality studies that are adequately powered to confirm these benefits are still lacking [50].

32.3.6 Sepsis

Overwhelming infection and sepsis can occur in the setting of oncology as patients are immunosuppressed due to the disease, treatment, and following myeloablative therapy for bone marrow transplant. Mortality of sepsis is associated with the underlying organ dysfunction rather than the characteristics of malignancy such as neutropenia or disease progression [51]. The pathophysiology of sepsis and septic shock remains the same to noncancer patients, and no clinically significant differences in the macrocirculation or the microcirculation have been demonstrated [52]. Oncology patients are usually neutropenic (absolute count of polymorphonuclear neutrophils (PMNs) less than 500/mm^3) due to the disease involvement or treatment complication (chemotherapy and radiotherapy). Profound neutropenia (absolute count of PMN less than 100) and duration of neutropenia for more than 7 days are risk factors for severe infections. These patients seldom mount an immune response to infections, and hence, there is a delay in identifying infections in these patients. Febrile neutropenia (FN) is defined as a single reading of oral temperature more than 38.3 °C (101 °F) or an oral temperature recording of more than 38.1 °C (100.4 °F) sustained over a 1-h period in patients with an absolute neutrophil count less than 500 cells/mm^3 or in whom absolute neutrophil count is expected to decrease to less than 500 cells/mm^3 during the next 48 h [53, 54]. Patients usually present with pneumonia, gastroenteritis, urinary tract, or primary bacteremia. Sepsis is a medical emergency similar to polytrauma, acute myocardial infarction, and stroke. The Surviving Sepsis Campaign stresses early identification and management of sepsis with appropriate measures such as initial hydration (30 ml/kg crystalloids), hemodynamic monitoring, and use of vasopressors and antibiotics. They suggest a 1-h bundle approach that incorporates initial resuscitation with ongoing evaluation [55]. With early identification and improved care, the mortality rate of sepsis has come down and is currently reported as low as 40% in cancer patients [55, 56]. Currently, sepsis is managed in lines with the management protocols of patients without malignancy. Adjuvant G-CSF in neutropenic sepsis, and rather it may worsen the respiratory status due to pulmonary infiltration by leucocytes [57].

The dilemma in the management of this emergency is that all these patients will be either hospitalized or having frequent contact with the hospital and already might have received multiple antibiotics. Hence, these patients are at increased risk for severe infections by multidrug-resistant organisms. The treating intensivist will have to choose the initial empirical antibiotic therapy based on the treatment history, and local antibiogram, and later deescalate according to culture reports and treatment response. Consideration should be given to multidrug-resistant (MDR) organisms, rare opportunistic organisms, and fungal organisms while selecting the initial empirical treatment regime. Patients who present with organ dysfunction and septic shock should be treated with a broad-spectrum agent such as carbapenem or even polymyxins like colistin and polymyxin B, depending on the local antibiogram and the presence of shock and organ failure. Multidrug combination therapy with a third-generation or fourth-generation cephalosporin and an aminoglycoside [53] or meropenem and polymyxin targeting most aerobic gram-negative bacteria may also be used. The empiric gram-positive cover needs to be added if the local incidence of MRSA is high, if patients present with hemodynamic instability, or there are infiltrates on chest X-ray suggestive of pneumonia [54]. Patients in shock or those who fail to improve should be treated with additional antifungal agents such as echinocandins or amphotericin B [54, 58]. Patient characteristics such as neutropenia, diabetes mellitus, chronic renal failure, invasive vascular devices, prolonged broad-spectrum antibiotics, multisite fungal infection, or colonization are considered high risk for invasive candidal infection. If the risk of Candida sepsis is high, empiric antifungal therapy may be initiated on admission itself [59].

32.3.7 Airway Emergencies

Airway obstruction from either local compression by mediastinal malignancies can cause mechanical respiratory compromise requiring ventilatory assistance. Patients present with stridor, dyspnea, hemoptysis, and cough, and some may have features of superior vena cava syndrome. An emergency CT scan of the thorax may help to differentiate among various causes of acute breathlessness and gives an idea of anticipated complications in securing the airway. Bronchoscopy (rigid or flexible depending upon expertise) can also be used as a diagnostic and curative tool. The treatment requires expedited management of the local cause and includes radiation therapy if the tumor is radiation sensitive or chemotherapy for highly chemosensitive malignancies like lymphomas, small cell lung cancers, and germ cell tumors [60]. Thymic tumors can cause myasthenia, as well as exert direct tracheal compression. In such cases, excision of the mass can alleviate the respiratory compromise and cure myasthenia in a significant percentage of patients. These groups of patients require constant vigil of the airway and urgent intubation in case of respiratory failure.

32.3.8 Acute Abdomen

Cardiac dysfunction can result from the mechanical effect of the malignancy on the heart, pericardium, and great vessels. The chemotherapeutic agents used for managing cancer can cause cardiomyopathy resulting in an impaired systolic and diastolic function of the heart. Commonly implicated agents are anthracyclines like doxorubicin, and newer chemotherapeutic agents like trastuzumab [61]. Patients present with arrhythmias or electrocardiography (ECG) changes such as QTc prolongation, breathlessness, or in frank cardiogenic shock. Cardiac failure is managed in similar lines of cardiac failure in noncancer patients with noninvasive ventilation, diuretics, vasodilators, and inotropes. Preemptive treatment with angiotensin-converting enzyme (ACE) inhibitors alone, or in combination with beta-blockers and dexrazoxane has been advocated in preventing cardiac failure among high-risk patients [62].

Radiation-associated cardiotoxicity is usually seen in young patients and presents later in life. The toxicities described include coronary artery disease, regurgitant or stenotic valvular pathologies, dilated

cardiomyopathy, conduction defects, and heart failure with preserved ejection fraction. Pericarditis can occur either acutely or as late as 6 months to 1 year after radiotherapy. Constrictive pericarditis presents with features of heart failure with a calcified noncompliant pericardium. These patients will require pericardiectomy although diuretics may provide temporary symptom relief [61].

Right heart failure and pulmonary hypertension (PH) can be associated with chemotherapeutic agents such as dasatinib or following pneumonectomy. Management guidelines for pulmonary hypertension have been published and treatment includes avoiding hypoxia, aggressive management of infections, diuretics, calcium channel blockers, anticoagulants, and pulmonary artery vasodilators [63].

Malignant pericardial effusion and cardiac tamponade due to massive pericardial effusion occur due to malignancies of the breast, lung, or direct involvement from melanoma or leukemia. Patients present with severe dyspnea and orthopnea and dry cough. Bedside echocardiography will reveal the diastolic collapse of cardiac chambers. Pericardiocentesis or pigtail insertion under image guidance may be needed for symptom relief [23, 60].

32.3.9 Cardiac Failure and Cardiac Tamponade

Abdominal malignancies can produce obstructive symptoms depending upon their location. Bowel involvement can lead to subacute intestinal obstruction, intestinal obstruction, bowel perforation, and can present as a surgical emergency. Local involvement of the gall bladder or biliary tract by the tumor can cause biliary obstruction, cholangitis, and jaundice. Tumor infiltration can cause massive bleeding and present as hemorrhagic shock. Compression of the ureters or bladder can cause hydronephrosis and postrenal kidney injury. The management will depend upon the cause and at times may require emergency laparotomy. Selective angiographic embolization can control tumor bleed, whereas local drainage by stenting such as biliary stenting and ureteric stenting can be done by the interventional radiologist for symptom relief and management. Hence, a good liaison between the surgical team, diagnostic and interventional radiology, and intensivist is required to manage these patients [64, 65].

32.3.10 Central Nervous System (CNS) Emergencies

Primary malignancies of the CNS can present with altered sensorium, seizures, or features of raised intracranial pressure (ICP). Unless intervened urgently, trans-tentorial herniation and death can ensue. The management in these cases remains surgical decompression. However, osmotherapy with mannitol or hypertonic saline, corticosteroids, and good ICU care, including sedation, paralysis, maintaining normothermia, maintaining normoxia, normoglycemia, eucarbia, may help as a temporary measure to reduce raised intracranial pressure. Epidural or bony metastasis from underlying lung cancer, breast cancer, and multiple myeloma, lymphoma, prostate cancer, etc. can cause cord compression and may present with features of paraplegia. Patients usually present with symptoms such as pain, motor weakness, sensory symptoms, bowel, and bladder involvement, early suspicion, diagnosis, and management are pivotal for recovery. Management includes immediate administration of glucocorticoids, surgery, radiotherapy, and systemic therapy in patients with chemosensitive tumors [66].

32.3.11 Adrenal Crisis or Adrenal Insufficiency

Adrenal insufficiency due to metastases or infiltration of bilateral adrenals with malignancy, surgical excision of both glands, or adrenal hemorrhage in severe sepsis, can cause adrenal insufficiency in patients with malignancy. At least 90% of functioning adrenal tissue must be lost for symptoms to manifest. Patients usually present with vague features like nausea vomiting, diarrhea, vague abdominal or flank pain, confusion, and vasopressor resistant hypotension. Hyponatremia, hyperkalemia, and mild acidosis may be seen in

biochemical analysis. Cancers of lung, breast, kidney, stomach, and pancreas are the common types to metastasize adrenals. A positive cosyntropin stimulation test suggests the diagnosis, and these patients need to be supplemented with daily physiologic doses of glucocorticoids [67].

32.4 Postoperative Care in Oncology

The back-up of critical care in postoperative care resulted in the undertaking of advanced and more aggressive procedures like tracheal resection and heated intraperitoneal chemotherapy (HIPEC) that have a positive influence on survival. Oncologic surgeries are associated with extensive tissue dissection, fluid shifts, and third space loss, cardiac arrhythmias, electrolyte imbalance, impaired glucose control, hypothermia, etc. Postoperatively, they are prone to a higher risk of surgery-related complications such as postoperative bleeding, respiratory failure, malnutrition, and venous thrombosis, which need to be addressed urgently. Apart from these, all patients will require routine post-operative care such as care till complete recovery from anesthesia, optimizing pain medications, managing postoperative nausea, vomiting, and other complications such as shivering [7, 68].

32.5 Transfusion Practices in Onco-Critical Care

Oncology patients are excluded from the majority of the blood transfusion trials, and hence, any evidence in these subsets of patients is patchy. In the general population, a restrictive strategy of transfusion for red blood cells is followed, targeting a hemoglobin level above 7 g/dl. This practice has been proved to be safe in a sicker group of patients with sepsis. There have been only two trials in cancer patients—TRISOP (surgical patients) and TRICOP (solid tumors with septic shock). These two trials seem to differ from the general practice of restrictive strategies in favoring a liberal transfusion strategy over a restrictive strategy and point toward the need for further research in this field. However, red blood cells should be transfused with caution in patients with hyperviscosity syndromes—hyperleukocytosis, multiple myeloma, etc. and a restrictive approach might be beneficial in these patients [69].

Cancer patients in ICU will be having a reduced platelet count from underlying malignancy, sepsis, chemotherapy or irradiation, immune destruction as in ITP, antibody-mediated as in heparin-induced thrombocytopenia, etc. Evaluation of the etiology for thrombocytopenia should be considered for platelet count less than 100,000/cc. The evidence regarding platelet transfusion is also limited, and transfusion is currently advocated only in cases of active bleeding or prophylactic when the platelet falls below a threshold of 10×10^9/l or 20×10^9/l, if the patient is febrile [70].

32.6 Chemotherapy in ICU

Administration of chemotherapeutic agents in the ICU is indicated to treat or prevent life-threatening malignancy-related emergencies such as hyperleukocytosis, hemophagocytic lymphohistiocytosis (HLH), and tumor lysis syndrome. Over the years, there has been more experience in administering chemotherapy in the ICU, and this has led to a decrease in the short-term and long-term mortality rates. Caution must be exerted while calculating the required doses, accounting for organ dysfunction, altered pharmacokinetics, and pharmacodynamics of critically ill patients and seeking help from the oncology team will be beneficial. The presence or presumed presence of infection need not hinder chemotherapy in ICU in case of life-threatening emergencies. The patient identity and the chemotherapeutic schedule should be confirmed, cross-checked, and documented and informed consent regarding the adverse effects of the same should be taken before the administration of chemotherapy. Care must be taken while administering these extremely toxic drugs and the recommendations regarding dilution, volume, infusion rate, etc. should be followed. In the case

of drug reactions or drug toxicities, or drug extravasations, the drug infusion should be stopped immediately and help from onco-hematology should be sought [71].

32.7 Infection Control in ICU

Cancer patients are at high risk for nosocomial infections, and the rates can be as high as 40% [72]. Hospital-acquired and ICU-acquired infections escalate the treatment cost and also increases morbidity, mortality significantly. The common nosocomial infections are ventilator/hospital-acquired pneumonia, skin and soft tissue infections, central-line-related bloodstream infections, and catheter-associated urinary tract infections. Because of the huge implication of these infections, a systematic approach to reducing the effects is required. Simple measures like maintaining hand hygiene have been proved to be effective in reducing infection rates in hospitals. All hospitals now adhere to the "five moments of hand washing" as suggested by the World Health Organization (WHO)—that is, before and after touching a patient, before any sterile procedure, after contact with fomites in patient surroundings, and after any high-risk procedures with body fluid exposure [73]. The hospital-acquired infection rates are considered benchmarks of poor compliance of healthcare staff with the handwashing guidelines. Apart from hand hygiene, many bundles (a group of interventions that performed together changes the outcome efficiently) have been suggested to reduce HAI. The bundles for infection control have been summarized in Table 32.5 [74].

Table 32.5 Common bundles in ICU for infection control

Ventilator-associated pneumonia (VAP) bundle	Head end elevation of the bed up to 30° Daily interruption of sedation and spontaneous breathing trials Aspiration of subglottic secretions Peptic ulcer prophylaxis in high-risk patients Deep vein thrombosis prophylaxis
Central line related blood stream infection (CRBSI) bundle	Maintaining good hand hygiene practices Strict aseptic precautions for line insertion Use of chlorhexidine for skin antisepsis Preference for subclavian and jugular sites than femoral sites Daily assessment of lines and prompt removal of unnecessary lines
Catheter associated urinary tract infection (CAUTI) bundle	Avoid unnecessary urinary catheterizations Catheterize in aseptic precautions Daily care of urinary catheter and remove if not required

32.8 Nutrition in Onco-Critical Care

Malnutrition is a common problem among critically ill oncology patients and is aggravated by infections, inflammation, stress, etc. The previous nutritional status of the patient is also an important factor affecting malnutrition. Most of these patients will be malnourished due to preexisting nausea, vomiting, and cachexia of malignancy. Malnutrition results in increased morbidity and mortality in all patients, and hence, nutritional support should be initiated early aiming to minimize the effects of starvation, support the immune system, prevent nutritional deficiencies, and facilitate wound healing. Screening tools like Nutritional Risk Screening 2002 (NRS 2002), the malnutrition universal screening tool (MUST) mini nutritional assessment (MNA), and the malnutrition screening tool (MST) are available to rapidly screen patients at risk for malnutrition. Clinical parameters that hinder nutrition like disease site, anorexia, asthenia, vomiting, dysgeusia, pain, depression should be actively searched for. A significant weight loss (>10% for 6 months) is the most reliable indicator of nutritional deficit. Albumin and prealbumin can be altered by infections, liver diseases, renal dysfunction, dehydration, anasarca, etc., and this limitation must be kept in mind. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend dual X-ray absorptiometry (DEXA) or bioimpedance analysis (BIA) to assess muscle

Table 32.6 Indications of total parenteral nutrition in ICU

Contraindication to enteral feeding	Chyle leak Intestinal obstruction
Malfunctioning gut	High-output enterocutaneous fistulas Paralytic ileus Massive resection of bowel Radiation enteritis Not attaining nutritional goals even after 2 weeks
Inadequate enteral feeding	Patients at high nutritional risk with anticipated delay in attaining nutritional gals by 7 days

mass and fat reserves, along with performance scales such as the Eastern Cooperative Oncology Group (ECOG), or Karnofsky and biomarkers such as serum C-reactive protein (CRP) and albumin for nutritional assessment in high-risk patients. Enteral feeding is safe and effective and if tolerated should be initiated early in the course of ICU stay. There has been no evidence for immune nutrients in cancer patients though it seems attractive and physiological. Those who have a high nutritional risk score and contraindications for enteral feeding may be considered for early parenteral nutrition. Patients with anorexia but a functioning intestinal tract have not been shown to benefit from parenteral nutrition, and, therefore, priority should always be given to the enteral route [75]. Total parenteral nutrition is indicated only in a select population in the ICU (Table 32.6).

32.9 ICU Outcomes of Cancer Patients

Patients with solid tumors seldom require ICU admission for medical reasons such as febrile neutropenia, septic shock, invasive fungal infection, acute respiratory failure, or other organ dysfunctions. The majority of these patients will be admitted to the critical care unit postoperatively. Excluding patients admitted for routine postoperative care, patients with solid tumors have almost double mortality rates as compared to patients without cancer (41% vs 21%) [76].

Hematological patients on the contrary are usually admitted to critical care units for life-threatening medical conditions such as oncologic emergencies, infections, or organ dysfunction. They generally tend to have higher disease severity scores [Simplified Acute Physiology Score (SAPS II)] or sequential organ failure assessment score (SOFA score) and a higher mortality rate (50–60%) [76].

Bone marrow transplant (BMT) recipient patients remain a separate subset with high ICU and in-hospital mortality, even though the mortality rates are decreasing. BMT patients require ICU admission for medical complications like acute respiratory failure, sepsis, cardiac dysfunction, neurologic disorders, and bleeding diathesis. BMT patients requiring mechanical ventilation still have an ICU mortality rate of 80% that further worsens with worsening organ dysfunction [16]. Various factors affect the prognosis of critically ill patients admitted to an ICU (Table 32.7).

32.10 Palliative Care in ICU

Palliative care is defined as a holistic approach to improving the quality of life of patients and their families by early identification, meticulous assessment, and addressing unmet needs such as pain and other physical, psychosocial, and spiritual problems [79]. The key domains include (1) symptom management; (2) empathetic and realistic communication about disease, possible treatment, and outcomes; and (3) support for both patient and family throughout illness. Palliative care is an integral component of multidisciplinary care and should be provided to all. The initiation of palliative care is associated with better control of symptoms, better utilization of hospice resources including ICU stay, increased satisfaction for patient and family, and reduced moral stress on the physician, thus minimizing burnout. The barriers to palliative care can be minimized by effective and realistic communication, discussing advance directives (if present), with care to avoid confusing words such as withdrawal of care and use simple realistic terms like

Table 32.7 Prognostic factors for critically ill oncology patients [76–78]

Negative prognosis	Positive prognosis	Neutral
Extreme ages Respiratory failure requiring mechanical ventilation Delay of >2 h in starting appropriate empirical antibiotics Multiple organ dysfunction score > 2 organ involvement Higher apache/sofa scores Invasive aspergillosis Poor response of cancer to chemotherapy Poor performance score before ICU admission—Karnofsky score <70 or higher Eastern Cooperative Oncology Group (ECOG) scale 3–4	Indication for ICU admission being primary postoperative care Disease in remission Good performance status before hospital admission Acute onset of critical illness (< than 7 days) Absence of fungal infection Absence of comorbidities Reversible cause for ICU admission	Type of tumor (solid vs hematological) Neutropenia Metastatic nature of the disease Prior ICU admission

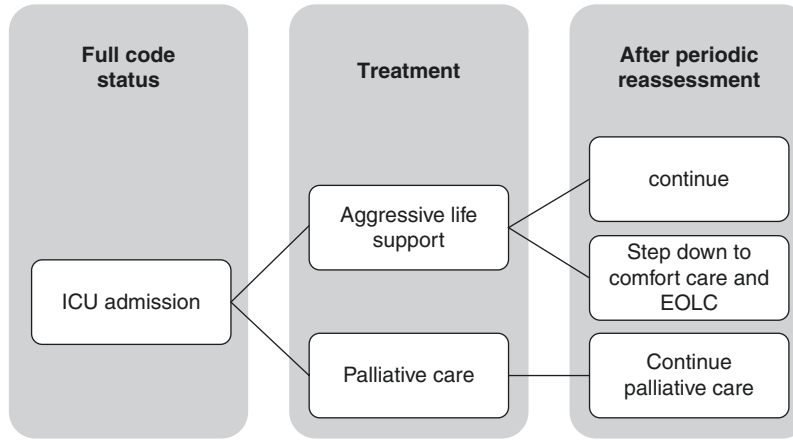

Fig. 32.3 Schematic representation of patient care in ICU

withdrawal of life-sustaining treatments [80–82]. A schematic representation of ideal patient care in ICU is represented in Fig. 32.3.

32.11 End-of-Life Care (EOLC) in ICU

Ideally, only those patients who have a reasonable chance of either cure or palliation from their disease or symptoms should be admitted to a critical care unit. However, many times patients with advanced disease or those with advanced directives will be admitted to the ICU for a time-limited full-code trial. Although seemingly straightforward, the transition from full-code status to EOLC is often vague, delayed, and an area of conflict. This creates a situation of dilemma, conflict of interests, and the increased patient suffering from simultaneous wastage of resources. At a stage of treatment futility or end of life, intensive care to the patient should mean comfort care, avoidance of inappropriate aggressive interventions clearly understanding that aggressive life-supporting interventions increase rather than alleviating the sufferings of the patient. The treatment plan of all critically ill patients should be revised frequently and monitored for futility. If futility is observed, it should be conveyed to the primary team and relatives. Open empathetic communication with relatives and the primary team is required to voice opinions while avoiding conflict. EOLC discussions require time and multiple sessions of discussions. Each session must be documented properly to maintain transparency. Once EOLC is decided, the site of care should be reviewed, with preference to patient comfort. Adequate space for the patient and relatives, adequate medications, adequate staffing needs to be

ensured and the patient should not be neglected at any point in time. Unnecessary monitoring may be avoided, and close relatives may be permitted to remain by the bedside, as per their wishes. All treatment orders should be reviewed, with unnecessary medications being avoided but retaining medications for symptom control. There should be regular assessment regarding the adequacy of treatment for symptom control. Spiritual care should also be taken care, and bereavement support to the family members should be offered to cope with their issues [83, 84].

32.12 Integrated Intensive Care Management of Onco-Critical Care

Intensive care for critically ill cancer patients requires an integrative approach from the oncologist, intensivist, primary physician (in case of surgical specialty, or nononcological specialty). Whenever a patient arrives at the hospital for the initial visit, the nature of the disease and possible treatment options should be realistically and empathetically explained to the patient and relatives. This allows them to be realistic and prepare for the disease and treatment complications. On follow-up, response to treatment must be evaluated and any change in the treatment plan should be discussed and documented. Addressing the patients' unmet needs like symptom management and palliative care should be involved at this stage, if not involved earlier.

When there are signs of organ dysfunction or sepsis, broad-spectrum antibiotics need to be administered while preparing for a discussion with intensive care. As none of the current tools can accurately predict patients who may benefit from intensive care, all patients willing to be shifted to ICU, and those without advanced directives may be shifted to the ICU. All patients with advanced disease and in whom no treatment can be offered for control of the primary disease may be refused ICU admission. During ICU stay, there should be daily interaction among the intensivist and oncologist regarding response to therapy and prognosis. All patients admitted to ICU should receive full-code treatment, similar to noncancer patients for the initial 3–5 days, unless specified. Patients identified for end-of-life care should be initiated for the same after detailed discussion and appropriate documentation among caregivers and relatives. Patients discharged from ICU should be followed up by the intensivist and screened for postintensive care syndrome. Those suffering from depression and other chronic illnesses post-ICU stay must be identified, and rehabilitation must be offered [8, 17, 76]. Figure 32.4 summarizes a flowchart of integrating care from an initial hospital visit to post-ICU discharge.

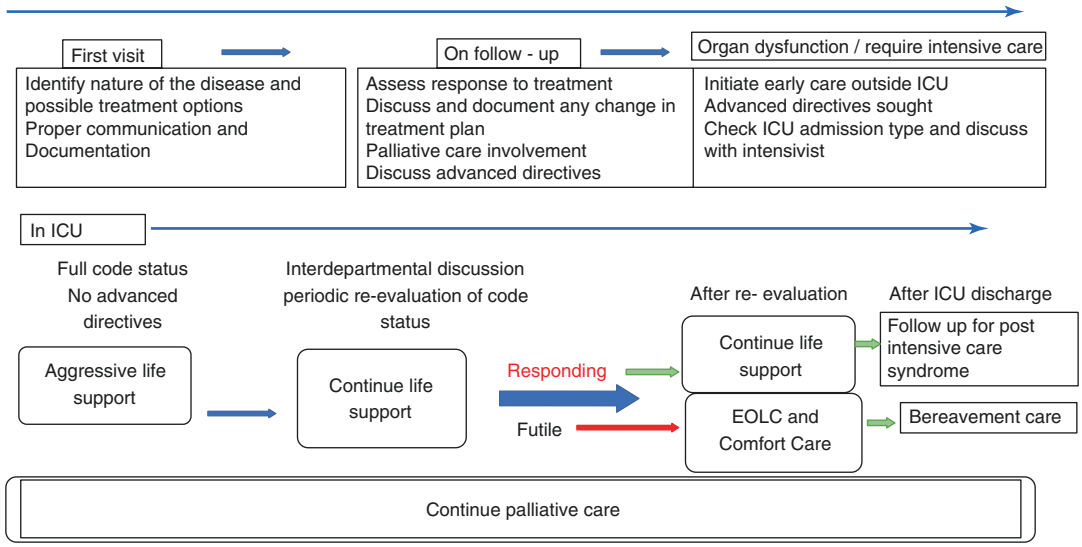

Fig. 32.4 Integrating various departmental services in oncology critical care

32.13 Summary

Intensive care in oncology has evolved over decades and is currently a rewarding profession. Properly selected patients admitted to the ICU have survival rates and quality of life identical to their noncancer counterparts. Early identification of organ dysfunction, potent antimicrobial therapies, and noninvasive diagnostic strategies for organ dysfunction and appropriate management are some of the factors responsible for the reduction in mortality rates. We need to develop a score that predicts benefits for early ICU admission in these subsets of critically ill patients. The strategies used to avoid intubation (like NIV and HFNC) need further evaluation before they are accepted as alternatives to mechanical ventilation. End-of-life care and palliative care are also integral parts of intensive care and should be offered to all eligible patients. For the better outcome of these patients, a multidisciplinary team including intensivist, oncologist, and palliative care specialist is essential.

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Part VII

Allied Onco-Specialties

Palliative and End-of-Life Care for Advanced Cancer

33

Sushma Bhatnagar

33.1 Introduction

Advanced cancer is defined as advanced stages of cancer that is not curable. In India, 70–80% of cases are diagnosed when they have reached stage 3 or 4. Around two thirds of cancer, diagnoses are incurable at presentation and require palliative care. But unfortunately, less than 1% gets the benefits of palliative care. The benefits of early integration of palliative care in the continuum of care in patients with advanced cancer are well established [1–3].

33.2 Palliative Care in Advanced Cancer

Palliative care services in advanced cancer help by palliating symptoms and improving the overall quality of life (QoL) and satisfaction. It improves pain, fatigue, dyspnea, nausea, vomiting, diarrhea, constipation, anxiety, and depression. The fear of dying further increases the distress of the patient and their family members. Palliative care follows the holistic approach and deals with physical, psychosocial, spiritual, and financial aspects. Palliative care provides added support to live and fight cancer.

Palliative care should be incorporated in the early phase as soon as the diagnosis of advanced cancer is made. It early recognizes, prevents, and manages symptoms and sufferings of patients with advanced cancer. It provides a common platform for patients, caregivers, and multidisciplinary team to discuss and set the goal of patient care. Various studies have demonstrated that integrating palliative care early leads to a better QoL, lesser depression, and more of end-of-life care (EOLC) discussions [4–6].

Despite knowing the terminal stage of the diseases, most of the patients rush to the hospital and get admitted for symptomatic management, and eventually land up on mechanical ventilator support and death in an intensive care unit (ICU). ICU support adds life to the patient as they are on life support care but at the cost of increased sufferings and declined QoL. ICU care also falsely raises the hope of the caregivers. This has a long-term effect on the relatives of those who die in ICU and are not able to spend the valuable last stage of their life with their loved ones. Thus, it is high time to spread awareness regarding palliative and EOLC.

