Difficult Decisions in Surgery:
An Evidence-Based Approach

Mark K. Ferguson *Editor*

Difficult Decisions in Thoracic Surgery

An Evidence-Based Approach

Fourth Edition

Springer

Difficult Decisions in Surgery: An Evidence-Based Approach

Series Editor

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The complexity of decision making in any kind of surgery is growing exponentially. As new technology is introduced, physicians from nonsurgical specialties offer alternative and competing therapies for what was once the exclusive province of the surgeon. In addition, there is increasing knowledge regarding the efficacy of traditional surgical therapies. How to select among these varied and complex approaches is becoming increasingly difficult. These multi-authored books will contain brief chapters, each of which will be devoted to one or two specific questions or decisions that are difficult or controversial. They are intended as current and timely reference sources for practicing surgeons, surgeons in training, and educators that describe the recommended ideal approach, rather than customary care, in selected clinical situations.

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To my wife for her endless patience and support.

Preface to the First Edition

Why do thoracic surgeons need training in decision making? Many of us who have weathered harrowing residencies in surgery feel that, after such experiences, decision making is a natural extension of our selves. While this is no doubt true, *correct* decision making is something that many of us have yet to master. The impetus to develop a text on evidence-based decision making in thoracic surgery was stimulated by a conference for cardiothoracic surgical trainees developed in 2004 and sponsored by the American College of Chest Physicians. During that conference it became clear that we as thoracic surgeons are operating from a very limited fund of true evidence-based information. What was also clear was the fact that many of the decisions we make in our everyday practices are not only uninformed by evidence-based medicine but often are contradictory to existing guidelines or evidence-based recommendations.

The objectives of this book are to explain the process of decision making, both on the part of the physician and on the part of the patient, and to discuss specific clinical problems in thoracic surgery and provide recommendations regarding their management using evidence-based methodology. Producing a text that will purportedly guide experienced, practicing surgeons in the decision-making process that they are accustomed to observe on a daily basis is a daunting task. To accomplish this it was necessary to assemble a veritable army of authors who are widely considered to be experts in their fields. They were given the unusual (to many of them) task of critically evaluating evidence on a well-defined topic and provide two opinions regarding appropriate management of their topic: one based solely on the existing evidence and another based on their prevailing practice, clinical experience, and teaching. Most authors found this to be an excellent learning experience. It is hoped that readers of this book will be similarly enlightened by its contents.

How should a practicing surgeon use this text? As is mentioned in the book, wholesale adoption of the stated recommendations will serve neither the physician nor the patient well. The reader is asked to critically examine the material presented, assess it in the light of his or her own practice, and integrate the recommendations that are appropriate. The reader must have the understanding that surgery is a complex, individualized, and rapidly evolving specialty. Recommendations made today for one patient may not be appropriate for that same patient in the same situation several years hence. Similarly, one recommendation will not serve all patients well.

The surgeon must use judgment and experience to adequately utilize the guidelines and recommendations presented herein.

To produce a text with timely recommendations about clinical situations in a world of rapidly evolving technology and information requires that the editor, authors, and publisher work in concert to provide a work that is relevant and up-to-date. To this end I am grateful to the authors for producing their chapters in an extraordinarily timely fashion. My special thanks go to Melissa Morton, Senior Editor at Springer, for her rapid processing and approval of the request to develop this book, and to her staff for the rapid processing of the manuscripts. My thanks go to Kevin Roggin, MD, for sharing the T.S. Eliot lines and the addendum to them. Finally, the residents with whom I have had the opportunity and privilege to work during the past two decades continually reinforce the conviction that quality information is the key to improved patient care and outcomes.

Chicago, IL, USA Mark K. Ferguson
March 27, 2006

Preface to the Fourth Edition

Much has changed in the 14 years since the first volume of this book was published. At the time of this writing, there is a growing desire among many people worldwide to live in a more insular and homogenous environment. Coupled with this is a growing population of implacable individuals who choose to deny science, either through ignorance, mistrust, or the fervent wish that the facts they choose not to like really do not exist. Leaders now offer "alternative truths," boldfaced falsehoods that, repeated often enough, acquire a ring of truth among those whose factual knowledge comes primarily from untrustworthy sources.

Fortunately, those who work in the medical sciences have not been influenced by these cultural changes. Medical science is built on a foundation of continuous questioning of accepted beliefs in the hope of improving our knowledge and our ability to care for our patients. Those who attack medical scientists for changing guidelines, standards, and algorithms for care as if being guided by whimsy do not understand the iterative process that is the scientific method. Change should not be seen as a sign of uncertainty, but as a hallmark of progress. It is evidence that our clinicians and scientists are adapting to new challenges and learning new facts, and applying this to the benefit of their patients. It is in the spirit of this process that the present volume was developed.

As always, recommendations made in this book are not meant to be followed blindly, but are intended as guides to the reader. Hopefully, a sufficient amount of data is presented in each chapter so that the interested reader can make an independent judgment about best decisions based on the practice setting, the individual patient, and the reader's own skills.

I am, and the reader of this book should be, grateful for the sacrifices that the authors made to complete their chapters. The level of enthusiasm among the authors was high, and each of the chapters had an assigned author within 1 week of the project launch date. The authors were tasked to complete their chapters in less than 80 days and were asked to not only bring their clinical expertise to bear, but at the same time were required to assume an attitude of equipoise in order to foster an objective view of the data. I think the reader will find that the authors succeeded admirably. My high esteem for the contributors is due to the fact that, despite their very busy clinical and academic schedules, not a single author asked for monetary or other compensation for the hours of work that was required.

Working in the environment in which I do is a blessing that is increasingly apparent to me every day. I am surrounded by smart, enthusiastic, and caring attendings, physician assistants, nurses, and trainees who comprise our thoracic surgery team. Our fellows, residents, and medical students are bright, inquisitive, and hardworking individuals who put our patients and their educational goals above any personal interests. I have colleagues around the world who are collaborative in advancing the art and science of surgery and who are supportive when I need help.

My hope is that readers will use this book as a source to enhance their knowledge, stimulate further learning, and improve the care of their patients. If the book succeeds in even one of those domains, I will consider these efforts to have been worthwhile.

Chicago, IL, USA
March 8, 2020

Mark K. Ferguson

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Part II Esophagus

Introduction

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Mark K. Ferguson

Introduction

Dorothy Smith, an elderly and somewhat portly woman, presented to her local emergency department with chest pain and shortness of breath. An extensive evaluation revealed no evidence for coronary artery disease, congestive heart failure, or pneumonia. A chest radiograph demonstrated a large air-fluid level posterior to her heart shadow, a finding that all thoracic and general surgeons recognize as being consistent with a large paraesophageal hiatal hernia. The patient had not had similar symptoms previously. Her discomfort was relieved after a large eructation, and she was discharged from the emergency room a few hours later. She was seen several weeks later in an outpatient setting by an experienced surgeon, who reviewed her history and the data from her emergency room visit. After evaluating a CT scan and barium swallow, the surgeon diagnosed a giant Type III paraesophageal hernia. The patient was told that an operation is often necessary to repair such hernias. Her surgeon indicated that the objectives of such an intervention would include relief of symptoms such as chest pain, shortness of breath, and postprandial fullness, and prevention of catastrophic complications of giant paraesophageal hernia, including incarceration, strangulation, and perforation. Ms. Smith, having recovered completely from her episode of a few weeks earlier, declined intervention, despite her surgeon's strong expression of concern.

She presented to her local emergency department several months later with symptoms of an incarcerated hernia and underwent an urgent operation to correct the problem. The surgeon found a somewhat ischemic stomach and had to decide whether to resect the stomach or just repair the hernia. If resection was to be performed, an additional decision was whether to reconstruct immediately or at the

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time of a subsequent operation. If resection was not performed, the surgeon needed to consider a variety of options as part of any planned hernia repair: whether to perform a gastric lengthening procedure; whether a fundoplication should be constructed; and whether to reinforce the hiatal closure with non-autologous materials. Each of these intraoperative decisions could importantly affect the need for a subsequent reoperation, the patient's immediate survival, and her long-term quality of life. Given the dire circumstances that the surgeon was presented with during the emergency operation, it would have been optimal if the emergent nature of the operation could have been avoided entirely. In retrospect, which was more correct in this hypothetical situation, the recommendation of the surgeon or the decision of the patient?

Decisions are the stuff of everyday life for all physicians; for surgeons, life-altering decisions often must be made on the spot, frequently without what many might consider to be the necessary data. The ability to make such decisions confidently is the hallmark of the surgeon. However, decisions made under such circumstances are often not correct or even well reasoned. All surgeons (and many of their spouses) are familiar with the saying "…often wrong, but never in doubt." As early as the fourteenth century physicians were cautioned never to admit uncertainty. Arnauld of Villanova wrote that, even when in doubt, physicians should look and act authoritative and confident [1]. In fact, useful data do exist that could have an impact on many of the individual decisions regarding elective and emergent management of the giant paraesophageal hernia scenario outlined above. Despite the existence of these data, surgeons tend to make decisions based on their own personal experience, anecdotal tales of good or bad outcomes, and unquestioned adherence to dictums from their mentors or other respected leaders in the field, often to the exclusion of objective data. It is believed that only 15% of medical decisions are scientifically based [2], and it is possible that an even lower percentage of thoracic surgical decisions are so founded. In addition, it has recently been reported that standards of care based on accepted clinical evidence have been debunked after begin in use for long periods of time, sometimes decades [3]. With all of our modern technological skills, big data, machine learning/artificial intelligence, and communication skills, why do we still find ourselves in this situation?

Early Surgical Decision Making

Physicians' diagnostic capabilities, not to mention their therapeutic armamentarium, were quite limited until the middle to late nineteenth century. Drainage of empyema, cutting for stone, amputation for open fractures of the extremities, and mastectomy for cancer were relatively common procedures, but few such conditions were diagnostic dilemmas. Surgery, when it was performed, was generally indicated for clearly identified problems that could not be otherwise remedied. Some surgeons were all too mindful of the warnings of Hippocrates: "…physicians, when they treat men who have no serious illness, … may commit great mistakes without producing any formidable mischief … under these circumstances, when they

commit mistakes, they do not expose themselves to ordinary men; but when they fall in with a great, a strong, and a dangerous disease, then their mistakes and want of skill are made apparent to all. Their punishment is not far off, but is swift in overtaking both the one and the other" [4]. Others took a less considered approach to their craft, leading Hunter to liken a surgeon to "an armed savage who attempts to get that by force which a civilized man would get by stratagem" [5].

Based on small numbers of procedures, lack of a true understanding of pathophysiology, frequently mistaken diagnoses, and the absence of technology to disseminate new information quickly, surgical therapy until the middle of the nineteenth century was largely empiric. For example, by that time fewer than 90 diaphragmatic hernias had been reported in the literature, most of them having been diagnosed postmortem as a result of gastric or bowel strangulation and perforation [6]. Decisions were based on dogma promulgated by word of mouth. This has been termed the "ancient era" of evidence-based medicine [7].

An exception to the empiric nature of surgery was the approach espoused by Hunter in the mid-eighteenth century, who suggested to Jenner, his favorite pupil, "I think your solution is just, but why think? Why not try the experiment?" [5] Hunter challenged the established practices of bleeding, purging, and mercury administration, believing them to be useless and often harmful. These views were so heretical that, 50 years later, editors added footnotes to his collected works insisting that these were still valuable treatments. Hunter and others were the progenitors of the "renaissance era" of evidence-based medicine, in which personal journals, textbooks, and some medical journal publications were becoming prominent [7].

The discovery of X-rays in 1895 and the subsequent rapid development of radiology in the following years made the diagnosis and surgical therapy of a large paraesophageal hernia such as that described at the beginning of this chapter commonplace. By 1908 X-ray was accepted as a reliable means for diagnosing diaphragmatic hernia, and by the late 1920s surgery had been performed for this condition on almost 400 patients at the Mayo Clinic [8, 9]. Thus, the ability to diagnose a condition was becoming a prerequisite to instituting proper therapy.

This enormous leap in physicians' abilities to render appropriate ministrations to their patients was based on substantial new and valuable objective data. In contrast, however, the memorable anecdotal case presented by master (or at least an influential) surgeons continued to dominate the surgical landscape. Prior to World War II, it was common for surgeons throughout the world with high career aspirations to travel to Europe for a year or 2, visiting renowned surgical centers to gain insight into surgical techniques, indications, and outcomes. An example is described in the memoir of Edward D. Churchill, who was being groomed for leadership at the Massachusetts General Hospital in the late 1920s [10]. In the early twentieth century Murphy attracted a similar group of surgeons to his busy clinic at Mercy Hospital in Chicago. His publication of case reports and other observations evolved into the Surgical Clinics of North America. Seeing individual cases and drawing conclusions based upon such limited exposure no doubt reinforced the concept of empiricism in decision making in these visitors. True, compared to the strict empiricism of the nineteenth century, there were more data available upon which to base

surgical decisions in the early twentieth century, but information regarding objective short-term and long-term outcomes still was not readily available in the surgical literature or at surgical meetings.

Reinforcing the imperative of empiricism in decision making, surgeons often disregarded valuable techniques that might have greatly improved their efforts. It took many years for anesthetic methods to be accepted [11]. The slow adoption of endotracheal intubation combined with positive pressure ventilation prevented safe thoracotomy for decades after their introduction into animal research. Wholesale denial of germ theory by physicians in the United States for decades resulted in continued unacceptable infection rates for years after preventive measures were identified [12]. These are just a few examples of how ignorance and its bedfellow, recalcitrance, delayed progress in thoracic surgery in the late nineteenth and early twentieth centuries.

Evidence-Based Surgical Decisions

There were important exceptions in the late nineteenth and early twentieth centuries to the empiric nature of surgical decision making. Among the first were the demonstration of antiseptic methods in surgery and the optimal therapy for pleural empyema. Similar evidence-based approaches to managing global health problems were developing in non-surgical fields. Reed's important work in the prevention of yellow fever led to the virtual elimination of this historically endemic problem in Central America, an accomplishment that permitted construction of the Panama Canal. The connection between the pancreas and diabetes that had been identified decades earlier was formalized by the discovery and subsequent clinical application of insulin in 1922, leading to the awarding of a Nobel Prize to Banting and Macleod in 1923. Fleming's rediscovery of the antibacterial properties of penicillin in 1928 led to its development as an antibiotic for humans in 1939, and it received widespread use during World War II. The emergency use of penicillin, as well as new techniques for fluid resuscitation, were said to account for the unexpectedly high rate of survival among burn victims of the Coconut Grove nightclub fire in Boston in 1942. Similar stories can be told for the development of evidence in the management of polio and tuberculosis in the mid-twentieth century. As a result, the first half of the twentieth century has been referred to as the "transitional era" of evidence-based medicine, in which information was shared easily through textbooks and peer-reviewed journals [7].

Among the first important examples of the use of evidence-based medicine is the work of Semmelweiss, who in 1861 demonstrated that careful attention to antiseptic principles could reduce mortality associated with puerperal fever from over 18% to just over 1%. The effective application of such principles in surgery was investigated during that same decade by Lister, who noted a decrease in mortality on his trauma ward from 45 to 15% with the use of carbolic acid as an antiseptic agent during operations. However, both the germ theory of infection and the ability of an antiseptic such as carbolic acid to decrease the risk of infection were not generally

accepted, particularly in the United States, for another decade. In 1877 Lister performed an elective wiring of a patellar fracture using aseptic techniques, essentially converting a closed fracture to an open one in the process. Under practice patterns of the day, such an operation would almost certainly lead to infection and possible death, but the success of Lister's approach secured his place in history. It is interesting to note that a single case such as this, rather than prior reports of his extensive experience with the use of antiseptic agents, helped Lister turn the tide towards universal use of antiseptic techniques in surgery thereafter.

The second example developed over 40 years after the landmark demonstration of antiseptic techniques and also involved surgical infectious problems. Hippocrates described open drainage for empyema in 229 BC, indicating that "when empyema are opened by the cautery or by the knife, and the pus flows pale and white, the patient survives, but if it is mixed with blood and is muddy and foul smelling, he will die" [4]. There was little change in the management of this problem until the introduction of thoracentesis by Trusseau in 1843. The mortality rate for empyema remained at 50–75% well into the twentieth century [13]. The confluence of two important events, the flu pandemic of 1918 and the Great War, stimulated the formation of the US Army Empyema Commission in 1918. Led by Graham and Bell, this commission's recommendations for management included three basic principles: drainage, with avoidance of open pneumothorax; obliteration of the empyema cavity; and nutritional support for the patient. Employing these simple principles led to a decrease in mortality rates associated with empyema to 10–15%.

The Age of Information

These surgical efforts in the late nineteenth and early twentieth centuries ushered in the beginning of an era of scientific investigation of surgical problems. This was a period of true surgical research characterized by both laboratory and clinical efforts. It paralleled similar efforts in non-surgical medical disciplines. Such research led to the publication of hundreds of thousands of papers on surgical management. This growth of medical information is not a new phenomenon, however. The increase in published manuscripts, and the increase in medical journals, has been exponential over a period of more than two centuries, with a compound annual growth rate of almost 4% per year [14]. In addition, the quality and utility of currently published information is substantially better than that of publications in centuries past.

Currently there are more than 2000 publishers producing works in the general field of science, technology, and medicine. The journals publish more than 2.5 million articles annually [15]. The annual growth rate of health science articles during the past two decades is about 3%, continuing the trend of the past two centuries and adding to the difficulty of identifying useful information [14]. The number of citations of medical publications has more than doubled in the past two decades, and in 2018 exceeded 900,000 [16]. As of 2009, over 50 million science papers had been published since the first paper in 1665. There is also a trend towards decentralization of publication of biomedical data, which offers challenges to identifying useful

information that is published outside of what are considered traditional journals [17]. For example, publication rates of clinical trials relevant to certain specialties vary from one to seven trials *per day* [18].

When confronting this large amount of published information, separating the wheat from the chaff is a daunting task. The work of assessing such information has been assumed to some extent by experts in the field who perform structured reviews of information on important issues and meta-analyses of high quality, controlled, randomized trials. These techniques have the potential to summarize results from multiple studies and, in some instances, crystallize findings into a simple, coherent statement.

An early proponent of such processes was Cochrane, who in the 1970s and 1980s suggested that increasingly limited medical resources should be equitably distributed and consist of interventions that have been shown in properly designed evaluations to be effective. He stressed the importance of using evidence from randomized controlled trials, which were likely to provide much more reliable information than other sources of evidence [19]. These efforts ushered in an era of high quality medical and surgical research. Cochrane was posthumously honored with the development of the Cochrane Collaboration in 1993, encompassing multiple centers in North America and Europe, with the purpose of "helping healthcare providers, policy makers, patients, their advocates and carers, make well-informed decisions about human health care by preparing, updating and promoting the accessibility of Cochrane Reviews" [20].

Methods originally espoused by Cochrane and others have been codified into techniques for rating the quality of evidence in a publication and for grading the strength of a recommendation based on the preponderance of available evidence. In accord with this, the clinical problems addressed in this book have been assessed using a modification of a single rating system (GRADE) that is outlined and updated in Chap. 2 [21].

Techniques such as those described above for synthesizing large amounts of quality information were introduced for the development guidelines for clinical activity in thoracic surgery, most commonly for the management of lung cancer, beginning in the mid-1990s. An example of these is a set of guidelines based on what were then current standards of care sponsored by the Society of Surgical Oncology for managing lung cancer. It was written by experts in the field without a formal process of evidence collection [22]. A better technique for arriving at guidelines is the consensus statement, usually derived during a consensus process in which guidelines based on published medical evidence are revised until members of the conference agree by a substantial majority in the final statement. An example of this iterative structure is the Delphi process [23]. The problem with this technique is that the strength of recommendations, at times, is sometimes diluted until there is little content to them. Some organizations that appear to have avoided this pitfall in the general of guidelines of interest to thoracic surgeons include The American College of Chest Physicians, the Society of Thoracic Surgeons, the European Society of Thoracic Surgeons, the European Respiratory Society, the American Thoracic Society, the National Comprehensive Cancer Network, the Society of

Clinical Oncology, the British Thoracic Society, the International Society for Diseases of the Esophagus, and the Society of Surgical Oncology, to name but a few.

Despite the enormous efforts expended by professional societies in providing evidence-based algorithms for appropriate management of patients, dissemination of and adherence to these published guidelines, based on practice pattern reports, is disappointing. Focusing again on surgical management of lung cancer, there is strong evidence that standard procedures incorporated into surgical guidelines for lung cancer are widely ignored. For example, fewer than 50% of patients undergoing mediastinoscopy for nodal staging have lymph node biopsies performed. In patients undergoing major resection for lung cancer, fewer than 60% have mediastinal lymph nodes biopsied or dissected [24]. Only one-third of physicians routinely assess diffusing capacity in lung cancer patients who are candidates for lung resection in Europe, and in the United States fewer than 60% of patients who undergo major lung resection for cancer have diffusing capacity measured [25, 26]. Even at centers with expertise in preoperative evaluation adherence to evaluation algorithms can be challenging, especially for higher risk patients [27]. There are also important regional variations in the use of standard staging techniques and in the use of surgery for stage I lung cancer patients, patterns of activity that are also related to race and socioeconomic status [28, 29]. Failure to adhere to accepted standards of care for surgical lung cancer patients results in higher postoperative mortality rates [30, 31], and the selection of super specialists for one's lung cancer surgery confers an overall long-term survival advantage [32]. Overall compliance with guideline recommendations for management of lung cancer is less than 45% [33].

The importance of adherence to accepted standards of care, particular those espoused by major professional societies, such as the American College of Surgeons, The Society of Surgical Oncology, the American Society of Clinical Oncology, the American Cancer Society, the National Comprehensive Cancer Network, is becoming clear as the United States Centers for Medicare and Medicaid Services develops processes for rewarding adherence to standards of clinical care. This underscores the need for surgeons to become familiar with evidence-based practices and to adopt them as part of their daily routines. What is not known is whether surgeons should be rewarded for their efforts in following recommended standards of care, or for the outcomes of such care? Do we measure the process, the immediate success, or the long-term outcomes? If outcomes are to be the determining factor, what outcomes are important? Is operative mortality an adequate surrogate for quality of care and good results? Whose perspective is most important in determining success, that of the patient, or that of the medical establishment?

The Age of Data

We have now entered into an era in which the amount of data available for studying problems and outcomes in surgery is truly overwhelming. Large clinical trials involving thousands of subjects render databases measured in megabytes. A National Cancer Institute Genomic Data Commons contains more than 14 petabytes of data.

Large databases in which surgical information is stored include the National Medicare Database, the Surveillance Epidemiology and End Results (SEER), Nationwide Inpatient Sample (NIS), the American College of Surgeons National Surgical Quality Improvement Program (NSQIP), and the Society of Thoracic Surgeons (STS) database. Other foreign national and international databases contain similar large amounts of information.

Medical databases are of two basic types: those that contain information that is primarily clinical in nature, especially those that are developed specifically for a particular research project, and administrative databases that are maintained for other than clinical purposes but that can be used in some instances to assess clinical information and outcomes, an example of which is the National Medicare Database. Information is organized in databases in a hierarchical structure. An individual unit of data is a field; a patient's name, address, and age are each individual fields. Fields are grouped into records, such that all of one patient's fields constitute a record. Data in a record have a one-to-one relationship with each other. Records are compiled in relations, or files. Relations can be as simple as a spreadsheet, or flat file, in which there is a one-to-one relationship between each field. More complex relations contain many-to-one, or one-to-many, relationships among fields, relationships that must be accessed through queries rather than through simple inspection. An example is multiple diagnoses for a single patient, or multiple patients with a single diagnosis. Ultimately, databases become four-dimensional complex clinical and research resources as time emerges as an important factor in assessing outcomes and the changing molecular signatures of cancers, as examples [34]. These latter characteristics are true of most electronic medical records that are used in routine medical care.