Palliative care physician needs to decide the transition from palliative care to EOLC. Often, oncologists delay planning for compassionate and EOLC. The transition from stopping treatment and focusing on EOLC requires good prog-

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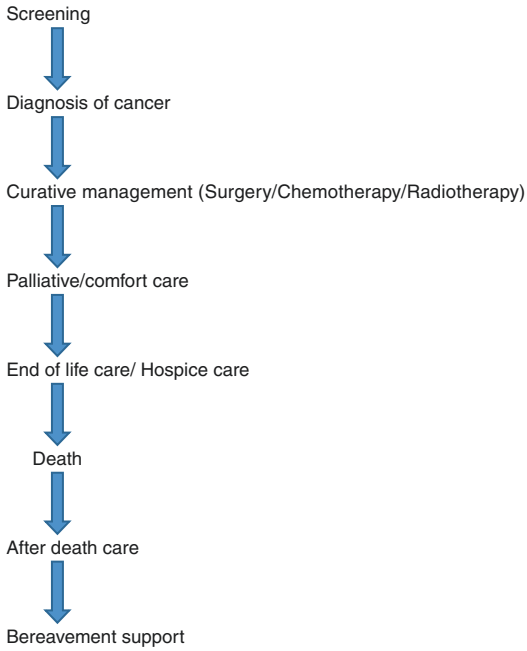

Fig. 33.1 Trajectory of cancer

nosticating skills and is a real challenge for both doctors and caregivers. Most of the time, end-of-life decisions are never discussed with the patient or caregivers because of a lack of communication between the primary physician and the patient. Thus, palliative, EOLC, oncology, and critical care should be integrated as early as feasible in the holistic management of cancer patients. The trajectory of cancer patients is typical (Fig. 33.1).

33.3 Palliative Care and ICU

Palliative care has also been integrated with critical care and has an impact on better symptom management, decreased pain scores, advanced care planning, and withdrawal and withholding of life-prolonging treatment [7, 8]. Honest and effective communication, prognostication, and well-conducted family conferences are important aspects. Palliative care in ICU can be provided by the easier visitation of family members, stopping of the diagnostic test, creating a spiritual environment, and the involvement of social workers and psychologists.

33.4 Palliative Onco-Surgery

Palliative care also includes surgery with the primary goal of improving QoL by providing symptomatic relief in advanced cancer [9]. Palliative oncosurgery is an evolving new concept that balances the risk–benefit ratio and its effectiveness depends upon the patient's symptomatic improvement [10]. However, the durability of surgery depends upon the stage of diseases, functional status of the patient, surgical morbidity and mortality, and prognosis of the disease. Palliative interventions like diversion stoma and stenting are often required in advanced colorectal and gastroesophageal malignancy. Even palliative care interventions have been reported among lung cancers involving major airways with improved QoL.

33.5 End-of-Life Care (EOLC)

EOLC care is challenging for both healthcare professionals and family members in advanced cancer. EOLC aims at symptom control, improving both qualities of life and quality of dying, a good death, and dying with dignity. All terminally ill patients have the human right of getting palliative and EOLC. EOLC acknowledges that every person has a human right to a good, dignified, and peaceful death. EOLC provides comfort and a compassionate approach not only during their last stage but also after death in the form of bereavement and social support.

Components of EOLC:

1. Early recognition of dying patients
2. Symptom control
3. Improvement of QoL
4. Psychosocial and spiritual support
5. End-of-life decision-making
6. Setting end-of-life goals
7. Good death

8. Empowering caregivers
9. Bereavement support to caregivers
10. Dealing with legal issues
11. Hospice services

Good EOLC includes good symptom management, the satisfaction of family members, and good quality and dignified death as demonstrated in Fig. 33.2.

The first component of EOLC is the early recognition of patients who are dying. Indicators of poor prognosis and decreased survival are a decrease in physical activity, inability to self-care, decreased oral intake, decreased talking, and skin changes. Besides these clinical and physiological parameters, there are certain scoring systems to guide us to follow EOLC. These are performance status, prognostic tools, and models.

The performance status can be measured by the Karnofsky Performance Status (KPS), the Eastern Cooperative Oncology Group (ECOG) scale, and the Palliative Performance Scale (PPS). KPS score < 50 and ECOG score of more than 2 on admission are associated with poor prognosis and survival of fewer than 6 months. KPS score of 10–20 is associated with poor survival of fewer than 2 weeks. PPS score of 30–50 is associated with a median survival of 41 days.

Other prognostic tools used in advanced cancer are Palliative Performance Index (PPI), Palliative Prognostic Score, Glasgow Prognostic Score, Cancer Prognostic Score (CPS), and Intrahospital Cancer Mortality Risk Model (ICMRM). PPI score of more than 4 corresponds to the survival of fewer than 6 weeks. "Adjuvant" is a web-based program that provides 10-year morbidity/mortality outcomes in breast and lung cancer. It can be searched at www.adjuvantonline.com. Out of all cancers, pancreatic adenocarcinoma and advanced non-small cell lung cancer have the shortest survival of around 2.5 months.

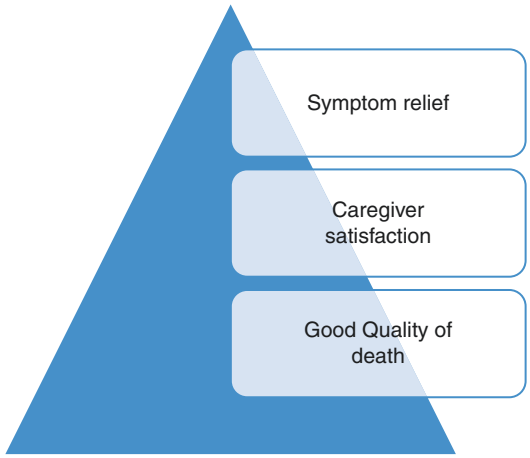

Fig. 33.2 Triad of good end-of-life care (EOLC)

Various scoring systems used for EOLC are the Supportive and Palliative Care indicators tool (SPICT), the Quality of Death-Hospice Scale (QOD-Hospice), Caregiver Evaluation of the Quality of End of Life Care (CEQUEL) scale, and Coping with Death Scale. SPICT is used to guide in identifying patients at risk of dying and patients in need of palliative care.

Good death includes adequate symptomatic relief, empowering caregivers in decision-making, death preparation, completion of unfinished business, spending last days with loved ones, respecting patient's preferences, and contributing to others in the form of organ donation. The Gold Standards framework has been developed to deliver standard care to people during the last stage of their life.

End-of-life decisions should be discussed transparently between physician and patients. It involves communication regarding the prognostication, expected survival, autonomy, resuscitation, advance care planning, and preferred place of care and death. Future EOLC goals should be set and documented. Most of the patients prefer home or hospice as the desired place of death rather than hospital wards or ICU [11, 12]. Hospice services are associated with better QoL and satisfaction drastically reducing the caregiver burden [13, 14]. Thus, EOLC reduces unnecessary hospital and ICU burden and thus decreases the wastage of hospital resources and financial distress of caregivers. Financial distress is very common in patients with advanced cancer but is often ignored and not discussed with the patients [15, 16]. When EOLC is not met, there is an increased risk of depression among caregivers [17, 18]. Timely EOLC by trained palliative care

Table 33.1 Barriers in providing end-of-life care (EOLC)

Patient related	Physician related	Caregiver related	Ethical/legal issues
Unrealistic hope	Lack of training in palliative care education	Inadequate coping skills	Lack of legal policies on EOLC
Denial	Lack of confidence in dealing with terminally ill patients	Lack of awareness regarding EOLC services	Lack of medical insurance
Lack of awareness of palliative care	Tendency of continuing aggressive treatment till the end		Lack of research
Fear and pain of dying	Deficiency of palliative care specialists		Lack of palliative care programs
	Lack of communication skills		Lack of legal backing and fear of litigation among doctors
	Lack of coordinated team-based care		
	Late referral to palliative physician [19, 20]		
	Lack of clarity and consensus within medical community		

physicians reduces medical futility. Despite all benefits, there exist many barriers in providing EOLC (Table 33.1).

Benefits of EOLC:

The integration of palliative care in the management of patients with cancer and timely sensitization and provision of EOLC has been found to improve the QoL not only of the patients but also of the caregivers. Various benefits include:

1. Better QoL
2. Less financial distress
3. Decreased hospital ICU Emergency services cost and burden [21, 22]
4. Treatment directed toward the patient's goals, needs, and preferences
5. Escape from ineffective or unwanted treatments
6. Provides emotional and spiritual support
7. Better communication between physician and caregivers
8. Avoids undue prolongation of the dying process
9. Avoids guilt and regret among caregivers
10. Better coping and family interactions
11. Prepares family for bereavement and legal issues
12. Respects patient autonomy
13. Provide proper patient information and education
14. Higher patient and caregiver satisfaction

33.6 Initiatives to Enhance EOLC

The Education in Palliative and End of Life Care (EPEC) is a project that started in India in 2007 to enhance the training and knowledge of doctors and volunteers in palliative care. Similarly, the End of Life Nursing Education Consortium (ELNEC) Training program has been started to enhance EOLC knowledge among undergraduate and graduate nurses. Such a training program is essential to sensitize healthcare professionals to the need for palliative care and EOLC.

33.7 Summary

Early integration of palliative care in the continuum of care in patients with advanced cancer is strongly recommended**.** Palliative care follows a holistic approach and deals with physical, psychological, spiritual, social, and financial aspects. Palliative care services in advanced cancer help by palliating pain and other symptoms, practical

support, improving quality of life, satisfaction, and good EOLC [23]. EOLC aims at symptom control, improving both qualities of life and quality of dying, a good death, and dying with dignity. Thus, integration of palliative, EOLC, oncology, emergency medicine, and critical care will improve patient outcomes. Palliative care should also be integrated into the medical education system so that more workforces can be trained to deliver palliative services. The concepts of medical futility and good death and recognition of the dying patient should be an integral part of the medical curriculum. More and more extensive research and evidence are required to support its integration into the present healthcare system. The regular audit should be done to evaluate the quality of EOLC.

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Part VIII

Miscellaneous

34 Perioperative Complications in Oncosurgeries

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34.1 Introduction

Due to the considerable burden of cancer today, oncosurgeries are being performed at many centers globally and comprise a significant proportion of the hospital workload. As technology evolves, surgical procedures become more complex and intricate requiring very astute perioperative care. Many more cancer patients with multiple comorbidities are now offered these procedures than ever before, with either an intent to cure or for palliation, and this makes the perioperative management very challenging. Despite better facilities, expertise, and equipment, certain complications do occur and remain inevitable, though lesser in frequency. This is partly due to the inherent nature of the surgical procedures, which may be over long hours, may be technically tedious, and may involve two or more body compartments with the additional challenge quite often of an immune-compromised patient. Then, there is always a lack of desirable length of time for adequate optimization preoperatively as there is this intent to contain the disease as early as possible. Most of the oncosurgical units have well-defined protocols and standards of care and are always in a state of readiness to deal with complications arising in patients undergoing oncosurgery. This chapter reviews the various complications occurring in the perioperative period in patients undergoing oncosurgeries.

34.2 Perioperative Complications in Oncosurgeries

Various perioperative complications encountered in oncosurgeries have been reported in the literature. These can be broadly divided into general complications and complications specific to oncosurgical patients (Table 34.1). In this chapter, some surgical complications have been mentioned too as they pose a challenge to both surgeons and anesthesiologists involved in perioperative care.

A proactive approach by the multidisciplinary perioperative team is desirable for the care of oncosurgical patients to foresee complications and chart a course right from the beginning. Every step must be taken to optimize adverse factors and prevent complications or at the very least reduce the impact on the outcome. Return to intended oncological therapy (RIOT) is the goal, and all the efforts must be directed toward ensuring this endpoint.

In patients with colorectal cancer, postoperative complications after curative surgery had a negative impact on overall survival and cancer recurrence.

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Table 34.1 Perioperative complications in oncosurgeries

General complications in oncosurgery	Inadvertent perioperative hypothermia
	Deep vein thrombosis and pulmonary embolism
	Perioperative injuries
	Postoperative lung complications
	Sepsis
	Postoperative nausea and vomiting (PONV)
	Postoperative atrial fibrillation (POAF)
	Chronic postsurgical pain (CPSP)
Specific complications in oncosurgery	Chemotherapy-related perioperative complications
	Opioid dependence
	Malnutrition and hypoalbuminemia
	Difficult access to the airway (tumor, postradiation, extubation dilemma)
	Problems of brachytherapy (nonoperating room, anesthesia, and patient transport)
	Carotid blowout syndrome
	Flap necrosis
	Chyle leak

The authors have suggested that in the future phase III trials for adjuvant chemotherapy in colorectal cancer, surgical morbidity must be incorporated as a stratification factor [1]. In a retrospective study of 239 patients undergoing gastrectomy for gastric cancer, postoperative complications were found to adversely affect the overall survival as also the disease-free survival [2]. So, utmost planning and care are desirable to prevent the occurrence of perioperative complications.

34.3 General Perioperative Complications in Oncosurgeries

Various factors have been reported in the literature which is related to adverse outcomes after oncosurgeries. The factors in general are detailed in the following section.

34.3.1 Inadvertent Perioperative Hypothermia (IPH)

Inadvertent perioperative hypothermia (IPH) where the core body temperature falls below 36 °C is encountered commonly in perioperative patients and requires well-placed strategies for its management. The higher American Society of Anaesthesiologists (ASA) physical status, combined general and regional anesthesia, emergency surgeries, major or intermediate-risk surgeries, and low body mass index (BMI) are some of the risk factors for IPH [3].

Perioperative hypothermia is a harbinger of dreaded complications like coagulopathy, surgical site infections, adverse cardiac events (myocardial ischemia and ventricular tachycardia), and increased length of stay. Updated National Institute for Health and Care Excellence (NICE) guidelines 2016 for prevention of IPH has suggested several preoperative, intraoperative, and postoperative preventive measures. Patients should not be transferred to operation theatre and anaesthesia should not be induced until core temperature has been documented as more than 36 °C. Forced-air warming, prewarmed fluids (within 30 min of removal from the warming device), adjustment of operating room ambient temperature, monitoring of core temperature and appropriate titration of active warming, use of heat and moisture exchange (HME) filters, and continuity of care in the postoperative period are some of the recommendations in this guideline [4]. In a systemic review in which 18 studies were included, forced-air warming was found to increase thermal comfort, reduce cardiac morbidity, and decrease the incidence of shivering and wound infection as compared to alternate forms of warming [5].

It has been reported that in patients with invasive urinary bladder malignancy and undergoing radical cystectomy, the occurrence of intraoperative hypothermia was a significant prognostic marker for overall survival, though, in this study, the patients in the hypothermia group had poor performance status and advanced disease as compared to the normothermia group [6].

34.3.2 Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)

DVT is another known complication in cancer patients. Acute PE can become life-threatening, and chronic pulmonary thromboembolism can have a significant impact on the quality of life. DVT and PE have a higher incidence in cancer patients as compared to noncancer patients undergoing surgical interventions. The guidelines published in CHEST in 2012 outline a well-researched management strategy to prevent DVT and PE in this group of patients [7]. But what is required is excellent communication between team members regarding the timing with regional anesthesia, interaction with co-administered anticoagulants, antiplatelet, or nonsteroidal anti-inflammatory drugs (NSAIDs), and a very close watch on surgical drains. Teams must be fully involved in the assessment of the risk of bleeding and perform a risk–benefit analysis every day. In the intraoperative and postoperative period, high alertness is required to detect this complication. Transesophageal echocardiography (TEE) can be used to evaluate the right heart function in the perioperative period. The hospital should have a robust PE/DVT protocol to detect and treat this life-threatening complication.

34.3.3 Perioperative Injuries

Perioperative injuries are unintentional injuries, which add to the postoperative morbidity, psychological distress, and have the potential for medico-legal concerns (Table 34.2). These injuries may be pressure ulcers, injury of muscles or tendons, and nerve injuries. Perioperative injuries may be related to either surgical factors or patient-related factors.

Table 34.2 Factors responsible for perioperative injuries

Surgical factors	Patient factors
Improper positioning Nerve injury (transection, pressure, stretching) Retractors [8, 9] Muscle and tendon injury (blood pressure cuffs, inadvertent pressure by the operating team, surgical mops, stretching)	Preexisting injuries Diabetes mellitus Hypertension Postchemotherapy Hypothermia Electrolyte imbalance

While positioning for surgical interventions and placement of surgical retractors, a fine balance is required so that the safety of the patient is ensured without obstructing surgical access and allowing adequate access to anesthesiologists. Patients undergoing oncosurgical procedures are more prone to these unintended harms as the surgeries are performed over a longer duration, some require wider surgical exposures, and there may be tissue insult due to prolonged unavoidable hypotension due to blood loss. Many of them may have had predisposing factors like preoperative chemotherapy, radiotherapy, and other comorbidities like diabetes or chronic renal insufficiency. Many assessment scales have been reported and validated for use for different injuries in the perioperative period. Braden scale is widely used for risk stratification of patients prone to pressure sores. This scoring is based on sensory perception, skin moisture, activity, mobility, nutritional status, and exposure to friction and shear. Assessment Scale for the Development of Injuries due to Surgical Positioning (ELPO version 2) incorporates seven factors namely "surgical position, duration of surgery, type of anesthesia, support surface, limb position, comorbidities, and patient age to assess the risk of perioperative injuries" [10].

Patients should be evaluated preoperatively for any preexisting injuries and predisposing factors for the occurrence of injuries. The assessment findings must be documented in the patient record and discussed with the patient as well. The informed consent must make a mention of these findings and the potential risk of injury must be explained. All care should be taken to prevent further exacerbation, and preventive strategies should be planned for the perioperative period. Postoperatively patients should be evaluated, any new finding should be documented, and appropriate steps should be taken to mitigate the harm.

The Amaerican Society of Anaesthesiologists (ASA) has published an updated practice advisory for the prevention of perioperative peripheral nerve injury in 2018 [11].

34.3.4 Postoperative Pulmonary Complications (PPC)

Postoperative pulmonary complications (PPCs) and its impact on mortality [12, 13] and the cost of care is well-recognized. There are several predisposing factors (Table 34.3), and some of them are amenable to optimization or modification before surgery [14]. Quite often, cancer patients lose out to ideal optimization as there is a resolve to operate as early as possible to contain the disease.

Table 34.3 Predisposing factors for postoperative pulmonary complications in cancer patients

Patient-specific factors	• Advanced age • Male sex • American Society of Anesthesiologist (ASA) physical status 3 or more • Malnutrition, hypoalbuminemia, anemia • Recovering chest infection • Preoperative sepsis • Impaired cognition • Obesity • Postchemotherapy • Depression • Poor cardiac reserve • Myelosuppression • Diabetes mellitus • Chronic liver disease • Chronic renal disease • Ascites
Procedure-specific factors	• Major surgery in the abdominal or thoracic cavity or involving both (e.g., esophagectomy) • Head and neck surgery (inability to cough) • Open surgeries (vs. minimally invasive surgery) • Multiple blood transfusions (acute lung injury) • Prolonged postoperative ventilator support • Emergent surgery (vs. elective procedure) • Redo surgeries • Surgical complication (postoperative pneumothorax, hemothorax, chyle leak, anastomotic leaks) • Use of nasogastric tube

The preventive strategies include optimization of all modifiable factors as much as achievable, pre- and postoperative physiotherapy and breathing exercises, acute pain management plan, and a low threshold for detecting infections. A preexisting plan or protocol is not sufficient. There must be frequent assessments for any such complication and its management at the earliest. The role of epidural analgesia in reducing the risk of postoperative pulmonary complications is well known [15, 16].

To reduce PPCs, a postoperative protocolized program based on patient education, early mobilization, and pulmonary interventions called "I COUGH" was found to appreciably reduce the incidence of postoperative pneumonia (from 2.6% to 1.6%) and unplanned intubation from 2% to 1.2% [17].

34.3.5 Perioperative Sepsis

Sepsis has been defined as "a life-threatening organ dysfunction caused by a dysregulated host response to infection." The presence of an infection, abnormal regulation of the host response to the infection and the organ dysfunction occuring as a result of this abnormal response comprise three critical components of sepsis [18].

Sepsis is the cause of 9% of all cancer-related mortalities in the United States of America [19]. The operated cases of cancer are more prone to sepsis due to an immune deficiency state causing cancer [20, 21] and/or chemotherapy-related depressed immune status, lymphadenectomy performed during surgery, indwelling central venous lines, or urinary catheters, and blood transfusion-related immunomodulation (TRIM) [22]. All guidelines regarding the prevention of surgical site infection (SSIs), catheter-associated urinary tract infection (CAUTIs), and catheter-related bloodstream infections (CRBSIs) should be strictly followed. Healthcare workers involved in the care must follow all hand hygiene protocols and wear appropriate personal protection equipment.

A heightened vigilance should be maintained to detect signs and symptoms of sepsis, and there must be no delays in obtaining cultures from drains, surgical wounds, and bronchoalveolar lavage fluid. Sequential Organ Failure Assessment score (SOFA) can be used to identify organ failure.

In the Surviving Sepsis Guidelines 2016, the 3- and 6-h bundles focus on time-targeted measurement and monitoring of lactates, the institution of fluid boluses, obtaining blood cultures, focused reassessment, and initiation of vasopressors. Noradrenaline is the vasopressor of choice, and phenylephrine is no longer recommended. Within an hour of diagnosis, empirical broad-spectrum antimicrobials covering all likely pathogens, including bacteria and any potential viruses and/or fungi based on the risk factors in the patient, must be commenced. This can be tailored once the results of cultures become available. Blood glucose levels above 180 mg/dL should be treated with a target of <180 mg/dL, continuous renal replacement therapy is indicated over intermittent therapy in hemodynamically unstable patients, stress ulcers and DVT prophylaxis should be given, and enteral nutrition should be started as early as possible. In patients with feeding intolerance, the use of prokinetic agents and the placement of feeding tubes in a postpyloric position have been suggested in this guideline [23].

34.3.6 Postoperative Nausea and Vomiting

Postoperative nausea and vomiting (PONV) are among the most distressing concerns for any patient. Usually, patients present for surgery after a gap of a few weeks after chemotherapy; hence, chemotherapy-induced nausea and vomiting have mostly subsided by then.

Hypercalcemia, uremia, ascites, brain metastasis, medication, gastritis, intestinal obstruction, and anxiety may cause nausea and/or vomiting in an oncosurgical patient and may subside once the cause is addressed. Apart from these, intraoperative factors like the use of opioids, bowel handling and bowel paresis, gastritis, use of NSAIDs etc. have been related to the occurrence of PONV.

The class of drugs commonly used for treating PONV are 5HT3 receptor antagonists, steroids, antihistamines, and butyrophenones. Neurokinin 1 (NK1) receptor antagonists were discovered in the 1990s. The NK1 receptors are present centrally as well as peripherally, and this receptor has substance P as its natural ligand. Aprepitant is an NK1 receptor antagonist and is commercially available in several countries. It has been used in patients of debulking surgery undergoing postoperative intraperitoneal chemotherapy [24]. In a systemic review, aprepitant was found to reduce the incidence of vomiting on the first two postoperative days (some heterogenicity was noted) with minimum need for rescue on the first postoperative day and a dose of 80 mg was found to be effective and safe [25].

In 2014, Society for Ambulatory Anesthesia published a comprehensive guideline for the management of PONV listing the risk factors (female gender, nonsmoker, previous history of nausea and vomiting, emetogenic surgeries), the scoring system for patients at risk, preventive strategies, and the dose and timing of antiemetics [26]. The choice and combination of drugs depend on the risk factors.

34.3.7 Postoperative Atrial Fibrillation (POAF)

New-onset postoperative atrial fibrillation (POAF) is the most common cardiac arrhythmia seen in oncosurgical patients after major surgery. Many patients undergoing noncardiac surgery develop clinically significant atrial fibrillation (AF) [27], and the incidence was reported as 12.3% in 2588 patients undergoing thoracic surgery for benign and malignant conditions [28]. Though mostly self-limiting, it results in a considerable increase in the cost of care, prolonged length of stay, and significant morbidity. Thromboembolic event is the most dreaded consequence of AF as it can cause a stroke or acute limb ischemia.

The American Association of Thoracic Surgeons (AATS) 2014 guidelines for the prevention and management of perioperative atrial

fibrillation and flutter for thoracic surgical procedures [29] has laid down definitions for the diagnosis of POAF following thoracic surgery. The AATS defines *electrophysiologic definition/diagnosis* as "ECG recordings (1 or more ECG leads)with ECG features of AF lasting at least for 30 seconds or the duration of the ECG (<30 s)" and *clinical definition/diagnosis* as "clinically significant POAF is intra- and postoperative AF requiring treatment, or anticoagulation, and/or extending the duration of hospitalization" [29].

Additionally, they have identified modifiable and nonmodifiable risk factors (Table 34.4) for POAF based on the American Heart Association Atrial Fibrillation guidelines and relevant literature on thoracic surgery. In this publication, thoracic surgical procedures have been divided into low-risk (5%), moderate-risk (5–15%), and high-risk (9.15%) categories based on their expected incidence of POAF.

For patients undergoing surgical interventions having high risk (>15%) of incidence of AF intermediate (5–15%) risk for POAF, a continuous ECG monitoring is suggested postoperatively for 72 h (or less if their shorter length of stay). This recommendation should also be followed in patients with significant additional risk factors (CHA2DS2-VASc > 2) for stroke or with a history of preexisting or periodic recurrent AF before their surgery. ECG monitoring must be continued in the postoperative period for patients who have received epidural catheters and regional anesthesia blocks, and similar are performed [29].

Table 34.4 Risk factors for postoperative atrial fibrillation

Modifiable risk factors	Nonmodifiable risk factors
Hypertension	Age
Myocardial infarction	Genetic variants
Valvular heart disease	Race – African American
History of heart failure	Family history
Obese	Male
Obstructive sleep apnea	History of arrhythmias
Chronic smoker	
Exercise	
Alcohol consumption	
Hyperthyroidism	
Increased pulse pressure	
Mitral regurgitation	
Left ventricular hypertrophy	
Increased left ventricular wall thickness	

The pharmacological control of heart rate in patients with AF is desirable. Various drugs have been suggested, and beta-blockers remain the drug of choice for control of rapid ventricular rate in patients with AF. Alternately, nondihydropyridine calcium channel blockers may be used in case beta-blockers are contraindicated like in patients with reactive airway disease. These drugs need to be used cautiously in patients with systolic heart failure. In such situations or when the response to these drugs is not optimal, amiodarone may be alternatively used. For patients with low left ventricular ejection fraction, the use of digoxin with beta-blocker or a calcium channel blocker may be administered to control the ventricular heart rate. Since postoperative patients have a high sympathetic tone, digoxin as a sole agent should not be used [30].

To mitigate the risk of thromboembolism, it is reasonable to initiate anticoagulation in patients in whom AF has persisted for 48 h or more. A CHADS2 score or CHA2DS2VASc score of 2 or more mandates the use of anticoagulants [31, 32]. Also, an appropriate risk–benefit analysis must be done to weigh the benefits of anticoagulation with the risk of postoperative bleeding. Toward this, HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history, or predisposition, labile INR, elderly, drugs/alcohol concomitantly) score can be calculated [33]. While making these decisions, it is of paramount importance that these measures and their implications are discussed and explained to the patient and the caregivers.

34.3.8 Chronic Postsurgical Pain (CPSP)

This is a well-known entity after any major or minor surgery, not necessarily oncosurgeries, and a high incidence of CPSP has been reported after breast surgery, amputations, and thoracic surgeries [34]. CPSP was defined based on the duration of pain, the association with a surgical procedure, and the exclusion of other causes [34]. The CPSP

definition proposed by Macrae (2001) was "pain should have developed after a surgical procedure; pain should be of at least 2 months' duration; other causes for the pain should be excluded, e.g. continuing malignancy (after surgery for cancer) or chronic infection; and in particular, the possibility that the pain is continuing from a pre-existing problem should be explored and exclusion attempted" [34]. It was redefined by Werner and Kongsgaard (2014) as "pain develops after a surgical procedure or increases in intensity after the surgical procedure; pain should be of at least 3–6 months' duration and significantly affect the quality of life; pain is either a continuation of acute post-surgery pain or develops after an asymptomatic period; pain is either localized to the surgical field, projected to the innervation territory of a nerve situated in the surgical field, or referred to a dermatome; and other causes of the pain should be excluded, e.g. infection, or continuing malignancy in cancer surgery" [35].

CPSP has a significant impact on the quality of life and increases the cost of medical care. The development of CPSP is multifactorial and can be broadly divided into nonmodifiable and modifiable factors (Table 34.5). Modifiable factors should be addressed as part of a well-planned perioperative strategy.

The role of preoperative counseling and allaying of anxiety and fear cannot be overemphasized. It has been reported that patients with a surgical outcome-related fear preoperatively have more pain, poor global recovery, and poorer quality of life after the surgical intervention as compared with patients who have an optimistic approach [36]. This aspect can be addressed with good preoperative counseling.

Table 34.5 Risk factors for chronic postsurgical pain

Nonmodifiable factors	Modifiable factors
Genetic predisposition Gender	Psychological factors Preemptive analgesia Better surgical techniques Shorter operating time Avoidance of nerve injury (cutting, stretching, crushing of nerves) Acute postoperative pain management

Laparoscopic surgeries offer an advantage as there is markedly reduced muscle injury and use of retractors; however, the incidence of post-thoracotomy pain syndrome was reported to be 25% after video-assisted thoracic surgery in a questionnaire-based study [37].

Better surgical skills can go a long way in reducing the incidence of CPSP. Breast surgery patients in a high-volume center are less likely to suffer from chronic pain, strange sensations in the ipsilateral arm, and phantom sensations in the removed breast, and this is due to higher surgical skills [38]. It is important to block or limit persistent pain sensitization in the postoperative period, and this requires newer therapies like multimodal pharmacological approaches. Future options like anti-nerve growth factor and Nav 1.7 antagonists to restore endogenous analgesia need to be explored [39].

34.4 Specific Perioperative Complications in Oncosurgeries

The oncosurgical interventions have some distinct complications that remain associated with patients with cancer. These specific cancer surgeries related complications are being discussed in the subsequent section.

34.4.1 Chemotherapy- and Radiotherapy-Related Perioperative Complications

The toxicity of chemotherapeutic agents can adversely impact cardiovascular, pulmonary, renal, hepatic, hemopoietic, and both central and peripheral nervous systems. There is a gap of about 3 weeks between neoadjuvant chemotherapy and surgery unless preoperative radiation has been given too wherein the gap may be as long as 10–12 weeks. All post-chemotherapy patients planned for surgery are high-risk patients. A thorough evaluation and optimization of chemotherapy-related side effects must be done preoperatively. The number of such patients

has risen in the last decade and a half due to the increasing use of neoadjuvant chemotherapy.

There must be all-time heightened awareness in the postoperative period for existing as well as hibernating chemotherapy-related issues (Table 34.6) and a well-chalked out plan to preempt any further deterioration in the affected organ system.

Apart from the hepatotoxic effects of chemotherapy agents, liver injury secondary to radiation therapy is well documented. The patients present within 4 months following hepatic radia-

Table 34.6 Adverse effect of chemotherapeutic agents and management in the postoperative period

Organs affected	Chemotherapeutic agents	Adverse effects	Suggested management
Cardiotoxicity [40, 41]	Anthracyclines Anthraquinolones	Congestive heart failure Left ventricular dysfunction Acute myocarditis Arrhythmia	General physical examination, preoperative ECG, evaluation of left ventricular ejection fraction by a 2D echo, stress echo if required, baseline B-type natriuretic peptide, and troponins Involvement of cardiologists as part of a multidisciplinary perioperative team Cardioprotection with ACE inhibitors, angiotensin II receptor blockers, and β-blockers may be considered Prophylaxis for thromboembolism after risk–benefit analysis
	Capecitabine 5-fluorouracil Cytarabine	Congestive heart failure and cardiogenic shock Myocardial ischemia Pericarditis	
	Paclitaxel Vinca alkaloids	Congestive heart failure Myocardial ischemia Hypotension Rhythms disturbances—block (atrioventricular, ventricular tachycardia, sinus bradycardia)	
	Cyclophosphamide	Valvular dysfunction—mitral regurgitation Neurohumoral activation	
	Imatinib	Congestive heart failure Left ventricular dysfunction arrhythmias Angioedema	
	Ifosfamide Gemcitabine Melphalan Cisplatin Docetaxel 5-fluorouracil Etoposide High doses of corticosteroid	Atrial fibrillation	
Hepatotoxicity [42–47]	Irinotecan	Steatohepatitis	Baseline liver functions and a close watch in the postoperative period Tests for assessing hepatic clearance of compounds like indocyanine green Imaging for residual liver remnant after hepatectomy Optimal recovery of the functional status of the organ system (5 weeks) [46, 47]
	Oxaliplatin	Sinusoidal dilation Vascular lesions requiring increased blood transfusion	
	Tamoxifen	Nonalcoholic fatty liver disease (NAFLD) Nonalcoholic steatohepatitis (NASH)	
	Methotrexate	Cirrhosis	

Table 34.6 (continued)

Organs affected	Chemotherapeutic agents	Adverse effects	Suggested management
Nephrotoxicity	Cisplatin Ifosfamide Mithramycin	Acute tubular necrosis	Preoperative evaluation of renal function, watchfulness in female patients, diabetics, age > 65 years, preexisting chronic renal disease Prevention of volume depletion and renal hypoperfusion Avoidance of nephrotoxic agents
	Methotrexate	Crystal nephropathy	
	Bevacizumab Tyrosine kinase inhibitors Mitomycin Gemcitabine	Thrombotic microangiopathy	
	IFN Pamidronate	Focal segmental glomerulosclerosis	
	Sorafenib Sunitinib	Acute interstitial nephritis	
Toxicity of central and peripheral and autonomic nervous system [48, 49]	Paclitaxel	Demyelination	Identification and documentation Measures to prevent postoperative cognitive dysfunction, assisted mobilization, prevention of falls, prevention of position-related injuries and pressure sores in the perioperative period with frequent changing of postures and padding Matching any deficit with the preoperative mapped areas
	Vinca alkaloids	Loss of deep tendon reflexes, numbness, and burning sensation in hand and feet Orthostatic hypotension Myalgia Loss of pain and temperature sensation	
	Cisplatin	Loss of deep tendon reflexes, ototoxicity, sensory ataxia	
	Ifosfamide	Somnolence, confusion, dizziness, cranial nerve dysfunction, depressive psychosis, seizures, coma	
	Methotrexate	Headache, lethargy, nuchal rigidity, cerebellar dysfunction	
	Oxaliplatin	Acute sensory symptoms and chronic sensory neuropathy	
	Bortezomib	Painful, small fiber sensory neuropathy	

tion therapy with classic symptoms of radiation-induced liver disease (RILD). These symptoms include ascites without icterus, hepatomegaly, and isolated disproportionate elevation of alkaline phosphatase. The same level of derangement is not seen in other liver enzymes. Patients with preexisting liver disease are more susceptible, and they may manifest as nonclassic RILD.

Radioembolization-induced liver disease (REILD) is also a recognized adverse effect of cancer-related therapy. It appears 4–8 weeks following radioembolization treatment for cancer and pathologically leads to sinusoidal obstruction syndrome. Patient presents with symptoms like jaundice and ascites with increasing levels of gamma-glutamyl transpeptidase (GGTP) and alkaline phosphatase [50]. Chemotherapeutic agents may injure vasculature of the kidney, glomerulus, proximal or distal tubules, and collecting ducts, and they may be classified accordingly [51].

It has been reported in a cross-sectional analysis of prospectively collected data from

3558 patients that the rate of acute kidney injury (AKI) in hospitalized cancer patients was much higher than those not suffering from cancer. Furthermore, irrespective of underlying cancer, those with diabetes and hyponatremia, on antibiotics and chemotherapy, with exposure to intravenous contrast, or with the history of ICU stay during hospital admission were at a higher risk for developing AKI in the hospital. There exist other several predisposing factors for AKI in cancer patients along with chemotherapy, and preemptive steps to prevent AKI may improve the clinical outcome [52].

While evaluating the patient for chemotherapy-related adverse effects on the central and peripheral nervous system, one must keep in mind other differential diagnoses like preexisting diabetic neuropathy, dementia, Vitamin B12 deficiency, Charcot–Marie–Tooth disease, peripheral vascular disease, and any paraneoplastic neuropathy like POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes). Any preexisting neuropathy should be mapped. Regional anesthesia should be avoided, or appropriate informed consent must be taken.

34.4.2 Challenges of Chronic Opioid Therapy

Management of anesthesia and postoperative pain can pose a challenge in cancer patients on chronic opioid use who are scheduled for palliative procedures. Unlike patients with addiction to recreational agents, the patient knows the drug and dosages, or his caregiver has all the details. These drugs are mostly according to the national health regulations in their country, and there is a prescription available.

The routine dose of analgesics that a patient is taking for his pain management needs to be continued until the day of surgery. A patient on pure μ agonist should not be shifted to a partial agonist or an agonist–antagonist. In India, morphine is the most prescribed opioid in cancer patients. Baseline opioid requirements should be met with an additional dosages of the same, or another short-acting pure mu agonist opioid can be added for acute pain in the perioperative period. As the acute pain following surgery subsides, these can be gradually reduced, and patients can then continue with the earlier or newly tailored opioid dose. Additionally, paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) remain an important component of multimodal management. Regional anesthesia can be given safely if there are no other contraindications. Other side effects of chronic opioid use like constipation, nausea, and cognitive impairment should be managed in the postoperative period.

34.4.3 Malnutrition, Hypoalbuminemia, and Anemia

Nutritional status is one of the important factors for an optimal perioperative outcome in oncosurgeries. Malnutrition has been reported to impact adversely the outcome parameters like morbidity, mortality, length of the hospital, and intensive care unit stay [53]. Hypoalbuminemia is one of the independent predictors for poor outcomes in oncosurgeries and is associated with an increased risk of deep vein thrombosis [54], surgical site infection [55], and nonhealing enteric fistula [56, 57]. Type, site of cancer, stage of cancer, apathy due to depression, and gastrointestinal side effects of preoperative radiation or chemotherapy can attribute to malnutrition. Patients undergoing palliative procedures may present with cachexia or sarcopenia.

Serum albumin levels correlated directly with perioperative morbidity and mortality. The mortality rate increases from less than 1% to 29% and morbidity rates increase from 10% to 65% when the serum albumin levels fall from greater than 46 g/L to less than 21 g/L in a cohort of patients scheduled for noncardiac surgeries. So, albumin may be considered one of the important perioperative predictors even in oncosurgeries. This prognostic tool is low cost, is easily available, and predicts accurately [58].

There are three key recommendations of the expert group of the European Society of

Parenteral and Enteral Nutrition (ESPN) [59]. The patients undergoing oncosurgeries should be screened for nutrition in the preoperative assessment irrespective of baseline BMI and weight. These assessments must be expanded to include body composition, anorexia, inflammatory biomarkers, physical function, and resting energy expenditure. The nutritional optimization should be initiated at the earliest. There must be individualized plans using multimodal interventions and should include appropriate planning and counseling for nutritional intake, physical activity, decreasing inflammation, and hypermetabolic stress [59]. The process must start as part of prehabilitation before surgery and continue during the perioperative period.

As per recommendations of ESPN guidelines on clinical nutrition in surgery in patients with poor nutritional risk, a wait of 7–14 days is appropriate even in cancer surgeries for nutritional therapy. The nutritional management should be initiated at the appropriate time in the preoperative period and should continue at the earliest after the surgery. It should be according to the tolerance of the patients, and the type of surgery and caution must be exercised with elderly patients. The selection of a route for nutrition needs to be selected as appropriate with preference enteral or oral route. Where enteral nutrition is contraindicated or not feasible or not tolerated, then parenteral nutrition should be instituted. In malnourished patients undergoing major upper gastrointestinal and pancreatic surgery, feeding through the nasojejunal tube or a feeding jejunostomy should be considered. If the requirement of tube feeding is longer than 4 weeks, then percutaneous endoscopic gastrostomy should be considered for optimal nutrition [60]. The combination of enteral with parenteral nutrition was found to be beneficial in elderly patients undergoing surgery for gastrointestinal malignancies [61].

Anemia in cancer patients may be due to malignancy-related blood loss, marrow infiltration, myelosuppression due to radiation or chemotherapy, poor intake, or chemotherapy-related chronic renal disease. Iron deficiency is one of the etiological reasons for anemia in cancer patients. Hence, assessment for the type of anemia in cancer patients should be done. Serum ferritin, C-reactive protein, and transferrin saturation aid in making a diagnosis of anemia. Of these, serum ferritin level < 30 μg/L has been recognized to be diagnostic for diagnosing iron deficiency anemia. Other markers like the levels of C-reactive protein>5 mg/L and/or transferrin saturation < 20% with a serum ferritin level < 100 μg/L indicated toward the diagnosis of iron deficiency anemia. If surgery is scheduled in less than 6 weeks, then parenteral iron should be given, but if surgery is 6–8 weeks later, then oral iron supplements and nutrition should be given for the management of anemia [62, 63]. Erythropoietin is used in treating anemia due to myelosuppression, but the threat of deep vein thrombosis should be kept in mind.

34.4.4 Difficult Airway

Cancers of head and neck (H&N) are a significant proportion of overall malignancy worldwide, and difficult airway remains challenging in these patients. These difficult airways comprise over 75% wherein difficulty in maintaining oxygenation or complete ventilation failure remains a possibility and mandates the needs of surgical access [64–66].

Apart from an infiltrating tumor, radiation renders tracheal intubation and mask ventilation difficult by causing tissue fibrosis, loss of tissue compliance, restricted mouth opening and neck extension, and glottic and epiglottic edema [67]. History suggestive of difficult airway is one of the important indicators of present difficult airway, but caution should be taken even if this was suggestive of a normal/easy airway [68]. Patients with H&N pathology have a high incidence of difficult video laryngoscopy than other patients. The strongest predictors of Glide Scope failure were conditions that are likely to exist in H&N cancer patients, including prior neck radiation, abnormal neck anatomy, and airway masses [69].

In advanced H&N disease, even a surgical airway becomes very challenging and sometimes impossible due to decreased mandibular protrusion and postradiation changes in the neck. A successful airway strategy requires a preformulated

plan for managing failed intubation attempts and for achieving and maintaining adequate ventilation, oxygenation, and protection against aspiration [70]. The optimal airway management approach depends on the surgical procedure, location of the lesion, patient symptoms, acuity of the situation, and the patient's tolerance of the airway management procedure. It may also be dictated by the anesthesiologist's skill set and equipment availability.

H&N tumors can cause airway distortion and can be friable, leading to bleeding, fragmentation, airway soiling, and rapid edema formation with laryngoscopy. Due to this, airway access may deteriorate even after a single aborted attempt and may worsen with repeated attempts at direct laryngoscopy in these patients. If direct laryngoscopy (DL) is chosen as a primary approach to tracheal intubation, multiple attempts should be avoided to avert total airway obstruction. The use of a flexible endoscope or video laryngoscope needs to be considered as a choice of equipment in patients with H&N cancers. At times, the use of a rigid bronchoscope remains a rescue measure especially in conditions of airway obstruction due to tumor mass, bleeding, etc. [71, 72]. The most common reasons for the failure of flexible scope tracheal intubation in these patients include the inability to identify the glottis, difficulty in passing the scope, bleeding, and airway obstruction [65]. Optical intubation stylets may have some advantages over flexible scopes. These rigid devices may bypass mobile supraglottic and glottic masses in situations when a flexible scope will not pass. Supraglottic airway devices may be difficult to insert or seat in patients with H&N pathology due to abnormal anatomy. History of neck radiation; limited mouth opening; and glottic, hypopharyngeal, and subglottic pathology, all of which may be present in these patients, are predictors of difficulty with supraglottic airway ventilation.

The combined use of video laryngoscopy with a flexible scope or optical stylet is increasingly common in complex airway management. Video laryngoscopy provides a clear view of the glottis and thus allows negotiation of the flexible scope or optical stylet in patients with distorted anatomy or airway tumors. The combined technique is thus useful for not only providing clear images but also providing dynamic images for observing the real-time intubation procedures and preventing any direct trauma to the mass lesion.

Oxygenation-centered airway management is critical for H&N cancer patients, who present with a higher incidence of failed tracheal intubation and "cannot intubate, cannot ventilate" (CICV) or complete ventilation failure situations. The use of high-flow nasal oxygen (transnasal humidified rapid insufflation ventilatory exchange [THRIVE]) is a useful technique and provides increased apnea time. The oxygenation throughout the intubation procedure remains an important step [73]. In selected cases, the use of transtracheal jet ventilation (TTJV) catheter or cannula or high-frequency TTJV [74] may be considered for preoxygenation before induction.

A tracheostomy may be planned as the primary intubation strategy for patients who are expected to have significant airway compromise after surgery. Most H&N cancer surgeons prefer to perform tracheostomies under controlled conditions, after induction of anesthesia, to avoid airway trauma, tumor disturbance, and tracheostomy tube displacement or obstruction. The final decision is usually taken in a controlled environment after the induction of anesthesia. In case, awake surgical access is deemed necessary, then a difficult airway cart should be ready and avoid any sedation. An awake dilator cricothyroidotomy is another good alternative [75]. For emergency airway management, surgical cricothyroidotomy is strongly preferred over percutaneous access through the cricothyroid membrane.

Inhalation induction should be considered for patients with H&N cancer only after consultation with the surgeon and evaluation of the predicted difficulty with mask ventilation and may be best reserved for patients with noncollapsing lesions [76]. Inhalation induction may be highly problematic for patients with difficult mask ventilation.

Emergence from anesthesia for H&N cancer patients should include a smooth, rapid awakening and extubation. Extubation should be devoid of coughing, bucking, and straining. Blood pres-

sure should be controlled during emergence and in the immediate postoperative period for many H&N procedures.

Endotracheal extubation should be planned as thoroughly as endotracheal intubation and requires a strategy for patients who undergo H&N procedures.

Compared with other elective surgeries, H&N surgeries are associated with higher rates of airway complications like laryngospasm, postextubation airway edema, postoperative airway obstruction, and need for reintubation during and immediately after emergence and well-planned extubation [77]. One-third of adverse events reported to the fourth National Audit Project (NAP) of the Royal College of Anaesthetists occurred during emergence and recovery from anesthesia [78]. The plan for extubation should be formulated with the surgeon and should consider the difficulty of initial intubation, the extent and duration of surgery, the potential for postoperative swelling or bleeding, and the patient's current and preoperative medical status. The algorithm of the Difficult Airway Society (DAS) and All India Difficult Airway Association (AIDAA) can be a good foundation for the extubation strategy. The use of a supraglottic airway device as a primary ventilatory device, instead of an endotracheal tube for smooth emergence and extubation (Bailey Maneuver), is a well-known strategy [79]. Extubation can be delayed in cases of anticipated extubation failure. Such patients must be managed in an intensive care setting allowing 24–48 hours for the surgical edema to subside. Thereafter extubation should be carried out under the supervision of personnel with expertise in airway management and with a difficult airway cart at bedside. The use of bridge adjuncts like airway exchange catheter remains useful.

34.4.5 Problems of Brachytherapy and Intraoperative Radiation

Brachytherapy is one of the modalities to provide radiation therapy and is being used for H&N cancers as well. Here, the catheters are placed at the site of cancer lesion at suitable distances and radiation is provided using these brachy-catheters. This technique provides radiation exposure to the cancer lesion without having adverse effects on other nearby structures even at high doses [80].

Advanced head and neck tumors and tumors of the pelvis and retroperitoneum may require intraoperative radiation therapy (IORT). After debulking of the tumor, the nearby normal vital organs/structures are manually moved out of the way and protected with the shield. The patient is then shifted from the operation room to the brachytherapy suite, and here, a high dose of radiation as per calculations is directed onto the target surface.

IORT necessitates the continuation of anesthesia care beyond the familiar operating room setup to a remote area. The patient is shifted to the brachytherapy suite while maintaining anesthesia with intravenous agents like propofol and opioids. Manual ventilation or portable ventilators are used if neuromuscular blocking agents are used. An anesthesiologist always accompanies the patient maintaining the standards of care and monitoring. The American Society of Anesthesiologists (ASA) guidelines for providing anesthesia in the nonoperating room must be followed [81]. The location should have an anesthesia machine with drugs and standard monitors, a resuscitation cart with the defibrillator and emergency drugs, a source of oxygen, suction, anesthesia gas scavenging, and trained support staff.

The radiation equipment is maintained at a low temperature to prevent overheating. Hence, it is important to maintain normothermia in anesthetized patients with warming blankets and warm intravenous fluids. Considering that levels of radiation in the brachytherapy suite are very high, the staff must be protected with lead aprons and thyroid shields [82].

To prevent radiation exposure-related health hazards, the anesthesiologist should not be present during radiation therapy. A remote-controlled duplicate set of monitors (master and slave concept) should be available outside the radiation area. Video cameras should be installed so that the patient can be monitored for any movement, displacement of the endotra-

cheal tube, invasive lines, or intravenous connections. There should be a provision to stop the radiation immediately if patient safety is compromised due to any reason.

34.4.6 Carotid Blow Out Syndrome

Carotid blow out syndrome (CBS) is one of the complications seen in patients undergoing cancer treatment (surgery and radiotherapy), especially for H&N cancers. It has been observed in around 3–5% of such patients [83]. The presentation is sudden massive trans-oral or trans-cervical bleeding with high rates of mortality and neurological morbidity.

CBS may present in three different clinical conditions depending on the severity. CBS may present with threatened blowout where vessels are clinically exposed or there is the invasion of vessels by the tumor as evident from imaging modalities. CBS may also be evident as an impending blowout where the bleeding from the vessel has stopped spontaneously. The most dreaded CBS presentation is acute, profuse, and uncontrollable bleeding [84].

The gold standard modality for diagnosis of CBS is angiography. This technique also provided therapeutic options simultaneously like endovascular stenting [85]. Computed tomographic and magnetic resonance angiography can also be used to identify the threatened lesions [86].

Early endovascular stenting is indicated in threatened lesions to prevent hemorrhage. But an impending or acute CBS requires volume resuscitation, application of pressure to stop the bleed, and earliest control of the airway. In successfully resuscitated and stabilized patients, endovascular procedures may be attempted. However, if interventional radiology therapies are unavailable or fail, then urgent surgical intervention is required. Suggested steps in the management of CBS include comprehensive management (Table 34.7).

In terminally ill patients with H&N cancers, if CBS appears to be likely, then an informed discussion must be held with the patient and the caregivers to plan the care and interventions. The wishes of the patient should be respected and care must focus on ensuring alleviation of symptoms and not prolongation of life.

Table 34.7 Suggested steps in the management of CBS

Pressure on the bleeding vessels using digital pressure or balloon tamponade
Initiate advanced trauma support protocol
Initiate massive transfusion protocol
Maintain oxygen saturation > 95%
Shift to operation room/endo-radiology suit
Surgical intervention includes debridement of the wound, excision of the malignant mass, closure of the fistula, coverage of the exposed vessel, and surgical site using a well-vascularized tissue graft.

34.4.7 Microvascular Flap Necrosis

The flap reconstruction is one of the important reconstructive aspects after H&N surgeries. These flaps could be either a free flap (microvascular flap) or a pedicle flap. These surgeries are frequently performed as part of cancer surgery for covering a resected area for functionality, protection, aesthetics, or a combination [87, 88]. The flap needs to be monitored in the postoperative period as flap loss remains a dreaded complication. Certain comorbidities in a patient and some perioperative conditions may predispose a patient to loss of a flap. Some of the risk factors considered to be responsible for flap necrosis are listed in Table 34.8.

The use of anticoagulants is one of the preventive measures, but no single anticoagulation regimen has been found to offer any significant advantage over others with regard to flap outcome including flap thrombosis and its loss [98]. The choice of anesthetic technique also has a role in the flap outcome. The principal goals in the perioperative period remain maintenance of low blood viscosity to maintain flap perfusion, better oxygenation, and vasodilation and maintain good perfusion pressure. The measures are required to prevent excessive blood loss during surgical resection. Balanced general anesthesia

Table 34.8 Patient and perioperative risk factors, which may result in flap necrosis

Patient risk factors	Perioperative risk factors
• Preoperative radiation [89] • ASA physical status III and higher [90, 91] • Age > 70 years [92] • Hypercoagulability (hereditary or acquired) [93] • Low cardiac output state, congestive cardiac failure, moderate-to-severe aortic stenosis, low cardiac index [94] • Preoperative anemia (<10 g/dL) [95]	• The length of the flap may lead to its kinking leading to compromised vascular supply and thus necrosis. Also, vessel compression, pedicle tension, external compression due to bandage, hematoma, neck position, etc. may lead to flap compromise [96] • Undetected ischemia of the flap • Hypotension • Prolonged surgical time [97]

with optimal vasodilation and minimal cardiac depression should be targeted during prolonged free flap procedures [99]. The use of regional blocks has been reported to be beneficial by vasodilation of the vessels, reduce vasospasm episodes of the grafted vessels, and thus maintain perfusion of the grafted flap. However, this has a limited role on H&N flap but good analgesia needs to be provided. Nonsteroidal anti-inflammatory drugs can increase the risk of perioperative bleeding and hematoma formation, and this effect may get potentiated in the presence of anticoagulation; hence, they should be avoided.

To avoid flap edema, crystalloids should be targeted to meet the basic physiological needs and its overloading should be avoided. The use of synthetic colloids is the other option to replace blood loss and maintain adequate tissue perfusion. Hematocrit and hemoglobin must be maintained with blood products to its physiological levels to maintain not only perfusion but also oxygenation. The vasopressors should be cautiously used, especially during the graft harvesting as vasopressors affect the vessel dimensions including perforators and its identification. This leads to the technical dissection of the flap with its blood supply [100]. Intraoperative hypothermia should be prevented by using fluid warmers and warm air systems.

34.4.8 Chyle Leak and Its Management

Chyle leak is an infrequent complication but it must be dealt with efficiently. In case it is leaking inside the chest or abdomen and not draining out then to prevent lung compromise, a chest tube insertion, repositioning of an existing one or a pigtail drain insertion, may be required. Most of these leaks resolve spontaneously though occasionally surgical intervention may be required. The main aim of the management of chyle leaks is to follow strategies that aid in decreasing the production of chyle itself. This shall in turn help in decreasing the ascites and pleural effusion, maintain fluid and electrolyte balance, and also prevent nutritional loss. Though there is no robust evidence, restricting lipids in the diet is widely practiced and the use of medium-chain triglycerides in enteral nutrition is encouraged [101].

34.5 Summary

The most effective step to prevent complications in oncosurgery is to keep all the complications on our clinical radar, ensure early detection, and prompt targeted treatment.

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35 Anesthesia for Operative Oncological Emergencies

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35.1 Introduction

Emergencies are a challenge for the treating team and can result in significant morbidity and mortality if not managed appropriately and urgently. An emergency can be defined as an acute life-threatening event related to tumor invasion (i.e., gastrointestinal tract or brain mass lesions), or complications of cancer directed therapy, such as radiotherapy, chemotherapy or immunotherapy (i.e., perforation). An undiagnosed malignancy may also present as an emergency. A cancer patient may present for an emergent surgery unrelated to the cancer for example a bowel perforation in a patient with a buccal mucosa carcinoma. For early detection and better outcomes, the oncologist must maintain a high degree of suspicion. Patients and families also need to be aware of warning symptoms and red flags so that they report early to the hospital. The chapter focuses on perioperative concerns and anesthetic implications of emergency oncological surgical interventions.

35.2 General Considerations

In the management of oncological emergencies, a meticulous assessment is required. In addition to routine preoperative assessment for onco-surgical intervention, there are aspects unique to cancer and cancer directed therapy that may complicate the course of management. For instance, prior cardiotoxic chemotherapy or neck radiotherapy needs to be factored in to the anaesthesia management. Perioperative optimization and effective coordination between oncology (surgical, radiation and medical), anesthesia and intensive care teams is key.

Cancer and/or its therapy may lead to metabolic or physiological abnormalities which may need to be addressed urgently prior to surgery. However, some abnormalities remain inherent to cancer and increase the risks associated with emergency surgery. Certain pathologies related to cancer like anterior mediastinal mass, superior venae cavae syndrome, brain metastasis, and effusions (pleural/pericardial) may complicate the management of anesthesia. The team needs to evaluate and plan for difficult venous access, difficult airway, postoperative respiratory support, and availability of blood products. Perioperative management of anemia, thrombocytopenia, or pancytopenia may be needed in the patient who is on active cancer therapy.

It may not be easy to stratify risk accurately using conventional tools like the American

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Society of Anaesthesiologists (ASA) physical status, especially for geriatric patients. This is primarily due to multiple factors apart from physical status and associated comorbidities. Factors like poor functional capacity, cognitive impairment, low serum albumin, low hemoglobin, history of falls, presence of fatigue, and other associated comorbidities have an association with increased perioperative morbidity and mortality [1].