In addition to collection of data such as those above that are generated in the process of standard patient care, new technological advances are providing an exponential increase in the amount of data generated by standard studies. An example is the new 640 slice computed tomography scanner, which has vastly expanded the amount of information collected in each of the x-y-z axes as well as providing temporal information and routine 3-D reconstruction capabilities during a routine CT scan. The additional information provided by this technology has created a revolutionary, rather than evolutionary, change in diagnostic radiology. Using this technology, virtual angiograms can be performed, three dimensional reconstruction of isolated anatomic entities is possible, and radiologists are discovering more abnormalities than clinicians know what to do with.

A case in point is the use of CT as a screening test for lung cancer. Rapid low-dose CT scans were introduced in the late 1990s and were quickly adopted as a means for screening high risk patients for lung cancer. The results of this screening were mixed. Several reports suggested that the number of radiographic abnormalities identified was high compared to the number of clinically important findings. For example, in the early experience at the Mayo clinic over 1500 patients were enrolled in an annual CT screening trial, and in the 4 years of the trial, over 3100 indeterminate nodules were identified, only 45 of which were found to be malignant

[35]. Similar results were reported by others during screening or surveillance activities [36]. Many additional radiographic abnormalities other than lung nodules were also identified. In addition, the increase in radiation exposure owing to more complex exams and more frequent exams led to concerns about radiation-induced neoplasms, an unintended consequence of the good intentions of those performing lung cancer screening [37, 38]. However, recent reports of improved lung cancer survival resulting from screening appropriately selected individuals for screening has led to formal recommendations for screening such populations [39–41]. This is changing the practice of medicine, even though cost-effectiveness of such interventions has not been demonstrated.

What Lies in the Future?

What do we now do with the plethora of information that is being collected on patients? How do we make sense of these gigabytes or terabytes of data? It may be that we now have more information than we can use or that we even want. Regardless, the trend is clearly in the direction of collecting more, rather than less, data, and it behooves us to make some sense of the situation. In the case of additional radiographic findings resulting from improved technology, new algorithms have already been refined for evaluating nodules and for managing their follow-up over time, and have yielded impressive results in the ability of these approaches to identify which patients should be observed and which patients should undergo biopsy or surgery [42]. What, though, of the reams of numerical and other data than pour in daily and populate large databases? When confronting this dilemma, it useful to remember that we are dealing with an evolutionary problem, the extent of which has been recognized for decades. Eliot aptly described this predicament in *The Rock* (1934), lamenting:

> *Where is the wisdom we have lost in knowledge?Where is the knowledge we have lost in information?*

To those lines one might add:

> *Where is the information we have lost in data?*

One might ask, in the presence of all this information, are we collecting the correct data? Evidence-based guidelines regarding indications for surgery, surgical techniques, and postoperative management are often lacking. We successfully track surgical outcomes of a limited sort, and often only in retrospect: complications, operative mortality, and survival. We don't successfully track patient's satisfaction with their experience, the quality of life they are left with as a result of surgery, and whether they would make the same decision regarding surgery if they had to do things over again. Perhaps these are important questions upon which physicians should focus. In addition to migrating towards patient-focused rather than

institutionally-focused data, are we prepared to take the greater leap of addressing more important issues requiring data from a societal perspective, including cost-effectiveness and appropriate resource distribution (human and otherwise) and utilization? This would likely result in redeployment of resources towards health prevention and maintenance rather than intervention. Such efforts are already underway, sponsored not by medical societies and other professional organizations, but by those paying the increasingly unaffordable costs of medical care.

Insurance companies have long been involved, through their actuarial functions, in identifying populations who are at high risk for medical problems, and it is likely that they will extend this actuarial methodology into evaluating the success of surgical care on an institutional and individual surgeon basis as more relevant data become available. The Leapfrog Group, representing a consortium of large commercial enterprises that covers insurance costs for millions of workers, was founded to differentiate levels of quality of outcomes for common or very expensive diseases, thereby potentially limiting costs of care by directing patients to better outcome centers. These efforts have three potential drawbacks from the perspective of the surgeon. First, decisions made in this way are primarily fiscally based, and are not patient focused. Second, policies put in place by payors will undoubtedly lead to regionalization of health care, effectively resulting in de facto restraint of trade affecting those surgeons with low individual case volumes or comparatively poor outcomes for a procedure, or who work in low volume centers. Finally, decisions about point of care will be taken from the hands of the patients and their physicians. The next phase of this process will be requirements on the part of payors regarding practice patterns, in which penalties are incurred if proscribed patterns are not followed, and rewards are provided for following such patterns, even if they lead to worse outcomes in an individual patient.

Physicians can retain control of the care of their patients in a variety of ways. First, they must make decisions based on evidence and in accordance with accepted guidelines and recommendations. This text serves to provide an outline for only a fraction of the decisions that are made in a thoracic surgical practice. For many of the topics in this book there are precious few data that can be used to formulate a rational basis for a recommendation. Practicing physicians must therefore become actively involved in the process of developing useful evidence upon which decisions can be made. There are a variety of means for doing this, including participation in randomized clinical trials, entry of their patient data (appropriately anonymized) into large databases for study, and participation in consensus conferences aimed at providing useful management guidelines for problems in which they have a special interest. Critical evaluation of new technology and procedures, rather than merely adopting what is new to appear to the public and referring physicians that one's practice is cutting edge, may help reduce the wholesale adoption of what is new into patterns of practice before its value is proven.

Conclusion

Decisions are the life blood of surgeons. How we make decisions affects the immediate and long-term outcomes of care of our patients. Such decisions will also, in the near future, affect our reimbursement, our referral patterns, and possibly our privileges to perform certain operations. Most of the decisions that we currently make in our surgical practices are insufficiently grounded in adequate evidence. In addition, we tend to ignore published evidence and guidelines, preferring to base our decisions on prior training, anecdotal experience, and intuition as to what is best for an individual patient.

Improving the process of decision making is vital to our patients' welfare, to the health of our specialty, and to our own careers. To do this we must thoughtfully embrace the culture of evidence-based medicine. This requires critical appraisal of reported evidence, interpretation of the evidence with regards to the surgeon's target population, and integration of appropriate information and guidelines into daily practice. Constant review of practice patterns, updating management algorithms, and critical assessment of results is necessary to maintain optimal quality care. Documentation of these processes must become second nature. Unless individual surgeons adopt leadership roles in this process and thoracic surgeons as a group buy into this concept, we will find ourselves marginalized by outside forces that will distance us from our patients and discount our expertise in making vital decisions.

References

1. The KJ, Mortality G. An intimate history of the black death, the most devastating plague of all time. New York: Harper Collins; 2006.
2. Eddy DM. Decisions without information. The intellectual crisis in medicine. HMO Pract. 1991;5:58–60.
3. Herrera-Perez D, Haslam A, Crain T, Gill J, Livingston C, Kaestner V, Hayes M, Morgan D, Cifu AS, Prasad V. A comprehensive review of randomized clinical trials in three medical journals reveals 396 medical reversals. Elife. 2019;8. pii: e45183.
4. Hippocrates. The genuine works of Hippocrates. Charles Darwin Adams (Ed, Trans). New York: Dover; 1868.
5. Moore W. The knife man: the extraordinary life and times of John Hunter, Father of Modern Surgery. New York: Broadway Books; 2005.
6. Bowditch HI. A treatise on diaphragmatic hernia. Buffalo Med J Monthly Rev. 1853;9:65–94.
7. Claridge JA, Fabian TC. History and development of evidence-based medicine. World J Surg. 2005;29:547–53.
8. Hedblom C. Diaphragmatic hernia. A study of three hundred and seventy-eight cases in which operation was performed. JAMA. 1925;85:947–53.
9. Harrington SW. Diaphragmatic hernia. Arch Surg. 1928;16:386–415.
10. Churchill ED. Wanderjahr: the education of a surgeon. Boston: The Francis A. Countway Library of Medicine; 1990.

11. Robinson DH, Toledo AH. Historical development of modern anesthesia. J Invest Surg. 2012;25(3):141–9.
12. Farrar FL. The butchering art: Joseph Lister's quest to transform the grisly world of Victorian medicine. New York: Straus and Giroux; 2017.
13. Miller JI Jr. The history of surgery of empyema, thoracoplasty, Eloesser flap, and muscle flap transposition. Chest Surg Clin N Am. 2000;10:45–53.
14. Mabe MA. The growth and number of journals. Serials. 2003;16:191–7.
15. Ware M, Mabe M. The STM report. 4th ed. Hague: International Association of Scientific, Technical and Medical Publishers; 2015.
16. https://www.nlm.nih.gov/bsd/stats/cit_added.html. Accessed 8 March 2020.
17. Druss BG, Marcus SC. Growth and decentralization of the medical literature: implications for evidence-based medicine. J Med Libr Assoc. 2005;93(4):499–501.
18. Hoffman T, Erueti C, Thorning S, Glasziou P. The scatter of research: cross sectional comparison of randomised trials and systematic reviews across specialties. BMJ. 2012;344:e3223.
19. Cochrane AL. Effectiveness and efficiency. Random reflections on health services. London: Nuffield Provincial Hospitals Trust; 1972.
20. Cochrane Collaboration website. http://www.cochrane.org/. Accessed 8 March 2020.
21. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EH, Phillips B, Raskob G, Zelman Lewis S, Schunemann H. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. Chest. 2006;129:174–81.
22. Ginsberg R, Roth J, Ferguson MK. Lung cancer surgical practice guidelines. Society of Surgical Oncology practice guidelines: lung cancer. Oncology. 1997;11:889–92. 895.
23. https://www.rand.org/topics/delphi-method.html. Accessed 8 March 2020.
24. Little AG, Rusch VW, Bonner JA, Gaspar LE, Green MR, Webb WR, Stewart AK. Patterns of surgical care of lung cancer patients. Ann Thorac Surg. 2005;80:2051–6.
25. Charloux A, Brunelli A, Bolliger CT, Rocco G, Sculier JP, Varela G, Licker M, Ferguson MK, Faivre-Finn C, Huber RM, Clini EM, Win T, De Ruysscher D, Goldman L, European Respiratory Society and European Society of Thoracic Surgeons Joint Task Force on Fitness for Radical Therapy. Lung function evaluation before surgery in lung cancer patients: how are recent advances put into practice? A survey among members of the European Society of Thoracic Surgeons (ESTS) and of the Thoracic Oncology Section of the European Respiratory Society (ERS). Interact Cardiovasc Thorac Surg. 2009;9:925–31.
26. Ferguson MK, Gaissert HA, Grab JD, Sheng S. Pulmonary complications after lung resection in the absence of chronic obstructive pulmonary disease: the predictive role of diffusing capacity. J Thorac Cardiovasc Surg. 2009;138:1297–302.
27. Novoa NM, Ramos J, Jiménez MF, González-Ruiz JM, Varela G. The initial phase for validating the European algorithm for functional assessment prior to lung resection: quantifying compliance with the recommendations in actual clinical practice. Arch Bronconeumol. 2012;48(7):229–33.
28. Shugarman LR, Mack K, Sorbero ME, Tian H, Jain AK, Ashwood JS, Asch SM. Race and sex differences in the receipt of timely and appropriate lung cancer treatment. Med Care. 2009;47:774–81.
29. Coburn N, Przybysz R, Barbera L, Hodgson D, Sharir S, Laupacis A, Law C. CT, MRI and ultrasound scanning rates: evaluation of cancer diagnosis, staging and surveillance in Ontario. J Surg Oncol. 2008;98:490–9.
30. Birkmeyer NJ, Goodney PP, Stukel TA, Hillner BE, Birkmeyer JD. Do cancer centers designated by the National Cancer Institute have better surgical outcomes? Cancer. 2005;103:435–41.
31. Tieu B, Schipper P. Specialty matters in the treatment of lung cancer. Semin Thorac Cardiovasc Surg. 2012;24(2):99–105.
32. Freeman RK, Dilts JR, Ascioti AJ, Giannini T, Mahidhara RJ. A comparison of quality and cost indicators by surgical specialty for lobectomy of the lung. J Thorac Cardiovasc Surg. 2013;145(1):68–74.

33. Nadpara PA, Madhavan SS, Tworek C, Sambamoorthi U, Hendryx M, Almubarak M. Guideline-concordant lung cancer care and associated health outcomes among elderly patients in the United States. J Geriatr Oncol. 2015;6(2):101–10.
34. Surati M, Robinson M, Nandi S, Faoro L, Demchuk C, Rolle CE, Kanteti R, Ferguson BD, Hasina R, Gangadhar TC, Salama AK, Arif Q, Kirchner C, Mendonca E, Campbell N, Limvorasak S, Villaflor V, Hensing TA, Krausz T, Vokes EE, Husain AN, Ferguson MK, Karrison TG, Salgia R. Proteomic characterization of non-small cell lung cancer in a comprehensive translational thoracic oncology database. J Clin Bioinforma. 2011;1(8):1–11.
35. Crestanello JA, Allen MS, Jett JR, Cassivi SD, Nichols FC III, Swensen SJ, Deschamps C, Pairolero PC. Thoracic surgical operations in patients enrolled in a computed tomographic screening trial. J Thorac Cardiovasc Surg. 2004;128:254–9.
36. van Klaveren RJ, Oudkerk M, Prokop M, Scholten ET, Nackaerts K, Vernhout R, van Iersel CA, van den Bergh KA, van't Westeinde S, van der Aalst C, Thunnissen E, Xu DM, Wang Y, Zhao Y, Gietema HA, de Hoop BJ, Groen HJ, de Bock GH, van Ooijen P, Weenink C, Verschakelen J, Lammers JW, Timens W, Willebrand D, Vink A, Mali W, de Koning HJ. Management of lung nodules detected by volume CT scanning. N Engl J Med. 2009;361:2221–9.
37. Smith-Bindman R, Lipson J, Marcus R, Kim KP, Mahesh M, Gould R, Berrington de González A, Miglioretti DL. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. Arch Intern Med. 2009;169:2078–86.
38. Berrington de González A, Mahesh M, Kim KP, Bhargavan M, Lewis R, Mettler F, Land C. Projected cancer risks from computed tomographic scans performed in the United States in 2007. Arch Intern Med. 2009;169:2071–7.
39. Jaklitsch MT, Jacobson FL, Austin JH, Field JK, Jett JR, Keshavjee S, MacMahon H, Mulshine JL, Munden RF, Salgia R, Strauss GM, Swanson SJ, Travis WD, Sugarbaker DJ. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg. 2012;144(1):33–8.
40. Moyer VA on behalf of the U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2013. https://doi.org/10.7326/M13-2771.
41. Wood DE, Kazerooni EA, Baum SL, Eapen GA, Ettinger DS, Hou L, Jackman DM, Klippenstein D, Kumar R, Lackner RP, Leard LE, Lennes IT, ANC L, Makani SS, Massion PP, Mazzone P, Merritt RE, Meyers BF, Midthun DE, Pipavath S, Pratt C, Reddy C, Reid ME, Rotter AJ, Sachs PB, Schabath MB, Schiebler ML, Tong BC, Travis WD, Wei B, Yang SC, Gregory KM, Miranda Hughes M. Lung cancer screening, Version 3.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 16:4. https://doi.org/10.6004/jnccn.2018.0020.
42. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, Mehta AC, Ohno Y, Powell CA, Prokop M, Rubin GD, Schaefer-Prokop CM, Travis WD, Van Schil PE, Bankier AA. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology. 2017;284(1):228–43.

Evidence Based Medicine: Quality of Evidence and Evaluation Systems

2

Apoorva Krishna Chandar and Yngve Falck-Ytter

Introduction

Evidence based medicine is defined as "a systematic approach to clinical problem solving which allows the integration of the best available research evidence with clinical expertise and patient values" [1]. Arguably, the most important application of evidence based medicine is the development of clinical practice guidelines. Commenting on clinical practice guidelines, the Institute of Medicine [2] says:

> *Clinical Practice Guidelines are statements that include recommendations intended to optimize patient care. They are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. To be trustworthy, guidelines should be based on a systematic review of the existing evidence; be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups; consider important patient subgroups and patient preferences, as appropriate; be based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest; provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of recommendations; and be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations.*

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As knowledge grows exponentially, clinicians' treatment decisions increasingly depend on well done clinical practice guidelines [3]. However, a major impediment to the implementation and adoption of such guidelines is that they are often confusing and not actionable. The lack of clarity in guidelines creates confusion for not only the healthcare provider, but for patients as well. On the other hand, good clinical practice guidelines are actionable and easy to understand. In order to formulate clinical practice guidelines that can effectively guide clinicians and consumers, guidelines need to be derived from the best available evidence from which information can be obtained to support clinical recommendations.

Systematically developed guidelines have the potential to improve patient care and health outcomes, reduce inappropriate variations in practice, promote efficient use of limited healthcare resources and help define and inform public policy [4]. Despite an explosion in the field of guideline development in recent years, guidelines often lack transparency and useful information.

In the past, guideline developers usually relied solely on evidence hierarchies to determine the "level of evidence" with randomized controlled trials (RCTs) always being considered high level evidence and observational studies to be of lower quality. Such hierarchies suffer from oversimplification as RCTs can be flawed and well done observational studies may be the basis of higher quality evidence. Although the past 30 years have shown an enormous increase in evidence rating systems, almost all relied on a variation of those simple hierarchies. In addition, strong recommendations were routinely attached to high levels of evidence without regard to potentially closely balanced benefits and harms trade-offs which usually does require eliciting patient values and preferences and instead should result in conditional recommendations.

GRADE began as an initiative to offer a universally acceptable, sensible and transparent approach for grading the quality of evidence and strength of recommendations (http://www.gradeworkinggroup.org/). With the overarching goal of having a single system that avoids confusion and is methodologically rigorous, yet avoids the shortcomings of other systems, the GRADE framework helps to formulate clear, precise and concise recommendations. The uses of the GRADE framework are two-fold:

1. Defines the strength recommendations in the development of clinical practice guidelines
2. Assist in rating the quality of evidence in systematic reviews and other evidence summaries on which those recommendations are based

The GRADE framework has been widely adopted (>80 societies and organizations) including the WHO, the COCHRANE collaboration, the American Thoracic Society, and the European Society of Thoracic Surgeons [5]. In this chapter, we elaborate the GRADE approach to rating the quality of evidence and implications for strong and weak guideline recommendations and how patient values and preferences as well as resource use considerations can change those recommendations.

The GRADE Approach

Defining the Clinical Question

In GRADE, the starting point is the formulation of a relevant and answerable clinical question. It is essential to formulate a well-defined clinical question for more than one reason: On the one hand, it helps to bring emphasis on the focus and scope of the guideline and, and on the other, it helps to define the search strategy which will be used to identify the body of evidence. The PICO strategy that assists in defining a clinical question is detailed in Table 2.1.

What Outcomes Should We Consider for Clinical Decision Making?

Not all outcomes are equally important. Clinical questions in practice guidelines often contain several outcomes, some of which may or may not be useful for decision making. GRADE categorizes outcomes in a hierarchical fashion by listing outcomes that are critical to decision making (such as mortality), outcomes that are important but not critical for decision making (post-thoracotomy pain syndrome) and outcomes that are less important (hypertrophic scar resulting from thoracotomy incision). Such a step-wise rating is important because in GRADE, unlike other guideline systems that rate individual studies, quality of the available evidence is rated for individual outcomes across studies. The reasoning behind this is that quality frequently differs across outcomes, even within a single study.

Guideline panels should specify the comparator explicitly. In particular, when multiple treatment options are involved (such as surgical vs. nonsurgical treatments for symptomatic giant bullae in COPD), it should be specified whether the recommendation is suggesting that all treatments are equally recommended or that some interventions are recommended over others. In the same context, the choice of setting (such as resource poor vs. adequate resources or high volume vs. low volume centers) needs to be taken into consideration. Guideline panels should be aware of the audience and the setting they are targeting when formulating guidelines. We will elaborate further on resource use later in this chapter.

Table 2.1 The PICO approach to define a clinical question

P	Patient population	Describes the patient population being targeted by the intervention (e.g., patients with Barrett's esophagus)
I	Intervention	Describes the intervention that is being studied (e.g., minimally invasive esophagectomy for Barrett's esophagus with high grade dysplasia)
C	Comparator	Describes the intervention to which the study intervention is being compared to (e.g., radio frequency ablation)
O	Outcomes	Describes the outcomes which includes benefits and downsides (e.g., all-cause mortality, progression to esophageal adenocarcinoma, quality of life)

Grading the Quality of Evidence

The quality of evidence is the extent to which our confidence in a comparative estimate of an intervention effect is adequate to support a particular recommendation. For the rest of the chapter we will therefore use the terms "confidence in the evidence" and "quality of evidence" interchangeably.

Following the formulation of a PICO based clinical question is the crucial process of reviewing and grading the quality of evidence associated with the clinical question. For instance, a question like 'surgical management of non-small cell lung cancer' might give us a large number of studies, which might include randomized clinical trials (RCTs), observational studies and case series conducted in different settings, involve various kinds of surgeries and target different patient populations. Indeed, this becomes a challenge for review authors and guideline developers alike as they are presented with an enormous body of evidence. GRADE offers a formal way of rating the quality of this large body of evidence by providing detailed guidance for authors of systematic reviews and guidelines. GRADE defines the quality of evidence as the confidence we have in the estimate of effect (benefit or risk) to support a particular decision [6]. Although confidence in the evidence is continuous, GRADE uses four distinct categories to conceptualize evidence quality (Table 2.2).

Rating the Quality of Evidence from Randomized Controlled Trials

In GRADE, outcomes that are informed from RCTs start as high quality evidence. However, RCTs vary widely in quality. Methodological limitations (risk of bias), particularly related to the design and execution of RCTs can often lower the quality of evidence for a particular outcome. GRADE uses five different, well defined criteria to rate down the quality of evidence from RCTs (Table 2.3).

Limitations in Study Design

Proper randomization and adequate allocation concealment, which prevents clinicians and participants becoming aware of upcoming assignments are important strategies to protect from bias. Inadequate allocation concealment leads to exaggerated estimates of treatment effect [9]. Major limitations in study design may lead to rating down the quality of evidence for an outcome. However, assessment of whether or not a methodological shortcoming, such as lack of blinding, may have had a substantial impact on an estimate of effect is important as there are situations where

Table 2.2 Quality of evidence

High quality	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality	We are moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of effect, but possibility to be substantially different
Low quality	Our confidence in the effect is limited: The true effect may be substantially different from the estimate of the effect
Very low quality	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 2.3 Rating the quality of evidence for each important outcome

- For outcomes informed by RCTs, start as high confidence, then rate down to moderate, low or very low confidence in the evidence
- For outcomes informed by observational studies, start as low confidence, then either rate down or, on rare occasions, rate up to moderate or high confidence in the evidence

Checklist	*Things to look out for*
Risk of bias	RCTs: Major limitations, such as lack of allocation concealment, lack of blinding, large losses of follow-up, failure of intention-to-treat analysis, and a study terminated early for benefit. Consider using the Cochrane risk of bias tool [7] Observational studies: assess risk of confounding by examining the selection of exposed and non-exposed cohort, comparability of the cohort and issues with assessment and adequacy of follow-up of the outcomes of interest. Consider using the Newcastle-Ottawa quality assessment tool [8]
Inconsistency	Widely differing estimates of the treatment effect (variability in results or heterogeneity)
Indirectness	Population: e.g., differences in age, gender, comorbidities Intervention: e.g., similar but not identical intervention Comparator: e.g., difference in comparator intervention Outcomes: e.g., use of surrogate outcomes, short-term vs. long-term No head-to-head comparison of two interventions
Imprecision	Wide confidence intervals/small sample size/few events that make the result uninformative
Publication bias	High probability of failure to report studies (likely because no effect was observed)
Magnitude of effect	Large magnitude of association: RR > 2.0 or RR < 0.5 Very large magnitude of association: RR > 5.0 or RR < 0.2 Two or more observational studies, direct evidence, no plausible confounders, no threats to validity, sufficiently precise estimate
Dose-response	Presence of a dose-response gradient
Plausible confounders	Unaccounted, plausible biases from observational evidence that moves the result in the direction of underestimating the apparent treatment effect (all plausible confounding would reduce a demonstrated effect; all plausible confounding would suggest a spurious effect when results show no effect)

lack of blinding may not materially impact a particular outcome. Another issue that is commonly encountered with RCTs is losses to follow up. Again, losses to follow up may not always require rating down if there are few and proportionate losses to follow up in both treatment and control groups. However, disproportionate losses to follow up can either increase (due to greater losses in the control group) or decrease (due to greater losses in the treatment group) the treatment effect [10]. The way in which RCTs are analyzed is another important criterion to consider in study design. Intention-to-treat (ITT) analysis is the preferred method of analysis of RCTs. However, it is documented that the intention-to-treat approach is often inadequately described and inadequately applied in RCT and deviations from ITT analysis are common [11]. RCTs should be carefully reviewed to determine if they adopted the

ITT approach for a particular outcome. Lastly, authors of systematic reviews and guideline developers should exercise caution when they encounter trials that are stopped early for benefit, particularly when such trials contribute considerable weight to a meta-analysis as they might produce a spurious improvement in the treatment effect [12, 13].