The functional capacity of the cancer patient can reliably predict perioperative cardiac morbidity. The cancer patient may present acutely and be chronically debilitated and have a poor cardio-respiratory reserve. The patient's baseline functional status is a predictor of perioperative risk. The functional capacity of the cancer patients has an inverse relationship with the perioperative major cardiac events. The conventional assessment tools like stair climbing tests have been found to have a good relationship with the prediction of postoperative complications. The inability to climb two flights of stairs has a positive predictive value of 82% for the occurrence of postoperative complications: cardiac (arrhythmias, heart failure, and myocardial infarction); pulmonary (pneumonia, embolism), and mortality [2].

Onco-surgical emergencies give little time for the optimization of concurrent comorbidities like ischaemic heart disease. The main cause of perioperative myocardial infarction is the imbalance in demand–supply of oxygen to cardiac muscles. Therefore, the perioperative plan goals include monitoring for ischaemia and the prevention of tachycardia, hypotension and decreased cardiac output.

In onco-surgical patients, the focus of the perioperative physician is the maintenance of physiology. This requires appropriate fluid resuscitation, preventing dyselectrolytemia and optimizing acid–base disturbances. Prevention and aggressive management of sepsis is paramount in the immunocompromised cancer patient. Correction of anemia, coagulopathies, and acute bleeding needs to be done on an urgent basis. The goal in such a patient is to maintain optimal tissue and organ perfusion and thereby optimal delivery of oxygen. The fluid requirement varies depending on the overall patient status, the underlying pathology, and the presence of associated conditions like sepsis. Judicious fluid administration will ensure an effective circulating volume and can be monitored by measures like urine output and lactate levels. The perioperative optimal fluid management decreases the length of hospital stay, postoperative morbidity, and mortality. The choice of fluid (crystalloids, colloids, and blood products) influence the overall outcome after the surgical intervention. The main guiding principle of fluid management includes the prevention of organ hypoperfusion including vital organs like the renal system, dyselectrolytemia, avoidance of fluid overload and tissue oedema.

Perioperative fluid may be administered according to the precalculated fluid volume based on estimation using patient body weight, deficit, type of surgery, and third space fluid loss during surgery. This traditional type of fluid administration is often inaccurate given emerging evidence of its deleterious effects. It also does not consider other comorbidities like cardiovascular status [coronary artery disease (CAD), sepsis, and cardiac failure].

Goal-directed therapy (GDT) for fluid management is increasingly being recommended. This is based on measuring the variables that guide the appropriate use of fluids and drugs to maintain organ perfusion. The various physiological variable that have been used includes stroke volume variation (SVV), cardiac output, tissue oxygen contents, systemic vascular resistance (SVR). These guide selection and appropriate use of crystalloids, colloids including red blood cells, inotropes, and vasopressors. Failure to maintain adequate circulating volume may lead to hypoperfusion and diversion of blood from non-vital organs like the gastrointestinal tract, skin, and liver to vital organs like the brain, heart, and kidney. This leads to tissue hypoxia and increases perioperative morbidity. With large fluid shifts and surgery, fluid therapy can be a challenge [3–5].

The perioperative anesthesia plan for oncological emergency surgical interventions needs to be individualized based on patient assessment, and the proposed surgical intervention. The time avail-

able for optimization, that is, urgency of the surgery also remains the deciding factor for the anesthesia plan. The various options include general anesthesia, regional anesthesia, and/or in combination. At times, certain minor surgical interventions, for example, percutaneous drainage, especially in the sick patient may be done under sedation and monitored anesthesia care. An optimal anesthetic technique depends on an individualized assessment of patient and surgical requirements. There is dearth of robust evidence to guide clinicians managing surgical emergencies [6].

The key points for perioperative management of the patients presenting with emergency onco-surgery recommendations that have been found to decrease the in-hospital mortality include [7–9]:

- A proactive approach with early surgical intervention after quick optimization of the patient status.
- Sepsis is common in patients presenting for emergency surgery.
- Patients for onco-surgical emergencies need to be considered as high risk and a high index of suspicion is mandated for its assessment. Look for tachypnoea, tachycardia, altered mental status, early identification through a reliable scoring system (like Sequential Organ Failure Assessment, SOFA), and treatment based on surviving sepsis guidelines.
- Protocolized fluid therapy as guided by dynamic indices like SVV besides standard hemodynamic parameters.
- Continuous involvement of a multidisciplinary team including the senior anesthesiologist, intensivist, and surgeon.
- Postoperative intensive care unit (ICU) or high dependency unit (HDU) care.

Literature reports high 30-day mortality ranging from 15% to 18% in a subgroup of patients presenting specifically for emergency laparotomy—the commonest causes being intestinal obstruction and perforation. This mortality is even higher rising to 25% in elderly patients with advanced malignancy and comorbidities [10, 11].

The conventional recommendations of fasting for 2 h for clear liquids, 6 h for a light meal, and 8 h for a fatty meal depend on the urgency and emergency of the surgical interventions. Emergent surgery may not permit adherence to strict fasting protocols and appropriate protective measures including prokinetics (like metoclopramide), H2 receptor blockers, and Sellick's maneuver may reduce the risk of aspiration.

35.3 Malignant Bowel Obstruction

The overall prevalence ranges from 3% to 15%, most seen in ovarian and colorectal malignancy. Other primary sites of malignancy causing intestinal obstruction are the pancreas (6–13%), urinary bladder (3–10%), endometrium (3–11%), breast (2–3%), stomach (6–9%), and melanoma (3%). In advanced stages of ovarian malignancy, the prevalence can be as high as 50% [12].

Nine to 16% of newly diagnosed colorectal malignancies present to hospitals in an emergency setting [13]. Emergent surgery has a ten times higher mortality than elective surgery in colorectal cancer [14]. Emergency surgery has mortality rates of up to 15% [15]. The cancer lesion can directly lead to obstruction of the bowel via external compression, direct invasion, or peritoneal carcinomatosis. This leads to the clinical features of perforation and infection.

Various advanced malignancies like ovarian cancers present with malignant bowel obstruction. At times, such bowel obstruction is indicative of advanced malignancy and hence the perioperative team should consider the trajectory of disease for an optimal decision related to surgical intervention. Surgery used to be the mainstay but increasingly less invasive techniques (endoscopic, radiologic) have found a place in management. A patient may undergo an ileostomy, diverging colostomy, stent placement, stenting followed by secondary surgery, palliative bypass procedure, palliative chemotherapy, or radiotherapy, and at times, even radical resection. The selection of these interventions depends on individual patients' assessment and disease status. A systematic review has reported alleviation of obstructive symptoms with the success-

ful discharge of 34–87% of patients with bowel obstruction after palliative surgery. The mortality reported was 6–32% [16].

The various determinants of the perioperative morbidity and mortality include age > 65 years, American Society of Anesthesiologists physical status ≥2, advanced disease, medical comorbidities, malnutrition with hypoalbuminemia, high blood urea nitrogen, ascites, leukocytosis, and multifocal obstruction, and emergency surgery [15, 17–22]. The significance of prior radiotherapy (RT) as a prognostic indicator in patients with gynecological malignancy presenting with obstruction for palliative surgery is not clear. Fernandes et al. [23] reported that previous RT decreases the chances of survival after surgery while according to Krebs and Goplerud [24] RT alone poorly predicts the clinical benefit of surgery. Sjo et al. compared the elective vs emergency colonic cancer surgery and observed higher complication rate (38 vs. 24%) and mortality (10 vs. 3.5%) in patients undergoing emergency surgeries [25].

35.3.1 Preoperative Optimization

The main goals are correction of fluid and electrolyte imbalance, acid–base disturbance, and restoration of hemodynamic instability especially in patients with perforation and impending sepsis. Broad-spectrum antibiotic prophylaxis is recommended in all patients with signs suggestive of sepsis and requiring emergency surgical exploration.

Hypochloremic metabolic alkalosis, hypovolemia, and hypokalemia due to loss of potassium and hydrogen ion-rich fluid are usually seen in patients with upper bowel obstruction. Additionally, small bowel obstruction causes abdominal distension with the upward displacement of the diaphragm and increased chances of atelectasis and pneumonia preoperatively. Large bowel obstruction is associated with metabolic acidosis due to the loss of bicarbonate rich fluid. With increasing inflammation, there is increased protein loss. Methane accumulation can also cause hyperammonemia and alkalosis. Sequestration of fluid and gas proximal to obstruction leads to fluid leaking into the peritoneum and peritonitis. The subsequent vascular shifts lead to hypovolemia, shock, and dehydration.

The preoperative fluid deficit cannot be assessed accurately as it is difficult to estimate the third space (third space is considered by some as a fictional construct) and intraluminal losses. Sometimes compensatory mechanisms due to gradual fluid sequestration could be misleading. Hypoalbuminemia due to loss of protein-rich fluid from the gut and nutritional deficiency further complicates the intravascular volume depletion. The fluid status needs optimization and goals of preoperative fluid therapy aim at replacing vascular and interstitial fluid loss, optimization of electrolyte, and metabolic abnormalities. This ensures adequate circulatory fluid and thus improves oxygen delivery to tissues. The response of fluid resuscitation is ensured by adequate urine output, improving the trend in hemodynamic and oxygenation. Crystalloid including balanced salt solution remains the fluid of choice for resuscitation and fluid replacement. Colloids may be considered if substantial crystalloids have been used for resuscitation. Starches need to be used carefully as these fluids are associated with kidney injury especially in patients with sepsis. Most of the available data comparing colloids with crystalloid use have been extrapolated from critically ill patients; however, a few small studies on surgical patients have reported no difference in postoperative acute kidney injury and mortality on comparing crystalloid with low molecular weight 6% hydroxyethyl starch (HES) [26, 27].

Goal-directed fluid therapy is well accepted and endpoints like pulse pressure variation (PPV) and transesophageal Doppler-based algorithms for stroke volume have been used [28, 29]. It has been reported that PPV-directed fluid replacement led to more stable cardiovascular status, lesser hospital stay, and earlier return of bowel function, hemodynamics as compared to restrictive fluid management in ASA physical status I/II patients undergoing open gastrointestinal surgery

[28]. The choice between crystalloids and colloids in ASA physical status I/II patients undergoing open gastrointestinal surgery remains and controversial with regard to beneficial outcomes and overall, renal dysfunction. The colloids should be cautiously and judiciously selected for the selected group of patients. Balanced HES (130/0.4, 6%) solution is associated with stable hemodynamics with a lesser requirement of fresh-frozen plasma (FFP) in patients undergoing laparotomies for gynecological surgeries [30]. Yates [30] however reported no added advantage of colloids over crystalloids in terms of reducing the surgical morbidity after goal directed fluid therapy in colorectal surgery. On the other hand there were no signs of renal dysfunction attributable to colloid administration when fluid therapy is targeted to optimize cardiac preload.

35.3.2 Anesthetic Management

A large-bore intravenous line or central venous catheter as appropriate should be secured preoperatively for fluid resuscitation. H2 receptor antagonists may be given due to the high risk of aspiration. Intraoperative monitoring includes standard monitoring and the use of invasive and advanced monitoring tools are based on the patient clinical status and type of surgical intervention. Invasive hemodynamic monitoring is required for elderly patients with comorbidities, patients with signs of sepsis, or hemodynamic instability at presentation for emergency intervention. It also serves the purpose of frequent sampling for arterial blood gas (ABG) analysis in perioperative settings.

The choice of anesthetic technique depends on the patient's status including fasting and rapid sequence induction and intubation. The anesthetic agents for induction and maintenance are determined by the condition of the patient. Induction of anaesthesia and incremental doses of all anesthetic drugs including analgesics need to be titrated judiciously in the sick patient. There is no specific recommendation about anesthetic agents in emergency bowel surgery apart from avoiding the use of nitrous oxide [31]. An epidural block may be considered only if the benefits of reduction of perioperative pain, stress, and pulmonary complications outweigh the risks of cardiovascular instability and coagulopathy. A tense abdominal wall can decrease venous return and increase anesthetic and relaxant requirements. Hypotension can lead to end-organ hypoperfusion in patients with already compromised hepatic and renal blood flows due to long-standing intraabdominal hypertension. Central venous pressure does not serve as a guide for intravascular volume status in patients with a distended abdomen. Although hypovolemia is the major contributor to intraoperative hypotension, overzealous fluid administration can lead to postoperative salt and fluid overload. Fluid overload worsens the bowel edema and surgical outcome. Fluid management in these patients is a challenge. Goal-directed fluid therapy is the gold standard by transoesophageal Doppler, stroke volume variation, or lithium dilution cardiac output monitoring. Real-time data from these monitoring tools can be used to titrate intravenous fluids, blood, and inotropes. Recent evidence suggests that although it reduces the postoperative morbidity, length of hospital and ICU stay, it does not reduce the overall mortality. However, evidence for its use in emergency cancer surgery is scarce. In low resource settings a fluid regimen with a urine output of 0.5–1 ml/kg/hour may be practiced [3, 4, 32–34].

Prevention of hypothermia using warmed intravenous fluids, forced-air warming, and heated under blankets is vital. At surgical closure too, the tense and distended abdomen may lead to postoperative respiratory difficulty.

35.3.3 Postoperative Period

In the postoperative period, the goals of care are hemodynamic stability, respiratory support, and pain relief. The analgesic technique would be multimodal management. The use of epidural analgesia may be unsafe in these subsets of the surgical population due to sepsis and associated risk of coagulopathy and lack of time to assess

the coagulation parameters. The nonsteroidal anti-inflammatory (NSAIDs) may be contraindicated or prescribed with due caution. Dynamic pain relief is important to allow early physiotherapy to prevent atelectasis. Thromboprophylaxis, antibiotics, early enteral nutrition, and physiotherapy will help in enhancing the recovery and decreasing perioperative morbidity.

35.4 Bowel Perforation

Common causes of perforation of the gastrointestinal tract in cancer patients are spontaneous perforation due to the primary tumor of the gut or metastatic growth of a distant primary [35]. Other causes include long-term steroids or use of NSAIDs, chemotherapy, immunotherapy, and radiotherapy-induced tumor necrosis of an infiltrating gut wall tumor or severe gastroenteritis-induced bowel distension. In patients with perforation, peritonitis-induced fever and leukocytosis should be interpreted cautiously with the background use of cytotoxic drugs or neutrophil-stimulating factors [36, 37].

The clinical picture includes hypotension, tachycardia, and oliguria which may require prompt fluid resuscitation and vasopressor support preoperatively. Broad-spectrum antibiotics should be instituted at the earliest. A two-stage procedure with initial laparotomy, peritoneal lavage, and drain insertion with or without ileostomy/colostomy followed by resection at a later stage is more appropriate for patients who are septic and have poor performance score. The underlying physiological derangements mandates titration of various anesthetic agents the requirement of various drugs is reduced minimum alveolar concentration (MAC) is reduced in sepsis. Perforation of the gut in an oncological setting carries a grave prognosis due to the immunosuppression and seedling of cancer cells in the peritoneal cavity. These patients usually have an advanced stage of cancer (stage 3 or 4) [38, 39]. Perforation peritonitis carries a high risk of mortality especially in patients with a delayed presentation to hospital.

35.5 Malignant Spinal Cord Compression

One of the commoner oncological emergencies is malignant spinal cord compression (MSCC). It can lead to a permanent neurological deficit if not addressed urgently. It is the first presenting feature in 23% of patients with malignancy and can appear as an additional clinical manifestation in 77% cases with an established diagnosis of cancer [40]. The commonest site of vertebral metastasis is the thoracic vertebrae (70%), followed by lumbar vertebrae (20%) and cervical vertebrae (10%).

The neurological compromise can occur due to various pathologies including neural compression from extradural tumors from adjacent vertebral metastasis, pathological vertebral fracture, or direct spread of tumor in the epidural space. Also, in 10% of cases, the direct paravertebral spread to epidural space can lead to neurological insult. This is commonly the mechanism of MSCC in these are usually caused by lymphoma and myeloma [41].

Certain etiologies and presentation warrant early surgical intervention. The urgent surgical intervention for MSCC include:

- Deteriorating neurological function or paraplegia of fewer than 48 h duration
- Spine instability in the background of cancer and suggestive of structural failure (as assessed with radiological imaging) and with increased risk of progression to cord compression
- Uncontrollable mechanical pain originating from spine instability
- No histological of malignancy

Surgical intervention varies from minimally invasive procedures like vertebroplasty and kyphoplasty to vertebrectomy with spinal stabilization using implants. The surgical spinal stabilization is usually reserved for patients with a good performance status and a good disease prognosis. Simple decompression at one or two vertebral levels without fusion is classified as a low-risk

surgery while those involving instrumentation and fusion are classified as intermediate-risk surgeries [42].

35.5.1 Preoperative Evaluation

The decision for surgery depends on extent of invasion, histology of the tumour (response of cancer to therapy), mechanical stability and ASA physical status. The vertebral column involvement in a cancer patient is usually due to vertebral metastasis. Chemotherapy and radiotherapy-related cardiac and pulmonary toxicities need to be evaluated and addressed before surgery. Respiratory assessment should take into consideration pleural effusion, infection, therapy-related pulmonary toxicity (cyclophosphamide, chlorambucil, busulfan, or antimetabolites).

Patients with thoracic cord compression levels may have decreased vital capacity and overall reduced respiratory reserve. Baseline arterial blood gas analysis can serve as a guide for postoperative management and postoperative respiratory insufficiency and/or elective postoperative ventilation. Hypercalcemia, commonly seen with multiple bone metastases, needs to be corrected beforehand.

Acute cord compression can cause neurogenic shock. This occurs due to the absence of sympathetic tone below spinal cord compression. This manifests as hypotension, bradycardia, and arrhythmias which should be kept in mind during cardiac evaluation. Motor and sensory neurological deficits need to be evaluated and documented. This would help in recognizing new postoperative deficits.

Cancer is a hypercoagulable state the risk of deep vein thrombosis is enhanced because of limited mobility in MSCC. Significant blood loss is expected in reconstructive spine surgeries and blood bank support is necessary.

The outcome with regard to ambulation after the urgent surgical intervention for MSCC depends on presurgical neurological status [43, 44].

35.5.2 Intraoperative Management

As a part of multimodal pain management, acetaminophen 1000 mg orally (PO) or intravenous, gabapentin 300–600 mg PO, or pregabalin 75–150 mg PO may be used as premedication. Anxiolytics and narcotics should be prescribed with care, as these patients may already be using opioids.

Large-bore intravenous access should be established as procedures involving multiple levels can bleed profusely. These need to be secured appropriately, as it may dislodge during positioning. Invasive blood pressure monitoring is indicated for cervical and high thoracic spine surgery, expected blood loss, multiple comorbidities, and hemodynamic instability. These become essential as the risk of hemodynamic instability exists due to the site of surgery and associated blood loss. It also allows frequent intraoperative and postoperative blood investigations. Central venous catheter placement may be necessary for the administration of anaesthesia vasoactive drugs if intraoperative hypotension or massive blood loss is anticipated. Hypotension and a low hematocrit increase the risk of optic neuropathy in a prone position.

The intravenous administration of anaesthesia inducing agents should be slow and in reduced doses, especially in patients with cervical and high thoracic spine surgery as exaggerated hypotension is expected owing to sympathetic denervation which may further compromise the cord perfusion and lead to secondary injury to the spinal cord. Succinylcholine is generally not used as it may cause life-threatening hyperkalemia 24–48 h postinjury. The choice of nondepolarizing muscle relaxants depends on the use of neuromonitoring. Short-acting agents like atracurium and cis-atracurium may be useful if the assessment of motor-evoked potentials is being done intermittently.

The airway management remains challenging as spine movement during assessment or management can further exacerbate neurological insult. This is more of a concern in patients with

cervical spine metastasis. Airway management strategies depend on airway assessment, cervical spine instability, and the clinician's expertise. In patients with difficult airway including cervical spine involvement, the patient should be prepared for airway management using a fiberoptic bronchoscope or video laryngoscope. The choice between awake or asleep under anesthesia and the use of neuromuscular blocking agents should be based on patient assessment. The position and extent of surgery will determine the need for an armored or double-lumen tube. The tracheal tube should be fixed securely, as intraoperative displacement of a tube in a prone patient is very difficult to manage. Procedures involving higher thoracic levels with an anterior approach may require one-lung ventilation.

Neurophysiological monitoring is used in patients with impending injury to the spinal cord or nerve roots. Somatosensory-evoked potentials (SSEP) are used intraoperatively for neurological monitoring. This is affected by various anesthetic agents including intravenous induction agents, inhalational agents, opioids, and local anesthetics. Several other factors like hypothermia, hypotension, and hypoxia interfere with the interpretation of motor and sensory evoked potentials intraoperatively. Various inhalational agents like nitrous oxide, isoflurane, and sevoflurane have been found to reduce the amplitude and prolong latency of SSEP and motor evoked potentials (MEP) in a dose-dependent manner. When using inhalational anesthesia for maintenance, concentrations of more than 0.5 MAC may interfere with reliable monitoring. The use of neuromuscular blocking drugs carefully as their use intereferes with MEP monitoring. Remifentanil is the preferred opioid because it has a minimal effect. It also has a short context-sensitive half-life and thus its effect wears off faster after its infusion is stopped. Propofol causes a dose-dependent decrease in cortically evoked responses but the effect is of smaller magnitude. So, propofol-based anesthetic technique (total intravenous anesthesia, TIVA) remains the preferred technique. Depth of anesthesia monitoring is recommended in patients receiving TIVA. However, interpretation of neurophysiological monitoring remains vital and the impact of the anesthetic agents should be cautiously interpreted. Usually, a decrease in amplitude or latency by 35–50% that is not related to drug dosing is significant for possible neurological damage. The interpretatation of evoked potential monitoring is difficult and a "wake up test" may be required. The "wake-up test" involves decreasing anaesthetics to lighten the plane of anaesthesia in order to observe the patients motor ability on command.

The hemodynamics should be maintained near the baseline as any fall in blood pressure may not be compensated due to a lack of autoregulatory mechanisms [45]. On the other hand, hypertension can lead to excessive blood loss and a bloody surgical field. Deliberate hypotension is not recommended as it increases the risk of cord ischaemia and further compromises cord perfusion especially after instrumentation and retraction [46]. Patients with neurogenic shock will require initial volume resuscitation and should be guided for an endpoint like urine output, pulse pressure variation and stroke volume variation as undue volume overload may result in cord edema or pulmonary edema. The newer advanced hemodynamic tools using arterial waveform contour analysis by minimally invasive cardiac output monitors or use if transesophageal Doppler provides useful information. Urine output monitoring is a useful tool for assessing vital organ perfusion. A distended urinary bladder may lead to increased intraoperative blood loss as pressure is transmitted to the valve-less epidural veins. Temperature monitoring and maintenance are essential in patients with spinal cord insults. MSCC can lead to loss of sympathetic tone and thus vasodilation below the level of cord compression. This leads to excess heat loss. Fluid warmers and forced air warming body warmers can prevent hypothermia in the perioperative period.

Positioning the patient with care to avoid traction over the unstable spine is imperative. Excessive neck movement, unrecognized rotation, and a neck extension can compromise flow in the carotid and vertebral arteries. Surgery is often conducted in a prone or knee-chest position. Risks inherent to patient position need to be addressed meticulously. Risks of inferior vena cava compression, abdominal compression, optic

neuropathy, neck vein obstruction, and eyeball compression should be kept in mind during prone position and pressure points should be protected [46–48]. Specially designed operating tables and devices like the use of Wilson frame are being used to ease positioning and surgery [49]. The appropriate selection of devices is important as these devices may put unnecessary pressure on the abdomen and ventilation may be impaired. Similarly, undue focal pressure needs to be prevented on vulnerable areas like the face, breast genitalia, and abdominal organs and appropriate padding of bony prominences needs to be ensured. The Postoperative Visual Loss Study Group, POVL group [47] suggested that dependent position of the head could lead to ischaemic optic neuropathy. Meticulous initial positioning of the head and frequent intraoperative monitoring (in case of movement) decreases the risk. Documentation of these eye checks is recommended in long surgeries [48]. Horseshoe-shaped head rests have been implicated in cases of Central Retinal Artery Occlusion (CRAO) in surgeries in prone position and should be avoided. Decompressive surgery for metastatic tumors is prone to major bleeding. The availability of blood products should be ensured. Autologous blood transfusion and Red cell salvage and not considered in Cancer due to the possibility of dissemination of tumour cells. Deep vein thrombosis preventive strategies need to be followed in the perioperative period. If there are contraindications to the use of anticoagulants, mechanical prophylaxis using an electronic pneumatic compression device or even the use of graduated compression stocking should be used.

35.5.3 Postoperative Management

The postoperative management requires monitoring of neurological function, analgesia, and judicious fluid management. The multimodal analgesic technique remains the preferred choice. Patients may be already be taking preoperative analgesics including opioids and needs to be modified to treat surgical pain. Other analgesic adjuvants like ketamine, gabapentinoids, etc., may also contribute to analgesia [50–55]. These patients are frequently on steroid therapy perioperatively (to decrease cord oedema) NSAIDs carry the risk of hematoma formation at the surgical site and subsequent neurological compromise. Paracetamol remains safe and should be considered for analgesia.

The postoperative period close monitoring of complications or deterioration in neurological function. Postoperative visual loss (POVL) has been reported after spinal surgery and is attributed to direct pressure on the globe leading to compromised retinal perfusion, ischemic optic atrophy (ION), and CRAO. ASA advisory for visual loss recommends the regular monitoring of haemoglobin during spine surgery [56, 57]. The visual loss is usually on one side and associated with other pressure effects like ptosis, ophthalmoplegia, or symptoms due to supraorbital nerve compression may be seen. In the case of POVL, ophthalmologist consultation should be sought and treatment includes correction of anemia, optimization of oxygenation and blood pressure [47].

The risk of extubation failure after spine surgery includes multiple spine surgeries, blood loss>300 mL, long-duration surgery, and combined anterior and posterior surgical approach [58]. Hence, extubation should be carefully planned and the use of an airway exchange catheter may be considered. Hematoma or supraglottic oedema because of venous and lymphatic obstruction can compromise the airway [59]. Neck swelling, change in voice, agitation, and respiratory distress may manifest 3–6 hours after surgery. Other presentations can include tracheal deviation, and carotid sinus compression (bradycardia with hypotension). Emergency airway standard operating protocols (SOPs) are useful. Evacuation of hematoma can relieve compression if initial intubation is unsuccessful. The hemodynamic fluctuations should be controlled during the extubation procedure to prevent exacerbation of edema or hematoma [59].

35.6 Surgery for Brain Metastases

Brain metastases are often indicative of excessive disease burden and if untreated life expectancy is not more than 2 months. Surgery is indicated in young patients with controlled disease, minimal extracranial metastases, and a high-performance score, single surgically accessible metastatic lesion, and prolonged survival [60]. The goal of surgical intervention for brain tumor metastasis is to relieve the mass effect due to tumor mass, decompress the tumors lesion, and thus prevent life-threatening neurological symptoms [61].

Neuroanesthesia is a rapidly evolving field. The approach to a case must include the principles of anesthesia, neurosurgery, and neurology. The main guiding principles of perioperative care for brain surgery include the provision of optimal operative conditions, maintenance of neurocognitive function, avoiding hemodynamic fluctuations (maintaining optimal cerebral perfusion pressure), maintaining oxygenation, avoiding hypercapnia, optimal conditions for electrophysiological monitoring, and smooth recovery. The introduction of newer image-guided microscopic techniques, neurological monitoring, and awake craniotomy has significantly decreased the incidence of postoperative complications, neurological deficit, and infection to less than 5% [62, 63].

Preoperatively, the pre-existing neurological deficit needs to be assessed and documented. These patients usually are started on brain decongestant therapy including osmotic diuresis (e.g., mannitol), diuretics (furosemide), and steroids. Steroids like dexamethasone decrease the vasogenic edema and reduce intracranial pressure [64]. Timely administration of steroids has been found to reduce symptoms severity and increase survival [65–67]. The steroids-related side effect like increased blood sugar needs to be monitored and managed accordingly [68, 69]. Prophylactic administration of anticonvulsant drugs is not recommended due to drug interaction with corticosteroids (cytochrome P450 pathway) [70].

The ventilatory strategies need to ensure optimal oxygenation (partial pressure of oxygen, PaO_2 80–100 mmHg) and eucarbia (partial pressure of carbon dioxide, $PaCO_2$ 30–35 mmHg) and an inspiratory pressure as low as possible [71–73]. Most of the anesthetic agents excluding ketamine decreased intracranial pressure (ICP), reduced cerebral metabolic rate (CMR), decreased cerebral metabolic rate (CMR), decreased cerebral blood flow (CBF), and decreased cerebral blood volume (CBV). Total Intravenous anaesthesia (TIVA) and inhalational techniques have both been used safely. Propofol administration leads to decreased CBF, decreased ICP, preserved autoregulation but causes hypotension to a greater extent than barbiturates. Barbiturates have been reported to provide cerebral protection against ischemia [74–77]. A Cochrane review reported that there was no significant difference in emergence when comparing inhalational (sevoflurane) at minimum alveolar concentration (MAC) < 1 or propofol infusion in patients being operated for a brain tumor. However, intraoperative brain relaxation was better with intravenous propofol [78, 79]. Also, etomidate is not a suitable anaesthesia inducing agent in these patients as even a single dose inhibits steroid production for up to 24 hours with a higher incidence of PONV [72]. While comparing TIVA with the inhalational technique for anesthesia maintenance for brain surgeries, factors like emergence (short-term outcome), ease of titration, administration, hemodynamic stability, and brain conditions are to be assessed [80, 81]. Opioids minimally disturb the cerebral physiology and are used along with lidocaine 1–1.5 mg/kg IV during induction. Remifentanil seems to be promising for maintenance along with propofol as a target-controlled infusion (TCI) due to its easy titratability. Succinylcholine may be required while attempting rapid sequence induction or dealing with difficult intubation. Though it causes a transient increase in CBF, it can be attenuated using low-dose non-depolarizing neuromuscular blocking drugs (defasciculating dose) [75]. The superiority of one technique over the other is a matter of debate given the lack of substantial evidence, especially in patients with mass effect undergoing emergency craniotomy.

Management of ICP, CPP, and CBF is critical in patients with mass effect and raised ICP and therefore hypotension, hypertension, hypercarbia, and hypoxia should be avoided. The use of nitrous oxide for these surgeries should be discouraged as not only increases ICP and CBF but also leads to the expansion of trapped space in the cranium once the dura is closed [82, 83]. Though there were no significant differences in respiratory and cardiovascular parameters in patients undergoing craniotomy for cancer when comparing fentanyl alfentanil, and remifentanil. The recovery was faster with remifentanil which remains desirable for brain surgeries [84, 85]. The hemodynamic fluctuations at emergence needs to be obtunded and drugs like remifentanil and dexmedetomidine effectively blunt the stress responseblunt can be used [86–90]. Postoperative analgesia of paramount, importance as uncontrolled pain may have a detrimental effect after brain surgery [91]. Multimodal analgesia including scalp block and paracetamol help reduce the dose of opioid analgesics. However, the use of nonsteroidal antiinflammatory drugs may be avoided because of associated concerns of bleeding and in a closed space and its fatal consequences [92, 93]. PONV remains a concern and thus its control should be emphasized [92, 94].

Anesthetic management can influence intraoperative brain swelling. Various factors associated with an increased risk of brain swelling include the baseline ICP, degree of midline shift, and underlying pathology [94, 95]. Strategies for intraoperative brain relaxation include frusemide 10–20mg IV, dexamethasone 10mg IV, mannitol (20%), 0.5 to 1g/kg intravenous administered over 10 to 15 minutes, and hyperventilation (targeted to maintain $PaCO_2$ of 30 to 35 mmHg); 3% hypertonic saline has also been used as it has comparable efficacy to mannitol [96]. Awake craniotomy is a technique that aids resection of brain lesions close to eloquent areas more precisely functional cortical mapping minimizes postoperative neurological deficit with improved survival in addition to the shorter hospital stay and reduced cost of care [97, 98]. Deep venous thrombosis (DVT) remains a risk and its prophylaxis should be initiated timely and appropriately using pharmacological and nonpharmacological strategies [99, 100]. The role of positioning (head-up position) to decrease brain edema by increased drainage is reported [101, 102]. The role of hypothermia for neurological outcome remains controversial [103, 104]. Some studies have observed a decrease in ICP during cooling and significant improvement in the outcome while others failed to show improved outcomes [103, 104]. High-quality evidence is needed to formulate protocol and recommendations for therapeutic hypothermia during and after craniotomy in patients with raised intracranial tension. In neuro-anesthesia, the emphasis is on the quality of wakening the patient as well as sending him to sleep. Meticulous planning, preoperative medications, monitoring, and postoperative care can impact results.

35.7 Tumor Bleeding

The incidence of significant bleeding is 6–14% in cases of advanced cancer and could be life-threatening [105]. It could be caused by major vessel damage by tumor invasion—carotid artery blow out or due to coagulopathies induced by systemic therapy, abnormalities of platelet function, and its number. Severe intrabdominal bleeding can occur from solid vascular tumors like hepatocellular carcinoma, renal cell carcinoma, or spontaneous rupture of the spleen in lymphomas and leukemias. Chronic use of NSAIDs as analgesics can cause upper gastrointestinal (GI) bleeding while pelvic malignancies especially after radiotherapy can be a cause of lower GI bleeding.

Immediate management before surgical intervention includes applying pressure to the external bleeding site, correction of the underlying coagulopathy by administering platelets, FFPs, hemostatic agents, and resuscitation with fluids and packed cells in patients with hemodynamic instability. The embolization of bleeding vessels is a minimally invasive procedure

[106] and is useful in bleeding that is difficult to access surgically and in patients not willing or unfit for surgery. The anesthetic techniques are based on patient assessment and the target vessel to be embolized and both local and general anesthesia may be chosen. Resuscitation, optimization, and anesthesia management are as in other bleeding emergencies—large bore intravenous cannula, active warming to prevent hypothermia, correction of acidosis due to circulatory failure, hypocalcemia, and a close watch on urine output.

35.8 Summary

The perioperative physician needs to evaluate and plan for difficult venous access, difficult airway, postoperative respiratory support, and blood products in patients presenting with oncological emergencies. The side effects and sequelae of prior therapy need to be kept in mind while planning for any intervention. Problems peculiar to each tumor and its site will influence the perioperative care plan.

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Enhanced Surgical Recovery and Cancer

36

Doreen S. Agboh and Anoushka M. Afonso

36.1 Introduction

Globally cancer is increasingly being reported and is the second commoner cause of morality [1, 2]. It is estimated that up to 50% of inpatient admissions worldwide are for a diagnosis of cancer [3]. With increasing cancer prevalence over time, the patients presenting for surgical intervention shall also increase leading to the increasing role of anesthesiologists for perioperative and periprocedural care. Despite significant immunological advances in cancer care, surgery will continue to be a mainstay strategy for reducing tumor burden, particularly for solid tumors. Frequently, chemo-radiation therapies are administered before the surgical resection as neoadjuvant therapy or after the surgical resection as an adjuvant treatment modality. This is primarily to ensure tumor regression for optimal surgical resection and prevention of cancer recurrence in case of any residual lesion or micrometastasis. In the routine presurgical evaluation and optimization, patients with cancer need special perioperative considerations. These relate to evaluating and optimizing the anatomic, physiological, paraneoplastic effects of cancer and its treatment on different organ function. Anesthesia providers should therefore be cognizant of immediate, and long-term systemic effects of cancer therapies (organ toxicities), and the effects of chemo-radiation on nutrition, fatigue, anemia, and physical deconditioning all of which could influence the recovery profile after major surgery.

To optimize surgical care and enhance oncological outcomes, a multidisciplinary perioperative program including various aspects of patient care should be followed. This is aimed at reducing symptom burden and increasing quality of life with enhanced functional recovery. Such steps also avoid or at least minimize the various perioperative complications. These coordinated multidisciplinary care pathways and principles of care aimed to enhance functional recovery of the surgical patient are the enhanced surgical recovery programs (ESRP). ESRP focus on minimizing the neuroinflammatory signaling (stress) response to surgery trauma through minimally invasive surgery when indicated, utilizing procedure-specific multimodal opioid-sparing strategies, minimizing periprocedural oxygen debt, providing optimal anesthesia care with an emphasis on rapid emergence, utilizing lung-protective ventilatory strategies, and ensuring complete reversal from neuromuscular blockade. Also, the postoperative phase demands a focused

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approach to safely implement early drinking, eating, and ambulating measures. An important postoperative component of enhanced recovery principles is procedure-specific pathway-based care and institution of monitoring systems for rapid rescue from postoperative complications [4]. Various specific multimodal elements are planned in the preoperative, intraoperative, postoperative, and post-discharge phases of surgical practice as a part of enhanced recovery pathways. Adherence to the key elements in each of these phases of care is vital to improving outcomes for surgical patients. Gustafsson et al. indicated a dose–response relationship with enhanced recovery after surgery (ERAS) protocols adherence and clinical outcomes after major colorectal surgery [5].

While earlier recovery to baseline function without major postoperative complications is important for any surgical patient population, this is particularly relevant for patients with cancer as frequently adjuvant therapies are part of the cancer care plan for many diseases. In pancreatic [6], thoracic [7], and breast cancer [8], there is a correlation between postoperative complications, timely delivery of adjuvant therapies, and survival. Delaying adjuvant therapies after a successful ablative surgery leads to a worse prognosis. Frequently, common causes for delayed adjuvant therapies are postoperative complications, postoperative fatigue, and poor general physical condition (a general measure of recovery after major surgery). One of the major goals for surgical patients with cancer should, therefore, be faster recovery after surgery so that they can get back to their intended oncologic therapy. Thus, every enhanced recovery protocol implemented for cancer patients should consider the stage of the disease, overall prognosis, appropriateness of therapy and risks associated with therapies, and patient's wishes.

36.2 Preoperative Preparation

In addition to routine presurgical evaluation and medical optimization of comorbidities, surgical patients with cancer have certain special considerations. The critical components that encompass preoperative care of patients with cancer are advanced care planning, patient education to engage and empower patients in their perioperative journey, nutritional optimization, prehabilitation, and anemia management.

36.2.1 Advanced Care Planning

In the United States, cancer treatments utilize an exorbitant amount of resources, particularly during advanced stage disease with little to no chance for a cure, and often at the expense of offering a meaningful quality of life that meets the patient's wishes. This is also true during the end of life care, with consistently high rates of terminal hospitalizations including intensive care and treatment [9]. Approximately one-third of patients with terminal illnesses are admitted to hospital in the last days of their life [9]. Additionally, research demonstrates that terminally ill patients often receive more intensive care regimens than their stated preferences for treatment [9].

Unlike noncancer conditions, the functional decline is an innate characteristic of cancer's trajectory and thus is a distinct period in which patients can benefit from advanced care planning (ACP) and palliative care [9, 10]. Professional oncologic organizations like the National Comprehensive Care Network (NCCN) and the American Society of Clinical Oncology (ASCO) have long emphasized the importance of ACP in providing optimal palliative care [9, 11]. ACP should therefore be routinely discussed with all patients timely [12].

36.2.2 Education

Effective preoperative education of patients allows them to further understand the risk and benefits associated with their surgery and allows for psychological preparation before their surgery. Additionally, because of the high-stakes nature associated with many oncological procedures, it is important to provide patients with a detailed understanding of their surgical proce-

dure so that they may have clear expectations of and anticipation for potential events that could happen intraoperatively and postoperatively. Setting patient expectations in terms of pain management, ambulation, and resuming oral intake can pave the way for accelerated recovery. It has been demonstrated that perioperative education has been associated with decreased anxiety, better postoperative outcomes, and improved patient and family satisfaction [4]. While patient education is important during the perioperative process, physicians must familiarize themselves with the health literacy of their patients for effective engagement of patients and caregivers. Providing patients with educational materials that they can read and detailed instructions that they can follow that is written in clear, simple language can also facilitate clear learning [4].

36.2.3 Nutritional Concerns

The nutritional status of the cancer patient has an impact on the overall outcome and thus the need for its optimization at all stages of cancer and therapy. So, a preoperative screening protocol for nutritional assessment before surgery should be an integral part of the preoperative assessment as malnourishment remains an important parameter affecting perioperative complications, morbidity, mortality, and even the oncological outcome [13–15]. The assessment includes a history of nutritional intake, physical examination, and/or biochemical parameters. Use of validated tools like nutritional risk indicator (NRI), the patient-generated subjective global assessment (PG-SGA), the nutritional risk screening tests, and Reilly's NRS for nutritional assessment helps not only detection of the malnourishment, but also categorizes the severity [4, 16]. This assessment shall help in nutritional optimization by triaging the patient. Malnutrition and subsequent weight loss in cancer may be related to an amalgamation of factors including undernutrition, cancer catabolism, and inflammation, which can further lead to cachexia and sarcopenia [14]. When managing the nutritional status of a cancer patient before surgery, strategies should be implemented that avoid decreased insulin resistance, prevent negative protein balance, and modulate the immune system [13]. Additionally, when determining the proper nutritional intervention necessary for treating the cancer patient, it should be determined if a patient's cancer therapy is high risk or low risk with regard to its impact on the patient's nutritional status [16]. Based on baseline and change in nutritional assessment during the disease and its treatment, nutritional intervention can be determined for those who fall below the threshold for adequate preoperative nutrition [16].

For those that are deemed as malnourished before surgery, nutritional supplementation should be implemented 5–7 days before surgery via enteral nutrition or total parenteral nutrition as an alternative, if needed [4, 13, 17]. However, total parenteral nutrition should be implemented 7–10 days before surgery [17]. Enteral feeding is preferred to total parental feeding [13]. In addition to optimization for any nutritional deficiencies before surgery, there are key steps that should be taken immediately before surgery to optimize recovery. Rather than fasting before surgery, patients should consume clear carbohydrate beverages to allow for the replication of normal metabolic responses and place the patient in a fed state before surgery [4, 17]. This method can decrease the body's metabolic stress response to surgery, thereby decreasing the risk of postoperative complications [4, 17]. Furthermore, a carbohydrate drink may decrease protein loss by placing patients in an anabolic state [13].

36.2.3.1 Prehabilitation

Various strategies may be intervened in the preoperative period to decrease the psychological and physiological stress associated with surgery [18]. Cancer prehabilitation is outlined as "a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment, includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a patient's health to reduce the incidence and the severity of current and future impairments" [19].

Physical activity, in particular, can attenuate the perioperative risks associated with surgery [18]. Those who implement an exercise regimen before surgery have a faster return to baseline and have enhanced recovery after surgery [20]. Exercise can also decrease mortality and increase functional status and serves as a strong marker for health status [13]. Because delays in cancer treatment can lead to poor outcomes, the timing of prehabilitation implementation as it relates to the anticipated date of surgery is critical to take into account when building an exercise regimen [19]. As little as 3 weeks before surgery may be sufficient time to build up a physiological reserve, which can further improve surgical outcomes [18]. Additionally, the integration of neoadjuvant radiation therapy and chemotherapy expands the window in which exercise prehabilitation can be implemented [4, 18]. Prehabilitation also serves psychologically to benefit cancer patients by decreasing anxiety [20]. Psychological interventions should also be implemented in the prehabilitation landscape to address any psychiatric disturbances (i.e., depression, anxiety, etc.) and provide psychosocial support [19], as a cancer diagnosis can be particularly burdensome both mentally and emotionally.

Cancer patients who undergo neoadjuvant chemotherapy often have a decline in overall physical fitness, which has been associated with the worst outcome after surgery [21]. Preoperative exercise training may have an important benefit for surgical outcome and recovery after surgery in cancer patients. For those awaiting oncological surgery, preoperative exercise training programs a feasible option in regard to participation and adherence [22]. Licker and colleagues showed in a randomized controlled trial, high interval training (HIT) resulted in "significant improvement in aerobic performances, but failed to reduce early complications after lung cancer resection" [23]. The use of newer assessment modalities like cardiopulmonary exercise testing (CPET) is useful for assessing the comprehensive cardiorespiratory status and has an association with postoperative morbidity and decreased CPET [24]. The effect of exercise on cancer patients was evaluated by Loughney and colleagues [25] with acceptable safety, feasibility adherence rates in patients scheduled for neoadjuvant chemotherapy and surgery. The concept of the "dual hit" of neoadjuvant chemotherapy and surgery was explored in the context of preoperative exercise training.

In addition to an appropriate exercise regimen tailored for the cancer patient, nutritional optimization is important to increase anabolism and minimize the catabolic state in the postoperative period. Malnourished surgical patients benefit from perioperative nutrition. Klek S et al. aimed to assess the clinical significance of route and type of nutritional support (enteral, parenteral, standard, or immunomodulating) in the perioperative setting of malnourished cancer patients with comparable results [26]. In another study, the beneficial effect of preoperative enteral nutrition in terms of infection and hospital stay was noted [27]. Protein supplementation has also been used in prehabilitation programs. Another study concluded the clinical meaningful improvement in functional walking capacity by prehabilitation intervention including nutritional counseling with protein supplement along with an exercise regime initiated in the preoperative period [28].

The nutritional deficiency may also manifest as anemia and is seen in cancer patients because of variable reasons. Anemia has been found to have an increased need for blood transfusion and associated morbidities as well [29]. The pathophysiology of anemia in the cancer patient, who has nutritional deficiencies, chronic anemia, and concurrently on chemotherapeutic agents that affect red blood cell production, is multifactorial. Given the association with preoperative anemia and patient morbidity, there is a need to reduce perioperative transfusions and its risks and lessen the impact of postoperative anemia. Enhanced recovery from surgery in cancer patients can potentially be improved with an opportunity to intervene in the preoperative window in patients with treatable anemia. For example, Munoz et al. [30] describe a patient blood management strategy that involves a multidisciplinary multimodal individualized strategy for addressing perioperative anemia in the colorectal cancer

patient. They report that treating anemia early and aggressively in colorectal patients allows for optimization of preoperative hemoglobin, which transforms transfusion risk from high to low and improves outcomes overall [30]. Iron therapy, erythropoiesis-stimulating agents (ESAs) under appropriate recommendations, restrictive transfusion protocols, and other measures to decrease blood loss should be undertaken. Follow-up in these cancer patients is important as they often receive adjuvant chemotherapy and radiotherapy.

36.3 Intraoperative Management

36.3.1 Postoperative Nausea and Vomiting (PONV) Prophylaxis

PONV is one of the concerns in postoperative cancer patients and is seen in a large number of patients depending upon various risk factors [31, 32]. It directly impacts the quality of life by leading to concerns like fluid and electrolyte imbalance, pain, wound dehiscence, etc. [31, 33]. So, it is essential that PONV needs to be controlled optimally to avoid these potential adverse effects. PONV prophylaxis before surgery is recommended rather than reactively treating addressing PONV as it occurs [4]. A risk assessment of PONV can be conducted using the Apfel score [4]. The Apfel score evaluates the risk of PONV based on parameters including female gender, nonsmoking status, history of PONV, and administration of postoperative opioids as predictive measures [4, 32]. The PONV prophylaxis modality and drug(s) need to be administered based on risk stratification [34]. Low-risk patients should not receive prophylaxis for PONV unless the surgery which they are undergoing is emetogenic [34]. However, for those that are moderate to high risk for PONV, combination therapy that targets more than one type of receptor may be more effective than single therapy for prophylaxis.

For surgeries that are high risk for PONV such as gynecological, laparoscopic, HEENT (head, eyes, ears, nose, throat), intra-abdominal, breast procedures as well as those that are of longer duration, PONV prophylaxis should be administered regardless of Apfel score [34]. In the context of cancer patients, preoperative psychological factors are associated with the risk of increased PONV [31, 35]. Even by multiple antiemetic agents administration, almost 30% of women after breast cancer surgery had experienced nausea, with 10% having both nausea and vomiting [31].

36.3.2 Fluid Management

Fluid management of the patient should be optimized throughout the perioperative period with the goal of a euvolemic, and hydrated state before surgery [36]. For the cancer patient, preoperative radiation and chemotherapy can cause treatment-related diarrhea, which can lead to dehydration and fluid depletion [37]. Radiation can cause increased intestinal motility, while chemotherapy causes damage to the intestinal mucosa and leading to decreased absorption [37]. Prolonged fasting and bowel preparations should be avoided, as they may lead to dehydration before surgery [36]. Perioperative goal-directed fluid therapy is defined as "the concept of using indices of continuous blood flow and/or tissue oxygen saturation to optimize end-organ function" [4]. Monitoring dynamic flow indices can be used to predict the hemodynamic effects of fluid administration to optimize oxygen delivery to tissues [13]. Goal-directed fluid therapy (GDFT) should be customized to the basis of patients' surgical risk, vascular access, monitoring needs, and the operating context to optimize hemodynamic stability [4, 36, 38]. During surgery, fluid administration should be carefully adjusted to reduce perioperative organ dysfunction and to restoring tissue perfusion and cellular oxygenation [4]. The aim of intraoperative fluid management is homeostasis by optimal fluid and electrolyte replacement to maintain euvolemia and electrolytes level through low-crystalloid therapy and fluid boluses (when necessary) to replace blood/fluid loss and maintain intravascular volume [36]. GDFT may decrease major complications, length of stay, and improve outcomes [4, 36]. A recent

meta-analyses for the beneficial effect of GDFT noncardiac surgical patients reported comparable effects on mortality, ICU stays, and hospital stay as compared to standard fluid management but with lesser wound infection, hypotension, and abdominal complications [39]. There is no evidence of benefit for the use of crystalloid or hydroxyethyl starch (HES) for colorectal cancer surgery for GDFT, despite a lower 24-hour fluid balance with HES [39, 40].

36.3.3 Multimodal Pain Management

Because pain can prolong recovery time and delay discharge, it is important to optimize the management of pain throughout the perioperative period [41]. Multimodal analgesia remains the most accepted key strategy for the ERAS pathway [41]. The concept of a multimodal analgesic plan allows us to improve postoperative analgesia through different mechanisms and reduce the incidence of any opioid-related effects due to lower dosages. Multimodal pain management consists of the combinatory use of analgesics with different modes of action to minimize side effects and maximize analgesic effects [42]. Multiple agents with action on different receptors improve pain control should be utilized intraoperatively and postoperatively. Non-opioid analgesics include NSAIDs, acetaminophen, paracetamol, alpha-2 agonists, ketamine, gabapentin-type drugs, dexamethasone, neuraxial/regional techniques using local anesthetics, hypnosis, and acupuncture. Ultimately, multimodal analgesia serves to minimize the post-surgical length of stay, accelerate recovery, and improve outcomes [41]. Pain management strategies should be carefully planned, initiated before incision, tailored precisely to patient-specific considerations, and geared toward the surgical procedure in which the patient is undergoing. This careful selection of pain management can allow for the best outcomes for cancer patients [2]. Because pain secondary to cancer is a common occurrence due to both the pathophysiology of cancer and as a result of therapeutic interventions [2], anesthesiologists must take cancer pain into account when planning an analgesic regimen for their cancer patients. Additionally, surgical interventions for cancer therapies are complex—adequate analgesia should be administered that allows for improved functionality to allow patients to return to chemotherapy and radiation therapy expeditiously [2]. Analgesic plans should aim for early mobilization, decreased perioperative complications, and the improvement of quality care, in addition to lowering pain in the cancer patient [42]. Avoiding hypothermia, a complete reversal of neuromuscular blockade, and lung-protective ventilation strategies are also part of the optimal anesthetic plan for cancer patients undergoing an enhanced recovery protocol.

36.4 Postoperative Care

36.4.1 Pain Management Maintenance

In the realm of postoperative care during the perioperative period, continued effective pain management, complication-free recovery, reduced symptom burden, and enhanced quality of life should be emphasized for the cancer patient. Post-surgically, major physiological changes can occur which can delay recovery [4]. Pain, in particular, can amplify these physiologic changes thereby increasing the time to restoration to baseline function [43]. Similarly to intraoperative multimodal pain management strategies, this approach should also be utilized postoperatively [41]. Postoperative analgesia should focus on maximizing the pharmacologic benefits while minimizing side effects to allow for enhanced recovery and functional restoration to ultimately improve outcomes [4, 41].

36.4.2 Postsurgical Complications and Return to Intended Oncological Therapies (RIOT)

The measurement of outcome to intervention in cancer patients has been variously recorded. RIOT has emerged as a novel metric tool for func-

tional recovery after various cancer-related interventions [44]. It includes two important aspects of initiation to the intended therapy after surgery and time taken for such initiation [45]. When RIOT was introduced into the enhanced recovery pathways, the team noted significant practice change management. For example, in colon cancer patients with metastases to the liver, the identified RIOT rate was 75%. During the introduction of enhanced recovery pathways in liver surgery, the RIOT rate increased to 95% [46]. Similarly in pancreatic surgery, the patients with complications has lesser and early as compared to those with complications [47]. Breast cancer overall survival is dependent on both completion and amount of adjuvant chemotherapy. If there is a delay, greater than 12 weeks, recurrent-free survival and overall survival are adversely affected [8]. Enhanced recovery pathways can potentially allow for a more rapid recovery and shortened time to patient oncologic therapy.

36.4.3 Health-Related Quality-of-Life Assessment

The outcome measures after surgical intervention are important parameters for confirming the effectiveness of any protocol like enhanced recovery protocol [4]. The usual parameters reported for surgery include morbidity and mortality. But the health-related quality-of-life assessment tools should be included to assess the impact of overall perioperative care [48]. Health-related quality-of-life assessments are subjective multidimensional measures answered by the patient that is used to determine how the patient's health state impacts the quality of life through the evaluation of various health domains [48, 49]. These include not only physical but also psychological, social, and physical well-being. Each of these measures should be globally assessed in the cancer patient to allow for the optimization of treatment and overall well-being [48]. Such assessment can serve to evaluate complications and side effects [48], both of which can have deleterious effects on standards of living. Additionally, quality-of-life assessments can help to determine the most appropriate surgical procedure [48]. The treatment of cancer patients can be rather complex [50]—often utilizing chemotherapy or radiation in addition to surgery as treatment modalities. While this multifactorial approach may serve as a curative treatment, the morbidities associated with these therapies may influence the patient's quality of life. The prospect of cure may make toxicity associated with cancer treatment tolerable [49]. However, for cancer patients who have a decreased probability of cure, these adverse side effects may be less acceptable [49].

36.5 Summary

The rate of survival of cancer patients undergoing surgical procedures is highly dependent on the various factors including cancer-related comorbidities, cancer biology, the impact of cancer and therapy per se, and overall quality of life [45]. Enhanced recovery after surgery protocols for cancer patients should encompass the risks associated with both oncological pathologies and surgical procedures to allow for optimization of patient outcomes. Preoperatively, patients should maintain adequate nutrition through supplementation if necessary and engage in prehabilitation exercises in preparation for their surgery in the weeks before surgery. On the day of surgery, postoperative nausea and vomiting prophylaxis should be implemented timely. During surgery, it is critical to tailor fluid management through goal-directed therapy that maximizes oxygen delivery to tissues and prevents hypovolemia or hypervolemia. Pain management during and after surgery should be multimodal and include non-opioid analgesics to allow for enhanced recovery to baseline. Additionally, cancer patients who recover quickly after surgery can, in turn, return to their intended therapy expeditiously as well. This can further serve to improve the overall outcomes of cancer patients undergoing postoperative oncologic treatment postoperatively. By adhering to ERAS protocols and tailoring treatment with specific regards for the clinical sequelae associate with cancer pathophysiology and cancer treatment regimens,

physicians can increase the odds of favorable outcomes for cancer patients undergoing surgical therapy, decrease morbidity and mortality, and alleviate suffering.

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37 Anesthesia for Cytoreductive Surgery (CRS) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Rakesh Garg

37.1 Introduction

Optimal cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is the treatment modality for the management of primary peritoneal malignancy, pseudomyxoma peritonei, and peritoneal carcinomatosis from colorectal, gastric, ovarian, and cervix malignancies [1]. Sugarbaker remains a pioneer in describing the technique wherein cytoreduction of macroscopic tumor was followed by locoregional chemotherapy to treat peritoneal tumors [2]. CRS with HIPEC remains a long-duration, complex surgical intervention with multisystemic derangement along with metabolic and physiochemical perturbations. Such procedures require appropriate patient selection, planning, and vigilance in the perioperative care for an optimal outcome [3]. CRS and HIPEC impacts respiratory, hemodynamic, renal, hepatic systems, hematologic, metabolic, fluid, and thermal homeostasis not only intraoperatively but may continue in the early postoperative period as well [1, 4]. The concerns remain of toxicity of chemotherapeutic agents and occupational hazards with HIPEC. A good understanding of the physicochemical impact of the CRS and HIPEC is essential. Despite many advancements and better understandings in medical sciences with better monitoring tools, the patients undergoing CRS and HIPEC has morbidity and mortality of 12–65% [1, 4].