Inconsistency of Study Results

Confidence in the estimate of effect may require rating down for inconsistency, if the magnitude and direction of effects across different studies varies widely (heterogeneity of study results). Variability in treatment effects across studies usually is the result of varying populations or interventions. However, when the reasons for inconsistency across studies cannot be identified, the confidence in the evidence may be lower. Consider for example the effect of suction vs. non-suction on prolonged air leakage to the underwater seal drains following pulmonary surgery. A meta-analysis of available RCTs showed varying effect estimates and direction of effect resulting in an I-squared of residual heterogeneity of close to 60%, which could be considered substantial and it would not be unreasonable to rate down for inconsistency [14].

It is particularly important to remember that in GRADE, the quality of evidence is not rated up for consistency, it is only rated down for inconsistency. Several criteria may help decide whether heterogeneity exists: the point estimates vary widely across studies; minimally or non-overlapping confidence intervals; statistical test for heterogeneity shows a low p-value; I-squared value (percentage of variability due to heterogeneity rather than chance) is large [15].

Indirectness of Evidence

GRADE defines several sources of indirectness. For example, differences in patient characteristics (age, gender and race), differences in interventions or comparators (similar but not the same intervention or comparators), indirectness of outcomes (direct outcome measures vs. surrogate outcome measures) and indirect comparisons (e.g., lack of head-to-head trials of competing surgical approaches). All sources of indirectness can result in lowering our confidence in the estimate of effects. However, it is necessary to remember that when direct evidence is limited in quantity or quality, indirect evidence from other populations may be considered and the quality need not necessarily be rated down with proper justification for not doing so. For example, although direct evidence about the safety and effectiveness of prophylaxis of VTE prevention in patients undergoing thoracic surgery is limited, the ACCP anti-thrombotic guidelines did not rate down for indirectness as they felt that the evidence about relative risks from studies of patients undergoing general or abdominal-pelvic surgery could be applied with little or no indirectness to thoracic surgery [16]. Another domain of indirectness is duration of follow-up for certain outcomes. GRADE recommends that guideline developers should always indicate the length of follow up to which the estimate of absolute effect refers. This length of follow up is a time frame judged appropriate to balance the risk-benefit consequences of alternative treatment strategies. Longer follow up periods are associated with higher risk differences between intervention and control. This could

potentially lead to important differences in readers' perception of the apparent magnitude of effect. Often, extending the time frame involves the assumption that event rates will stay constant over time [17].

Of particular importance is the categorization of outcome measures into direct and surrogate outcomes. In the absence of data on patient-important outcomes, surrogates could contribute to the estimation of the effect of an intervention on the outcomes that are important. Post-surgical asymptomatic deep vein thrombosis detected by screening venography or ultrasound surveillance is an example of a surrogate outcome [18]. It is to be noted that despite the relative importance of direct outcomes, both direct and surrogate outcomes should be reported in studies because the audience for guideline developers and systematic reviews might want to see both before making appropriate decisions.

Imprecision

Imprecision is usually determined by examining the confidence intervals. Usually, studies with few enrolled patients and / or few events have wider confidence intervals. Additionally, our confidence in the evidence is lowered when the 95% confidence interval fails to exclude important benefit or important harm. Consider for example the long-term outcome of dilation requirements when using 180° laparoscopic anterior fundoplication (180° LAF) versus laparoscopic Nissen fundoplication (LNF) for GERD [19]. Although the partial fundoplication showed less than half the rate of dilatations, few events in the studies and generally low sample sizes did not allow for a precise estimate even after pooling the results, and the 95% confidence interval crosses one.

Publication Bias

When there is sufficient evidence that trials have not been reported (especially when treatment effects are negligibly small or absent), this may lead to an overestimation of effect and decrease our confidence in the evidence. Such trials, more commonly than not, are industry funded and small. Authors of systematic reviews and clinical guidelines should show due diligence in checking for any unreported trial results by verifying with clinicaltrials.gov for registered, but potentially unpublished, trials. Systematic reviews provide a way of detecting publication bias by examining the funnel plot, for example, to help detect potential publication bias.

Rating Up the Quality of Evidence from Observational Studies

Outcomes deriving their evidence from observational studies usually start as low confidence in the evidence (low quality evidence). The reason for this is that observational studies are unable to fully control for unknown confounders. However, there are situations where evidence from observational studies should be considered to provide higher quality evidence. GRADE recommends rating up the quality of evidence in several instances. Evidence from well-done observational studies without known residual confounding, large magnitude of effect will usually increase our confidence that an effect exists and it would be reasonable to rate up the quality of evidence. For example, surgical resection with

curative intent of esophageal cancer shows a very large relative magnitude of effect in reduction of mortality compared to best supportive care [20]. Another reason for rating up the evidence quality is the presence of a dose response gradient. Table 2.3 gives an overview of when to rate up or rate down the quality of evidence obtained from observational studies.

Moving from Quality of Evidence to Formulating Recommendations

Strength of a recommendation reflects the extent to which we can be confident that the beneficial effects of an intervention clearly outweigh its undesirable effects [21]. Even though GRADE suggests rating the quality of evidence for each outcome in an ordinal fashion to assist systematic review authors and guideline developers to arrive at an outcome-specific rating of confidence, the final rating of confidence in the evidence (overall quality of evidence for a particular PICO question) will need to be determined before making recommendations. GRADE specifies that the overall quality of evidence is driven by the lowest quality of evidence of an outcome that is critical for decision making [22]. For instance, we might be confident about an intervention's benefit, but as long as there is a harm associated with this intervention that is considered critical for decision making (and, for example, rated as moderate quality of evidence), the overall quality of evidence across all critical outcomes in regards to the PICO question should remain at moderate despite the high quality of evidence for benefit.

While acknowledging that the strength of recommendations is, in fact, a continuum, GRADE offers a binary classification for strength of recommendations: strong and weak (conditional). Such a dichotomous system provides clear, simple, easily understandable, and readily implementable directions with clear implications for patients, clinicians and policy-makers. Table 2.4 provides an overview of this classification.

The strength of recommendation is guided not merely by the quality of the evidence—high quality evidence doesn't necessarily always indicate strong recommendations, and strong recommendations can sometimes arise from lower quality evidence [23]. Though the quality of evidence is the primary starting point in guiding the strength of a recommendation, additional, but separate factors such as balance between desirable and undesirable effects, patients' values and preferences, and uncertainty regarding wise use of resources arising from a recommendation are equally important in the GRADE system and may change the strength or even the direction of a recommendation [6]. When guideline panels strongly recommend an intervention, they are confident that the desirable effects clearly outweigh the undesirable effects and that almost all fully informed patients, with reasonable certainty will opt for the intervention. GRADE identifies four important factors that can impact the overall quality of evidence and thereby influence the strength of recommendations (Table 2.5).

Table 2.4 Health care implications of GRADE defined strengths of recommendations

Strength of recommendation	Implications for patients	Implications for clinicians	Implications for policy makers
Strong	Most individuals in this situation would want the recommended course of action and only a small proportion would not Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences, but could help with the implementation	Most individuals should receive the intervention Adherence to this recommendation according to the guidelines could be used as a quality criterion or a performance indicator	The recommendation can be adopted as a performance indicator in most situations
Weak (conditional)	The majority of individuals in this situation would want the suggested course of action, but many would not Decision aids may be useful in helping individuals make decisions consistent with their values and preferences	Be prepared to help people to make a decision that is consistent with their own values and preferences Use decision aids and implement shared decision making approaches	Policy-making will require substantial debates and involvement of many stakeholders

Table 2.5 GRADE determinants of the strength of recommendation

GRADE category	Example of a **strong** recommendation	Example of a **weak** (conditional) recommendation
Quality of evidence	A large number of high quality RCTs has shown that plain chest X-ray screening does not reduce lung cancer mortality	Only case series have examined the effectiveness of diaphragmatic repair for the treatment of hepatic hydrothorax in patients who are not eligible for TIPS
Balance of benefits versus harms and burdens	The success of an initial pleural aspiration attempt in stable patients with large spontaneous pneumothorax is sufficiently high with acceptable risks and low costs compared to VATS	180° laparoscopic anterior fundoplication compared to Nissen fundoplication reduces the incidence of procedure related dysphagia and need for dilatation, but at a cost of increased rate of re-operation and residual reflux symptoms
Values and preferences	Younger patients with early stage non-small cell lung cancer will invariably place a higher value on the life prolonging effects of post-surgical adjuvant chemotherapy over treatment toxicity	Older patients with early stage non-small cell lung cancer may not place a higher value on the life prolonging effects of post-surgical adjuvant chemotherapy over treatment toxicity
Resource use (e.g., cost)	The relative low cost of chest catheter insertion for the treatment of large primary spontaneous pneumothorax	The high cost of adding bevacizumab to initial chemotherapy regimens in patients with advanced non-small cell lung cancer

Resource Use

Resource use varies widely over time and across geographical settings. While an intervention with higher costs is unlikely to be strongly recommended over an equally effective lower cost alternative, it is essential to consider the context of recommendation and hence, guideline panels must be specific about the setting to which a recommendation applies [21].

Resource use studies might be conducted concurrently within the framework of an empirical study such as clinical trial or using a decision model that typically uses secondary data collected from several sources. Cost utilization and resource utilization might be particularly important in surgical treatments.

GRADE recommends assessing resource implications in two steps [24]. First, consider whether resource use is important (or critical) for making the recommendation. Second, consider specific items of resource use and their potential impact on different strategies. For a detailed explanation of application of GRADE to resource use, we refer the readers to other relevant GRADE publications [24, 25].

Presenting Summary of Findings

GRADE offers a way of displaying a comprehensive, but condensed summary of key outcomes and their importance in a summary of findings (SoFs) table. A SoFs table usually contains all important outcomes necessary for clinical decision making, shows the quality of evidence across studies for a particular outcome and the associated relative and absolute effects [22]. When meta-analyses are accompanied by such SoFs tables, they can prove useful for guideline developers while developing recommendations. GRADE recommends limiting the number of outcomes to approximately seven for each SoFs table, as it is unlikely that more outcomes will lead to better overview of the data and judgments made [17]. If there are more than seven outcomes, combining certain similar outcomes might become necessary (such as symptomatic deep vein thrombosis and pulmonary embolism into one category of "venous thrombotic events"). It is not uncommon to find systematic reviews that address more than one comparison, evaluate an intervention in two disparate populations or examine the effects of a number of interventions for the same clinical problem. Such systematic reviews are also likely to be accompanied by more than one SoFs table [26].

How Should Clinical Guidance Be Worded?

Guideline authors should choose appropriate phrasing to disseminate their findings. GRADE advises the use of standardized language to express strong and weak recommendations for or against an intervention. Such standardized wording would be: "We recommend to use…" or "We recommend against the use of …" for strong recommendations and "We suggest to use…" or "We suggest against the use of…"

for weak recommendations [22]. For example, a weak recommendation would be worded like this: "For thoracic surgery patients who are at high risk for major bleeding, we suggest the use of mechanical prophylaxis, preferably with optimally applied intermittent pneumatic compression, over no prophylaxis" [16].

Applying GRADE

With its clarity, simplicity and methodological rigor, GRADE lends itself for application to grading the quality of evidence for a wide range of evidence summaries, from systematic reviews of interventions, diagnostic tests and strategies to formal health technology assessments or presentations that can be more easily utilized by health care providers by including actionable recommendations, such as clinical practice guidelines, care paths, or decision support systems (top half illustrating the supporting systematic review; lower half the moving-to-recommendations process).

Conclusion

A common, simple, yet rigorous rating system can reduce confusion and increase the transparency when formulating recommendations in guidelines, textbooks and other evidence summaries. It allows surgeons to engage the patient in a shared decision-making process when recommending care based on varying levels of confidence in the evidence and different trade-offs between benefits and downsides as well as uncertainty of patient's values and preferences [27].

Although evidence quality ratings within the GRADE approach have shown to be reproducible [28], the main goal is to provide transparent and explicit judgments. GRADE is the only system to recognize that quality may differ across outcomes and specifically addresses this issue by being outcomes-centric. GRADE provides explicit, detailed and comprehensive criteria for rating the quality of evidence. Finally, not only does GRADE define quality of evidence and strength of recommendations as two related but separate concepts, but also makes the transition from rating the quality of evidence to formulating clinically sensible recommendations a transparent process by including additional domains important for decision making: patient's values and preferences, balance between harms and burdens, and resource use.

References

1. Sackett D, Strauss S, Richardson W, et al. Evidence-based medicine: how to practice and teach EBM. 2nd ed. Edinburgh: Churchill Livingstone; 2000.
2. IOM (Institute of Medicine). Clinical practice guidelines we can trust. Washington, DC: The National Academies Press; 2011.
3. Mendelson D, Carino TV. Evidence-based medicine in the United States--de rigueur or dream deferred? Health Aff (Millwood). 2005;24(1):133–6.

4. Sultan S, Falck-Ytter Y, Inadomi JM. The AGA institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol. 2013;11(4):329–32.
5. Organizations that have endorsed or that are using GRADE: GRADE Working Group; 2013 [cited 2013 October 30]. Available from: http://www.gradeworkinggroup.org/society/.
6. Falck-Ytter Y, Kunz R, Guyatt GH, Schunemann HJ. How strong is the evidence? Am J Gastroenterol. 2008;103(6):1334–8.
7. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. Lancet. 2002;359(9306):614–8.
8. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011;64(4):407–15.
9. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. BMJ. 1999;319(7211):670–4.
10. Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q, et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. JAMA. 2010;303(12):1180–7.
11. Guyatt GH, Briel M, Glasziou P, Bassler D, Montori VM. Problems of stopping trials early. BMJ. 2012;344:e3863.
12. Deng B, Tan QY, Zhao YP, Wang RW, Jiang YG. Suction or non-suction to the underwater seal drains following pulmonary operation: meta-analysis of randomised controlled trials. Eur J Cardiothorac Surg. 2010;38(2):210–5.
13. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol. 2011;64(12):1294–302.
14. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S–77S.
15. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013;66(2):158–72.
16. Guyatt GH, Norris SL, Schulman S, Hirsh J, Eckman MH, Akl EA, et al. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):53S–70S.
17. Broeders JA, Roks DJ, Ahmed Ali U, Watson DI, Baigrie RJ, Cao Z, et al. Laparoscopic anterior 180-degree versus nissen fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. Ann Surg. 2013;257(5):850–9.
18. Lee JS, Urschel DM, Urschel JD. Is general thoracic surgical practice evidence based? Ann Thorac Surg. 2000;70(2):429–31.
19. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
20. Wells G, Shea B, O'Connell J. The Newcastle-Ottawa Scale (NOS) for Assessing The Quality of Nonrandomised Studies in Meta-analyses. Ottawa Health Research Institute web site. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 2 June 2020.
21. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. BMJ. 2008;336(7652):1049–51.
22. Falck-Ytter Y, Guyatt GH. Guidelines: rating the quality of evidence and grading the strength of recommendations. In: Burneo JG, Demaerschalk BM, Jenkins ME, editors. Neurology: an evidence-based approach. New York: Springer; 2012. p. 25–41.
23. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6.
24. Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol. 2013;66(2):140–50.

25. Guyatt GH, Oxman AD, Kunz R, Jaeschke R, Helfand M, Liberati A, et al. Incorporating considerations of resources use into grading recommendations. BMJ. 2008;336(7654):1170–3.
26. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94.
27. Feuerstein JD, Gifford AE, Akbari M, Goldman J, Leffler DA, Sheth SG, et al. Systematic analysis underlying the quality of the scientific evidence and conflicts of interest in gastroenterology practice guidelines. Am J Gastroenterol. 2013;108(11):1686–93.
28. Mustafa RA, Santesso N, Brozek J, Akl EA, Walter SD, Norman G, et al. The GRADE approach is reproducible in assessing the quality of evidence of quantitative evidence syntheses. J Clin Epidemiol. 2013;66(7):736–42.

Decision Analytic Techniques and Other Decision Processes

3

Varun Puri and Bryan F. Meyers

Introduction

Nearly all clinical care results from some sort of decision process. Decisions that influence patient care can range from bedside choices concerning routine laboratory testing to health policy decisions about permitting and paying for new and expensive treatment options for specific illnesses. Similarly, the consequences of healthcare decisions can be seen in the outcomes of individual patients as well as generational shifts in the management of disease processes.

Decision making in healthcare is inherently complex and often influenced by a multitude of factors. These include the availability of competing alternatives; information about the risks, costs and downstream effects of these individual options; and the point of view or perspective from which one must make the decision. The process of formally and simultaneously considering the available evidence and comparing options with the objective of maximizing desirable outcomes is called decision analysis. Though decision analysis has its roots in engineering and economic systems, it has been increasingly utilized in the field of medicine to clarify thinking and guide management decisions [1, 2]. Several authors have also applied this methodology to common thoracic surgical problems [3–13].

Application of Decision Analytic Techniques

Common scenarios in clinical medicine where decision analysis might be most useful fall into one of three categories which are described below with relevant examples.

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Action Versus Inaction

Certain clinical situations require an active choice between an intervention and watchful waiting. A common scenario in thoracic surgery is an incidentally detected solitary pulmonary nodule [5]. The framework for decision analysis here begins with a consideration of all the available options. These include watchful waiting with a further CT scan in 3–6 months (relative inaction) or immediate action alternatives which include CT-PET scan, percutaneous or bronchoscopic biopsy, or proceeding directly with surgery. Proper consideration of the risk of malignancy prior to any of these interventions is of paramount importance. As an example, the risk of a nodule being malignant is higher in a 65 year old smoker than in a 45 year old non-smoker. Similarly, the likelihood of cancer in a 2 cm spiculated lesion is much higher than that in a 9 mm ground glass opacity. These defining characteristics greatly influence the positive and negative predictive values of the tests (also called post-test probabilities) and must be considered and defined in the decision analysis. The careful formulation of the question is paramount in the construction of a worthwhile decision analysis. In the examples above, one would expect a different answer for the two extreme examples, so it would be unlikely that those two patients would be evaluated with the same decision analysis. The question must be very specific, and the results of the subsequent decision analysis would only generalize to situations consistent with the specific parameters defined in advance.

Next, one looks at each of the possible options for action and considers the consequences of each of these choices. For this, it is important to consider the sensitivity, specificity, and accuracy of each of these tests, in the setting in which they will be employed. A false positive test will lead to an unnecessary operation while a false negative test might result in a missed or delayed cancer diagnosis and the potential for progression and increased long term risk of mortality. The consequences of inaction (watchful waiting) may be the appropriate avoidance of an unnecessary operation in the event that the lesion is actually benign, or an inappropriate delay in treatment for what turns out to be a lung cancer. Finally the advantages of treatment, such as an early diagnosis and an increased chance of avoiding cancer-related mortality, and the disadvantages, such as perioperative costs and adverse outcomes, are factored into the decision analysis. The end-points in analysis can vary and range from minimizing costs, to minimizing cancer deaths, to minimizing intervention-related adverse effects, or to maximizing overall length of life. Although superficially these objectives appear similar, the analysis is usually performed with a specific end-point in mind. Rarely, the decision analysis will evaluate two options that result in the same qualitative outcome and they are compared on measures of cost or time efficiency. More commonly, the measured endpoints are more complex like a simultaneous assessment of costs, length of life, and quality of life. The more complex the endpoint, the more likely that decision analysis techniques will be helpful in elucidating and clarifying the differences between the choices studied.

Choice Among Various Actions That Seem Plausible

Another common application of decision analytic techniques is a comparison of viable alternatives when one option is not known to be clearly superior. As an example, unsuspected mediastinal lymph node metastases may be encountered at the time of proposed resection for lung cancer [3]. The two principal alternatives are: A. Proceed with the planned resection; or, B. Stop the operation without a resection in order to administer neoadjuvant chemotherapy or chemoradiotherapy, and then attempt resection at a later date in the absence of progression or clinical decline. In this cited example, the authors considered an array of possible events after the primary resection option including operative mortality, survival with adjuvant treatment, and survival with no adjuvant treatment. Similarly, for the scenario where resection is postponed until after induction therapy, they considered the probabilities of various consequences; mortality related to the exploration, the receipt of chemoradiation without a subsequent resection, and successful progression from induction therapy to resection. Investigators may estimate the likelihood of each of these scenarios from previously published literature, utilize their own clinical data, or employ a combined approach. In this particular study, the authors chose to perform a cost-effectiveness analysis. The enquiry shed light on that clinical decision by estimating the overall costs of treatment and the expected survival and quality-adjusted survival for the two competing treatment options to facilitate a decision and subsequent research.

Optimizing Timing or Interval of Action

Decision analysis can also be employed to propose the appropriate timing of interventions. As an example, the optimal follow-up strategy after resection for esophageal cancer is a matter of debate. Various groups advocate frequency of follow-up ranging from 3 to 12 month intervals. An appropriate use of decision analysis could be to compare two alternatives; intensive follow-up with axial imaging, clinic visits, and lab tests every 3 months, versus a less intensive approach with imaging performed at annual clinic visits only. For both strategies, one would consider the probabilities of detection of recurrence and the likelihood of survival with and without treatment for recurrence. Subsequently a model could be created to with a view towards optimizing resource utilization and avoiding unnecessary interventions.

Technical Aspects

The decision analysis process is best conducted using a standard approach. Briefly, one must first define the problem and clarify the objectives in the problem-solving process. Next, one must enumerate the alternatives and how these choices affect downstream events with their probabilities and values. Finally, we consider the

balance of benefits and adverse outcomes of each option. Weinstein et al. [14] have described this **PROACTIVE** approach to decision analysis.

P: Problem(s)—Define Problem Explicitly

The details of the problem must be described as precisely as possible because the performance characteristics of the intervention and many of the subsequent probabilities and outcomes will be highly associated to those defining details. This step also involves a consideration of the natural history of the problem and likely consequences of inaction. It is often useful to create a "consequence table" enumerating outcomes for the watchful waiting approach.

R: Reframe

Consider the problem from multiple perspectives including those of the patient, family members, society, and the clinician. This is useful as it is common for a disease process to pose different challenges to these stakeholders. For example: a screening question might pose minimal health impact on the vast majority of patient stakeholders who do not have the screened condition, but a huge impact on the small minority who are found to have the disease being sought. The answer in such a decision analysis will often hinge on the costs of screening and the costs of care prevented or required as a result of a positive screen. Certainly, the net benefit of such a program might vary if you consider from various perspectives: patient, society, or payor.

O: Objective—Focus on the Objective(s)

Is the goal to save lives, or save money or to strike a balance between the two? There may be more than one objective and it is important to understand any trade-offs between objectives. A "means" objective is an intermediate step (e.g. performing surgery for lung cancer) and is not considered to be intrinsically valuable while a "fundamental" objective (e.g. long-term survival after surgery for lung cancer) has intrinsic value. Means objectives might be useful for surrogate endpoints when the downstream events from that point are predictable and the fundamental objective is either distant in time or expensive to measure.