Perioperative management of CRS and HIPEC remains challenging [5]. A good outcome requires a team approach inclusive of onco-anesthesiologist, onco-surgeon, intensivist, and other specialties like cardiologists, nephrologists, pulmonologists, etc. for appropriate consultations as per associated comorbidities. This also requires the involvement of nursing staff, physiotherapists, dieticians, and other ancillary support services for an uneventful outcome. The definite protocol and recommendations for CRS and HIPEC have not been reported due to lack of robust evidence and the existing literature remains scarce for definite perioperative anesthetic management. This chapter provides an overview of the perioperative anesthetic management of CRS and HIPEC based on existing literature and the author's interpretation of the existing literature and experience of such procedures.

37.2 Patient Selection/Indications

The patient's selection for these complex surgical procedures requires diligent assessment and consideration of many factors. The surgery- and patient-related factors need to be assessed and

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identified for a final decision on surgical intervention. The patient and family member need to be discussed as regards the procedure and probable outcome. The various factors for patient selection include [6, 7]:

- Tumor:
  - Pseudomyxoma peritonei
  - Peritoneal carcinomatosis from stomach, colorectal, ovary, or cervix
  - Malignant peritoneal mesothelioma
  - Sarcoma peritoneum
  - As an adjunct HIPEC for the management of uncontrolled malignant ascites.
- Tumor confined to the abdominal cavity
- Feasibility of optimal surgical cytoreduction and removal of all macroscopic lesions.
- Tumor load expressed as the Peritoneal Carcinoma Index (PCI) <20 (maximum 39)
- Karnofsky Index of >80% and without any uncontrolled major comorbidity

37.2.1 Methods of HIPEC

CRS with HIPEC remains an extensive surgery. It involves exploratory laparotomy, extensive peritoneal/multivisceral resection, instillation of hyperthermic chemotherapy, multiple visceral anastomosis/reconstruction, and finally abdominal closure [1, 2, 8] (Fig. 37.1). Depending on the type and site of the tumor, surgical resection of the peritoneum (parietal and visceral), omentum, bowel (small, colon, rectal), stomach, pancreas, ovary, uterus, fallopian tube, cervix, urinary bladder, spleen, liver capsule, pancreas, and lymph nodes is performed [9]. The goal of the CRS phase remains to surgically remove all the macroscopic tumor mass before the institution of HIPEC [10].

After the CRS phase (major surgical debulking/cytoreduction) and before reanastomosis and reconstructions, HIPEC is initiated [9]. It can be delivered and circulated in the peritoneal cavity by the two described techniques as follows:

- *Open Abdomen HIPEC Technique* (Coliseum Technique): This technique is the conventional technique and described initially by Sugarbaker. After the CRS phase (Fig. 37.2), the abdomen remains open and hyperthermic infusate is circulated into the peritoneal cavity using a dedicated machine (Fig. 37.3). Direct manipulation by the surgeon is done for uniform distribution of the drug in the abdomen (Fig. 37.4). This technique is limited by a decrease in temperature of the instillate due to direct heat loss in the open abdomen, and the risk of spillage of chemotherapy drug directly or by aerosolized particles.

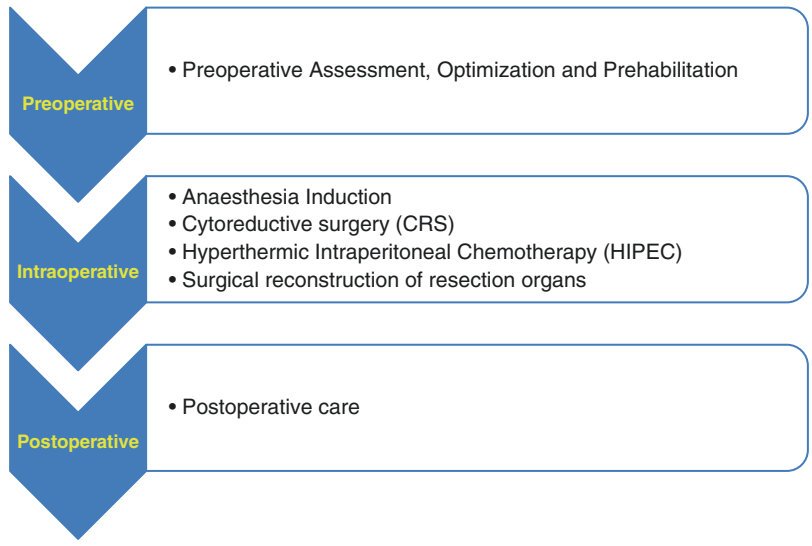

Fig. 37.1 Sequence of CRS with HIPEC surgical procedure

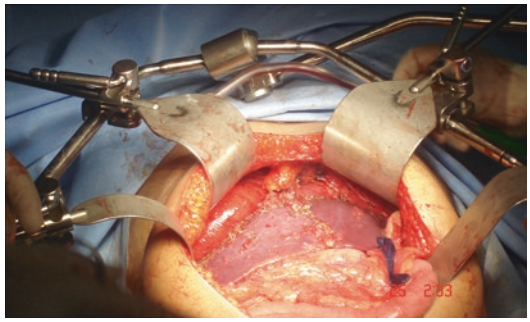

Fig. 37.2 CRS phase: surgical intervention for cytoreduction

Fig. 37.3 Hyperthermic intraperitoneal chemotherapy equipment

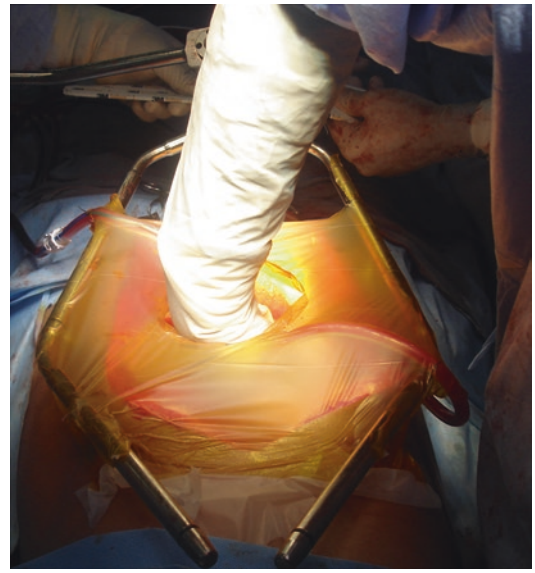

Fig. 37.4 HIPEC phase: manipulation for even distribution of infusate

The open technique has been modified to the peritoneal cavity expander (PCE) technique that allows even circulation of the hyperthermic chemotherapeutic agent. This technique uses an acrylic cylinder with inflow and outflow tubes along with an expander reservoir. These are secured over the wound and the tips remain inside the abdominal cavity wherein the bowel floats freely and manually manipulated in the PCE filled with heated infusate.

- *Closed Abdomen HIPEC Technique:* This technique involves the placement of HIPEC tubing (Tenckhoff catheter) along with temperature probes and thereafter the abdominal wall is closed. Then using roller pump forces, the hyperthermic infusate is circulated in the abdominal cavity through the inflow tubing and is removed from the abdomen via outflow tubing connected to the HIPEC machine. This technique generates higher pressures, maintains the temperature, and thus aids in a deeper penetration of the drug. It also decreases the risk of contamination. This technique may be limited by the generation of higher intraabdominal pressures and cephalad shifting of the

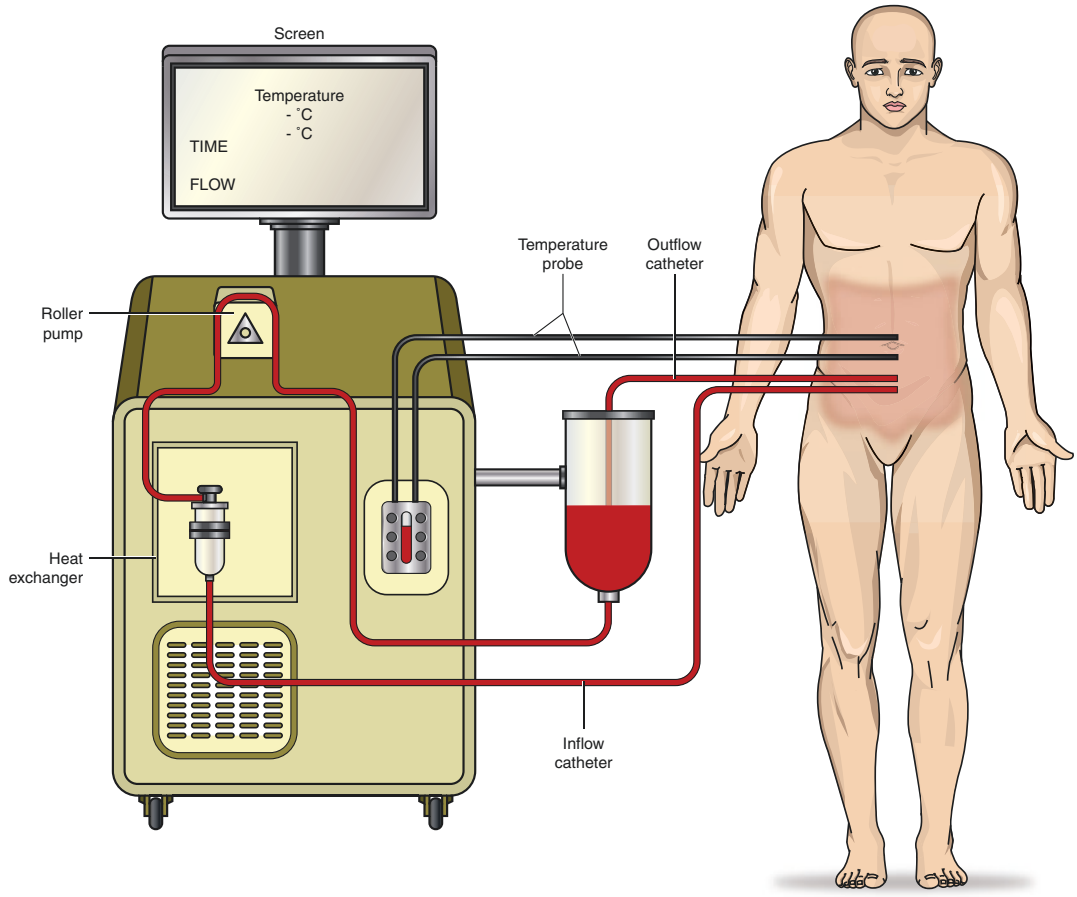

Fig. 37.5 Process of HIPEC

diaphragm, leading to hemodynamic and respiratory compromise. Also, the drugs may not be circulated evenly; this could cause an increase in contact time to the bowel (the possibility of a localized bowel injury due to the pooling of heat and chemotherapeutic agent), risk of splanchnic hypoperfusion, and the manipulation for even circulation of infusate may not be feasible.

In both the techniques, the heat exchanger equipment maintains the infusate temperature at 44–46 °C at the machine level, so as to maintain the intraperitoneal infusate temperature around 41–43 °C to achieve the tumoricidal activity (Fig. 37.5).

37.2.2 Mechanism of Action of HIPEC

The hyperthermic intraperitoneal chemotherapy can penetrate the tissues up to the depth of 5 mm. This mandates optimal CRS of tumor load to ensure sufficient penetration of the agent into the residual tumor [1, 3, 4, 11]. Thereafter, chemotherapy in carrier solution is instilled and circulated in the abdominal cavity using specific equipment at the high controlled temperature of 41–43 °C for 30–90 min.

During HIPEC, the delivery of the chemotherapeutic agent administered intraperitoneally is dependent on the flow rate of perfusate, the temperature of the perfusate at the patient end, dose of the chemotherapeutic drug, and

the duration for which the hyperthermic chemotherapeutic drug is circulated in the abdominal cavity [12]. The circulation and maintenance of the temperature of perfusate are essential for its optimal effect on tumor lesions after CRS. This provides a high local concentration of the chemotherapeutic drug in the abdomen and decreases its systemic absorption [1]. The action on tumor cells is via reversible nonselective inhibition of RNA synthesis, mitosis arrest and inhibition of DNA repair mechanism, denaturation of protein, and activation of heat shock protein leading to the tumor cells' damage [13]. The other reported mechanism includes immune-mediated damage to cancer cells. Hyperthermia increases drug penetration and metabolic activity into the malignant cells (increases the cytotoxicity/tumoricidal activity) and thus the synergistic effect of hyperthermia and chemotherapeutic effect [3, 12, 14]. Also, hyperthermia causes microcirculation flow stasis in malignant cells, in contrast to increased flow in normal cells' blood flow. The damaged cells accumulate lactic acid, get an acidic milieu, and get lysed by released lysosomal enzymes.

The effect of HIPEC is optimal when the drug is perfused soon after CRS and before surgical anastomosis and reconstruction are performed. This avoids the trapping of cancer cells along with the scar tissue, adhesions, or anastomotic sites [15]. The intracavitary hyperthermic chemotherapy achieves higher doses at the direct tumor site that otherwise would not be tolerated with systemic administration (20–1000 times higher than plasma concentrations) [9, 12]. This is due to the peritoneal–plasma barrier and allows a slow rate of absorption across the peritoneum to the plasma. The absorbed drug from peritoneal drains in the portal vein with first-pass detoxifying effect and remains beneficial for potential hepatic micrometastases. In some circumstances, concurrent intravenous chemotherapy may also be administered to increase the tumoricidal effect. For example, patients requiring instillation of hyperthermic intraperitoneal oxaliplatin for HIPEC receive intravenous systemic chemotherapy like fluorouracil and folinic acid administered 1 h before the initiation of HIPEC.

37.2.3 Concerns for CRS and HIPEC

CRS and HIPEC interventions are peculiar and anesthesiologists play an important role in an optimal outcome. The malignancies may have an impact on organ systems directly and indirectly. These may be related to cancer itself or related to preoperative treatment like chemotherapy. In addition to issues related to major surgical resection, the addition of HIPEC introduces more challenges with specific issues of hyperthermic chemotherapy drug administration in the peritoneal cavity. It not only has a direct systemic effect and hyperdynamic metabolic response but is also related to notable increases in core temperature and circulating inflammatory cytokines [3, 16]. This impact may persist in the postoperative period for several days. The following description provides an overview of the impact on various body systems for patients scheduled for CRS and HIPEC.

37.2.3.1 Cardiovascular Changes

Patients undergoing CRS and HIPEC have an impact on the cardiovascular system in multiple ways. The existence of abdominal tumors per se and prior treatment like chemotherapy may be associated with cardiovascular morbidity. The disease itself causes abdominal distension, ascites, and organ involvement. These factors may lead to decrease in return and loss of protein-rich fluid in ascitic fluid. This along with preoperative chemotherapy may cause pronounced cardiovascular impact and needs assessment before surgical intervention. CRS and HIPEC surgery is associated with major fluid shift and blood loss, especially in the initial phase of CRS, as large areas of the peritoneum are exposed (evaporative fluid loss) along with major tissue debulking. The drainage of protein-rich ascitic fluid occurs during the CRS phase. The direct surgical impact on abdominal resection leads to major vascular compression (narrowing of the vena cava) and elevation of the diaphragm leading to decreased venous return, inferior vena cava collapse, and thus decrease in the cardiac output [4, 9, 16]. The HIPEC phase is a hypermetabolic, hyper-

dynamic phase due to an increase in body temperature and have associated metabolic acidosis. The change in hemodynamic parameters includes increased heart rate, increased central venous pressure (CVP), increased cardiac index (CI), and increased intrathoracic blood volume index [4, 9, 16–20]. There is a decrease in systemic vascular resistance (SVR) and a decrease in mean arterial pressures (MAPs). The abdominal distension and increased intraabdominal pressure during surgery and due to circulating perfusate during HIPEC lead to reduced blood circulation in the abdomen, elevated splanchnic vascular resistance, and reduced venous return [21, 22]. Thus, both the phases of CRS and HIPEC are linked to a variable amount of hemodynamic fluctuations. However, it needs to be noted that CVP and pulmonary capillary wedge pressure (PCWP) do not correctly assess the volume status [17, 23, 24]. Chemotherapeutic agents during the HIPEC phase may have direct cardiac toxicity like intraperitoneal cisplatin which may lead to amiodarone-refractory pulseless ventricular tachycardia and is discussed in detail in the later section [6, 25]. These specific toxicities need to be assessed with QT interval prolongation on ECG and plasma magnesium levels [6].

37.2.3.2 Respiratory Changes

The peritoneal and gynecological malignancies may be associated with ascites and pleural effusion. Both of these may lead to mechanical effects on pulmonary function by causing atelectasis, decreased functional residual capacity (FRC), and thus decreased respiratory reserves due to direct pressure effects [4]. Preoperative chemotherapy may be associated with pulmonary toxicity as well. Direct surgical retraction and abdominal filling of hyperthermic perfusate lead to increased abdominal pressures. These increased pressures cause a cranial shift of the diaphragm, which in turn leads to reduced FRC and increased airway pressures. End-tidal carbon dioxide ($EtCO_2$), decrease in the alveolar–arterial (A–a) gradient, and arterial pH oxygen. Increased oxygen extraction and consumption occurs during the HIPEC due to hypermetabolism [26, 27]. These changes are usually transient and get reversed with conservative ventilatory measures, except the component of acidosis which has a metabolic component as well and needs to be managed in the postoperative period as well [28].

37.2.3.3 Renal Changes

Patients requiring CRS and HIPEC may manifest renal and electrolyte derangements and etiology remains multifactorial. Acute kidney injury has an incidence of 1.3–5.7% in such surgeries and is usually reversible if appropriately managed [15, 29]. The factors responsible for such derangements include [30]:

- Preoperative (cancer itself, nutritional issues, presence of ascites, and prior chemotherapy)
- Intraoperative
  - CRS phase (extensive surgery, major fluid shift, and blood replacements; hemodynamic fluctuations, and systemic inflammation)
  - HIPEC phase (impact of hyperthermic chemotherapeutic agent toxicity—hyperthermia and direct drug toxicity)
- Postoperative (direct renal toxicity of hyperthermic chemotherapeutic agent, major fluid loss, and fluid replacements).

Various modalities need to be planned including hemodynamic optimization to prevent renal injury. Patients with renal dysfunction have been associated with increased cardiovascular adverse events in patients undergoing CRS and HIPEC. The hemodynamic needs to be maintained with the goal of maintenance of tissue perfusion and oxygenation. This can be attained by optimal fluid maintenance and optimal use of vasopressors and inotropes [2, 31].

37.2.3.4 Coagulation Alterations

CRS and HIPEC are associated with coagulation abnormalities due to multifactorial etiology, though the exact pathophysiology is not completely understood [2–5, 8, 32–35]. The coagulopathy occurs due to the impact of:

- Preoperative chemotherapy
- Nutritional deficiencies
- Cancer per se (thrombotic state)
- Prolonged surgeries
- Major fluid shifts
- Blood loss with dilutional coagulopathy, transfusion coagulopathy
- Protein loss (leak and ascitic fluid drainage)
- Temperature fluctuations: hypothermia in CRS and hyperthermia in HIPEC
- Metabolic acidosis
- Decreased serum calcium levels
- Impact of the hypermetabolic phase of hyperthermic chemotherapy
- Liver and renal dysfunction during the HIPEC phase

The loss of ascitic fluid also contributes to the loss of protein components including albumin (50–70%), globulins (30–45%), and fibrinogen (0.3–4.5%), and affects coagulation [28]. The altered coagulation parameters include [3–5, 27, 36–38]:

- Thrombocytopenia
- Decreased antithrombin (AT) III
- Decreased fibrinogen value
- Prolonged activated partial thromboplastin time (aPTT)
- Prolonged prothrombin time and international normalized ratio (PT-INR)
- Decreased coagulation factors like factor XIII, not measured by standard coagulation tests.

Due to these deficits, coagulopathy peaks around 24–48 h in the postoperative period and resumes normality around 3–4 days usually [39].

37.2.3.5 Metabolic Perturbations

The hypoperfusion state during the CRS and hypermetabolic phase of HIPEC lead to metabolic perturbations, in addition to other perioperative factors. The metabolic disturbances occur in both phases of CRS and HIPEC due to factors including [1]:

- CRS phase: hypothermia, fluid/blood loss leading to hypoperfusion, and increased intraabdominal pressure
- HIPEC phase: hyperthermia, chemotoxicity, and increased intraabdominal pressure

Acidosis (both metabolic and respiratory) has been reported in CRS and HIPEC [1, 3, 4, 6]. Metabolic acidosis remains more common. The hypermetabolic state of HIPEC leads to elevated the arterial partial pressure of carbon dioxide ($PaCO_2$) and thus respiratory acidosis [1, 4]. The metabolic acidosis with low bicarbonate levels and increased serum lactate occur in the HIPEC phase [1, 3, 4, 6]. Usually, these changes settle with appropriate fluid resuscitation and bicarbonate infusion is generally not required.

37.2.3.6 Nutrition

The nutritional deficit may occur due to cancer per se, decreased intake, and the impact of preoperative treatment like chemotherapy. Also, it may be related to the loss of proteins from ascitic fluid. The incidence of malnutrition remains high in ovarian cancer (67%), colorectal cancer (54%), and gastric cancer (83%) [4, 19, 40]. The CRS and HIPEC surgery remains a catabolic and pro-inflammatory state mandating nutritional optimization before surgery. Poor nutritional status remains an independent predictor of poor outcome. Malnutrition delays wound healing, causes increased risk of infections, and prolongs hospital stay [13, 19, 41]. The presence of skeletal muscle depletion (sarcopenia) in patients planned for CRS and HIPEC has been found to have poorer prognosis with an increased incidence of perioperative complications [13, 42].

37.2.4 Preoperative Assessment

A thorough history and examination is the key aspect for patient's assessment scheduled for CRS and HIPEC. This not only helps in planning the perioperative care, risk stratification but also the need for additional tests, referrals, and

plan for optimization. The assessment should include prior drug therapy including chemotherapy, analgesics, or drugs for associated comorbidities apart from routine assessment similar to other major surgical procedures. The presence of comorbidities like cardiac diseases, renal dysfunction, and presence of diabetes mellitus has been observed to have poorer outcome [43]. It has been reported that patients with diabetes mellitus have an increased incidence of infections and their related complications, cardiac events like arrhythmias, renal dysfunction, and respiratory failure in the perioperative period [3, 4, 44].

The specific scoring system for assessment and risk stratification does not exist for CRS and HIPEC procedure. The routine assessment tools for associated comorbidities like cardiac diseases, hypertension, and diabetes mellitus disease need to be used for risk stratifications. The tools like the American Society of Anaesthesiologists (ASA) physical status and Eastern Cooperative Oncology Group (ECOG) performance status are useful for risk stratification [33, 45, 46].

The following is an overview of assessment in patients with CRS and HIPEC to be interpreted in the context of systemic changes as discussed:

37.2.4.1 Cardiovascular System

The main goal of cardiac assessment is to identify the preexisting cardiac disease and to assess the compensatory reserves for adverse physiological changes during CRS and HIPEC [4, 15, 47]. The CRS and HIPEC cause increased cardiac work and increased myocardial oxygen demand, so it is essential to assess for any preexisting coronary heart disease. Any decrease in the left ventricular function may lead to decompensation and heart failure due to the intolerance of aggressive fluid therapy and hyperthermia. The cardiovascular system assessment is primarily based on the findings of history and examination. The majority of patients would require 12 lead electrocardiograms (ECGs), echocardiograms, and stress testing because of compromised cardiovascular reserves due to diseases or preoperative chemotherapy. The stress test need would base on decrease in functional capacity or having an underlying cardiac disorder or for those patients whose functional capacity could not be assessed. Cardiopulmonary exercise testing (CPET) provides a comprehensive assessment of cardiovascular compromise and may be indicated in a select patient with associated cardiac or respiratory comorbidities.

37.2.4.2 Respiratory System

Pulmonary function needs to be assessed clinically, physical examination, imaging (chest X-ray), and by specific lung evaluation like spirometry. Lung recruitment for atelectatic lung may be initiated at the earliest possible time. Respiratory physiotherapy avoids many perioperative respiratory-related adverse impacts. At times, as per patient initial assessment, CPET may be required in patients with limited reserves as assessed clinically.

37.2.4.3 Renal

Because of renal and electrolyte imbalance, patients for CRS and HIPEC are assessed for renal function (blood urea and serum electrolytes—calcium, potassium, sodium, and magnesium) [3, 4, 40]. Renal function needs further assessment in case of tumor per se or treatment-related renal dysfunction. The assessment of a calculated glomerular filtration rate would aid in the identification of at-risk patients for renal dysfunction during and after CRS and HIPEC [15]. The assessment of the urinary pathway needs to be assessed as at times, the tumor causes mechanical obstruction. Patients may be having ureteric stent and its patency needs to be confirmed.

37.2.4.4 Coagulation Status

Assessment of the coagulation profile using INR, aPTT, and platelet count is desirable in these patients to rule out any baseline coagulation abnormality [3–5].

37.2.4.5 Nutrition Status

The nutritional status needs to be assessed clinically. The presence of sarcopenia, low albumin levels, and low hemoglobin levels has been found to have increased perioperative adverse events [42, 43].

37.2.5 Preoperative Optimization

CRS and HIPEC surgeries remain time-sensitive surgeries and complete optimization may not be feasible due to time constraints. However, initiation of the optimization process should start in the preoperative period for whatever time possible. The first visit to such a patient should be an opportunity to teach and involve the patient for optimization and prehabilitation. The various optimization issues may be summarized as:

37.2.5.1 Cardiovascular System

As per time permits, the cardiac status needs to be optimized. In the case of hypertension, the optimization steps need to be initiated. However, complete normalization may not be feasible due to time constraints for such time-sensitive surgical intervention.

37.2.5.2 Respiratory System

The presence of atelectasis due to the presence of abdominal mass, ascites, and pleural effusion is commonly seen in patients undergoing CRS and HIPEC. Patients should be taught deep breathing exercises, incentive spirometry, and encouraged to perform these before surgery. Respiratory physiotherapy for loosening and removal of lung secretions should also be initiated preopertively. The initiations of pulmonary physiotherapy recruits lungs, and thus lesser chances of respiratory morbidities [48].

37.2.5.3 Renal System

The renal function needs to be assessed preoperatively. At times, due to direct compression over the kidney and the presence of gross ascites with deranged renal function, the patient should be assessed for the need of ureteric stent placement to optimize the renal function preoperatively. In cases, if the stent is already present at the time of preoperative assessment, the patency of the stents needs to be checked and ensured.

37.2.5.4 Nutrition

Preoperative low serum albumin levels remain the predictor for adverse outcomes, including the increased length of hospital stay and overall survival [42, 49]. So, the patient needs to be optimized nutritionally preoperatively as per time permits for such time-sensitive surgical intervention. Appropriate dietician consultation with an increase in oral intake is beneficial. The role of parenteral nutrition remains controversial.

37.2.5.5 Prehabilitation

The initial strategies by appropriate prehabilitation improve the overall surgical outcome. The literature is scarce for specific prehabilitation strategies for patients undergoing CRS and HIPEC. However, it may be extrapolated from similar major abdominal surgeries. The improvement in lung function, and nutritional status is one of the important components of prehabilitation that appears suitable to these surgical interventions. It has been reported that the explanation given to the patient and training by physiotherapists along with optimal pain management improve the postoperative recovery and reduce the length of critical care unit stay [23].

37.3 Temperature Regulation

Patients manifest variations in temperature in the perioperative period and have a variable impact on body functions. Both hypothermia and hyperthermia are seen in patients undergoing CRS and HIPEC. The CRS phase is usually associated with a fall in core body temperature and HIPEC leads to hyperthermia. The temperature fluctuations are primarily related to long-duration and extensive surgical resection/exposure, loss of body fluids (ascitic fluid, blood loss), major fluid shifts, and fluid/blood replacements for hypothermia and hyperthermic chemotherapeutic agent instillate for hyperthermia [17]. The core temperature significantly decreases during CRS and before HIPEC than the baseline (33.5 ± 1.7 °C and 36.5 ± 0.6 °C, respectively) [1, 9, 23, 50–52]. It significantly increases during HIPEC (38.2 ± 1.1 °C) and persists after completion (38 ± 0.8 °C) than before this phase.

Temperature fluctuations lead to metabolic alterations (metabolic acidosis, electrolyte

imbalance, and elevated serum lactate levels), coagulation abnormalities, anti-inflammatory cascade activation, adverse myocardial events, surgical wound infection, and neurological insult [3–5, 53]. Hyperthermia during the HIPEC phase results in a hypermetabolic state. This leads to increased heart rate, peripheral vasodilatation (further associated with decreased MAP and reflex increase in heart rate), raised $EtCO_2$, and increased oxygen requirement which peaks at the end of the HIPEC phase. Hyperthermia also leads to the risk of pulmonary edema, ventilator-related acute lung injury, neurocognitive dysfunction, and electrophysiological alterations in peripheral nerves [4, 13, 54]. HIPEC-induced hyperthermia impacts postoperative recovery and it has been observed that a higher delta temperature correlates with the need for prolonged mechanical ventilation and prolonged critical care unit stay [34, 35].

Normothermia maintenance remains an important goal and requires proper planning (Table 37.1) [1, 3–6, 13, 34, 55]. This requires temperature monitoring and its optimal control for an uneventful outcome. Continuous core body temperature (nasopharynx/esophagus) monitoring is deemed necessary. Use of warming devices like warming blankets, water-based warming mattresses, forced-air warming blankets (Bair hugger ®), and fluid warmers are desirable during the CRS phase. The optimal control of operating room (OR) temperature is necessary [4–6]. During the HIPEC phase, abdominal cavity temperature and temperature of chemotherapeutic perfusate including the warming device temperature need to be monitored. During this phase, warming blankets and warming fluid infusers need to be stopped and cooling strategies should be initiated. These include the infusion of cooled intravenous fluids, ice packs at vascular areas like axilla, and keeping the warming blankets to ambient flow or switching them off [4, 5, 34, 55]. In extreme cases, even the instillate temperature needs to be reduced. Usually, after the HIPEC, the temperature starts normalizing but remains above the baseline for the variable period in the postoperative period.

Table 37.1 Management of temperature during CRS and HIPEC

Context	Hypothermia prevention	Hyperthermia prevention
Monitoring	Core body temperature	Core body temperature Abdominal cavity temperature and temperature of chemotherapeutic perfusate Temperature of warming device for HIPEC
Fluids and blood products	Fluid warmers' infusers	Stop fluid warmers Cool fluids
Warming blankets	Water-based warming mattress Forced-air warming blankets	Warming blankets/ mattresses switched off or on ambient temperature mode
Operating room temperature	Optimal level of operating room temperature	Optimal level of operating room temperature
Others		Monitoring and control of perfusate temperature

37.3.1 Perioperative Pain Management

CRS and HIPEC are associated with severe pain, as compared to other major abdominal surgeries [4, 5, 15, 56]. The CRS and HIPEC require a large abdominal incision, tissue cutting, resection, manipulation, and have an intense inflammatory phase. These elicit the pain fibers/pathways and thus need optimal planning and administration of analgesics and analgesic technique.

Optimal pain management causes a reduction in need and duration of postoperative mechanical ventilation, better breathing function, lesser pulmonary complications, lesser incidence of postoperative chronic pain syndrome, early ambulation, and better patient satisfaction with improved overall recovery [2, 5, 50, 57]. These malignancies are extensive and may present with pain in the preoperative period itself and require

aggressive pain management with analgesics titrated as per the pain score. The analgesics are prescribed as per the World Health Organization (WHO) analgesic ladder. It needs to be ensured that analgesics are continued until surgery and its supplementation should be accordingly adjusted in the perioperative period.

Pain management is preferably a multimodal analgesic technique inclusive of the regional block and intravenous analgesics including paracetamol. Though a single technique may not be considered as the gold standard for analgesia, however, majority of published literature favors the use of intravenous opioids and thoracic epidural analgesia for analgesia in such surgeries [4, 23, 27, 34, 35]. This technique has been reported to have better pain scores and better bowel function recovery with lesser side effects [5]. Epidural analgesia requires a combination of local anesthetics (bupivacaine, ropivacaine) and opioids and continues for 5–7 days in the postoperative period [33, 34]. This may be administered as boluses or infusions. The contradictory concerns of hypotension related to local anesthetic-induced sympathetic block in the epidural block and HIPEC-induced vasodilatation and decreased systemic vascular resistance (SVR) exits [34, 35, 58]. However, the majority of studies found epidural block to be useful without significant concern of hemodynamic instability attributed to the epidural block itself. The concern over the removal of the catheter in the postoperative period due to coagulopathy is not much, as coagulopathies usually resolve in the postoperative 2–3 day period and epidural analgesia is usually required for 5–7 days. Also, it has been reported that intraoperative hyperthermia does not lead to significant coagulation abnormalities and thus central neuraxial block remains safe from the risk of hematoma formation [59]. The standard protocol of epidural catheter removal needs to be followed in cases of postoperative coagulation abnormalities [6, 7]. The risk of epidural analgesia in the form of hemodynamic instability, epidural hematoma, and infections due to massive blood loss, coagulopathy, and immunosuppression is very rare and can be easily managed [3–5].

Other analgesic options include the administration of intrathecal opioids, intravenous patient-controlled analgesia (IV-PCA), use of other regional blocks like paravertebral blocks, transverse abdominis plane (TAP) block, rectus sheath block, etc. At times, the patient may be on anticoagulants as part of deep vein thrombosis (DVT) prophylaxis. Caution needs to be exercised with regard to associated coagulation issues (preoperative due to nutritional deficiencies and chemotherapy and postoperative due to the impact of dilution and HIPEC-related coagulopathy) for placement and removal of central neuraxial catheters. The recent concerns on the use of opioids and cancer recurrence have led to the use of opioid-sparing analgesic techniques and thus local anesthetic-based central neuraxial analgesia is being considered [60, 61]. However, no concrete evidence has emerged to date. Another impact of opioids relates to the delayed return of bowel function [62, 63].

37.4 Drugs for HIPEC

The HIPEC requires the selection of appropriate chemotherapeutic drugs for instillation in the peritoneal cavity along with carrier solution. These drugs are hydrophilic, have high molecular weight, and slow peritoneal clearance. The peritoneal fluid–blood barrier prevents the clearance of chemotherapeutic drugs [10, 37]. This allows more contact time at higher concentrations locally to tumor cells without an increased risk of systemic effects even at this higher dose. The drug selection is based on the type of tumor and the dose of the drug is based on patient demography including height, weight, and body surface area (Table 37.2) [1, 3–8, 10, 11, 25, 34, 37, 38, 47]. The dose modification is required in associated renal, hepatic, and cardiac dysfunction. These drugs have specific side effects that need to be preempted and managed accordingly [10].

Table 37.2 Chemotherapeutic drugs used in HIPEC [1, 3–8, 10, 11, 25, 34, 37, 38, 47]

Chemotherapy drug class	Chemotherapeutic agent	Malignancies	Mechanism of action	Adverse effects	Remarks
Alkylating agents: Platin	Cisplatin	Ovary Stomach Mesothelioma	DNA replication inhibition	Nephrotoxicity: Renal failure, acute tubular necrosis Hypomagnesemia: Pulseless ventricular tachycardia Hypocalcemia Neurotoxicity: Convulsions, peripheral sensory neuropathy, ototoxicity, cortical blindness Myelosuppression Acute hypersensitivity reactions	Monitor: Magnesium plasma levels and QT interval prolongation Renal failure is generally reversible and requires conservative management Carrier solution: 1.5% dextrose containing peritoneal dialysate Avoid chloride-containing solution
	Oxaliplatin	Colon Appendix Rectum Pseudomyxoma peritonei	DNA replication inhibition	Immune-mediated platelet dysfunction Hemoperitoneum Neurotoxicity: laryngeal/pharyngeal dysesthesia Gastrointestinal bleeding	Carrier solution: 1.5% dextrose containing peritoneal dialysate Avoid chloride-containing solution
Antimetabolites: Anthracyclines	Doxorubicin	Ovary Stomach Mesothelioma	DNA synthesis interruption with type II isomerase inhibition	Cardiotoxicity (arrhythmia, cardiomyopathy) Myelosuppression Gastrointestinal: Mucositis	–
Antimetabolites: antitumor antibiotics	Mitomycin C	Colorectal Pseudomyxoma peritonei Mesothelioma	DNA and RNA synthesis interruption	Nephrotoxicity, hemolytic uremic syndrome Hematologic toxicity: leukopenia, thrombopenia Pulmonary toxicity: pulmonary hypertension, pneumonitis, pulmonary fibrosis Myelosuppression Gastrointestinal toxicity: nausea, vomiting, diarrhea	Carrier solution: 1.5% dextrose containing peritoneal dialysate

Antimetabolites: Pyrimidine analogs	5-fluorouracil	Stomach	Interfere with DNA synthesis via action as pyrimidine antimetabolites	Cardiac toxicity: Chest pain, ST-T wave changes, arrhythmias (atrial fibrillation, ventricular ectopy, ventricular fibrillation), cardiogenic shock, ventricular dysfunction, acute coronary syndrome	Management by pharmacotherapy: nitrates, calcium channel blockers Cardiotoxic effects prominent after repeat doses
Alkylating agents: Nitrogen mustards	Melphalan	Peritoneal carcinomatosis	Interfere with DNA function	Pericarditis, pericardial effusion Seizures Bone marrow suppression	–
Topoisomerase 1 inhibitors	Irinotecan	Colorectal Appendix	DNA rupture	Myelotoxicity Cholinergic syndrome Neutropenia	–
Microtubule assembly inhibitors: Taxanes	Paclitaxel, Docetaxel	Stomach Ovary	Inhibition of microtubule assembly	Cardiac rhythm changes: Bradycardia, dysautonomia Peripheral neuropathy	–

37.4.1 HIPEC: Carrier Solution

The chemotherapeutic drug for perfusion in the abdominal cavity during HIPEC requires a carrier solution (Table 37.3) [1, 3–7, 10–12, 34, 38]. Various solutions like isotonic saline, 5% dextrose, or peritoneal dialysate solution (containing 1.5% dextrose) have been used as a carrier solution. Lactated Ringer's solution as a carrier solution has also been reported [47]. The selection of solutions is based on the type of chemotherapeutic agent being used. The volume of the carrier solution for perfusion ranges from 3 to 4 L (open technique) to 6 L (closed technique) (more commonly, perfusate volumes of 0.5 L/m^2 or 2 L/m^2) [47, 64]. The fluid is circulated in HIPEC at a rate of 0.6–1 L/min flow rate. The chemotherapeutic drug is added to the carrier solution, once the carrier solution achieves a temperature of around 41–42 °C [3, 4, 47, 64].

These carrier solutions themselves have peculiar concerns. The distribution and dose of the chemotherapeutic agent in perfusate are altered by the absorption of the carrier solution across the peritoneum. The selection of a particular carrier solution is based on the interaction and compatibility of mixed solutions. It has been reported that oxaliplatin interacts with chlorine (degradation of oxaliplatin) and this chloride-containing carrier solution is not used with oxaliplatin. Carrier solution causes hyperglycemia, hyponatremia, hyperlactatemia, or metabolic acidosis. Oxaliplatin is used with a 5% dextrose containing carrier solution. The 5% dextrose as a carrier solution may lead to hyponatremia via various mechanisms. The occurrence of hyperglycemia leads to an extracellular shift of water, loss of sodium into the peritoneal perfusion fluid, and absorption of free water into the plasma leading to dilutional hyponatremia [65]. However, it shows spontaneous recovery within a few hours. In severe cases, it requires antihyperglycemic therapy. The 5% dextrose as a carrier solution is also associated with hyperlactatemia via hyperglycemia-induced glycolysis and hypoperfusion. Dextrose (1.5%) containing peritoneal dialysate for the administration of cisplatin or mitomycin causes lesser hyperglycemia and no significant dyselectrolytemia but has a higher incidence of renal injury.

Table 37.3 Carrier solution used in HIPEC [1, 3, 5–7, 10–12, 34, 38]

Carrier solutions
• Isotonic saline
• 5% dextrose
• Peritoneal dialysate solution (containing 1.5% dextrose)
• Lactated Ringer's solution

37.4.2 Intraoperative Period

37.4.2.1 Intraoperative Monitoring

Appropriate monitoring is essential in patients undergoing CRS and HIPEC. Apart from routine conventional monitoring, certain additional monitoring is required for such interventions. Specific monitoring is also required based on associated patients' conditions and comorbidities. The monitoring required in these groups of patients includes:

- Cardiovascular:
  - Electrocardiogram (ECG)
  - Invasive arterial pressure monitoring
  - Transesophageal Doppler
  - Continuous cardiac output using pulse contour analysis monitors
- Respiratory:
  - Pulse oximeter
  - Capnography
  - Oxygen and gas analyzers
- Urine Output:
  - Hourly during CRS and every 15 min during the HIPEC phase
- Temperature:
  - Core body temperature
  - Instillate (chemotherapeutic temperature) temperature
  - Intravenous fluid temperature
  - Warming blankets' temperature
- Blood loss estimation
- Neuromuscular monitoring
- Arterial blood gas monitoring
- Platelet function analyzer or thromboelastogram (TEG)

37.4.2.2 Airway and Ventilatory Management

Due to decreases in respiratory reserves, adequate preoxygenation should be done before the induction of anesthesia [66]. Head up position may be beneficial but no evidence exists for such positioning during induction in CRS and HIPC. The presence of abdominal mass and/or ascites and/or possible bowel obstruction may lead to increase in intraabdominal pressures and thus the risk of regurgitation and aspiration [66]. So, preoperative fasting needs to be ensured along with the need for rapid sequence induction and intubation.

The technique of induction of anesthesia is based on the tumor site and extent. It requires rapid sequence, modified rapid induction, or conventional induction and tracheal intubations as per patient assessment. The choice of induction drugs and neuromuscular blocking agents is based on the anesthesia technique and patient assessment. The choice of airway equipment remains to be a cuffed endotracheal tube. The technique of securing the airway remains as per the airway assessment and has been discussed elsewhere. The endotracheal tube cuff pressure increases in CRS and HIPEC and thus cuff pressure monitoring and its pressure readjustment are required [4, 66, 67].

Based on the extent of abdominal mass and patient clinical condition, ventilator strategies may be planned. In the presence of large mass, lung-protective strategy like smaller tidal volumes with the application of positive end-expiratory pressure (PEEP) along with intermittent lung recruitment maneuvers are beneficial [19]. When significant respiratory compromise is preexisting in patients, the open technique of HIPEC may be preferable to a closed technique [68]. Also, in the HIPEC phase, not only oxygen requirements increase but also impaired oxygenation ratio and tissue oxygenation occur in addition to increased airway pressures due to diaphragm elevation [34, 36, 53]. It requires the modification of ventilator strategies to counter oxygenation-related concerns.

37.4.2.3 Hemodynamic Management

Intraoperatively, hemodynamic shows variable dynamic changes. This mandates constant and continued monitoring and attention to manage as per hemodynamic fluctuations. Optimal hemodynamic is clued from signs of adequate tissue/organ perfusion without being overloaded with fluids. The monitoring requires an arterial line, central venous catheter, and a urinary catheter. The other least invasive hemodynamic monitoring devices used in such procedures include esophageal Doppler and FloTrac/Vigileo® and are useful for assessing the fluid status [13]. These provide real-time dynamic parameters like stroke volume variation (SVV), pulse pressure variation (PPV), aortic blood flow, and left ventricular ejection time [3, 4, 13, 67].

Though urine output is a good marker for fluid appropriateness, it may be affected by direct renal handling during surgery and the impact of hyperthermic chemotherapeutic instillate on kidney function. The central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) remain inappropriate due to mechanical effects by surgical retractors, compressions, and raised intraabdominal pressures [4, 6].

In HIPEC with closed technique, the intraabdominal pressure increases and ranges between 12 and 26 mmHg, leading to decreased perfusion pressure of abdominal organs with increased splanchnic pressures [3, 5, 15]. It has been reported that despite an optimal fluid status, increased abdominal pressures led to a marked decrease in hepatic blood flow, as confirmed using transesophageal echocardiography Doppler signals, and decreased liver function [69]. It is desirable to maintain abdominal perfusion pressures > 60 mmHg. This can be achieved with an adequate fluid infusion or the use of vasoactive medications.

37.4.2.4 Fluid and Blood Management

The fluid management has to be meticulously and dynamically planned. Maintaining euvolemia

and thus cardiovascular stability along with correction of electrolyte/metabolic changes remains challenging. Such procedures require fluid differently in different phases of the surgery (CRS vs HIPEC vs postoperative period). It aims at maintaining optimal perfusion pressure to vital organs with optimal urine output [1, 4, 13, 67]. Goal-directed balanced isotonic crystalloid infusion appears to be an acceptable technique for maintaining optimal organ perfusion [34, 70, 71]. This improves perioperative outcomes with the reduction of complications [3–5, 71]. It has been reported that goal-directed therapy aimed at maintaining the cardiac index (CI) ≥ 2.5 L/min/m^2 and restrictive fluid regimen improves perioperative outcome when compared to traditional fluid regimen strategy [66, 71, 72]. The use of liberal or massive fluid infusion needs to be discouraged. Such regimen increases adverse events due to fluid overload-induced tissue edema, decreased cellular perfusion, and also other abdominal, cardiac, or pulmonary complications [5, 13, 34]. The underlying pathophysiology for this outcome relates to endothelial glycocalycial system damage affecting the overall recovery. Caution is required during fluid administration as tissues receive prolonged mechanical, thermal, and chemical damage and thus are prone to leaky capillaries and thus remain prone to interstitial edema in any fluid status phase. Optovolemia (regime tailored to the individual patient basis) appears to be the correct approach for such surgical interventions. This individualized approach of fluid management may be done by goal-directed assessment tools like stroke volume variation and cardiac output [13, 34, 66, 71]. In the HIPEC phase wherein vasodilatation occurs, the need for inotropes/vasopressors is desirable in addition to appropriate fluid resuscitation [4, 71, 72]. However, no evidence exists with regard to the timing and type of the inotropes/vasopressors. The excessive fluid loading to compensate for vasodilatation is not desirable, as vasodilatation reduces to a larger extent after completion of the HIPEC phase. The advanced versions of the cardiac output monitoring system measure extravascular lung water (EVLW) as well in addition to other hemodynamic variables [Vigileo (EV1000)]. Such measurement of EVLW measures lung water as well and thus would be useful to avoid morbidity due to hypervolemia [44, 72].

It has been observed that patients receiving fluids over 15.7 ml/kg/h have increased complications with regard to those receiving less than this volume [73]. It was also reported that the rate of fluid administration and blood loss was an independent predictors of perioperative morbidity [73, 74]. The usual requirement of 6–8 ml/h of fluid in other abdominal surgeries appears insufficient and the reported fluid volume is 12–20 ml/kg/h and depends on the patient status and extent of debulking [9, 13]. The endpoint of fluid administration is the maintenance of optimal end-organ perfusion [20, 75].

Urine output remains a well-accepted monitoring tool. The adverse impact on kidney function during the HIPEC phase mandates well perfusion of the kidney and thus higher urine volume to keep the kidney flushed of toxic effects of drugs and hyperthermia. Though not well reported, it is prudent to maintain a urine output of 0.5 ml/kg/h during CRS, around 4 ml/kg/h during HIPEC. Due to the continued impact of CRS and HIPEC in the postoperative period, it is suggested to maintain a urine output of 1–2 ml/kg/h after the HIPEC [3, 4, 6, 17, 20]. The urine monitoring needs to be done more frequently (every 15 min) during the HIPEC phase to assess the dynamic and acute impact.

The choice of fluid with regard to crystalloid or colloid remains debatable and definite scientific evidence is lacking [76]. However extrapolating from other major surgeries, it appears that the infusion of balanced salt solutions is preferable and maintains adequate preload, colloid oncotic pressure, perfusion of tissues, and electrolyte balance. Draining of ascitic fluid, debulking of tumor, and drain placements during CRS are associated with perioperative protein loss. The protein loss in a day is around 700 g [77]. The occurrence of hypoalbuminemia leads to increased perioperative morbidity and thus protein supplementation (oral preoperatively and intravenous perioperatively) appears acceptable in patients with low serum protein levels [1, 51,

77]. The transfusion of fresh frozen plasma (FFP) should be given only for clinically manifested coagulopathy.

The CRS is extensive surgery with major blood loss due to surgical dissection and coagulopathy. Intraoperatively, the patient may manifest bleeding due to dilutional coagulopathy (use of the large volume of fluids), transfusion coagulopathy (use of red blood cell transfusions to replace blood loss), and preexisting protein loss associated coagulopathy [2–5, 13, 18, 19]. Additionally, patients may have platelet dysfunction due to extreme variation in the temperature. The recommendations for optimal fluid and blood replacement in the perioperative period have not been reported conclusively. The risk factors for the need for blood transfusion include surgical duration >9 h, preoperative INR >1.2, preoperative hemoglobin <12.5 g/dl, and PCI > 16 [1]. The specific management of blood replacement may be done as per assessment by the point-of-care tool thromboelastogram (TEG) [78, 79]. It assesses the coagulation derangements, identifies the specific coagulation abnormality, and guides the replacement of specific blood products [9, 18]. The blood transfusion practices remain restricted as in most cancer surgeries because of increased morbidity/mortality, risk of immunomodulation, and cancer recurrence [80, 81]. The use of irradiated salvaged blood transfusion needs further evaluation in this group of patients [13, 18]. The role of preemptive administration of the antifibrinolytic tranexamic acid for reducing blood loss appears promising and needs to be studied further [13, 18].

37.4.2.5 Renal System and Electrolyte Balance Management

The CRS and HIPEC require urine output monitoring and optimal urine output is desirable. This monitoring becomes more frequent during the HIPEC phase due to an increased risk of renal injury. Though not recommended, low-dose dopamine and loop diuretics have been reported during HIPEC, especially when platinum-based chemotherapeutic agents are used intraoperatively to mitigate nephrotoxic insult by the chemotherapeutic agent [13, 19, 23, 34, 75, 82]. Even in such situations, euvolemia needs to be maintained and monitored with appropriate hemodynamic monitoring [19]. However, its protective effect is yet to be proven in such surgeries [83].

The electrolyte imbalance occurs intraoperatively due to fluid shifts and toxicity of the hyperthermic chemotherapeutic agent. Cisplatin and oxaliplatin lead to electrolyte disturbances like hyponatremia, hypocalcemia, and hypomagnesemia [3–5, 18, 19]. The carrier solution may cause electrolyte disturbances and thus electrolyte monitoring is desirable during HIPEC (preferably every 15 min during HIPEC and every 30 min up to 2 h of HIPEC and subsequently as per patient condition).

37.4.2.6 Antiemetics

Though there is no specific literature, there appears the need for prophylactic antiemetic in patients undergoing CRS and HIPEC. This may be due to the emetic potential of chemotherapy like cisplatin-induced nausea and vomiting and also risk factors for vomiting potential like in gynecological surgeries [84, 85].

37.4.3 Postoperative Management

The CRS and HIPEC phases are complex interventions with alterations and fluctuations in almost all body systems. These patients require high dependency on the care given by the critical care unit due to the possible need for mechanical ventilation, lung recruitment, chest physiotherapy, organ function assessment, assessing and managing complications, fluid management, analgesia, and identifying and correcting coagulation abnormalities. The postoperative period also requires the assessment for complications like bowel injuries, bile leak, pancreatitis, bleeding, deep vein thrombosis, and embolic phenomenon [15]. So, it is preferable to monitor these patients in the postoperative period in a monitored area, preferably the critical care unit, for at least 1–2 days for the normalization of various deranged body functions, as discussed in previous sections [1, 3]. The occurrence of cognitive dysfunction

due to increased perioperative inflammatory marker levels (systemic and central inflammatory response) after CRS and HIPEC has been reported [86]. It was suggested that excessive systemic inflammation triggers the inflammatory process in the brain, which produces neurotoxic responses, affects neuronal function, and causes cognitive impairments [86]. So, the patient needs assessment and appropriate management from this aspect as well.

The specific considerations in the postoperative period are summarized in the following section:

- *Analgesia*: Optimal analgesia is paramount for decreasing postoperative morbidity, early ambulation, decreased deep vein thrombosis, and better respiratory function. Multimodal analgesia needs to be continued postoperatively and may require aggressive management at least initially for 3–5 days and may continue even up to 7 days. Epidural analgesia using local anesthetics and opioids along with acetaminophen needs to be continued. Epidural analgesia may be administered as boluses, infusion, or patient-controlled. Nonsteroidal anti-inflammatory drugs (NSAIDs) need to be avoided, due to the possibility of coagulation abnormalities and the risk of renal dysfunction.
- *Airway Management, Ventilator Support, and Oxygen Therapy*: The airway management with regard to the timing of extubation depends on the intraoperative respiratory and hemodynamic status. Postoperative mandatory mechanical ventilation is not essential and usually, the majority of patients could be extubated soon after surgery [3, 13, 34, 87]. However, if mechanical ventilation is required, weaning needs to be tried, once the patient is stabilized. The use of noninvasive techniques in the postoperative period may mitigate atelectasis and bring about better recovery [19]. Given increased oxygen therapy, oxygen supplementation may be required for a few hours to a day depending on the patient need and assessment. However, these may be weaned at the earliest. The chest physiotherapy including incentive spirometry needs to be continued to prevent atelectasis.
- *Hemodynamics and Fluid Management*: These patients require hemodynamic monitoring to assess and manage hemodynamic status and optimal perfusion of the vital organs. The fluid shift and loss persist for 2–3 days postoperatively and thus its monitoring and appropriate replacement are required. Fluid and protein loss may occur through drains in the postoperative period. Protein loss due to the loss of protein-rich fluid in the exudates in drains and hypermetabolic phase may persist in the postoperative period. Goal-directed fluid management needs to be continued [87]. Protein levels need assessment and protein supplementation needs to be done with exogenous albumin, if the protein levels are <3.0 g/dl.
- *Electrolyte abnormalities:* The postoperative period requires electrolyte and metabolic monitoring. These abnormalities may continue in the immediate postoperative period due to ongoing fluid loss and hypermetabolic phase. Management needs to be planned as per the report outcome.
- *Coagulation and Blood Products:* Blood product transfusion needs to be individualized as per patient's clinical assessment and using a point-of-care tool like TEG. During the assessment of hemoglobin level and TEG interpretation, specific blood products like packed red cells, cryoprecipitate, or fresh frozen plasma may be transfused. Coagulation abnormalities may peak at 24–48 h postoperatively when associated liver and renal dysfunction also occurs. Accordingly, blood products may be administered and may be guided by the point-of-care tool like TEG. Usually, such derangements settle down by the third day. The routine requirement of blood product transfusion is not desirable.
- *Thromboprophylaxis*: Such surgical procedures remain prothrombotic. Since these patients are prone to coagulation abnormalities, so the need and technique of thromboprophylaxis have to be individualized. Until coagulation abnormalities are corrected or

optimized, mechanical devices for the prevention of deep vein thrombosis (DVT)-like intermittent pneumatic compression and graduated compression stockings are preferred. Once the coagulation parameters are normalized and there is no excessive ooze from drain sites, pharmacological agents like low molecular weight heparin (LMWH) or heparin may be initiated.

- *Temperature Monitoring:* Temperature remains elevated for initial 1–2 days postoperatively and subsequently gets normalized. This is related to the inflammatory response and may be confused with the onset of sepsis. A careful assessment is required for differentiating these etiologies. The phenomenon of high-inflammatory syndrome following HIPEC is reported and relates to hyperthermia, increased fibrinogen levels, and increased gastric secretions [1, 18].
- *Nutrition:* Nutrition needs to be restarted at the earliest. The preferred mode remains enteral nutrition, as it allows a faster bowel activity, reduces the risk of translocation of bacteria, and thus the risk of infection. The use of a nasojejunal catheter may be considered for early enteral nutrition [19]. Only in selected cases with prolonged recovery like the presence of postoperative ileus, stress ulcer, or anastomotic leak, parenteral nutrition may be considered. Albumin may be considered if serum levels are less than 3 g/dl.
- *Infection Control/Prevention*: These patients are immunocompromised. All procedures including epidural catheter drug administration, infusion of intravenous drugs, and fluids need to be aseptically managed [3, 4, 13]. Antibiotics should be selectively provided as per patient assessment and institutional protocol.
- *Other System Monitoring*: Hyperthermic chemotherapeutic agents used for HIPEC have systemic toxicity. The various manifestations may occur due to bone marrow suppression, heart (cardiomyopathy, arrhythmias)/renal (deranged urea, creatinine)/liver (increased bilirubin, transaminases, and cytolysis without cholestasis) toxicity and associated adverse events [34, 88]. This mandates monitoring of the organ function in the postoperative period. Coagulation parameters need an assessment on a regular basis, peaks on 1–2 days, and take up to 5 days for normalization [1, 13, 34].