A: Alternatives

Consider all relevant alternatives. It is useful to broadly consider alternatives in three categories; inaction, intervention, and information (e.g. ordering more tests before making a decision).

C: Consequences/Chances

Model the consequences and estimate the chances, or probability, of these consequences. The consequences (positive and negative) of each alternative can be tabulated into a balance sheet. The likelihood of each of these consequences needs to be estimated and the search for these probabilities can be an important part of the entire decision analysis. The sum of all outcome probabilities for an individual action always adds up to 1.

T: Trade-Offs

Identify and estimate the value trade-offs. Valuation of consequences requires assessing the importance of each potential consequence. Here, patient reported outcomes are often a key. As an example, if one is interested in survival after treatment for cancer, quality of life estimates further refine the valuation. A more meaningful assessment of utility of an intervention is quality-adjusted survival. The Quality Adjusted Life Year (QALY) is a measure that integrates the length of life and the quality of life. The basic idea underlying the QALY assumes that a year of life lived in perfect health is worth 1 QALY (1 Year of Life × 1 Utility value = 1 QALY) and that a year of life lived in a state of less than perfect health is worth less than 1 QALY. A variety of techniques are available to assess the utility of each disease state and thus calculate QALYs.

I: Integrate

To integrate the evidence and values, one formally calculates the expected value of each option. In some analyses, this is referred to as "rolling up" the decision tree to come up with a preferred alternative and some numerical estimates that justify the preference. Sophisticated computer programs are available to perform this step.

V: Value

Optimize the expected value. The underlying principle of decision analysis is to maximize the expected utility. The probability of reaching each outcome (e.g. survival free of disease, survival with burden of disease, death) is multiplied by the calculated value of that outcome, and for each choice in the decision tree, the sums of these products are added to create the expected average value for that choice. The choice of the expected value to measure may stem from an aim to maximize desirable outcomes (QALYs) or to minimize cost or harm. Alternatively, a more complex end-point may be chosen like in a cost-effectiveness analysis.

E: Explore/Evaluate

Explore the assumptions and evaluate uncertainty. Decision analysis uses locally observed or researched values as estimates of both probabilities and value of outcomes. If there is uncertainty about these numbers, it may change the recommendation. Hence it is imperative to determine if the recommendation is "sensitive" to plausible changes in probabilities and utility values. Such an analysis is called a "sensitivity analysis" and may be conducted by varying one (1-way sensitivity analysis) or more than one (n-way sensitivity analysis) variable simultaneously across the range of clinically meaningful values and reassessing the model. In some cases, the outcome will change very little in response to large swings in a data point (insensitive) while in other cases, a particular data input will be very influential and thus more important to the analysis.

Creating a Decision Tree

Now let us examine how these principles can be applied in creating a decision tree. A decision tree (Fig. 3.1) reads from left to right and begins with a decision node (square) that frames the question being evaluated. At this point in the analysis, an intervention is selected, in this case a choice between two competing treatment options for lung cancer. From there, a series of probability nodes (circles) reflects the likelihood of downstream events for patients subjected to any of the interventions. In this overly simplistic model, the possible outcomes with either treatment arm are limited to success and failure. The probabilities of these outcomes (a number between 0 and 1) are indicated. The probabilities of outcomes for each intervention add up to 1. Finally, the terminal nodes (triangles) represent final states for the analysis and are labeled with the costs expended to reach that state (for cost effectiveness analyses) as well as the estimated utilities for patients reaching that terminal state. In this case, the costs are provided in dollars and beneficial outcomes are described in QALYs. Figure 3.2 shows a decision tree after rolling it back.

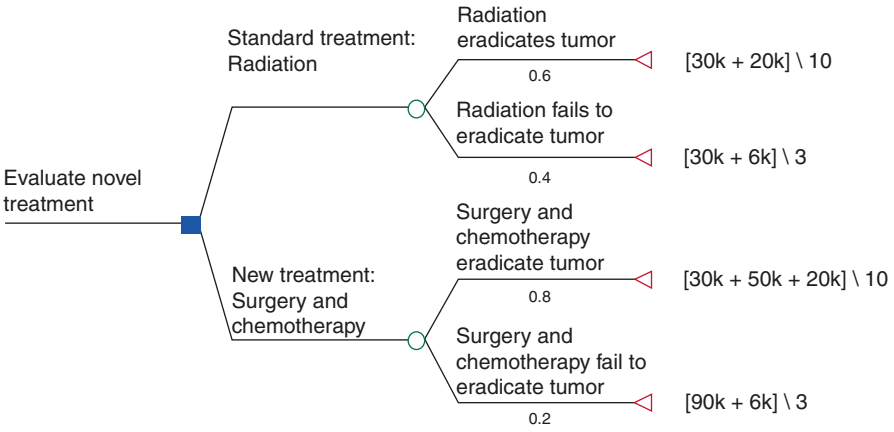

Fig. 3.1 A generic decision tree for cost-effectiveness analysis for treatment of cancer

Fig. 3.2 Rolled back decision tree depicting the overall costs and the utilities associated with either treatment option

"Rolling back" a decision tree refers to an analysis that starts at the terminal nodes of the tree and works backward to the initial decision node, determining the costs expended and the values achieved for each decision pathway. In this example, the proposed alternative treatment costs more, but provides a longer expected survival. The standard treatment, or base case, has been recommended in this model as the decision tree here aims to minimize cost. Different end points (e.g. maximizing survival or minimizing cost for life years gained) can be selected that may alter the recommendation. While this is a very simple example, more complexity can be introduced by acknowledging finer grades of difference in outcomes. For instance, cure without any complication would be the ideal outcome in any decision tree, but cure with minor or major complications might lead to similar life expectancy with increased cost (to manage the complications) and decreased quality of life (as a consequence of the complications). The real value of these decision trees increases as their complexity begins to approximate that seen in clinical outcomes.

Special Situations

Cost-Effectiveness Analysis (CEA)

CEA refers to a unique situation in decision analysis whereby the objective is to maximize population health benefits for any given level of resources. The same approach may be used given a preset health benefit goal, with the objective of minimizing the cost of attaining it. Such an analysis is often performed from a payer's perspective. In this perspective the costs of therapy are those experienced by the payer of treatment. Alternate approaches are to consider the societal perspective or a combined approach. In a combined perspective analysis, the costs of treatment are those experienced by the payer, minus the monetary gains to society from an individual who lives longer due to a more effective treatment. The costs of therapy may include direct medical costs, non healthcare costs (transportation, dietary changes, exercise programs etc.), caregiver time costs, loss of productivity, and costs of future healthcare interventions with longevity gained by treatment. Effectiveness of therapy is typically measured in QALYs. In a typical CEA, the incremental cost-effectiveness ratio (ICER) is estimated as the cost per life year (or quality-adjusted life year) gained over the patient's remaining lifetime by using a decision model and is a measure of cost-effectiveness. If one treatment modality is less costly and more effective than the other, it is labeled as dominant.

Markov Modeling

Thus far we have considered a linear model in the decision tree where a cohort moves forward in time. A state-transition model, also called a Markov model, is also commonly utilized in decision analyses. Markov models allow patients or groups of patients to transition from one state of health/disease to another as they move through the model. The specific strength of Markov models is this ability to reflect disease progression over time by using different health states or events. Therefore, these models are usually well understood by clinicians and can make direct use of traditional

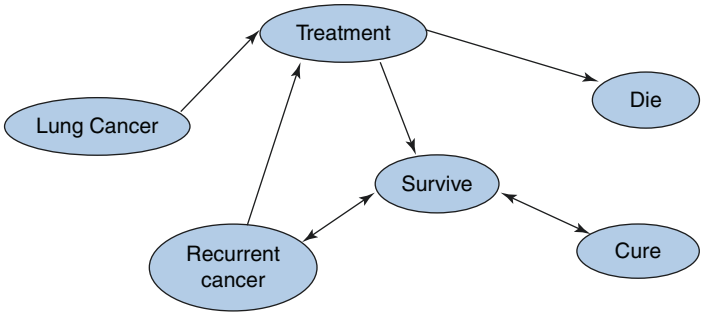

Fig. 3.3 A simple Markov model depicting the transition from one state of health to another

epidemiological survival data (e.g. annual rates, Kaplan-Maier curves, time-to-event distributions). A Markov model can be used to simulate both short-term processes (e.g. recovery after an operation), and long-term processes (e.g. an individual's life span).

Markov models can be analyzed in several ways. One of the most common is known as cohort simulation (Fig. 3.3). A cohort of patients begins the model in any of the disease states and the cohort is then tracked for the duration of the model. The proportion of the cohort in any of the states at any point in time, and the mean duration in each state can be calculated. Alternatively, the Monte Carlo simulation (microsimulation) approach operates at the level of the individual patient. Many hypothetical patients are passed individually through the model and their disease pathways recorded, replicating as closely as possible the process of interest. This allows investigators to simulate variability in outcome on both the individual and population level.

Other Clinical Applications of Decision Analysis

Healthcare Policy

Decision analysis techniques are implicitly and explicitly employed in the development of health policy. These applications range from recommendations from national and international working groups about management of specific disease processes, to cost-effectiveness analyses that inform whether or not certain treatment options are viable.

Clinical Protocols

Clinical protocols can be developed using the "PROACTIVE" approach and by eliminating the nonoptimal alternatives in a decision tree. This approach is relatively rigid and is most suitable when patient preference is less likely to alter the decision.

Patient Decision Aids

These are tools designed to inform patients about the alternatives where patient preference is critical in the decision making process. Decision analysis methodology is at the core of developing these instruments. These decision aids provide detailed information to patients but generally avoid making a specific recommendation and leave the final decision up to the patient-clinician team.

Benefits of Decision Analysis

Although decision analysis is not suitable for all clinical questions, it is clearly a useful technique for assisting complex and uncertain decisions, where the best option is not immediately apparent. Studying and performing DA clarifies the thinking of clinicians by forcing them to explicitly consider the known and the unknown elements of the decision process. Additionally, since decision analyses include the results of the most relevant research studies in the field, they promote evidence-based decisions. Also, it is likely that formal DA studies incorporate a more specific yet a comprehensive range of evidence than would be used in a more unstructured approach to decision making. Decision analysis provides a framework whereby clinicians can objectively communicate with colleagues and patients about the decision making process [1, 2]. By incorporating patient-centered outcomes like quality adjusted survival as measures of utility in decision processes, it encourages patients to be more involved in the decision process [1]. Decision analysis can be a catalyst for encouraging focused research in an area. This is particularly true when sensitivity testing leads to a change in the recommendation and thus generates both active discussion and testable hypotheses.

Drawbacks and Limitations of Decision Analysis

Since decision analysis is conducted with a specific end-point and a base case analysis which mirrors a clinical scenario, clinicians may have some difficulty applying the recommendations or thinking in the same framework when either the end-point or the clinical situation is altered. The methodology for decision analysis inherently requires making assumptions about the probabilities of events and values and these are supported by literature that may be of varying quality. Clinicians who are trained to interpret measurable individual data points and make decisions based upon them may be skeptical of recommendations generated by utilizing assumptions even though they may be based upon sound evidence.

Conclusion

Clinical decision making is complex and guided by a number of factors including medical evidence, personal experience, and intuition. “Decision analysis” provides a framework for examining the clinical scenario, synthesizing the available

evidence, and providing a recommendation for action. Decision analysis techniques are valuable tools in clinical medicine to develop health policy, clinical algorithms, and for cost-effectiveness analysis.

References

1. Elwyn G, Edwards A, Eccles M, Rovner D. Decision analysis in patient care. Lancet. 2001;358:571–4.
2. Richardson WS, Detsky AS. Users' guides to the medical literature. VII. How to use a clinical decision analysis. B. What are the results and will they help me in caring for my patients? Evidence Based Medicine Working Group. JAMA. 1995;273:1610–3.
3. Ferguson MK. Optimal management when unsuspected N2 nodal disease is identified during thoracotomy for lung cancer: cost-effectiveness analysis. J Thorac Cardiovasc Surg. 2003;126:1935–42.
4. Ferguson MK, Lehman AG. Sleeve lobectomy or pneumonectomy: optimal management strategy using decision analysis techniques. Ann Thorac Surg. 2003;76:1782–8.
5. Tsushima Y, Endo K. Analysis models to assess cost effectiveness of the four strategies for the work-up of solitary pulmonary nodules. Med Sci Monit. 2004;10:MT65–72.
6. Puri V, Crabtree TD, Kymes S, et al. A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: a decision analysis. J Thorac Cardiovasc Surg. 2012;143:428–36.
7. Puri V, Pyrdeck TL, Crabtree TD, et al. Treatment of malignant pleural effusion: a cost-effectiveness analysis. Ann Thorac Surg. 2012;94(2):374–80.
8. Shah A, Hahn SM, Stetson RL, et al. Cost-effectiveness of stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. Cancer. 2013;119:3123–32.
9. Meyers BF, Haddad F, Siegel BA, et al. Cost-effectiveness of routine mediastinoscopy in computed tomography- and positron emission tomography-screened patients with stage I lung cancer. J Thorac Cardiovasc Surg. 2006;131:822–9.
10. Samson P, Patel A, Robinson CG, Morgensztern D, Chang SH, Colditz GA, Waqar S, Crabtree TD, Krupnick AS, Kreisel D, Patterson GA, Meyers BF, Puri V. The role of surgical resection in stage IIIA non-small cell lung cancer: a decision and cost-effectiveness analysis. Ann Thorac Surg. 2015;100(6):2026–32.
11. Hu Y, Puri V, Shami VM, Stukenborg GJ, Kozower BD. Comparative effectiveness of esophagectomy versus endoscopic treatment for esophageal high-grade dysplasia. Ann Surg. 2016;263(4):719–26.
12. Semenkovich TR, Panni RZ, Hudson JL, Thomas T, Elmore LC, Chang SH, Meyers BF, Kozower BD, Puri V. Comparative effectiveness of upfront esophagectomy versus induction chemoradiation in clinical stage T2N0 esophageal cancer: a decision analysis. J Thorac Cardiovasc Surg. 2018;155(5):2221–30.e1.
13. Semenkovich TR, Meyers BF, Kozower BD, Puri V. The role of a decision analysis in treatment of T2N0 esophageal cancer. J Thorac Dis. 2018;10(Suppl 26):S3309–10.
14. Hunink MGM. Elements of decision making in health care. In: Decision making in health and medicine. 1st ed. Cambridge: Cambridge University Press; 2001. p. 1–33.

Decision Making: The Surgeon's Perspective

4

Thomas K. Varghese Jr

Introduction

The history of lung volume reduction surgery (LVRS) in the United States exemplifies the influence of nonclinical determinants of care. LVRS was first used to treat emphysema in the 1950s. However, the procedure didn't catch favor until the early 1990s when reported successes from small case series led to a dramatic increase in its use nationwide despite variability in results, incomplete follow-up, and lack of data on patient selection criteria [1]. Factors that contributed to this included favorable media reports, patient advocacy group testimonials that influenced patient and surgeon attitudes about LVRS, the relative inexpensive nature of the procedure and generous reimbursement [2]. A National Heart, Lung, and Blood Institute (NHLBI) workshop of medical experts in September 1995 as well as critical analysis commissioned by the Centers for Medicare and Medicaid Services (CMS) concluded that the data on risks and benefits of the procedure were too inconclusive to warrant unrestricted Medicare reimbursement. However, as the analysis showed some patients appeared to benefit from the procedure, a clinical trial demonstrating the effectiveness of surgery was recommended [3].

The announcement of the National Emphysema Treatment Trial (NETT) was met with resistance from some in the surgical community who felt that there was enough evidence to warrant reimbursement in all cases [4]. The suspension of Medicare reimbursement in December 1995 until NETT was completed led to a dramatic decrease in the number of LVRS procedures [5]. As many third-party payers base their coverage plans on CMS guidelines, the policy likely influenced Non-Medicare patients and providers. Whether surgeons stopped performing the

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procedure because of lack of reimbursement or as an acknowledgement of scientific uncertainty is unknown. But the sharp decline in LVRS temporally related to CMS intervention is clear. NETT determined that a subgroup of patients with localized apical emphysema and poor exercise tolerance after exercise training were the most likely to benefit from LVRS [6], and subsequent CMS policy partly limited surgical decision-making as reimbursement was limited to eligible patients and surgeons.

Delivery of medical advice is characterized by a process of weighing, prioritizing and structuring information given to a patient into a decision. In the ideal world, this is evidence-based. However, non-clinical factors can influence the surgical decision-making process. There is a growing expectation for patient participation in their care, and passage of the Affordable Care Act (ACA) encourages greater use of shared decision-making [7]. Government policy is an example of how non-clinical factors can influence the surgical decision-making process.

Models of the Surgeon-Patient Relationship

The surgeon-patient relationship can be described based on the degree of decisional authority assumed by patients as the surgeon as agent, shared decision-making, and informed decision-making models (Fig. 4.1). The surgeon as agent is one where the physician is the expert adviser who incorporates the values of the patient when making a treatment recommendation. The surgeon elicits or assumes these values from the patient, and has total command over the decision-making process. As patient participation is limited, they may be subjected to biased treatment if the surgeon only gives limited treatment options or in the delivery of the same. On the other end of the spectrum is informed decision-making. Although the surgeon is recognized as the one who has technical expertise, in this model patients are the ones who elicit

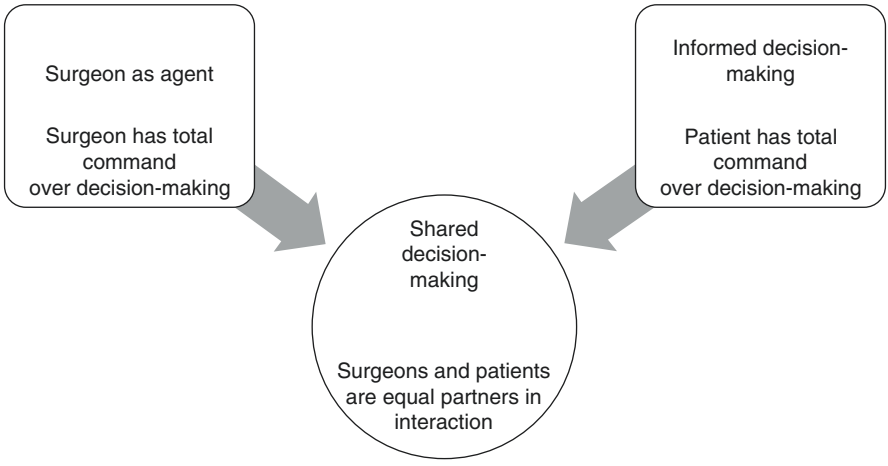

Fig. 4.1 Surgeon-patient relationship models

and understand information about their treatment choices. The surgeon in this instance doesn't give his/her opinion, but rather presents the patient with various options, allowing patients to arrive at their own conclusions.

In between these two models is shared decision-making. Surgeons and patients are equal partners in this interaction, where each freely exchanges information and preferences about treatment options so that a mutually acceptable decision can be made. For situations where there isn't only one clearly superior course of treatment, shared decision-making can help to better align medical care with patients' preferences and values.

In surgery, the decision-making process is often situational. Patient autonomy and participation can be influenced by medical condition, surgeon factors, patient educational level, and availability of evidence-based information on the particular condition. We'll continue to explore the factors that influence the decision-making process from the surgeon's perspective, while a subsequent chapter will focus on issues from the patient's perspective.

Methodology for Evaluating Decision-Making Factors

Studies of nonclinical factors influencing clinical decision-making use qualitative or semi-quantitative research methodologies (surveys, case vignettes, decision-analysis modeling) that have methodological limitations [8]. Qualitative research (focus groups and key informant interviews) helps develop hypotheses that can then be evaluated using semi-quantitative methods. Surveys are at times difficult to interpret because limited generalizability to those who respond to the questionnaire, the degree of understanding of the questions by the responders, and the extent of socially normative responses by physicians. Socially normative responses occur when members of a group provide "acceptable" answers to questions when the "real" answer would generate negative social judgment. Socially normative answers are more common where responding individuals are identified. Subsequent quantitative evaluations of these issues may become difficult to do if the number of variables of interest and potential for confounding become overwhelming. Methods less familiar to surgeons, such as the factorial experimental design, may overcome these obstacles. Factorial design allows comparison of different groupings of categorical variables. For example, five dichotomized variables have 32 (2^5) unique groupings that can be analyzed using hierarchical logistic regression. The complexity of the calculations rises with the number of variables and combinations of variables, and thus even this study design has limitations. It is thus imperative that surgeons involved in these type of studies work with behavioralists and biostatisticians who are well-versed in alternative research designs.

Surgeon Factors Related to Clinical Decision-Making

The clinical decision-making process is often influenced by non-clinical factors from the surgeons' perspective. These factors include the surgeons' tolerance of uncertainty, risk-taking attitude, demographic characteristics, and their level of training.

Table 4.1 Questions used to assess relative risk preferences of surgeons

1. In a choice between two therapies for an otherwise healthy person
(a) Treatment A: 100% chance of increase in survival by 5 years as compared to the average person, 0% chance of no increase in survival
(b) Treatment B: 50% chance of increase in survival by 10 years as compared to the average person, 50% chance of no increase in survival
2. In a choice between two therapies for a sick person
(a) Treatment A: 100% chance of decrease in survival by 5 years as compared to the average person, 0% chance of decrease in survival by 10 years as compared to the average person
(b) Treatment B: 50% chance of decrease in survival by 5 years as compared to the average person, 50% chance of decrease in survival by 10 years as compared to the average person

Impact of Risk-Taking Attitude on Clinical Decision-Making

Reactions to uncertainty and attitudes towards risk intuitively have implications on clinical decision-making. However, there is a limit in our understanding of the degree to which this issue influences surgical care [9]. Instruments have been developed in an attempt to assess risk-taking in general among physicians. Nightingale [10] developed a two-question test that has been frequently used to assess the degree to which physicians view themselves as risk seeking or risk averse (Table 4.1). These questions assess respondents' willingness to gamble for their patients in both the face of gain and in the face of loss. Those who refuse to gamble for their patients in the face of loss are considered risk averse. In three studies that Nightingale conducted [10–12], a significant correlation was found between resource utilization and risk preference in the face of loss. The more often physicians chose the risk averse gamble, the more likely they were to utilize additional resources to rule out uncertain outcomes. Most physicians in the setting of certain loss would rather minimize loss and fail in half of these attempts, than accept a certain loss. This fear of risk taking has been found to be less consistent in other studies [13], and varies based on mode of testing and across different cultures [14].

Impact of Surgeon Age

There is little data looking specifically at the impact of surgeon age and clinical decisions. Anecdotes have suggested many surgeons lack insight into the gradual degradation of their own skills. Age causes deterioration in physical and cognitive performance. Greenfield and Proctor identified cognitive factors that declined with age in surgeons including the ability to focus attention, the ability to process and correlate information and native intelligence [15]. Trunkey and Botney developed a series of tests, the "MicroCog", that were designed to detect impaired competence occurring late in a physician's career [16]. The tests measure reactivity, attention, numeric recall, verbal memory, visuospatial facility, reasoning and mental calculation. The authors found in all physicians (including non-surgeons) that although

they perform better than non-physicians, by age 75 they lose 25% of their starting score. In a meta-analysis looking at all types of physicians, Choudhry and colleagues found that half of the 59 articles included for study reported declining measures of quality of care with increasing physician years in practice [17]. Other studies have shown that older physicians were less likely to adopt newly proven therapies, and may be less receptive to new standards of care [18–20]. In a study of 93 surgeons and anesthesiologists in Japan by Nakata and colleagues, the relationship between risk attitudes and demographic characteristics were explored in case vignettes assessing whether respondents were risk averse, risk neutral and risk seeking [21]. The only positive finding was with regards to age—the older the physician, the more risk averse they were. The study concluded that older physicians might shy away from risk, while younger physicians may be more willing to gamble.

However, it is unknown what influence emergence of the evidence-based care movement and maintenance of certification programs will have on any interaction of surgeon age and decision-making.

Impact of Surgeon Gender

There has been a dramatic change in the number of women entering the physician workforce over the past three decades [22]. Women make up close to half of all US residents and fellows—increasing from 21.5% in 1980 to 45.4% in 2010. Change however is coming more slowly in many of the surgical specialties, where women are still a distinctly small minority. As fewer than 5% of cardiothoracic surgeons are women [23], the impact of surgeon gender and decision-making have not been assessed. There have been small studies comparing communication styles between male and female physicians [24]. Female doctors were found to actively facilitate patient participation on medical decisions by enacting methods such as partnership building, positive talk, question asking, and information giving [24–26]. Female doctors were less dominant verbally during clinic visits as compared to males and engaged in active discussions with patients.

Impact of Specialty Training

Surgeon specialty has been shown to be associated with better post-operative outcomes among high-risk operations [27]. Goodney and colleagues [28] demonstrated that board-certified thoracic surgeons have lower rates of operative mortality with lung resections compared to general surgeons, although they noted that other factors such as hospital volume also influenced a patient's operative risk of mortality. In a lung cancer resection study conducted by our group in the SEER-Medicare population [29], we found that board-certified general thoracic surgeons had greater long-term survival rates than those treated by general surgeons. General thoracic surgeons performed preoperative and intraoperative staging more often than general surgeons or cardiothoracic surgeons (those who performed both cardiac and thoracic

procedures as part of their practice). In esophageal cancer surgery, Dimick and colleagues [30] found that specialty board certification in thoracic surgery was independently associated with lower operative mortality rates. Common themes in these studies were influence of provider volume on the overall effect, as well as more consistent process-of-care measures by specialty surgeons. As there is a trend towards increasing specialization amongst surgeons, other factors that may have influenced decision-making include training in the modern era, with inclusion of evidence-based protocols, and multi-disciplinary participation in tumor boards amongst specialists. It is unknown if subspecialty-trained surgeons are more risk seeking in their treatment options in light of additional training experience.

Healthcare System Factors Related to Clinical Decision Making

Impact of Practice Environment

The Patient Protection and Affordable Care Act (ACA) signed into law in March 2010 seeks to improve health care delivery in several ways, from access to quality to cost. ACA's goal was to create a movement of payment reforms, in which private insurance companies would follow the lead of successful government payment reforms, such as bundled payments, and ultimately create system-wide changes for reimbursement [31]. Changing the reimbursement structure for providers will inevitably create new issues for surgeons who are making decisions for their patients. Most of the payment reforms began in 2011 and 2012, and will continue through 2016. Two programs designed to restructure the way health care is delivered have been proposed under ACA, namely Patient-Centered Medical Homes (PCMHs) and Accountable Care Organizations (ACOs). These programs are designed to improve care coordination by encouraging use of electronic medical records, changing providers' financial incentives by including quality measures in reimbursement, and ultimately moving away from a fee-for-service to one where quality of care is valued [32].

The ACO movement has led to increased consolidation and integration in the medical marketplace. Hospitals are buying practices, which means that physicians are ceding autonomy to belong to the organizations to keep their market share intact and to have access to electronic record systems and other infrastructure that are expensive to capitalize. Awareness emerges for surgeons that their medical decisions can potentially negatively influence their income. This is not necessarily unethical, as cost containment has been recognized as an important circumstance in good decision-making [33]. There will be penalties, which could affect physician reimbursement. Adoption of rigid guidelines for the treatment of patients may limit individual surgeon decision-making, as well as expansion of treatment pathways and care plans. All of these are attempts at decreasing variation in care, decreasing length of stay, and reducing use of resources.

Surgeons in the Veterans Administration hospital system have participated for more than a decade in a systematic data-gathering and feedback system of outcomes

for major surgery [34]. The National Surgical Quality Improvement Project (NSQIP) works to decrease variation in clinical outcomes by demonstrating to surgeons when their center is an "outlier" in performance. This system allows hospitals to target QI activities that may influence components of care, and subsequently decision-making.

Impact of Political Environment

Professional organizations can play a role in decision-making by effectively regulating surgeon-directed clinical practice. One example is the guidelines for laparoscopic resection of curable colon and rectal cancer [35] written by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and endorsed by the American Society of Colon and Rectal Surgeons (ASCRS). These guidelines give recommendations on tumor localization, diagnostic evaluation for metastases, preparation for operation, surgical technique, as well as minimum number of cases to gain proficiency. The society also noted that while robotic surgery appears feasible, that in the absence of long-term oncologic outcome studies, no clear recommendations were made. Guidelines such as these influence members, and are in stark contrast to the situation of non evidence-based decision-making that existed for LVRS prior to NETT.

The reporting of surgeon-specific outcome data is another example of the influence of the political environment. Outcome data were rarely reported prior to the mid-1980s [36]. The first release of hospital open heart surgery risk-adjusted mortality rates in December 1990 [37] and the first formal public report in December 1992 [38] marked the start of a new era. These performance reports, or physician report cards, have increased in frequency in recent years [39]. Advocates of this form of reporting believe they provide information about quality of care that consumers, employers, and health plans can use to improve their decision-making and to stimulate quality improvement among providers [40]. They may also appropriately promote regionalization of medical centers and consolidation of resources. However, physicians are concerned that risk adjustment strategies in these reports are not adequate. Without this confidence, publication of procedural mortality rates may result in physicians withholding procedures in high-risk patients. In a study by Narins and colleagues [39], the attitudes and experiences of cardiologists were surveyed about the influence of the New York Percutaneous Coronary Intervention (PCI) report card on their decision-making process. 89% agreed or strongly agreed that patients who might benefit from PCI may not receive the procedure as a result of public reporting of physician-specific mortality rates. Seventy percent agreed or strongly agreed that the presence of a scorecard influences whether they treat a critically ill patient with an expected high mortality rate. The authors concluded that unintended consequence of scorecards might be to adversely affect healthcare decisions for especially high-risk patients. Scorecards may also impair the development of new treatments because of the more restrictive clinical practice environment [40].

In light of these drawbacks, many have proposed revamping the current system to facilitate rapid and accurate access to outcome data in the local practice environment. Adoption of these efforts is often embraced as this occurs on a voluntary basis rather than in response to punitive restrictions. Examples of such grass-roots initiatives on a state level that are surgeon-led include those in the states of Michigan [41] and Washington [42, 43]. On a national level, the Society of Thoracic Surgeons (STS) is a leader in the development of a society-based, publicly reported, volunteer registry database that has made a tremendous impact on risk-stratification and outcomes in cardiothoracic surgery [44, 45]. Surgeons who participate in such database initiatives can utilize risk-stratified models to better inform their decision-making process.

The Choosing Wisely® initiative helps physicians and patients have important conversations necessary to ensure that timely and optimal care is delivered. Launched by the American Board of Internal Medicine (ABIM) Foundation, Choosing Wisely® enables physicians and patients to engage in conversation about the overuse of tests and procedures, and helps patients make smart and effective care choices [46]. The original campaign has evolved into a multi-year initiative where the ABIM Foundation has reached out to specialty societies to identify a list of five tests or procedures that may be overused or misused. Criteria for developing these lists include limiting to items that fall within the specialty; supported by evidence; documented and publicly available upon request; frequently ordered/costly; easy for a lay person to understand; and measurable/accountable. The STS participated in the February 2013 phase II release [47] (Table 4.2). These specialty generated lists help to empower physician-patient conversations and to avoid unnecessary procedures that may harm patients while driving up health care costs. Sixty-three specialty societies have joined the campaign, with additional lists targeted for early 2014.

Impact of the Medico-Legal Environment

Fear of lawsuits has had a dramatic effect on many specialties. Surgeons may be influenced by medico-legal risks in terms of their decision-making with certain

Table 4.2 Society of Thoracic Surgeons Choosing Wisely® List

1.	Patients who have no cardiac history and good functional status do not require preoperative stress testing before non-cardiac thoracic surgery
2.	Do not initiate routine evaluation of carotid artery disease before cardiac surgery in the absence of symptoms or other high-risk criteria
3.	Do not perform routine predischarge echocardiogram after cardiac valve replacement surgery
4.	Patients with suspected or biopsy proven stage I non-small cell lung cancer do not require brain imaging before definitive care in the absence of neurologic symptoms
5.	Before cardiac surgery there is no need for pulmonary function testing in the absence of respiratory symptoms

operations in high-risk populations. The exact extent of this influence is unclear in the field of thoracic surgery. However, as a specialty that deals with a significant proportion of high-risk patients, it is certain that the cardiothoracic surgeon will face such a challenge in their career [48].

Summary

Although the ideal is to practice evidence-based medicine at all times, there are many non-clinical factors that influence the care that we provide. For every procedure there is sadly variability in operative and periprocedural care, with associated variations in outcomes between centers. Lapses in quality are a main driver in this variation. Further investigation into non-clinical factors may not only help to explain variation, but also serve as targets for change to improve outcomes. Areas of non-clinical influences include surgeon factors (such as risk-taking attitudes, age, gender, specialty training), and healthcare system factors (practice, political and medico-legal environment). Better assessment and control of these factors can lead to rational, consistent and appropriate care for our patients.

References

1. Cooper JD, Trulock EP, Triantafillou AN, et al. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg. 1995;109:106–19.
2. Ramsey SD, Sullivan SD. Evidence, economics and emphysema: Medicare's long journey with lung volume reduction surgery. Health Aff (Millwood). 2005;24:55–66.
3. Rationale and design of the National Emphysema Treatment Trial (NETT): a prospective randomized trial of lung volume reduction surgery. J Thorac Cardiovasc Surg 1999;118:518–28.
4. Cooper JD. Paying the piper: the NETT strikes a sour note. National Emphysema Treatment Trial. Ann Thorac Surg. 2001;72:330–3.
5. Huizenga HF, Ramsey SD, Albert RK. Estimated growth of lung volume reduction surgery among Medicare enrollees: 1994 to 1996. Chest. 1998;114:1583–7.
6. National Emphysema Treatment Trial Research Group. A randomized trial comparing lung volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med. 2003;348:2059–73.
7. Lee EO, Emanuel EJ. Shared decision making to improve care and reduce costs. N Engl J Med. 2013;368(1):6–8.
8. Clark JA, Potter DA, McKinlay JB. Bringing social structure back into clinical decision making. Soc Sci Med. 1991;32:853–66.
9. Tubbs EP, Broekel Elrod JA, Flum DR. Risk taking and tolerance for uncertainty: implications for surgeons. J Surg Res. 2006;131:1–6.
10. Nightingale SD. Risk preference and laboratory use. Med Decis Making. 1987;7:168–72.
11. Nightingale SD. Risk preference and admitting rates of emergency room physicians. Med Care. 1988;26:84–7.
12. Nightingale SD. Risk preference and decision making in critical care situations. Chest. 1988;93:684–7.
13. Holtgrave DR, Lawler F, Spann SJ. Physicians' risk attitudes, laboratory usage, and referral decisions: the case of an academic family practice center. Med Decis Making. 1991;11:125–30.

14. Zaat JOM. General practitioners' uncertainty, risk preference and use of laboratory tests. Med Care. 1992;30:846–54.
15. Greenfield LJ, Proctor MC. When should a surgeon retire? Adv Surg. 1999;32:385–93.
16. Trunkey DD, Botney R. Assessing competency: a tale of two professions. J Am Coll Surg. 2001;192:385–95.
17. Choudhry NK, Fletcher RH, Soumerai SB. Systematic review: the relationship between clinical experience and quality of health care. Ann Intern Med. 2005;142:260–73.
18. Freiman MP. The rate of adoption of new procedures among physicians. The impact of specialty and practice characteristics. Med Care. 1985;23:939–45.
19. Hlatky MA, Cotugno H, O'Connor C, Mark DB, Pryor DB, Califf RM. Adoption of thrombolytic therapy in the management of acute myocardial infarction. Am J Cardiol. 1988;61:510–4.
20. Young MJ, Fried LS, Eisenberg J, Hershey J, Williams S. Do cardiologists have higher thresholds for recommending coronary arteriography than family physicians? Health Serv Res. 1987;22:623–35.
21. Nakata Y, Okuno-Fujiwara M, Goto T, Morita S. Risk attitudes of anesthesiologists and surgeons in clinical decision making with expected years of life. J Clin Anesth. 2000;12:146–50.
22. Fraher EP, Knapton A, Sheldon GF, Meyer A, Ricketts TC. Projecting surgeon supply using a dynamic model. Ann Surg. 2013;257(5):867–72.
23. Antonoff MB, David EA, Donington JS, Colson YL, Litle VR, Lawton JS, Burgess NL. Women in thoracic surgery: 30 years of history. Ann Thorac Surg. 2016;101(1):399–409.
24. Roter DL, Hall JA. Why physician gender matters in shaping the physician-patient relationship. J Womens Health. 1998;7:1093–7.
25. Roter D, Lipkin M Jr, Korsgarrd A. Sex differences in patients' and physicians' communications during primary care medical visits. Med Care. 1991;29:1083–93.
26. Van den Bronk-Muinen A, Bensing JM, Kerssens JJ. Gender and communication style in general practice. Differences between women's health care and regular health care. Med Care. 1998;36:100–6.
27. Cowan JA Jr, Dimick JB, Thompson BG, et al. Surgeon volume as an indicator of outcomes after carotid endarterectomy: an effect independent of specialty practice and hospital volume. J Am Coll Surg. 2022;195:814–21.
28. Goodney PP, Lucas FL, Stukel TAA, Birkmeyer JD. Surgeon specialty and operative mortality with lung resection. Ann Surg. 2005;241:179–84.
29. Farjah F, Flum DR, Varghese TK Jr, et al. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. Ann Thorac Surg. 2009;87:995–1006.
30. Dimick JB, Goodney PP, Orringer MB, Birkmeyer JD. Specialty training and mortality after esophageal cancer resection. Ann Thorac Surg. 2005;80:282–6.
31. Lee PV, Berenson RA, Tooker J. Payment reform – the need to harmonize approaches in Medicare and the private sector. N Engl J Med. 2010;362:3–5.
32. Ein D, Jefferson A. The Patient Protection and Affordable Care Act: causes and effects. Ann Allergy Asthma Immunol. 2014;112:6–8.
33. Devettere RJ. Making health care decisions. In: Devettere RJ, editor. Practical decision making in health care ethics. Washington, DC: Georgetown University Press; 2000. p. 94.
34. Itani KM. Fifteen years of the National Surgical Quality Improvement Program in review. Am J Surg. 2009;198(5 Suppl):S9–S18.
35. SAGES. Guidelines for laparoscopic resection of curable colon and rectal cancer. 2012. http://www.sages.org/publications/guidelines/guidelines-for-laparoscopic-resection-of-curable-colon-and-rectal-cancer/. Accessed 8 March 2020.
36. Topol EJ, Califf RM. Scorecard cardiovascular medicine. Its impact and future directions. Ann Intern Med. 1994;120:65–70.
37. Hannan EL, Kilburn H Jr, O'Donnell JF, et al. Adult open heart surgery in New York State. An analysis of risk factors and hospital mortality rate. JAMA. 1990;264:2768–74.
38. Epstein A. Performance reports on quality – prototypes, problems and prospects. N Engl J Med. 1995;333:57–61.

39. Narins CR, Dozier AM, Ling FS, Zareba W. The influence of public reporting of outcome data on medical decision making by physicians. Arch Intern Med. 2005;165:83–7.
40. Schneider EC, Epstein AM. Use of public performance reports: a survey of patients undergoing cardiac surgery. JAMA. 1998;279:1638–42.
41. Prager RL, Armenti FR, Bassett JS, et al. Cardiac surgeons and the quality movement: the Michigan experience. Semin Thorac Cardiovasc Surg. 2009;21:20–7.
42. Flum DR, Fisher N, Thompson J, et al. Washington State's approach to variability in surgical processes/outcomes: Surgical Clinical Outcomes Assessment Program (SCOAP). Surgery. 2005;138:821–8.
43. Aldea GS, Mokadam NA, Melford R, et al. Changing volumes, risk profiles, and outcomes of coronary artery bypass grafting and percutaneous coronary interventions. Ann Thorac Surg. 2009;87:1828–38.
44. Clark RE, The STS. Cardiac Surgery National Database: an update. Ann Thorac Surg. 1995;59:1376–81.
45. Wright CD, Gaissert HA, Grab JD, et al. Predictors of prolonged length of stay after lobectomy for lung cancer: a Society of Thoracic Surgeons General Thoracic Database risk-adjustment model. Ann Thorac Surg. 2008;85:1857–65.
46. Cassel CK, Guest JA. Choosing wisely: helping physicians and patients make smart decisions about their care. JAMA. 2012;307:1801–2.
47. Wood DE, Mitchell JD, Schmitz DS, et al. Choosing wisely: cardiothoracic surgeons partnering with patients to make good health care decisions. Ann Thorac Surg. 2013;95(3):1130–5.
48. Mayer JR Jr. Ethical, legal and health policy challenges in contemporary cardiothoracic surgery: introduction. Semin Thorac Cardiovasc Surg. 2009;21:1–2.

Involving Patients in Difficult Decisions About Having Surgery

5

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Introduction

Traditional healthcare was characterized by physician paternalism in guiding patients towards what treatment the physician determined was best to address the patient's condition [1]. Healthcare and decision making about treatments is evolving towards a practice referred to as Shared Decision Making (SDM), especially for problems for which there is no single standard of care. SDM requires the participation of both the physician and the informed patient. This paradigm shift is expanding rapidly owing to the availability of patient-oriented information on the internet and through social media.

The change extends beyond the primary care setting, where patients and physicians often have a well-established relationship, to include surgical clinics, where the surgeon is charged with relatively limited, short-term care of the patient [2]. With more patients seeking an active role in SDM for difficult decisions, failing to ensure patients are sufficiently informed when taking part in SDM is likely to have negative, dramatic, and irreversible consequences in surgical care.

In decisions where relevant evidence is limited and patient values and goals can be diverse, informed patient preferences should be incorporated into making the choice. Consequently, this requires the sharing of information with the patient so that they are equipped with a good understanding of their situations and options. If the growing demand for SDM is to be met and executed appropriately, surgeons must be prepared to inform patients and foster healthy SDM.

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What Is Shared Decision Making?

SDM is a clinical approach in which informed patients actively share in making choices about their own care with their physicians. SDM is specifically required when, due to limitations of medical evidence, none of the options is considered a true standard of care. For some health problems requiring SDM, there are trade-offs between options. Options are linked to various probabilistic outcomes that make the right decision reliant on patients' preferences [3]. The SDM process is a compound and ordered one that typically takes place in a face-to-face consultation between the patient and physician. The goal is to first deliver the important information and ensure its comprehension, then deliberate over the options to settle on the preferred course of action.

Driving this transition from traditional paternalism towards SDM is the evolution of the physician-patient relationship towards a more collaborative model. It likely reflects changes in population demography as more paternalistic pre-baby boomers pass away and are replaced by later generation autonomous healthcare consumers, but it also receives pro-active international advocacy from many medical care providers, researchers, and ethicists as a moral imperative.

Call for Shared Decision Making

The practice of SDM has gained proponents, critics and researchers from all around the world over the decades. An international panel of medical experts convening in Salzburg in 2010 came to a consensus and released the Salzburg Statement on Shared Decision Making declaring that the implementation of effective SDM would make the single most profound improvement to healthcare quality [4]. The statement included instructions for health policy makers as well as physicians and patients. It asserted that physicians have an ethical imperative to practice SDM with patients, engage in two way communication, field and answer patients' questions, and solicit patients' values and personal preferences. Physicians should also provide accurate and individually tailored information about options and the uncertainties, benefits, and harms of treatment options. They must allow patients sufficient time to consider their options and recognize that most decisions need not be made immediately. The Salzburg Statement implored patients to recognize their right to participate, to voice their concerns, questions, and values, and seek out and utilize the highest quality information available [4].

Survey data indicate that patients express a desire for SDM, but that significant variance still exists in patient preferences for decisional control, as some patients still desire the physician to take a guiding role [5]. A qualitative interview study indicated that older frail patients expressed a desire for information but not necessarily to have input into the treatment choice [6]. Cancer patients often desire to have important information even when they indicated that they don't prefer a very active role in settling on the treatment choice. Although there will continue to be an

overall increasing desire for information and continuing evolution towards more patients wanting to be active participants in SDM, multiple decision making styles will persist.

Meeting the Requirement of Informed Patients in SDM

SDM is said to be performed effectively when patients accurately comprehend all of the necessary information regarding their options, identify their values and preferences, and determine which treatment choice gives them the best odds of realizing their goal [7]. Having a more equal informational footing, the patient and physician can often come to an agreement about what treatment best fits an individual patient's health state preferences and tolerance for risks, but if an agreement is not struck, the patient's preferences should ultimately prevail [4].

In much of the SDM literature, the "important information" is only vaguely if ever defined, but it is to some degree specific to the diagnosis and available treatment options. When considering surgery, it is important that the patient know the essential information at the critical time because this treatment cannot be discontinued and is irreversible. This is a serious concern with older patients who are observed to take different strategies in decision making and bias their attention in ways that younger patients do not [8].

Unfortunately, nationally representative survey data suggest that patients do not know the relevant information about a disease, prognosis and available options at multiple important points in care [9]. As a result, an entire decision support aid movement has started with the mission of developing and verifying the quality of tools intended to improve patient knowledge, including tools relevant to surgery [10, 11]. Many of these tools are intended to avoid ineffective SDM participation by uninformed or confused patients that could lead to treatment choices that do not match the patient's preferences and goals.

Several barriers to patient participation in SDM, which all could jeopardize patient education, have been identified and include dealing with multiple professionals unfamiliar with their preferences, diverse treatment strategies among physicians, fast patient turnover in hospitals, stressed medical personnel, and communication barriers [6]. All of these factors are risks that hinder the communication between patients and surgeons and contribute to leaving patients in a state of poor comprehension.

Impact of SDM on Clinical Outcomes

Currently, the downstream consequences for succeeding or failing to practice good SDM are not well-documented or understood. The rationale is that if a patient is to express their values, goals, and preferences and work with the physician to choose the treatment option that best fits, they must have an accurate model of the problem

in their mind. There is some evidence that the quality of SDM is predictive of patient-centered, clinical and care-cost outcomes. Decision conflict is a construct that largely reflects how satisfied a patient is about their treatment decision shortly after making it and usually prior to fully realizing the outcome. There is debate about the tenability and value of lowering patients' decision conflict [12], but helping patients feel secure and confident in their treatment choice will benefit overall satisfaction with care.

Although, the ethics of SDM should make it immune to cost considerations, the potential to lower or raise costs is of growing interest. Good SDM could improve satisfaction and functional outcomes, but poorly executed SDM could disproportionately increase costs and worsen clinical outcomes, satisfaction with care, and quality of life. Patients are unlikely to be as influenced by financial incentives as much as physicians often are, but it is not a certainty how SDM will influence the cost of care until more appropriate and longitudinal data are available. Some theories have been proposed as to how SDM might lower costs, and one in particular, costs of litigation, is highly relevant to surgery. Some data indicate that it is health care professionals' style and not the content of their communication that predicts litigation. There is evidence that failures of SDM such as devaluing patient or family views, delivering information poorly, and failing to understand the patient's perspective of the problem were predictive of litigation [13–15]. Improving patient comprehension and participation in SDM could lower the high rate of litigation in surgery, and therefore potentially decrease health care costs.

The Need for SDM in Surgical Care

The global population is growing older because there are more people who are living to an older age. The U.S. population over age 65 is estimated to increase from 40 million in 2010 to 88 million in 2050 [16]. Surgeons deliberate over details, including patient age and frailty. They take into account the characteristics of the patient, their diagnosis, and the risks associated with surgery, and then formulate a recommendation about whether or not having surgery is the best course of action. Although there are professional and financial biases pushing surgeons to recommend surgery, they recognize when a patient is not an ideal surgical candidate and that it might be advisable to consider other options.