37.4.3.1 Anesthesiologists and Operating Room Safety Issues with HIPEC

The HIPEC procedure is associated with exposure of chemotherapy drugs to the personnel [4, 6, 13, 89, 90]. The source of exposure to chemotherapeutic agents is via aerosolization, direct contact with the drug, contact with perfusate solution, tubing, and tissues/objects contaminated with chemotherapeutic agents. At high temperatures, the chemotherapeutic agents are aerosolized and released into the atmosphere, which could be inhaled by the operating room personnel. The body fluids of patients remain to be contaminated with chemotherapy in the postoperative period for up to 48 h. Such exposures may be significant in centers of high volume and the team involved in performing regular HIPEC procedures. The team also needs to be educated on the care of preventing spillage and using appropriate universal precautions. Utmost care should be taken and a protocol needs to be in place for the disposal of residual drugs and tubing used during the HIPEC procedure. Certain high-risk groups like pregnant women or lactating mothers, immunocompromised persons, and those with allergic reactions should remain away from the timing of the HIPEC procedure [6, 89].

Concerns also remain of the electrosurgical smoke (that contains polycyclic aromatic hydrocarbons, blood particles, viruses, and bacteria) during the CRS phase and have been reported to be associated with nausea, headache, eye irritation, respiratory tract irritation, and cardiovascular impact on the OR team personnel [89, 90].

Education and training of personnel, routine medical surveillance of personnel, ambient air, and biological monitoring may help reduce such

exposures. The institute should have its protocol to take care of these safety concerns of the professionals involved in CRS HIPEC. The use of personal protective equipment and careful handling of chemotherapy are desirable. Other protective strategies include the change of mask and gloves, ensure adequate ventilation, avoid unnecessary entry into the room, and the use of a smoke evacuator [89, 90].

37.5 Predictors/Markers of Perioperative Morbidity and Mortality

The literature reports variable factors that can be used for predictors of complications in the perioperative period (Table 37.4). HIPEC is associated with hypermetabolic response and returns to normal in 2–3 days postoperatively [6, 16]. Elevated body temperature and impaired renal function have been reported as the most common predictors of major complications [13, 16]. The early elevation in blood urea nitrogen, creatinine, and potassium levels are also considered as predictors of complications. Whereas the potassium and blood urea nitrogen levels were predictive in the early period, the creatinine level was more helpful in the later period. The hemodynamic changes like increased pulse rate and decreased arterial pressures on the background of elevated body temperature are accepted predictors of a patient's clinical status and complicated postoperative course. Failure of these changes to return to baseline at the expected rate or time should prompt to evaluate patients for major complications [16]. Higher PCI, longer duration of surgery, higher delta temperatures, increased blood loss with increased blood replacement, high intraoperative fluid infusion, and lower mean arterial pressure were predictors of postoperative morbidity with regard to the need for ventilation and critical care unit stay [82]. In another study, peritoneal carcinoma index over 14, diaphragmatic peritonectomy, fluid leaks in drains over 1500 ml during the first 24 h, need of vasopressors, and fluid infusion >70 ml/kg on day 1 were reported predictors of morbidity [91]. On acid–base assessment, the presence of delta base excess > +4.3 mmol/L at 48 h remains a morbidity predictor [92].

Table 37.4 Predictors of perioperative morbidity and mortality after CRS and HIPEC [6, 13, 16, 82, 91, 92]

	Predictors	Remarks
1	Elevated body temperature	Higher delta temperatures
2	Impaired renal function	Early elevation in blood urea nitrogen, creatinine, and potassium levels
3	Sustained postoperative hemodynamic changes	Increased pulse rate and decreased arterial pressures on the background of elevated body temperature Failure of these changes to return to baseline at the expected rate or time
4	Increased blood loss Need of vasopressors Fluid infusion >70 ml/kg on day 1	
5	Fluid leaks in drains over 1500 ml during the first 24 h	
6	Delta base excess > +4.3 mmol/L at 48 h	
7	Higher peritoneal carcinoma index (PCI)	Peritoneal carcinoma index over 14
8	Longer duration of surgery	
9	Diaphragmatic peritonectomy	

37.6 Other Hyperthermic Chemotherapy Surgical Procedures

37.6.1 Pressurized Intraperitoneal Aerosolized Chemotherapy (PIPAC)

In certain patient groups who have high tumor load or cannot tolerate HIPEC, another technique of chemotherapy administration has been reported. This technique is labeled as pressurized intraperitoneal aerosolized chemotherapy (PIPAC). In this technique, after the optimal cytoreduction, the chemotherapeutic drugs are delivered into the peritoneal cavity as a pressurized normothermic aerosol [93]. This therapy has been suggested to be repeated as part of palliative chemotherapy and of the disease response, and then the HIPEC may be considered.

37.6.2 Hyperthermic Intrathoracic Chemotherapy (HITHOC)/ Hyperthermic Intraperitoneal Chemotherapy

The use of intrapleural hyperthermic chemotherapy has been reported for patients with lung cancer with pleural seeding and primary malignant pleural tumors [94–96]. The perioperative anesthetic management remains challenging because of many pathophysiological changes (Table 37.5). The literature remains scarce for these procedures, as specific definite indications are not many. The majority of concerns are related to the use of hyperthermia and the use of chemotherapeutic agents' toxicity. Additional concerns are related to the need for one-lung ventilation and a direct hyperthermic impact on thoracic organs. The instillation of hyperthermic perfusate leads to an increase in the intrathoracic pressure, which in turn obstructs the inferior and superior vena cava and causes direct cardiac compression. This leads to a decrease in venous return and cardiac output [96]. Increased myocardial wall tension due to direct compression, increased heart rate, and reduced coronary perfusion can lead to decompensation of heart function [96]. The mediastinal shift also occurs resulting in these procedures and thus leads to decreased pulmonary blood flow due to hyperthermia and due constriction of pulmonary vasculature [97]. The mediastinal shift also causes increased airway pressure and reduced functional residual capacity [96]. To prevent this sequel further, care should be taken to avoid hypoxemia, acidosis, and hypercapnia [95]. Goal-directed fluid therapy remains a mainstay as liberal fluid therapy

Table 37.5 Pathophysiological changes in HITHOC

Organ system	HITHOC
Cardiovascular/ hemodynamics	Reduced venous return Reduce cardiac output Increase in oxygen demand Increased myocardial wall tension Cardiomyopathy Arrhythmias
Respiratory	Increased intrathoracic pressures Mediastinal shift Direct myocardial stimulation Respiratory acidosis-increased $ETCO_2$ Increased oxygen extraction and consumption Pulmonary edema Interstitial pneumonitis
Coagulation	Thrombocytopenia Prolonged PT, aPTT, INR Decreased fibrinogen
Renal, electrolytes	Renal dysfunction due to cytotoxicity Hypomagnesemia Hyponatremia
Metabolic	Metabolic acidosis Increased lactate Hyperglycemia
Postoperative complications	Empyema Air leaks/bronchopleural fistula Pneumothorax Pneumothorax Cytotoxic agent induced pleural inflammation

leads to pulmonary complications, including pulmonary edema and acute lung injury [96]. Thoracotomy causes severe pain and respiratory compromise. Multimodal analgesia technique including the use of thoracic epidural analgesia with local anesthetics and opioids appears acceptable [96, 98, 99].

HIPEC Using a New Hybrid Carbon Dioxide (CO_2) System This is a newer technique in which intraperitoneal chemotherapy is administered by the peritoneal recirculation system that uses the carbon dioxide (CO_2) technology. Here, CO_2 aids in a better fluid circulation of the hyperthermic infusate [100]. Though the perioperative concerns have not been studied, they however appear to cause concern on the creation of pneumoperitoneum. This technique needs further assessment for its utility and outcome in the CRS HIPEC.

Sequential HIPEC In this technique, CRS and HIPEC phases are performed sequentially in two separate sittings [12]. After the CRS, once the patient is stabilized, early postoperative HIPEC is administered subsequently. Not much literature is available for the same and requires further studies to look for its benefit versus its limitations with regard to oncologic recovery.

37.7 Summary

The CRS and HIPEC have emerged as an important surgical intervention for the management of peritoneal surface malignancies, gynecological and colorectal surgeries. These are complex procedures and show many dynamic changes in the perioperative period. The anesthesiologists should be well versed in the assessment of these patients, their optimization, and optimal perioperative care. The impact of the hyperthermic phase on the body needs to be understood and its appropriate and timely management is essential for an uneventful outcome. However, due to the scarce literature in this field, more robust, well-planned studies are desirable, especially in the field of monitoring, fluid management, and analgesia in patients undergoing CRS and HIPEC. The impact of prehabilitation and optimization strategies specific to CRS and HIPEC also needs further assessment.

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38 Perioperative Anemia Management for the Onco-Surgical Patient

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38.1 Introduction

The World Health Organization (WHO) defines "anemia as hemoglobin less than 120 g/L (12.0 g/dL) for a non-pregnant woman and less than 130 g/L (13.0 g/dL) for males." This definition has not been universally adopted in all clinical settings, largely because of the discrepancy between these values and the actual data collected from population databases. If you use the WHO standard, a large percentage of otherwise healthy persons could be identified as anemic [1]. However, there is clear prognostic value in these criteria. Four large retrospective studies based on data from National Surgical Quality Improvement Program (NSQIP), the Veterans Affairs' NSQIP, and the European Surgical Outcome Study (EuSOS) [2–5] reported the prevalence of anemia, using the WHO criteria, to range from 28% to 44% in preoperative patients. The presence of preoperative anemia is associated with various perioperative adverse effects like increased cardiovascular, respiratory, urinary, thrombotic, and systemic morbidity, as well as increased critical care unit admissions, and overall hospital length of stay. Even when controlling for confounding factors and mediating variables, Saager et al. [2] reported an association between anemia and poor outcomes, albeit to a lesser extent than the other large studies.

Anemia prevalence among cancer patients is around 30–90% [3]. This wide range reflects the different hemoglobin levels used to define anemia among studies. As expected, the prevalence of anemia varies with cancer type and increases with more advanced disease [3]. On average, about 40% of all cancer patients, and over 50% of patients receiving chemotherapy, are anemic [4]. Etiologies of anemia in cancer patients can be cancer specific (i.e., leukemia, anemia of chronic disease), related to iron or vitamin deficiencies (i.e., gastrointestinal losses or malabsorption), treatment related, or related to other noncancer causes (i.e., acute surgical blood loss). Interestingly, while the cause of anemia is often multifactorial in cancer patients, folate and B_{12} deficiencies are rare [5]. The presence of anemia in cancer patients is associated with increased rates of morbidity and, mortality, decreased quality of life (QoL), and worse performance scores [3, 4, 6]. The reason for poor outcomes in cancer patients with anemia is complex.

It is known that anemia can cause secondary tissue hypoxia. Local tumor hypoxia (often defined as a partial pressure of oxygen, pO_2 of

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<10 mmHg) can decrease the effectiveness of chemotherapy and radiation [7]. As solid tumors grow, structural and functional abnormalities of the tumor microvascular beds occur simultaneously. This exacerbates hypoxia and thus decreases the effectiveness of these therapeutic modalities [8]. It is also hypothesized that local hypoxia can alter gene expression, which can further decrease the number of cells destroyed by these therapies [7, 8].

Standard therapy modalities for anemia include administration of erythropoiesis-stimulating agents (ESAs), iron supplements, blood transfusions, and cell saver technology for surgical blood loss. Optimal management of anemia during cancer treatment improves the QoL [6, 9, 10]. Unfortunately, each treatment has inherent risks and can also impact survival and outcomes.

38.2 Erythropoiesis-Stimulating Agents and Iron

As perioperative physicians, anesthesiologists must be familiar with preoperative alternatives to blood transfusions, namely erythropoiesis-stimulating agents (ESAs) and iron. Onco-surgical patients require special consideration because, in many cases, surgery is carefully timed to optimize cancer therapy. In some cases, time from diagnosis to treatment is often only a matter of weeks. In other cases, surgery is carefully planned within a specific time interval relative to chemotherapy and radiation. In either case, delaying surgery can result in cancer progression or a reduction in the effectiveness of treatment. This time-sensitive schedule often does not confer enough time for nontransfusion modalities to reach peak therapeutic effect. These therapies also carry unique risks for cancer patients. However, these interventions are appropriate in certain settings, and if patients are appropriately educated about the risks.

Erythropoietin is the principal hematopoietic growth factor regulating erythrocyte proliferation [11]. Epoetin alpha, the first of the ESAs, was initially approved for use anemia of chronic renal failure. Subsequently, the indications for its use expanded to include the treatment of anemia in patients with non-myeloid malignancies. This agent was found to decrease the need for blood cell transfusion and improve the QoL [9, 12, 13]. In 2002, the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) concluded, “The guideline panel found good evidence to recommend the use of epoetin alpha as a treatment option for patients with chemotherapy-associated anemia with a hemoglobin concentration below 10 g/dL” [14]. As the body of literature became more robust, darbepoetin alfa was found to have similar clinical efficacy as epoetin alpha. Therefore, the term ESAs replaced epoetin alpha alone in future versions of the ASCO/ASH guidelines.

In the next decade, a series of studies showed an association between ESA use in cancer patients and increased mortality [15–17], venous thromboembolism [18], and tumor progression [19]. These data have been summarized in several meta-analyses [15, 20] and have resulted in updated versions of the ASCO/ASH guidelines [21], first in 2007, and then again in 2010. In 2008, the FDA issued a Boxed Warning summarizing the risks of increased mortality and/or worse tumor outcomes obtained in randomized studies in patients with cancer. They also made it mandatory from 2011 to 2017 for healthcare providers to complete training before prescribing these agents [22]. In 2010, ASCO/ASH guidelines stated, “It is worth reinforcing the point that the decision to limit the indication for ESAs to patients undergoing chemotherapy for palliation (treatment intent) is not based on direct comparative analyses of data from clinical trials of ESA treatment” [21, 23]. Therefore clinical judgment must be used when initiating ESA therapy for patients, including those who are on chemotherapy.

Because of the controversies related to the clinical use of ESA, other modalities like iron supplements gained momentum for managing anemias due to cancer and/or chemotherapy. Iron supplements are available in various forms for administration including oral, intravenous (IV), and intramuscular. Oral iron is usually prescribed as ferrous sulfate. While safe, it is not often stud-

ied or utilized in the perioperative setting for cancer patients to decrease blood transfusions as absorption of the oral preparation can be impaired by inflammatory mediators [24]. The IV formulation of iron is available in various forms like iron dextran, iron sucrose, iron gluconate, and ferumoxytol. Many studies demonstrate IV iron is a safe and effective option for reducing allogenic blood transfusions [25–28], even for cancer patients [29–31]. Most of these studies demonstrated the safety of the use of IV iron and found it to be a suitable modality for reducing allogeneic blood transfusions. The optimal timing of administration has yet to be established. Most studies administered IV iron at least 2 weeks preoperatively, but at least one study suggests that even a single postoperative dose of IV iron can decrease blood transfusion requirements [27]. Like all treatments for anemia, IV iron is not without risks. Anaphylaxis has long been a concern but is much less common in newer non dextran formulations [32]. The increased risk of infection with IV iron administration has been refuted, particularly with newer iron preparations like non-dextran IV preparations [33]. Finally, while studies evaluating the effects of IV iron on perioperative outcomes are promising, it must be mentioned that the long-term effects of IV iron on oncologic outcomes have not been established and need further research.

38.3 Blood Transfusions

Millions of units of red blood cells (RBCs) are transfused in the United States each year [35]. The decision to transfuse a patient is multifactorial. The perioperative blood management guidelines by the American Society of Anesthesiology (ASA) [35] state *"The determination of whether hemoglobin concentrations between 6 and 10 g/dL justify or require red blood cell transfusion should be based on potential or actual ongoing bleeding (rate and magnitude), intravascular volume status, signs of organ ischemia, and adequacy of the cardiopulmonary reserve."*

In other words, unless the patient is profoundly anemic (hemoglobin less than 6g/dL), clinical judgement drives the decision to transfuse. An absolute hemoglobin threshold to trigger transfusion may not be applicable across all surgical patients. Studies evaluating patients who refuse transfusions (i.e. Jehovah's Witness patients) found that postoperative mortality rises sharply when hemoglobin levels fall below 6g/dL, and about half of patients with a hemoglobin less than 3.0g/dL die during their hospital stay [36–38]. Most anesthesia providers determine a transfusion threshold during preoperative assessment by taking into consideration the patient's comorbid diseases, the baseline hemoglobin, the risk of ongoing bleeding, the availability of blood, surgeon preference and skill, and patient wishes.

It is important to mention that while treating anemia per se can improve QoL [9, 10], transfusions themselves have not been shown to have a mortality benefit. In 1999, the Transfusion Requirements in Critical Care (TRICC) trial compared the effect of a liberal (transfusion threshold of 10 g/dL) vs. a restrictive (transfusion threshold of 7 g/dL) transfusion protocol on mortality rates in intensive care patients. Except in patients with clinically significant cardiac disease, they found lower mortality rates in the restrictive-strategy group [39]. Similar outcomes were reported in other studies in patients undergoing cardiac and hip surgeries as well [40, 41]. Initially published in 2000, and later updated in 2010, 2012, and 2016 [42–45], a Cochrane review related to transfusion practices concluded the absence of impact on 30-day mortality or morbidity with restrictive blood transfusion protocols. But other evidence favors the beneficial effect of restrictive transfusion policy compared to liberal transfusion policy. Clearly, there is evidence that a restrictive transfusion policy is as safe as, and perhaps preferable to, a liberal transfusion policy for many patients. But can data for cardiac, intensive care and hip fracture patients be extrapolated to onco-surgical patients? Recent data from a prospective, randomized controlled trial [46] suggests that cancer patients may present a unique subset of all surgical patients, in that there may be a mortality benefit from a more liberal transfusion threshold. Currently, the

appropriate threshold for transfusing cancer patients remains unclear.

The inherent risks of blood product transfusions include infection (viral and, bacterial), allergic reaction, hemolytic reaction, febrile nonhemolytic reaction, transfusion-related acute lung injury (TRALI), and transfusion-related circulatory overload (TACO). While these complications are well understood by anesthesiologists, most of them apply to all patients. Transfusion-related immunomodulation (TRIM), which carries specific risks for cancer patients, will be the focus of the following discussion.

38.4 Transfusion-Related Immunomodulation

In the 1970s, a series of articles were published which reported the beneficial effects of pretransplant blood transfusions on kidney graft survival [47–49]. As a result, many institutions started routinely administering blood products preoperatively in kidney transplant patients. As the mechanism of transfusion-induced immunomodulation (later called TRIM) was unclear, some questioned whether this effect, while beneficial in the setting of transplant surgery, could have detrimental effects on cancer patients [50]. Consequently, many animal studies were conducted in the next two decades to examine the effect of transfusion on cancer cells [51–54]. Many of these animal studies involved researchers inoculating animals with tumor cells and transfusing varying components of allogeneic blood. They found that blood transfusions did have effects on patterns of tumor growth and metastasis. Further, they found that manipulating the components of blood transfused, that is, leukodepletion, could modulate these effects.

The results of initial animal studies and the fear of AIDS transmission spurred an explosion of clinical studies in the next decade that further elucidated the clinical risks of blood transfusions including increased risk of cancer recurrence and post-operative infections. In 1996, Landers et al. [55] published a review article in *Anesthesia and Analgesia* with over 200 references summarizing the state of the science on the immunomodulatory effects of transfusion therapy at that time. He concluded that blood products increase the risks of cancer recurrence. Since then, there has been an abundance of studies evaluating the effects of blood transfusions on oncologic morbidity that challenge these conclusions. Naturally, the studies have gotten more granular, and have evolved with the changes in transfusion practices (i.e., component separation and leukoreduction). To understand why this topic continues to be a point of debate after many years of scientific inquiry, a discussion of the literature in regard to one cancer type, prostate cancer, will be utilized as a framework to discuss the challenges of examining this very complex subject.

38.5 Blood Transfusions and Its Impact on Prostate Cancer

In the late 1980s and early 1990, six separate studies, investigated the association among blood transfusion, prostate cancer surgery, and outcomes [56–61]. Some studies reported an increase in mortality, and cancer recurrence in surgical patients with prostate cancer who received blood transfusion when compared to patients who did not receive a blood transfusion [56, 57, 59]. On the contrary, *improved* survival with blood transfusion for perioperative prostate cancer patients was also reported [58]. Ness [60] reported that homologous allogeneic blood transfusions as compared to autologous transfusions in patients with prostate cancer have no association with mortality or cancer recurrence. Velagapudi [61] reported "clear statistical evidence for lack of earlier tumor progression or cause-specific death in patients with prostate cancer treated with radical prostatectomy who receive perioperative homologous blood transfusions." To summarize, in the 1980s and 1990s, three studies reported worse outcomes with blood transfusions, two studies were equivocal, and one study reported improved survival.

These early data suggested that blood transfusions for patients undergoing surgery for prostate

cancer were associated with worse outcomes. A full understanding of these findings requires historical context as surgical techniques and indications for prostate surgery have evolved considerably in the last 20 years. These initial reports were before the use of prostate-specific antigen (PSA) for prostate cancer screening modality [62]. The patients in these reports probably presented with urinary obstruction due to locally advanced cancer, indicating more advanced disease [62]. Transurethral resection served as the primary surgical approach for many of these patients. The alternative surgical approach, the open radical prostatectomy, carried numerous risks of its own, notably significant blood loss. Proven reduction in intraoperative bleeding [63] and other factors propelled robotic surgeries to quickly and widely usurp the open approach to prostatectomy.

Like surgical techniques, transfusion practices have changed considerably in the past 20 years. Thresholds for transfusing and terminology were far from uniform in the 1980s. Unfortunately, several of these initial studies evaluating the effects of blood transfusions on prostate cancer did not identify what type of blood product was administered.

In the 2000s and 2010s, seven more studies [64–70] examined the relationship between surgery for prostate cancer, blood transfusions, and outcomes. These studies are more applicable to current practice as they aimed to address some of the shortcomings discussed above. There is more uniformity in the study variables: prostate specific antigen (PSA) screening is widely utilized, leukoreduction is universally implemented, and surgical technique is largely standardized. Several editorials [62, 71] and one meta-analysis [72] have synthesized these more recent data. They summarized that while allogeneic blood transfusion is associated with diminished survival after prostate cancer surgery, the same might not hold for autologous blood transfusions. Finally, at least one editorial posited that the process of leukoreduction for preventing the risk of prostate cancer recurrence has little advantage [62].

Screening and treatment of prostate cancer have influenced the perioperative management of patients for the anesthesiologist. Cancer as a disease state encompasses such an enormous spectrum of biologic and physiologic abnormalities that it is impossible to describe it in a single process; even describing it in a series of processes risks oversimplification. This complex variability impairs the generalization of transfusion trial results from one type of cancer to another. What may hold for prostate cancer may not hold for virus-associated cancer such as cervical cancer, and the data from 10 years ago might not apply to current patients as a result of changes in screening, adjunct therapies, and surgical techniques. As anesthesia providers care for a wide range of patients, it is not practical to be an expert on each cancer type. However, a firm grasp of different types of blood preparation is essential.

38.6 Blood Products: Leukoreduction

While the data on TRIM and leukoreduction continue to be perplexing, leukoreduction offers benefits to certain cancer patients as they are often immunocompromised from chemotherapy and/or they are prospective bone marrow transplant candidates. White blood cells (WBCs) in whole blood (WB) or RBCs can expose recipients to foreign Human Leukocyte Antigen (HLA) which are strongly immunogenic. The reduction in WBCs in the transfused product can reduce the incidence of infections (cytomegalovirus), alloimmunization, febrile, nonhemolytic reactions, and platelet refractoriness [73]. This is particularly important for chronically transfused oncology patients. The American Association of Blood Banks (AABB) industry standard for leukocyte-reduced RBCs is $<5 \times 10^6$ WBCs per unit. Neither buffy coat removal nor washing of the red blood cells adequately meets this standard. Instead, leukocyte filters are necessary and can be used at the time of collection or poststorage. Prestorage leukoreduction is preferred, as it is thought to reduce inflammatory cytokine accumulation due to WBCs during storage. While the FDA does not mandate universal leukoreduction, the American

Red Cross will only release leukoreduced blood products to hospitals.

38.7 Blood Products: Cytomegalovirus (CMV) Negative

CMV, a herpes virus, infections are usually asymptomatic but can be life-threatening in the immunocompromised, such as cancer patients [74]. Transfusion-transmitted CMV (TT-CMV) usually is transmitted via blood monocytes [75], which is why leukoreduction has been suggested to remove the potential source of this infection for blood transfusion. However, leukoreduction cannot eliminate the risk of CMV transmission [76] as the free virus can be detected in the blood of newly infected donors. Serology can identify CMV seronegative donors, but this approach has also been criticized as newly infected blood donors may be in the window period before seroconversion. Nucleic acid testing of donor blood has also been criticized for similar shortcomings [74, 75]. It is not surprising that an approach to protecting patients from CMV infection varies among settings [74, 77]. Strategies commonly involve using leukoreduced blood alone or in combination with using blood from CMV-negative donors. Trials are currently underway for identifying methods for pathogen inactivation [75].

38.8 Blood Products: Irradiated Blood Components

The risk of transfusion-associated graft-versus-host disease (TA-GVHD) remains after blood transfusion due to the potential replication of donor T cells. Such occurrence is more common in immunocompromised patients (such as those receiving chemotherapy, especially fludarabine [78] and those with a diagnosis of lymphoma or leukemia). The current leukoreduction methodology is not considered adequate to prevent TA-GVHD. By rendering donor lymphocytes incapable of proliferation, gamma irradiation of blood components prevents this rare but usually fatal disease. At least 25 gray should be the dosage for each cellular component. While most blood administered in the United states is leukoreduced, only about 20% blood is irradiated [34]. Components that contain no viable white cells, for example, fresh frozen plasma and cryoprecipitate, do not require irradiation.

38.9 Intraoperative Blood Salvage

The safety of intraoperative blood salvage (IBS) during cancer surgery is controversial [79]. Fear of the risk of cancer metastasis causes many providers to avoid this technique as tumor cells can be found in blood salvaged from the surgical field [80]. However, the filtration of tumor cells is feasible using a leukocyte filter [81]. Blood irradiation can be used to eliminate cancer cells from blood salvaged from the surgical field [82] although the logistics of this technique seem to limit its clinical use. Despite these concerns, several studies suggest that this technique does not increase risk of cancer recurrence [83–87], even if leukocyte depletion filters are not used [85, 86]. A recent meta-analysis failed to find an association between either cancer recurrence or metastasis and blood salvage [88]. As such, IBS remains an attractive option for patients undergoing surgeries with a high potential for blood loss (i.e., hepatic resections) who are opposed to blood transfusions (i.e., Jehovah's Witnesses).

38.10 Preoperative Blood Conservation Strategies: Acute Normovolemic Hemodilution and Preoperative Autologous Blood Donation

Various preoperative techniques like acute normovolemic hemodilution (PANH) and preoperative autologous blood donation (PAD) have been advocated for blood conservation strategies. Understandably, both techniques gained popularity during the Acquired immunodeficiency

syndrome (AIDS) epidemic. As screening techniques for infectious diseases have become more sensitive and specific, the utilization of both PANH and PAD has decreased. As of 2013, autologous blood transfusions made up only 0.2% of all blood transfusions in the United States [34]. Despite the shortcomings of these techniques discussed below, one scenario where they may be advantageous involves patients with multiple blood group antibodies which would make finding a compatible donor difficult.

For cancer patients, both PANH and PAD have limited utility. First, as stated, many cancer patients are anemic. While there is no absolute threshold beyond which these techniques are contraindicated, hemoglobin of >11 g/dL is generally needed to consider PAD. Studies evaluating these techniques are equivocal at best. A meta-analysis examining PANH published in 2015 concluded that while PANH was effective in reducing the intraoperative use of allogenic blood volume, it did not reduce overall perioperative allogenic transfusion volume [89]. Further, in this analysis, less than one-third of the studies were oncologic cases. The authors concluded that the significant heterogeneity of the studies "raises concerns about the true efficacy of PANH." Like PANH, evidence supporting preoperative autologous blood donation is fraught with concerns specific to cancer patients. Specifically, well-designed programs [90, 91] that have had reported success in decreasing autologous transfusions often utilize ESAs, the limits of which have been discussed. The cost factor associated with autologous blood transfusion also remains a concern [92].

38.11 Summary

Anesthesiologists often must choose between the lesser of two evils as anemic cancer patients find themselves in a place where Cata summarized "the problem, the solution and their combination are each associated with poor outcomes" [93]. As we expand our role as perioperative physicians, it is imperative that we become familiar with all treatment options available for the perioperative management of anemia and blood conservation strategies. We also must be cognizant of the effects our interventions have on long-term outcomes and how our treatment plans must evolve with scientific discovery.

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