When presenting to a surgery clinic for a condition that can be treated surgically, patients are regularly evaluated on their surgical candidacy. Although surgery is quite common for some conditions, the decision about having surgery is not obvious when the patient is at higher risk for complications or less likely to benefit from resection. Without additional concerns, surgery is often preferred because it is definitive and is associated with improved quality of life and decreased mental anguish. However, the immediate and long-term risks associated with surgery provide reason for pause, and more thorough pre-surgical assessment reveals that not all patients prove to be good surgical candidates.

Surgical evaluation often involves assessment of physiologic performance thresholds that predict good immediate surgical outcomes, but lower scores are not prohibitive, and the clinical complexity and diversity of patients has made it intractable to identify criterion values below which the surgical risk level should be considered excessive for all patients. In addition, some operations result in important long-term functional impairment that is permanent, and communicating how such impairments affect quality of life is often challenging.

There are often alternatives to surgery, including medical therapy or radiation therapy, depending on the condition. Some patients may simply be observed if their condition doesn't require immediate intervention, and when intervention ultimately is warranted the treatment options may be more clear to both the patient and the surgeon.

Many of the data upon which treatment decisions are based are from studies that did not include random assignment and that under-represented specific populations such as older patients and women. Consequently, there are insufficient data to provide guidelines for a diverse patient population that presents a complex array of variables and co-morbid conditions.

Problems with SDM and Surgery

The claim that patients are to be informed participants in SDM brings new challenges for both patients and their physicians because appropriate training and infrastructure for good SDM has largely not been put into place. As well, patients are usually not prepared to get the most out of their face-to-face time with the surgeon. Many patients are already predisposed for or against surgery prior to their initial consultation with a surgeon. This may be a result of their conversations with non-surgical specialists, family influences, personal biases, or misinformation. Many patients with a diagnosis of cancer are predisposed to surgery even if evidence demonstrates that surgery is not their best treatment option [17].

Older patients are likely to have greater difficulty participating in SDM for multiple reasons. Older people represent a more diverse population than their younger counterparts because of the prevalence of a wide variety of medical conditions and physical functioning. Some older patients have a combination of medical conditions to be managed and an array of medications carrying various risks and side-effects. As the large influx of older patients floods into surgical clinics, these surgeons will be faced with tremendous challenges of delivering appropriate treatment to a diverse patient population, for which there are few data to guide treatment choices.

Patient Clinical Complexity

Many factors can increase surgical risk and render the decision about whether or not to have surgery more difficult. When the patient is not otherwise healthy, but instead has significant co-morbid health conditions or significantly diminished cardiopulmonary function, they are less likely to benefit and are at higher risk for adverse

outcomes. Outcomes can be expected to be worse in patients with more co-morbid burden [18], and scoring systems have been developed that demonstrate the relationship of cumulative deficits to adverse outcomes [19]. Advanced age itself has become a difficult issue in surgical decisions as people are living longer and the population of advanced age adults is one of diverse health. Some patients of advanced age are robust and highly functional, while others have difficulty with day to day endeavors and are vulnerable to further degradations of function and looming mortality.

There is a potentially important impact on surgical outcomes of the widely-recognized but poorly understood geriatric syndrome of physiological frailty [20–22]. Surgical clinics are becoming increasingly adept at assessing patient frailty through assessment of physical and cognitive factors. Surgeons also put the patient to the "eyeball test" regarding their fitness for surgery, assessing the patient's surgical candidacy more intuitively and beyond what is captured in traditional pre-surgical evaluations, but much remains to be learned about the impact of frailty on surgical outcomes and how to predict it [23].

There is no clear criterion cutoff for any pre-surgical or physical evaluation that expressly prohibits sending a patient to surgery and the available published data are not of sufficient quality to set sound practice guidelines for a clinically diverse patient population. The process of assessing risk and probable outcomes for imperfect surgical candidates is rather fuzzy and speculative and, even with information on frailty, there remains a high amount of uncertainty regarding an individual patient's fate. Consequently, without strict guidelines, SDM is called for so that patients know that their options lead to uncertain outcomes, but that there is information about their own surgical fitness worth knowing when deciding on treatment.

Difficulties in Patient Comprehension

Patients are never standing on the same ground as surgeons regarding foundational knowledge about disease and surgery. A substantial barrier to implementing effective SDM is helping patients understand the important facts about their disease and treatment options so that they are accurately informed at the time that they are participating in the decision making process. The devil is in the details because patients must know how their own clinical characteristics might impact the perioperative risks and probabilities of different outcomes. A verbatim detailed comprehension of risk statistics appears to be neither necessary nor sufficient to guide decisions of physicians or patients if they do not derive the proper meaning [24, 25]. Educational barriers are important obstacles to patient comprehension [26]. What is important is that patients understand what can be expected to happen if the disease goes untreated, what options are available to them to combat the disease, the goals of each treatment, the advantages and disadvantages of those options, and the uncertainty inherent in all. This is not always feasible for surgeons to convey or patients to comprehend [27].

Non-demented older patients process information differently and sometimes implement strategies that are unlike those used by their younger counterparts. As cognitive abilities change over the life span, there is sometimes a shift towards

emotion-based information that can impact risk perception and decision making [8, 28]. Older adults often use religious coping for health related stressors, and that coping can come in positive or negative forms, such that they can either alleviate or bring on psychological morbidity [29]. However, it is not clear what impact religious thinking has on the treatment decisions of patients considering risky, but potentially curable, surgical treatment options with varying risk and promise.

Cancer patients deciding about surgery sometimes hold beliefs that contradict evidence-based medicine and can potentially misguide their decisions. In surgical oncology, some patients believe that cancer will spread during the surgery if the cancer, "hits the air" [30]. This belief is found to be retrospectively predictive of the decision to forego surgery [31] and it was found to be widespread among a national sample of healthy survey respondents [32]. It is clear that patients' abilities to process information and the mental representations that they ultimately construct can make a big difference in which choice they make about treatment.

Surgical Practice

The traditional practice of surgery might also provide barriers to effectively satisfying the requirement of an informed patient in SDM. Ultimately, the goal of all surgeons is to do the best that they can for their patients. However, this requires separating out the often influential institutional and financially-driven goals to more clearly determine what is preferred by the patient. It is likely that the professional culture of surgery has worked against the adoption of SDM as common practice. Surgeons focus on creating a feeling of confidence and optimism in their patients, which is somewhat at odds with delivering the "cold hard facts" and sometimes troubling risk information [2].

Surgeons strive to maintain an optimistic stance regarding the treatment that they provide and they often refer to an operation that removes all of the known cancer cells as a "cure" [1, 33]. This is thought to be integral part to the surgeon-patient relationship because putting patients into a positive state of mind is important to maximize hopes of a good outcome. The surgeon addresses the pre-surgical goal of comforting and convincing the patient that she or he is in good hands in the operating room and works to cultivate an optimistic attitude about surgery. The operation is typically performed only in cases in which the surgeon believes that it is justifiable, given the patients level of surgical risk, and the patient agrees to do what the surgeon believes is best. However, eliciting optimism in patients is difficult to balance with delivering important information about risk, uncertainty, or trade-offs that might be viewed as unfavorable by the patient in order to allow them to be fully informed participants.

Additionally, surgeons have other incentives to make specific choices [33]. There is little gain accrued when a patient is referred to radiation oncology, but surgeons receive financial incentives for patients going to the operating room [1]. Many factors cast doubt that popular current practices in surgical clinics effectively help patients to be informed and to share in difficult decisions about whether or not to undergo. Many of these motivations make assisting the patient in SDM a secondary concern, and even at odds with some of the surgeon's goals.

The Way Forward

It will become increasingly important for surgical clinic staff to be able to effectively educate patients on the important information and engage in SDM with patients, as it becomes the prevailing practice of healthcare. With a growing number of older, more clinically complex patients presenting to surgery clinics, some changes to surgical care practices will be necessary. These changes include a premium put on identification of patients' informational needs and desire for participation, well-designed external patient education resources, and decision support that is integrated into the individual patient's surgical consultation.

Surgeons should ascertain what level of involvement each of their patients want in the decision making process. Even when an older, sicker or frailer patient desires a passive role in SDM, the surgeon should take account of the patient's preferences and risk tolerances for different outcomes. For patients wishing to provide input into the choice, participation in SDM involves first education, confirming that they comprehend the essential information about their cancer diagnosis and treatment options, and inviting them to express their desires. Participation by an uninformed patient can be counterproductive and lead to choices that are a poor fit for patients' goals or leave them poorly prepared and in the dark about what lies ahead.

As difficult as it is to share such information, a patient should know the prognosis of their disease and the approximate time-frame in which it can be expected to advance and take their life. They should be told that there are options other than surgery, and that these might be worth exploring before making a choice, especially when they are not ideal surgical candidates. They should also know what treatment side-effects and health states are possible results from different treatments. A patient who wishes to eradicate their cancer in hopes of living as long as possible must be knowingly willing to accept a comparatively higher risk of treatment-related mortality and lasting morbidity. Such patients might choose to have surgery even if they are at a somewhat higher risk for complications or adverse outcomes because they desire what gives them the best hope of long-term survival. Conversely, a patient who believes that their remaining life-expectancy is too short to benefit from a high risk treatment offering a potential cure (5-year survival), should understand that they need not accept the risk of surgically-associated mortality and morbidities to do something to combat the malignancy, and instead could pursue radiation therapy which could slow the cancer's advancement and better preserve healthy lung tissue.

Further research is needed to understand SDM in surgery and how to improve and support it. The current theories of SDM and the instrumentation used to measure this process have been developed and used largely in primary care and, to a lesser degree, shown to be appropriate in oncology [34]. These instruments might not be well-tuned to measure and assess SDM or patient comprehension in surgical contexts and thus might have limited value in understanding the challenge that surgical professionals face when educating and sharing with their patients.

More research is needed to fully understand how to more reliably and consistently meet the unique decision support needs of older, clinically complex patients

faced with a decision about curative surgery as they are likely to differ from those of patients in a primary care or medical oncology setting. The relatively short-term doctor patient relationship in surgical clinics, the trust required for effectively delivering surgical consultation, the high-risk/high-reward prospects of surgery, and the relative urgency with which surgical patients must be made informed, all make SDM a more difficult endeavor for surgical specialists than primary care physicians or even oncologists,

The specifics of each kind of surgery are important to SDM. There is limited support available for higher surgical risk early-stage cancer patients. The majority of the decision research that has examined SDM in surgical oncology has focused on breast cancer patients. A formal review of 25 empirical articles published between 1986 and 2006 on breast cancer patients making surgical decisions report that patients' information needs were consistent and ranked (in order) were: chances for a cure, stage of disease, and treatment options [35, 36]. Patient age and education predicted information needs and source use [37]. However, some research has examined patient-centered factors that predict a choice regarding surgery and shows that negative perceptions of the patient-physician interaction on a communication scale importantly influences patients' decisions [31]. More research and development of sound SDM support aids and patient education are required to meet the needs for the growing population of older and clinically diverse patients deciding about surgery.

For the time being, surgeons should strive to inform the patients presenting to their clinic that there is no standard of care and that multiple courses of action are justifiable. They should also ascertain the degree to which each patient wishes to actively weigh options and participate in making the choice. As in all areas of health care, physicians should express an eager willingness to answer any questions the patient has, allow them time to think over surgery and other options, and permit them to explore information in greater detail before making a decision.

Summary

Patients' desired role in difficult decisions, such as whether or not to undergo curative cancer resection when deemed to be less than ideal surgical candidates, continues to shift towards active and informed participation in SDM with the physician. This change brings profound challenges to a specialty already overtaxed on time and resources because good SDM requires that patients are accurately informed at the time of sharing in the decision. They must understand options, uncertainties, risks and potential tradeoffs. Currently, there appear to be significant risks that patients presenting to a surgical clinic are not accurately informed and have misconceptions that might steer them away from a treatment that might suit their goals and preferences. Further research can help to illuminate the problems in SDM for surgery and how to solve them. It is likely that the burden of preparing patients for effective SDM in surgical clinics will have to be shared with professionals other

than the surgeons because the surgical clinics are too limited. For now, surgeons should be aware of the importance of striving to maximize patients' understanding about their disease and treatment options so that the patients' values and preferences guide a treatment choice that is right for them.

References

1. Katz P. The Scalpel's edge: the culture of surgeons. Needham Heights: Allyn and Bacon; 1999.
2. Hollingham R. Blood and guts : a history of surgery. 1st U.S. ed. New York: Thomas Dunne Books/St. Martin's Press; 2009. p. 319.
3. Taking shared decision making more seriously. Lancet. 2011;377(9768):784.
4. Salzburg Global Seminar. Salzburg statement on shared decision making. Br Med J. 2011;342:d1745.
5. Singh JA, Sloan JA, Atherton PJ, Smith T, Hack TF, Huschka MM, et al. Preferred roles in treatment decision making among patients with cancer: a pooled analysis of studies using the Control Preferences Scale. Am J Manag Care. 2010;16(9):688–96.
6. Ekdahl AW, Andersson L, Friedrichsen M. "They do what they think is the best for me." Frail elderly patients' preferences for participation in their care during hospitalization. Patient Educ Couns. 2010;80(2):233–40.
7. Elwyn G, Miron-Shatz T. Deliberation before determination: the definition and evaluation of good decision making. Health Expect. 2010;13(2):139–47.
8. Peters E, Hess TM, Västfjäll D, Auman C. Adult age differences in dual information processes: implications for the role of affective and deliberative processes in older adults' decision making. Perspect Psychol Sci. 2007;2(1):1–23.
9. Fagerlin A, Sepucha KR, Couper MP, Levin CA, Singer E, Zikmund-Fisher BJ. Patients' knowledge about 9 common health conditions: the DECISIONS survey. Med Decis Making. 2010;30(5 Suppl):35S–52S.
10. Fagerlin A, Lakhani I, Lantz PM, Janz NK, Morrow M, Schwartz K, et al. An informed decision? Breast cancer patients and their knowledge about treatment. Patient Educ Couns. 2006;64(1-3):303–12.
11. Whelan T, Levine M, Willan A, Gafni A, Sanders K, Mirsky D, et al. Effect of a decision aid on knowledge and treatment decision making for breast cancer surgery: a randomized trial. JAMA. 2004;292(4):435–41.
12. Nelson WL, Han PKJ, Fagerlin A, Stefanek M, Ubel PA. Rethinking the objectives of decision aids: a call for conceptual clarity. Med Decis Making. 2007;27(5):609–18.
13. Ambady N, LaPlante D, Nguyen T, Rosenthal R, Chaumeton N, Levinson W. Surgeons' tone of voice: a clue to malpractice history. Surgery. 2002;132(1):5–9.
14. Levinson W, Roter DL, Mullooly JP, Dull VT, Frankel RM. Physician-patient communication: the relationship with malpractice claims among primary care physicians and surgeons. JAMA. 1997;277(7):553–9.
15. Beckman HB, Markakis KM, Suchman AL, Frankel RM. The doctor-patient relationship and malpractice. Lessons from plaintiff depositions. Arch Intern Med. 1994;154(12):1365–70.
16. Projections of the population by age and sex for the United States: 2010 to 2050 (NP2008-T12). In: Division P, editor. U.S. Census Bureau; 14 Aug 2008.
17. Fagerlin A, Zikmund-Fisher BJ, Ubel PA. Cure me even if it kills me: preferences for invasive cancer treatment. Med Decis Making. 2005;25(6):614–9.
18. Battafarano RJ, Piccirillo JF, Meyers BF, Hsu H-S, Guthrie TJ, Cooper JD, et al. Impact of comorbidity on survival after surgical resection in patients with stage I non–small cell lung cancer. J Thorac Cardiovasc Surg. 2002;123(2):280–7.

19. Velanovich V, Antoine H, Swartz A, Peters D, Rubinfeld I. Accumulating deficits model of frailty and postoperative mortality and morbidity: its application to a national database. J Surg Res. 2013;183(1):104–10.
20. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–57.
21. Cicerchia M, Ceci M, Locatelli C, Gianni W, Repetto L. Geriatric syndromes in peri-operative elderly cancer patients. Surg Oncol. 2010;19(3):131–9.
22. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 2010;210(6):901–8.
23. Ferguson MK, Farnan J, Hemmerich JA, Slawinski K, Acevedo J, Small S. The impact of perceived frailty on surgeons' estimates of surgical risk. Ann Thorac Surg. 2014;98(1):210–6.
24. Reyna VF, Lloyd FJ. Physician decision making and cardiac risk: effects of knowledge, risk perception, risk tolerance, and fuzzy processing. J Exp Psychol Appl. 2006;12(3):179–95.
25. Reyna VF. A theory of medical decision making and health: fuzzy trace theory. Med Decis Making. 2008;28(6):850–65.
26. Gainer RA, Curran J, Buth KJ, David JG, Légaré JF, Hirsch GM. Toward optimal decision making among vulnerable patients referred for cardiac surgery: a qualitative analysis of patient and provider perspectives. Med Decis Making. 2017;37(5):600–10.
27. Mokhles S, Maat APWM, Aerts JGJV, Nuyttens JJME, Bogers AJJC, Takkenberg JJM. Opinions of lung cancer clinicians on shared decision making in early-stage non-small-cell lung cancer. Interact Cardiovasc Thorac Surg. 2017;25(2):278–84.
28. Finucane ML. Emotion, affect, and risk communication with older adults: challenges and opportunities. J Risk Res. 2008;11(8):983–97.
29. Pargament KI, Smith BW, Koenig HG, Perez L. Patterns of positive and negative religious coping with major life stressors. J Sci Study Relig. 1998;37(4):710–24.
30. DeLisser HM, Keirns CC, Clinton EA, Margolis ML. "The air got to it:" exploring a belief about surgery for lung cancer. J Natl Med Assoc. 2009;101(8):765–71.
31. Cykert S, Dilworth-Anderson P, Monroe MH, Walker P, McGuire FR, Corbie-Smith G, et al. Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer. JAMA. 2010;303(23):2368–76.
32. Margolis M, Kaiser L, Christie J. Patient decisions to undergo surgery for early-stage lung cancer. JAMA. 2010;304(11):1165.
33. Axelrod DA, Goold S. Maintaining trust in the surgeon-patient relationship: challenges for the new millennium. Arch Surg. 2000;135(1):55–61.
34. Butow P, Juraskova I, Chang S, Lopez A-L, Brown R, Bernhard J. Shared decision making coding systems: how do they compare in the oncology context? Patient Educ Couns. 2010;78(2):261–8.
35. Goel V, Sawka CA, Thiel EC, Gort EH, O'Connor AM. Randomized trial of a patient decision aid for choice of surgical treatment for breast cancer. Med Decis Making. 2001;21(1):1–6.
36. Lantz PM, Janz NK, Fagerlin A, Schwartz K, Liu L, Lakhani I, et al. Satisfaction with surgery outcomes and the decision process in a population-based sample of women with breast cancer. Health Serv Res. 2005;40(3):745–68.
37. O'Leary KA, Estabrooks CA, Olson K, Cumming C. Information acquisition for women facing surgical treatment for breast cancer: influencing factors and selected outcomes. Patient Educ Couns. 2007;69(1–3):5–19.

Part I

Lung

EBUS vs. Mediastinoscopy for Initial Pathologic Mediastinal Staging in NSCLC

6

Abhinav Agrawal and Septimiu Murgu

Introduction

Preoperative staging of the mediastinum in patients with non-small cell lung cancer (NSCLC) with computed tomography (CT) of the chest and positron-emission-tomography (PET) remains suboptimal. Initial pathologic pre-operative staging is usually comprised of two modalities: endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy. Recommendations have been published by the American College of Chest Physicians (ACCP) [1, 2], European Society of Thoracic Surgeons (ESTS) [3], National Comprehensive Cancer Network (NCCN) [4], and the European Society for Medical Oncology (ESMO) [5] regarding indications for invasive mediastinal staging in patients with NSCLC. In the following sections we review the landmark articles describing the techniques used for initial staging of patients with lung cancer. We provide an update of the literature since the publication of the above listed guidelines.

Search Strategy

Systematic methods were used to find relevant studies, assess their eligibility for inclusion, and evaluate study quality based upon the predefined-Patient, Intervention, Comparison, Outcomes (PICO) questions (Table 6.1). The online database MEDLINE was searched for papers published in English between January 1, 2000

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Table 6.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with known or suspected lung cancer	EBUS	Mediastinoscopy	Accuracy Completeness Safety Adjunct procedure utility

and September 30, 2019. All landmark articles prior to 2013 ACCP guidelines were included based upon references from the ACCP, ESTS, NCCN and ESMO guidelines if they were relevant to the PICO question. For the PICO question, the following terms were used in Pubmed: *endobronchial ultrasound, endosonography, mediastinoscopy, lung cancer, endoscopic ultrasound, lymph nodes, clinical N1, staging, N1 node, pre-operative, contralateral hilar nodes, contralateral interlobar nodes and N3 node*. Studies were also identified by use of the related articles' function in PubMed; the references of identified articles were searched manually. A total of 3651 articles were returned using the above search strategy. Additional articles were captured by reviewing the reference lists from identified studies and pertinent review articles and guidelines. After a thorough review, 42 articles (including 29 original studies or meta-analysis) were used in our assessment and recommendations.

Results

Is EBUS-TBNA More Accurate than Mediastinoscopy for Mediastinal Staging?

The performance of EBUS-TBNA for initial mediastinal staging of lung cancer has been compared to that of mediastinoscopy in prospective and retrospective studies as well as systematic reviews (Table 6.2). Yasufuku et al. compared EBUS-TBNA and mediastinoscopy in 153 patients and demonstrated equivalent results [6]. Ernst et al. showed similar results, where 93% of the patients who underwent EBUS-TBNA had appropriate identification of their pathologic state vs. 82% by mediastinoscopy (P = 0.083). They also demonstrated that per lymph node (LN) analysis, EBUS-TBNA had higher diagnostic accuracy (91%) compared to mediastinoscopy (78%) (P = 0.007) [7]. The major difference in the yield between the two procedures was primarily related to the difference in diagnostic yield at station 7 (98% for EBUS-TBNA vs. 78% for mediastinoscopy, P = 0.007), possibly because of EBUS access to the low and posterior subcarinal lymph nodes. This was re-demonstrated by Um et al. [8] who showed a trend towards inferior diagnostic yield at station 7 LN via mediastinoscopy (75% with mediastinoscopy vs. 82.5% with EBUS-TBNA). These authors also found a significantly lower yield at station 4L using mediastinoscopy (52.4%) as compared to EBUS-TBNA (81%) (P = 0.027). A 2015 systematic review, however, compared ten studies that used EBUS-TBNA to seven studies that used mediastinoscopy and demonstrated comparable sensitivity for staging of lung

Table 6.2 Evidence summarizing original research articles comparing EBUS-TBNA to mediastinoscopy for Initial Staging for NSCLC

References	Study design/patients	Interventions	Primary outcome	Adverse events	Comments	Evidence quality
Ernst et al. [7]	Prospective, Crossover trial/66 patients	EBUS-TBNA vs. CM	Staging of mediastinal lymph nodes: No significant difference between EBUS (93%) and CM (82%) ($p = 0.083$) in patients with lung cancer	EBUS-TBNA: 0 CM: Prolonged would infection (2), Prolonged bleeding (3), Prolonged ventilation (1)	Mediastinoscopy was performed combined with lung resection Higher accuracy for EBUS-TBNA at station 7 (98% vs. 79%)	Moderate
Yasufuku et al. [6]	Prospective Controlled trial/153 patients	EBUS-TBNA vs. CM	EBUS-TBNA: Sensitivity (81%), Specificity (100%), NPV (91%) and Accuracy (93%) CM: Sensitivity (79%), Specificity (100%), NPV (90%) and Accuracy (93%)	EBUS-TBNA: 0 Mediastinoscopy: Hematoma (2), left recurrent laryngeal nerve injury (1), wound infection (1)	Excellent agreement between EBUS-TBNA and mediastinoscopy for mediastinal staging in 136 patients (91%; Kappa, 0.8; 95% confidence interval, 0.7–0.9)	High
Um et al. [8]	Prospective Controlled Trial/127 patients	EBUS vs. CM	EBUS-TBNA (per-person analysis): Sensitivity (88.0%), Specificity (100%), Accuracy (92.9%), PPV (100%), and NPV (85.2%) CM (per-person analysis): Sensitivity (81.3%), Specificity (100%), Accuracy (89.0%), PPV (100%), and NPV (78.8%)	EBUS-TBNA: Minor bleeding (1), Transient hypoxemia (1) CM: Minor bleeding (1)	EBUS-TBNA was superior to CM in terms of its diagnostic performance for mediastinal staging of cN1–3 NSCLC Diagnostic performance Station 7—CM (75%) vs. EBUS-TBNA (82%) and Station 4L-CM (52%) vs. EBUS-TBNA (81%)	High

(continued)

Table 6.2 (continued)

References	Study design/patients	Interventions	Primary outcome	Adverse events	Comments	Evidence quality
Ge et al. [9]	Systematic Review/ EBUS-TBNA: 10 studies, 999 patients. CM: 7 studies, 915 patients	EBUS vs. CM	The pooled sensitivities for EBUS-TBNA and VAM were 0.84 (95% CI 0.79–0.88) and 0.86 (95% CI 0.82–0.90), respectively	EBUS-TBNA: atrial fibrillation (1), severe cough (2), pneumomediastinum (1) CM: hoarseness (2), pneumothorax (2), vascular lesions (4), perioperative bleeding (2), left recurrent laryngeal injury (4), chyle leak (1), esophagus injury (1), wound infection (1)	Pooled sensitivities calculated from EBUS and Mediastinoscopy studies, but patients did not have both procedures	Low
Zhang et al. [10]	Retrospective/ EBUS-TBNA: 55 patients. Systematic Mediastinal Lymphadenectomy: 190 patients	EBUS-TBNA vs. Mediastinoscopy	N staging accuracy: EBUS TBNA (83.6%) *vs.* Mediastinoscopy (78.9%) Lymph node diagnostic yield accuracy EBUS TBNA (92.9%) vs. Mediastinoscopy (98.8%) Lymph nodes diagnosis comparison (station #2, #4 and #7): Both EBUS-TBNA and CM showed high diagnostic sensitivity (82.4% *vs.* 94.7%, P = 0.130), specificity (97.4% *vs.* 100%, P = 0.173) and accuracy (98.8% *vs.* 92.9%, P = 0.025) respectively	EBUS-TBNA (1.6%): Severe cough (2), Oxygen desaturation (2) Mediastinoscopy (2.3%): Recurrent laryngeal nerve or vessel injury (6), post-operative infection (1)		Very Low

EBUS-TBNA endobronchial ultrasound with transbronchial needle aspiration, *CM* cervical mediastinoscopy, *NPV* negative predictive value, *PPV* positive predictive value, *EUS-FNA* endoscopic ultrasound with fine needle aspiration

cancer [9]. A 2018 retrospective original study suggested higher nodal staging accuracy using EBUS-TBNA compared with mediastinoscopy [10]. Thus, the current literature suggests that EBUS-TBNA and mediastinoscopy have similar performance in staging of lung cancer with likely higher accuracy of EBUS-TBNA for posterior station 7 and possibly for station 4L lymph nodes.

Should Sampling of N1 Nodes Using EBUS TBNA Be Routinely Performed as Part of Pre-operative Staging?

Some surgical series have reported that patients with hilar pN1 disease have a worse prognosis as compared to patients with more peripheral pN1 disease (interlobar nodes) [11]. In fact, the most recent IASLC staging data reported that patients with pN2 metastasis at a single lymph node station without hilar involvement (skip metastasis) had better survival than those with pN1 metastasis at multiple stations [12]. These findings may justify the use of neoadjuvant chemotherapy in patients with multiple N1 disease [13], however, routine sampling N1 nodes is not standard of practice in candidates for lobectomy. The role of EBUS for detecting N1 nodes has been reported by few investigators (Table 6.3). In one such study, Yasufuku et al. demonstrated a sensitivity, specificity, diagnostic accuracy, and NPV of 76.2%, 100%, 96.6%, and 96.2% to accurately differentiate between N0 and N1 disease [14]. Based on the current IASLC nodal staging system and available literature, we suggest that once the mediastinal staging is completed, sampling hilar and interlobar N1 nodes with EBUS should be performed as results are relevant for prognostication and possibly for induction therapy.

Given the fact that EBUS-TBNA can accurately assess the hilar and interlobar lymph nodes, it is important that non-surgical patients undergo EBUS-TBNA from ipsilateral hilar and interlobar lymph nodes for ruling out N1 disease prior to stereotactic body radiotherapy [15–17].

Should Routine EBUS-TBNA of the Contralateral Hilar and Interlobar Nodes Be Performed as Part of Pre-operative Staging?

It is important to note that in studies that compared EBUS with mediastinoscopy for staging NSCLC, the mediastinal lymph nodes were evaluated and sampled by EBUS if they were >5 mm, starting with mediastinal N3 (stations 2 and 4) and subsequently sampling N2 and N1 nodes. However, in those trials, the contralateral hilar (station 10) and interlobar (station 11) LNs were not sampled [6, 7, 18] and this did not affect surgical outcomes. In fact, if the contralateral mediastinal nodes (stations 2 and 4) are found to be positive on ROSE, then the contralateral hilar or interlobar nodes do not affect staging [12]. Thus, routine aspiration of CT-PET negative contralateral hilar or interlobar nodes is not warranted during routine EBUS-TBNA staging.

Table 6.3 PICO table of evidence summarizing studies comparing EBUS-TBNA to surgical staging in patients with NSCLC with clinical N1 (cN1) disease and studies assessing use EBUS-TBNA to distinguish N0 from N1 disease

References	Study design/patients	Interventions	Primary outcome	Comments	Evidence quality
Herth et al. [20]	Prospective/100 patents (with NSCLC with radiographically normal mediastinum and no PET activity)	EBUS-TBNA compared to surgical staging	EBUS-TBNA: Sensitivity (89%), specificity (100%), and NPV (98.9%)	Mean diameter of the punctured lymph nodes was 7.9 mm	Moderate
Dooms et al. [22]	Prospective Multicenter/100 patients	Endosonography compared surgical staging with mediastinoscopy	Endosonography alone: Sensitivity (38%), NPV (81%) Endosonography + Mediastino-scopy: Sensitivity (73%), NPV (91%)		Moderate
Vial et al. [25]	Prospective/72 patients with NSCLC staged as N0/N1 by PET/CT	EBUS-TBNA to surgical staging	36% patients with cN1 disease had N2 disease EBUS-TBNA identified 80% of these patients (Patients with cN1 diagnosed with N2 disease)		Moderate
Leong et al. [21]	Systematic review and meta-analysis/9 studies, 1146 patients	EBUS-TBNA for mediastinal staging in cN0/N1 disease	Mean prevalence of N2/N3 disease: 15% EBUS-TBNA: Pooled sensitivity (49%), pooled specificity (100%), mean NPV (91%) for detection of unsuspected N2/N3 metastases		Moderate

Bousema et al. [26]	Systematic review and meta-analysis/42 articles, 3248 patients	Rates of unforeseen N2 disease for endosonography (EBUS-TBNA and/or EUS-FNA) staging strategies with or without confirmatory mediastinoscopy Complication rate of mediastinoscopy was studied (eight studies, 1245 patients)	EBUS-TBNA or EBUS-TBNA plus EUS-FNA studies (1518 patients): Rate of unforeseen N2 disease was 9.6% EBUS-TBNA or EBUS-TBNA plus EUS-FNA with subsequent mediastinoscopy studies (1082 patients): Rate of unforeseen N2 disease was 9.9%	Complication rate of mediastinoscopy: 6%	Moderate
Yasufuku et al. [14]	Retrospective/163 patients	EBUS-TBNA to distinguish N0 from N1 disease	Sensitivity (76.2%), Specificity (96.6%), Diagnostic accuracy (100%), and NPV (96.2%) Accuracy of mediastinal staging: 95.7%		Low

If rapid onsite evaluation (ROSE) is used and N3 disease is found in the mediastinal lymph nodes, then contralateral lymph nodes 10 and 11 should be sampled (after changing the EBUS needle) as their involvement affects the radiation field.

Should EBUS-TBNA or Mediastinoscopy Be Used as the Initial Procedure for Pre-operative Staging in Patients with Clinical N1 (cN1) Disease?

There is reproducible evidence that preoperative staging of the mediastinum in cN1 disease (N1 nodes large on CT or positive on PET) is important due to a high prevalence of occult N2/N3 disease. The median range of occult N2/N3 disease in patient with cN1 disease is reported to be 20–42% based on prospective and retrospective studies [19]. Therefore, guidelines recommend routine pre-operative staging in these circumstances. The ACCP and ESTS guidelines provide slightly different recommendations regarding the best initial staging procedure in these patients. The ACCP guidelines suggest endosonography methods over surgical procedures as the best first test (ACCP, evidence level 2B). The ESTS guidelines state that the choice between mediastinoscopy with biopsies or with pre-surgical lymphadenectomies (VAMLA or TEMLA) and endoscopic staging by EBUS/EUS with FNA depend on local expertise (evidence Level V). It is important to note that VAMLA is only performed at certain expert thoracic centers in Europe and not routinely performed in the United States. Older studies showed the sensitivity of EBUS-TBNA for detecting malignancy is 89%, specificity 100%, and the negative predictive value is 98.9% in these patients [20]. A recent meta-analysis of patients with cN0/N1 disease showed that EBUS-TBNA had pooled sensitivity of 49%, pooled specificity of 100%, and a mean negative predictive value of 91% for detection of unsuspected N2/N3 metastases (mean prevalence of N2/N3 disease was 15%). The authors concluded that preoperative systematic staging by EBUS-TBNA of early lung cancer can reduce postoperative upstaging [21]. A prospective study of 100 patients with cN1 disease on imaging showed that endosonography (EBUS-TBNA or EBUS-TBNA combined with EUS-FNA) had a sensitivity of 38% to diagnose N2 disease, which could be increased to 78% by adding mediastinoscopy. This analysis concluded that ten mediastinoscopies were needed to detect one additional N2 disease missed by endosonography [22]. A subsequent non-randomized prospective study of 105 patients with cN1 disease showed that mediastinoscopy had a sensitivity of 73% to diagnose unsuspected N2 disease. It is important to note that 33 of these patients (31%) underwent a video mediastinoscopy with lymphadenectomy (VAMLA) with excellent results [23, 24]. More recently, Vial et al. showed that the prevalence of occult N2 disease in patients with cN1 disease can be as high as 36% and EBUS identifies 80% of these patients during pre-operative staging [25]. In this analysis, all EBUS procedures were performed under general anesthesia, with ROSE availability in a high-volume center. A recent meta-analysis

comprising of 3248 patients showed that the rate of occult N2 disease in patients with resected NSCLC was similar in patients staged with endosonography alone compared to those who underwent additional surgical staging with mediastinoscopy [26]. These authors also reported 6% morbidity in patients undergoing mediastinoscopy [26].

Based on the available evidence (Table 6.3), we conclude that in patients with CT-PET normal mediastinum and cN1 disease, a thorough EBUS-TBNA staging procedure is preferred over mediastinoscopy as the initial preoperative staging procedure, as is recommended by the ACCP guidelines.

What Are the Relevant Complication Rates for EBUS-TBNA and Mediastinoscopy?

The complication rate of mediastinoscopy reported in the literature is ~2.5% including pneumothorax, infection, injury to major mediastinal vessels, recurrent laryngeal nerve, airway and esophagus [27]. Mediastinoscopy-related mortality has been reported to be 0.08–0.1% [28]. The reported complication rate with EBUS-TBNA is 1–2% and includes bleeding, infection, and pneumothorax with a mortality of 0.01% [29, 30]. The available evidence demonstrates that EBUS-TBNA is a safer procedure compared to mediastinoscopy, which justifies the recommendation that EBUS-TBNA should be the first procedure offered for initial pathologic mediastinal staging.

Should Endoscopic Ultrasound Fine Needle Aspiration (EUS-FNA) Be Performed in Addition to EBUS-TBNA for Routine Pre-operative Mediastinal Staging?

As EBUS-TBNA does not provide access to stations 5, 6, 8 and 9, some authors have advocated adding endoscopic ultrasound (EUS-FNA) to EBUS-TBNA for complete sonographic staging of the mediastinum. Combined endosonography has been proposed to incorporate both procedures in a single sitting but this is not standard of practice.

A recent meta-analysis noted an increased pooled sensitivity of 12% by adding EUS-FNA to EBUS-TBNA during mediastinal staging [31]. However, the pooled sensitivity of EBUS alone in this analysis was much lower than that generally accepted for EBUS and reported in the ACCP guidelines (72% vs. 89%) [2, 31, 32]. Multiple studies assessed the value of combining EBUS-TBNA with EUS-FNA for initial staging of lung cancer. A careful review of those studies demonstrated that EUS-FNA added to the increased diagnostic yield by providing better access to LN stations 4L and 7 and on occasion access to station 5 rather than station 8 and 9 [33–38]. This suggests a lack of a thorough EBUS-TBNA staging practice and not necessarily a need for an additional technology. Furthermore, the involvement of station 8 and 9 in the

absence of upper mediastinal LN involvement (station 2, 4 and 7) is also extremely rare and thus unlikely to be even detected by pre-operative needle aspiration [13, 39, 40]. Stations 5 and 6 can be well visualized by EUS but can rarely be sampled without traversing the pulmonary artery or aorta. These stations are pre-dominantly involved in left upper lobe tumors and surgical staging with video-assisted thoracic surgery (VATS) is the method of choice for these nodes, as recommended by guidelines [2, 3, 41]. The 2015 ESGE/ERS/ESTS guidelines, however, recommend the use of combination of EBUS-TBNA and EUS-FNA (recommendation grade C) when available for diagnosis and staging of lung cancer [41]. The 2013 American College of Chest Physician's guidelines commented on unresolved issues regarding training and availability of combined endoscopic procedures but did not offer specific recommendation on their use for staging [1].

We conclude that routine use of combined EBUS-TBNA and EUS-FNA is not justified for improving accuracy of staging as long as all EBUS-TBNA accessible stations are being explored and sampled based on accepted criteria (>5 mm and relevant for staging). Routine preoperative sampling of PET-CT negative station 8 and 9 is not warranted to increase accuracy of initial pathologic staging. Selective use of combined ultrasound techniques may be applied in patients with a high suspicion of station 8 and 9 LN involvement based on pre-procedure imaging or when station 4L or 7 LNs greater than 5 mm are seen on EBUS but not sampled for technical reasons. In the absence of upper mediastinal lymph node involvement (station 2, 4 and 7), EUS-FNA should be performed for diagnosis and staging when lymph nodes in station 8 and 9 are positive on PET or CT imaging.

Conclusions and Recommendations

Based on the review of published evidence and consistent with existing guidelines, we found that EBUS-TBNA and mediastinoscopy have similar accuracy for initial pathologic staging of the mediastinum in lung cancer with likely higher accuracy of EBUS-TBNA for posterior station 7 and possibly for station 4L lymph nodes. We also conclude that EBUS-TBNA is a safer procedure compared to mediastinoscopy, which justifies the recommendation that EBUS-TBNA should be the first step for initial mediastinal staging for NSCLC. For patents with NSCLC with CT-PET normal mediastinum and clinical N1 (cN1) disease, a comprehensive EBUS-TBNA can detect occult N2/N3 disease. Given the minimally invasive nature of the procedure, a pre-operative EBUS is warranted in this patient population over a mediastinoscopy.

During EBUS staging procedures, sampling hilar and interlobar N1 nodes is feasible and may be relevant for prognostication and possibly induction therapy. This is especially important for non-surgical patients who are being considered for stereotactic body radiotherapy. On the other hand, routine aspiration of contralateral

hilar or interlobar nodes is not warranted during routine staging if they are CT-PET negative.

The routine use of combined EBUS-TBNA and EUS-FNA is not justified for improving accuracy of initial pathologic staging of the mediastinum as long as all EBUS-TBNA accessible lymph node stations are being explored and sampled. Routine sampling of CT-PET negative station 8 and 9 lymph nodes is not warranted and does not increase accuracy of staging given the low incidence of involvement of these stations in the absence of upper mediastinal LN involvement. Selective use of combined ultrasound techniques may be applied in patients with a high suspicion of station 8 and 9 involvement based on pre-procedure imaging or when station 4L or 7 are visualized on EBUS but not able to be sampled for technical reasons. An algorithm for the initial staging prior to curative intent treatment in patients with NSCLC is outlined in Fig. 6.1.

Recommendations

- We recommend EBUS-TBNA over mediastinoscopy for pre-operative mediastinal staging because of its higher accuracy and better safety profile (evidence quality high; strong recommendation).
- We recommend EBUS-TBNA over mediastinoscopy for patients with CT-PET normal mediastinum and tumors larger than 3 cm, central tumors or cN1 disease to detect occult N2/N3 disease (Evidence quality moderate, weak recommendation).
- We recommend sampling hilar and interlobar N1 nodes with EBUS as relevant for induction therapy and for non-surgical patients who are being considered for stereotactic body radiotherapy (evidence quality low, weak recommendation).

A Personal View of the Data

EBUS provides access to most mediastinal, hilar, interlobar and selected intralobar lymph nodes because of the adjacent anatomical relationship between lymph nodes and the airways. This explains why in certain studies, EBUS-TBNA was more accurate than mediastinoscopy for staging NSCLC. The accuracy of EBUS-TBNA is directly dependent on the thoroughness of the procedure. We believe that EBUS-TBNA procedure should be a complete mapping of the mediastinum with stations 2L, 2R, 4L, 4R and 7 being explored in every patient and each lymph node in these stations should be sampled if it is greater than 5 mm in its shortest diameter. EBUS exploration of a lymph node station should be performed by investigating the entire region based upon borders as defined by the IASLC lymph node map. This is extremely relevant especially for lymph node stations that cover large areas such as station 4R and 7 where more than one lymph node can be found in the station. In patients who are questionable or known poor surgical candidates, sampling of the ipsilateral hilar and interlobar lymph nodes (stations 10 and 11) should be

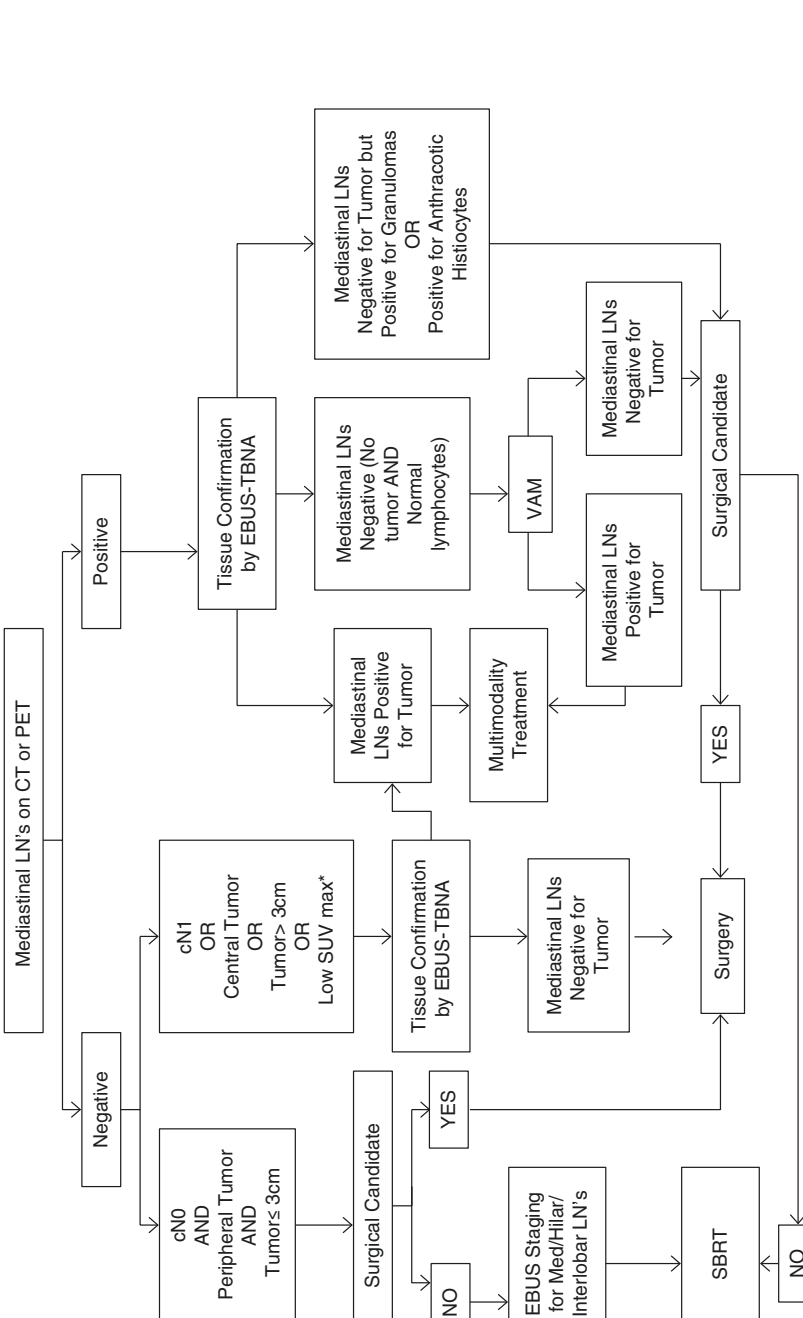

Fig. 6.1 Initial staging algorithm prior to curative intent treatment in patients with NSCLC. *LN* lymph node, *EBUS-TBNA* endobronchial ultrasound with transbronchial needle aspiration, *VAM* video-assisted mediastinoscopy, ∗ SEPAR guidelines for lung cancer staging [42]

performed at the time of EBUS-TBNA as these patients will not undergo surgical pathologic staging but may be candidates for stereotactic body radiotherapy and N1 nodal involvement needs to be ruled out.

A PET or CT positive mediastinal lymph node in which EBUS-TBNA identifies only normal lymphocytes (in the absence of granulomas or anthracotic histiocytes) requires surgical sampling. This is because the mere presence of lymphocytes is not a sufficient explanation for the positive PET or CT findings. This practice may change as more evidence is emerging that even these lymph nodes may end up being truly negative for malignancy as proven by surgical sampling. Future studies should be aimed at answering this question and define specific PET and CT characteristics for reactive and anthracotic lymphadenopathy.

Complications arising from EBUS-TBNA using the studied needles (21g and 22g) are very low. The safety and diagnostic yield of newer smaller (25g) or larger (19g) needles or the use of EBUS transbronchial forceps biopsy remain to be studied.

A bronchoscopy report of the EBUS-TBNA procedure should include documentation of exploration of the five mediastinal lymph node stations (2L, 2R, 4L, 4R and 7) and an explanation should be provided if any of these stations are not sampled during staging (size < 5mm, technical difficulty, or a malignant lymph node which upstages the tumor has already been identified on rapid on site cytology evaluation).

References

1. Detterbeck FC, et al. Executive summary: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):7S–37S.
2. Silvestri GA, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e211S–50S.
3. De Leyn P, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg. 2014;45(5):787–98.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-small cell lung cancer. 2019 Aug 30, 2019 [cited 2019 September 30th, 2019]; Version 7.0. Available from https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
5. Postmus PE, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(Suppl_4):iv1–iv21.
6. Yasufuku K, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. J Thorac Cardiovasc Surg. 2011;142(6):1393–400.e1.
7. Ernst A, et al. Diagnosis of mediastinal adenopathy-real-time endobronchial ultrasound guided needle aspiration versus mediastinoscopy. J Thorac Oncol. 2008;3(6):577–82.
8. Um SW, et al. Endobronchial ultrasound versus mediastinoscopy for mediastinal nodal staging of non-small-cell lung cancer. J Thorac Oncol. 2015;10(2):331–7.
9. Ge X, et al. Comparison of endobronchial ultrasound-guided fine needle aspiration and video-assisted mediastinoscopy for mediastinal staging of lung cancer. Lung. 2015;193(5):757–66.

10. Zhang R, et al. Endobronchial ultrasound-guided transbronchial needle aspiration and cervical mediastinoscopy for mediastinal staging of non-small cell lung cancer: a retrospective comparison study. J Thorac Dis. 2018;10(3):1951–9.
11. Rusch VW, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol. 2007;2(7):603–12.
12. Asamura H, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2015;10(12):1675–84.
13. Murgu SD. Diagnosing and staging lung cancer involving the mediastinum. Chest. 2015;147(5):1401–12.
14. Yasufuku K, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for differentiating N0 versus N1 lung cancer. Ann Thorac Surg. 2013;96(5):1756–60.
15. Rami-Porta R, et al. Lung cancer staging: a concise update. Eur Respir J. 2018;51(5). pii: 1800190.
16. Sarwate D, et al. Optimization of mediastinal staging in potential candidates for stereotactic radiosurgery of the chest. J Thorac Cardiovasc Surg. 2012;144(1):81–6.
17. Robson JM, et al. Occult nodal disease in patients with non-small-cell lung cancer who are suitable for stereotactic ablative body radiation. Clin Lung Cancer. 2014;15(6):466–9.
18. Annema JT, et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. JAMA. 2010;304(20):2245–52.
19. Call S, Obiols C, Rami-Porta R. Present indications of surgical exploration of the mediastinum. J Thorac Dis. 2018;10(Suppl 22):S2601–10.
20. Herth FJ, et al. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically and positron emission tomography-normal mediastinum in patients with lung cancer. Chest. 2008;133(4):887–91.
21. Leong TL, et al. Preoperative staging by EBUS in cN0/N1 lung cancer: systematic review and meta-analysis. J Bronchol Interv Pulmonol. 2019;26(3):155–65.
22. Dooms C, et al. Endosonography for mediastinal nodal staging of clinical N1 non-small cell lung cancer: a prospective multicenter study. Chest. 2015;147(1):209–15.
23. Decaluwe H, et al. Mediastinal staging by videomediastinoscopy in clinical N1 non-small cell lung cancer: a prospective multicentre study. Eur Respir J. 2017;50(6). pii: 1701493.
24. Bostantzoglou C, Iliopoulou M, Hardavella G. Mediastinal staging by videomediastinoscopy in clinical N1 non-small cell lung cancer. Breathe (Sheff). 2018;14(4):342–4.
25. Vial MR, et al. Diagnostic performance of endobronchial ultrasound-guided mediastinal lymph node sampling in early stage non-small cell lung cancer: a prospective study. Respirology. 2018;23(1):76–81.
26. Bousema JE, et al. Unforeseen N2 disease after negative endosonography findings with or without confirmatory mediastinoscopy in resectable non-small cell lung cancer: a systematic review and meta-analysis. J Thorac Oncol. 2019;14(6):979–92.
27. Czarnecka-Kujawa K, Yasufuku K. The role of endobronchial ultrasound versus mediastinoscopy for non-small cell lung cancer. J Thorac Dis. 2017;9(Suppl 2):S83–97.
28. Detterbeck FC, et al. Diagnosis and treatment of lung cancer: an evidence based guide for the practicing clinician, vol. 29. Philadelphia: WB Saunders; 2001.
29. von Bartheld MB, van Breda A, Annema JT. Complication rate of endosonography (endobronchial and endoscopic ultrasound): a systematic review. Respiration. 2014;87(4):343–51.
30. Yarmus LB, et al. Comparison of moderate versus deep sedation for endobronchial ultrasound transbronchial needle aspiration. Ann Am Thorac Soc. 2013;10(2):121–6.
31. Korevaar DA, et al. Added value of combined endobronchial and oesophageal endosonography for mediastinal nodal staging in lung cancer: a systematic review and meta-analysis. Lancet Respir Med. 2016;4(12):960–8.
32. Labarca G, et al. Is there added value in adding EUS to EBUS? Lancet Respir Med. 2017;5(2):e8.

33. Vilmann P, et al. Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. Endoscopy. 2005;37(9):833–9.
34. Wallace MB, et al. Minimally invasive endoscopic staging of suspected lung cancer. JAMA. 2008;299(5):540–6.
35. Herth FJ, et al. Combined endoscopic-endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes through a single bronchoscope in 150 patients with suspected lung cancer. Chest. 2010;138(4):790–4.
36. Szlubowski A, et al. A combined approach of endobronchial and endoscopic ultrasound-guided needle aspiration in the radiologically normal mediastinum in non-small-cell lung cancer staging--a prospective trial. Eur J Cardiothorac Surg. 2010;37(5):1175–9.
37. Hwangbo B, et al. Transbronchial and transesophageal fine-needle aspiration using an ultrasound bronchoscope in mediastinal staging of potentially operable lung cancer. Chest. 2010;138(4):795–802.
38. Kang HJ, et al. EBUS-centred versus EUS-centred mediastinal staging in lung cancer: a randomised controlled trial. Thorax. 2014;69(3):261–8.
39. Evison M, et al. Prevalence of nodal metastases in lymph node stations 8 & 9 in a large UK lung cancer surgical centre without routine pre-operative EUS nodal staging. Lung Cancer. 2018;115:127–30.
40. Obiols C, et al. Survival of patients with unsuspected pN2 non-small cell lung cancer after an accurate preoperative mediastinal staging. Ann Thorac Surg. 2014;97(3):957–64.
41. Vilmann P, et al. Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). Endoscopy. 2015;47(6):545–59.
42. de Cos S. J., et al., SEPAR guidelines for lung cancer staging. Arch Bronconeumol. 2011;47(9):454–65.

Does Preoperative Smoking Cessation Reduce Surgical Morbidity After Lung Resection?

7

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Introduction

As surgical resection is a potentially curative therapy for early-stage non-small-cell lung cancer (NSCLC), optimizing modifiable patient risk factors before surgery is important to minimize morbidity. A significant proportion of patients continue to smoke after being diagnosed with lung cancer and about 20% of patients who smoke may continue up to the time of surgery [1, 2]. Lung cancer patients who quit smoking have improved cancer prognosis and experience immediate functional benefits including decreased fatigue and shortness of breath [3]. Smoking cessation also benefits surgical outcomes, as tobacco use at time of surgery is a risk factor for pulmonary and overall complications [4, 5]. At the same time, delaying surgical resection for NSCLC is associated with upstaging and worse survival [6, 7]. These findings raise the question of whether there is value in delaying surgery for current smokers with resectable lung cancer to mitigate the negative effects of smoking on postoperative complications and improve patients' fitness for surgery. In this chapter we review the literature evaluating the effect of preoperative smoking cessation on surgical complications following lung resection for malignancy, focusing on the timing of smoking cessation relative to postoperative morbidity.

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Table 7.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcome)
Adults with cancer who smoke	Smoking cessation before surgery	Continued smoking at time of surgery	Morbidity after lung resection

Search Strategy

The PICO method was used to devise the search query (Table 7.1). The research question was, "In patients with lung cancer who smoke, does preoperative smoking cessation decrease morbidity after lung resection?" A search was conducted in the PubMed/MEDLINE database in August 2019 for English language studies published in the period from 1990 through August 2019. Medical Subject Headings terms were used to construct the search term: ("Lung neoplasms" [MeSH] OR "Lung diseases" [MeSH] OR "Pneumonectomy" [MeSH]) AND ("Smoking Cessation" [Mesh] OR "Tobacco Use Cessation" [MeSH]) AND "Postoperative Complications" [MeSH]. This search returned 41 results. Abstracts were reviewed for relevance to the PICO question. Review articles and meta-analyses were excluded.

Results

The search strategy returned 9 observational studies that addressed the PICO question (Table 7.2). The authors agreed that, given the overall health benefits from smoking cessation, patients should be encouraged to stop smoking as early as possible. However, published data was inconclusive about the effect of the timing of cessation on postoperative morbidity or whether there was an ideal period of preoperative cessation that would reduce the morbidity risk associated with tobacco smoking. The studies all analyzed smoking cessation duration as an ordinal variable, using intervals of preoperative smoking cessation duration to stratify patients into recent and distant smokers. Pulmonary and surgical complications were selected as outcome measures and differed among studies. Postoperative pulmonary complications of atelectasis and pneumonia were most commonly chosen. Most of the studies analyzed small cohorts from single institutions, which increases the risk of imprecision and limits generalizability of the observed effects. Prospective data was limited to two observational studies.

Three studies found evidence of a difference in postoperative morbidity between former smokers of different smoke-free periods before surgery. Nakagawa et al. examined the relationship between smoking cessation duration and postoperative pulmonary complications (PPCs) in patients undergoing pulmonary surgical procedures [8]. They performed a retrospective cohort study of 288 patients who underwent tumor enucleation, wedge resection, lobectomy, or pneumonectomy at their institution. Fourteen events were defined as PPCs (Table 7.2). Recent smokers who

Table 7.2 Effect of preoperative smoking cessation on postoperative morbidity after lung resection

Study	Study design and period	Cohort	Definitions of patient groups	Outcomes	Findings	Quality of evidence
Nakagawa et al. (2001) [8]	Retrospective cohort 1997–1998	N = 288 pulmonary surgical procedure	• Current smoker: smoked within 2 weeks before surgery • Recent smoker: smoke-free 2–4 weeks before surgery • Ex-smoker: smoke-free >4 weeks before surgery • Never smoker	Postoperative pulmonary complications: atelectasis prompting bronchoscopy; pneumonia; $Paco_2$ > 50 mmHg at 24 h after the surgery; air leak or effusion; bronchopleural fistula with large air leak or infection; empyema; chylothorax; hemothorax requiring drainage or reoperation; tension pneumothorax; pulmonary embolism; lobar gangrene; mechanical ventilation > 72 h; intercostal tube drainage > 14 days; required fraction of inspired oxygen > 0.6 or alveolar-arterial oxygen gradient > 300 mmHg 24-h postoperatively	Incidence of PPCs decreased for patient with preoperative smoke-free periods beyond 5–8 weeks. Incidence in patients with 9–12-week smoke-free period approached that of never-smokers	Low
Vaporciyan et al. (2002) [9]	Retrospective cohort Jan 1990–May 1999	N = 257 pneumonectomy for malignancy	• Quit <1 month before surgery • Quit 1 month or more before surgery • Never smoker	Major pulmonary events (MPE) (pneumonia or acute respiratory distress syndrome) LOS, mortality (in hospital or 30-day postop)	In multivariate analysis, only timing of smoking cessation of <1 month before surgery was a significant factor for development of MPE	Low

(continued)

Table 7.2 (continued)

Study	Study design and period	Cohort	Definitions of patient groups	Outcomes	Findings	Quality of evidence
Barrera et al. (2005) [15]	Prospective cohort 1999–2001	N = 300 thoracotomy for resection of primary lung cancer or metastatic cancer to lung	• Current smoker or quit <1 week before surgery • Quit between 1 week and 2 months before surgery • Quit >2 months before surgery • Never smoker	Postoperative pulmonary complications [respiratory failure requiring ICU admission and/or intubation; pneumonia (new pulmonary infiltrate with fever treated with IV antibiotics); atelectasis requiring bronchoscopy; pulmonary embolism; and the need for supplemental oxygen at hospital discharge]	Smokers had higher rate of pulmonary complications than nonsmokers. No difference in rate of complications between groups who had smoked	Low
Groth et al. (2009) [11]	Retrospective cohort April 2000–April 2006	N = 213 pulmonary resection for NSCLC	• Current smokers • Recent smokers: stopped within 1 month before surgery • Distant smokers: stopped more than 1 month before surgery	Preop and 1-year postop PFT results, length of stay, postoperative complications [prolonged air leak (more than 7 days), pneumonia, need for reintubation, atrial and ventricular arrhythmias, acute myocardial infarction, stroke, and death]	No significant differences between groups in change between preop and 1-year postop PFT results, length of stay, or complications	Low

Mason et al. (2009) [14]	Retrospective cohort January 1999–July 2007	N = 7990 primary resection for lung cancer	• Group 1: current smoker or cessation ≤2 weeks before surgery • Group 2: quit between 2 weeks to 1 month before surgery • Group 3: quit 1–12 months before surgery • Group 4: quit >12 months before surgery • Group 5: never smoked, or smoked <100 cigarettes in lifetime	Hospital mortality, pulmonary complications [prolonged ventilation (>48 h postoperatively), need for reintubation, atelectasis requiring bronchoscopy, tracheostomy, pneumonia, and development of acute respiratory distress syndrome]	Current or former smokers had higher risk of hospital mortality and complications than never smokers. No difference in risk between groups of current or former smokers	Low

(continued)

Table 7.2 (continued)

Study	Study design and period	Cohort	Definitions of patient groups	Outcomes	Findings	Quality of evidence
Seok et al. (2014) [12]	Retrospective cohort Jan 2005–June 2009	N = 232 with smoking history, received surgical resection for lung cancer	• Group 1: Quit <14 days before surgery • Group 2: Quit 15 days to 1 month before surgery • Group 3: Quit >1 month before surgery	Postoperative pulmonary complications (pneumonia, atelectasis, tracheostomy performed due to respiratory difficulty, repeated intubation episodes after surgery, and persistent air leak of more than 7 days)	No significant differences between groups in development of postoperative pulmonary complications	Low
Lugg et al. (2017) [16]	Prospective cohort April 2010–April 2014	N = 462 curative intent lung resection for NSCLC	• Current smoker • Quit <6 weeks before surgery • Quit >6 weeks or more before surgery • Never smoker	Postoperative pulmonary complications (defined by Melbourne Group Scale)	Current smokers had higher rate of complications than never smokers No significant difference in rate of complications between groups of ex-smokers	Low

Rodriguez et al. (2017) [13]	Retrospective cohort Jan 1994–May 2015	N = 378 active or former smokers, nonextended lobectomy for malignancy	• Current smokers: active smoker at time of surgery or quit within 16 weeks before surgery • Former smoker: quit up to 16 weeks before surgery	Postoperative pulmonary complications (pulmonary atelectasis requiring bronchoscopy, pneumonia or both)	No significant difference between current and former smokers in development of postoperative pulmonary complications	Low
Fukui et al. (2019) [10]	Retrospective cohort Jan 2012–March 2016	N = 666 pulmonary resection for primary lung cancer	• Current smoker • Quit >12 months before surgery • Quit 6–12 months before surgery • Quit 3–6 months before surgery • Quit 1–3 months before surgery • Quit <1 month before surgery • Never smoker	Operative mortality (30 and 90 days after resection), complications (hypoxia that required home oxygen therapy, pneumonia, intractable air leakage that required adhesion therapy or additional drainage, bronchopleural fistula, empyema, arrhythmias, pneumonia, atelectasis, uncontrolled sputum production that required bronchoscopy, and acute exacerbation of idiopathic interstitial pneumonias)	Significantly different rates of 90-day mortality and complications between groups of ex-smokers Risk of pulmonary complications decreased with increased period of smoking cessation	Low

stopped smoking 2–4 weeks before surgery had a higher incidence of PPCs (53.8%) than patients who smoked within 2 weeks of surgery (43.2%). Data were also presented as 4-week moving averages of PPC incidence among former smokers who were grouped into intervals from 0 to 15 weeks smoke-free before surgery. Incidence was highest for patients who had 1–4 weeks smoking cessation. The incidence of PPCs began to decrease for patients with smoke-free periods of 5–8 weeks and longer. Multivariate logistic regression analysis indicated no statistically significant increased risk for developing a PPC in current and former smokers compared to never smokers. Despite these findings, Nakagawa et al. concluded that patients should stop smoking for at least 4 weeks before surgery to reduce complication risk. Of the studies described in this review, only this publication by Nakagawa et al. made a recommendation for a smoke-free period before surgery.

Vaporciyan et al. and Fukui et al. also performed retrospective cohort studies at a single institution. Vaporciyan et al. reviewed data from 257 patients who underwent pneumectomy for malignancy for factors associated with major pulmonary events (MPE), defined as pneumonia or acute respiratory distress syndrome [9]. In a multivariate analysis, those who quit smoking less than 1 month prior to surgery were at increased risk of MPE compared to those who quit greater than or equal to 1 month prior, OR 2.70 (95% CI 1.18–6.17, $p = 0.018$). Fukui et al. reviewed records of 666 lung cancer patients who underwent pulmonary resection for factors associated with operative mortality and postoperative complications [10]. In the multivariate analysis, those with a history of smoking had a greater risk of pulmonary complications than those who had never smoked, OR 2.83 (95% CI 1.20–6.67, $p = 0.017$). In a separate, unadjusted analysis of smoking cessation duration, there was a statistically significant decrease in the risk of pulmonary complications with increased duration of cessation. Neither of these studies identified an inflection point of smoking cessation past which the pulmonary complication risk significantly decreased.

Six papers observed no effect of the timing of smoking cessation on postoperative morbidity. Groth et al. [11], Seok et al. [12], and Rodriguez et al. [13] performed single institutional retrospective cohort studies. Following results from Nakagawa et al., Groth et al. and Seok et al. selected 1-month smoke-free before surgery as a cut-off point to differentiate between recent and distant smokers. Groth et al. reviewed records of 213 NSCLC patients who underwent pulmonary resection. Seok et al. analyzed data from 232 patients who had a smoking history and underwent resection for lung cancer. They further stratified their cohort into a group of fewer than 14 smoke-free days before surgery. Both studies found no significant differences between groups of smokers in the rate of postoperative complications.

Rodriguez et al. used a cut point of 16 weeks before surgery to stratify current and former smokers in their study of 378 patients who underwent lobectomy for malignancy. Current smokers were defined as patients who had smoked within 16 weeks before surgery. Former smokers had refrained for at least 16 weeks before surgery. Although they described their study as a case-control, the authors separated the cohort by exposure (smoking status) rather than outcome (pulmonary complication), and thus performed a retrospective cohort study to evaluate the risk of

postoperative pulmonary complications associated with recent smoking. To minimize confounding, they matched 134 pairs of current and former smokers by age, body mass index, FEV1%, FEV1/FVC, surgical approach (VATS or minimally invasive thoracotomies) and NSCLC versus other diagnosis. There was no difference in the risk of developing a pulmonary complication between the two groups.

A retrospective review of Society of Thoracic Surgeons (STS) General Thoracic Surgery Database, including 79 participating institutions, found no association between timing of cessation and postoperative complications. Mason et al. collected STS General Thoracic Surgery Database records for 7990 patients who underwent pulmonary resection for primary lung cancer to analyze risks of hospital mortality and pulmonary complications associated with smoking status [14]. Patients were stratified by timing of smoking cessation according to STS data collection fields (Table 7.2). Only current smokers had a statistically significant increased risk of pulmonary complications compared to never smokers (OR 1.8, 95% CI: 1.05–3.1, $p = 0.03$). Odds ratios for patients who stopped between 14 days and 1 month before surgery (OR 1.6, 95% CI: 0.85–3.1, $p = 0.14$), 1–12 months before surgery (OR 1.5, 95% CI: 0.85–2.8, $p = 0.2$), and more than 12 months before surgery (OR 1.3, 95% CI: 0.77–2.2, $p = 0.3$) gradually decreased with increasing duration of cessation but did not approach statistical significance.

Two prospective observational studies found evidence that current smokers had higher complication rates than never smokers, but no difference in complication rates between groups of former smokers. Barrera et al. recruited 300 patients who underwent thoracotomy for resection of primary or secondary lung tumors at their institution [15]. The rate of pulmonary complications was significantly different between never smokers and all smokers (8% vs. 19%, $p = 0.03$), but there was no difference between groups of smokers stratified by smoking cessation duration. Lugg et al. recruited 462 patients who underwent NSCLC resection and analyzed frequency of PPCs according to smoking status [16]. Current smokers had a higher frequency of PPCs than never smokers (22% vs. 2%, $p = 0.004$). Among groups of former smokers, there was a trend of decreasing PPC frequency (ex-smoker <6 weeks, 10.9% vs. ex-smoker ≥6 weeks, 11.8%), but there was no statistically significant difference between the groups of former smokers, between former smokers and current smokers or between the former smokers and never smokers.

Conclusions and Recommendations

Based on the data presented, there is no ideal period of preoperative smoking cessation that would reduce morbidity risk associated with tobacco use in patients undergoing lung resection for NSCLC. Nakagawa et al.'s early study found an unexpected increase in complications for patients who underwent resection after 2–4 weeks of smoking cessation compared to those who smoked within 2 weeks before surgery. This prompted several follow-up studies to investigate this effect. Vaporyican et al. found evidence that smoking within 1 month of surgery was a significant factor for the development of postoperative pulmonary events, but other studies that evaluated

the 1-month cutoff point, such as those by Groth et al., Seok et al., and Mason et al. did not find an association between smoking within 1 month of surgery and increased morbidity. Studies by Mason et al., Barrera et al., and Lugg et al. provided evidence that an increased duration of smoking cessation before surgery was associated with decreased risk of complications, but there was insufficient evidence for a clear time point past which the risk was significantly reduced.

Delaying surgery for current smokers to extend preoperative smoking cessation is unnecessary. A prolonged interval between diagnosis of early-stage NSCLC and definitive surgical resection is associated with upstaging and decreased survival [6, 7]. In the absence of adequate evidence that postponing surgery to prolong the period of smoking cessation significantly decreases postoperative morbidity, surgical resection should proceed without delay.

Recommendations

- Smoking cessation should be encouraged, but there is no ideal period of preoperative smoking cessation to reduce the risk of surgical morbidity associated with smoking (evidence quality low; weak recommendation).
- Delaying surgery for active smokers to extend preoperative smoking cessation is unnecessary (evidence quality low; weak recommendation).

A Personal View of the Data

The quality of evidence available to answer the PICO question of whether preoperative smoking cessation decreases morbidity after lung resection is limited by the small cohorts and retrospective nature of the studies. Prospective data is limited to two observational studies with cohort sizes of fewer than 500 patients. Given the impractically of conducting a randomized controlled trial with smoking cessation as the intervention, future clinical studies may not be able to thoroughly eliminate bias.

Several sources of bias were found in the literature. All studies captured smoking cessation duration as an ordinal variable. The intervals of smoking cessation duration among groups were often inconsistent. Some groups were defined by broad intervals that may have grouped together patients with different degrees of risk. A group defined as patients who quit smoking 1–12 months before surgery, as in Mason et al.'s study for example, captures a wide range of possible morbidity risk. Also missing from the majority of these studies is a way to account for a patient who significantly decreased smoking before surgery. For example, a patient who smokes one pack of cigarettes per day but decreases to a few cigarettes per day is classified as a current smoker according to definitions used in the literature. This patient may be at a lower risk of pulmonary complications than those who continue to smoke one pack per day up to the time of surgery but the approach to patient stratification currently found in the literature would not capture this decreased risk. A third source

of bias in the literature is the patient-reported smoking cessation time, which risks errors in patient recall. Quantifying nicotine exposure with a biomarker such as serum or urinary cotinine may allow more accurate assessment of smoking exposure. Patients may underreport the time since they last smoked when presenting for preoperative evaluation and on the day of surgery [17]. Future investigators should take these considerations into account when designing studies.

At this time no society guidelines recommend a specific period of smoking cessation before cancer resection. Recent editions of the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology and the American College of Chest Physicians Lung Cancer Guidelines review much of the data referenced in this chapter and conclude that, while smoking cessation should be encouraged as early as possible, it should not delay the appropriate timing of lung cancer resection [18, 19].

Practices among individual cardiothoracic surgeons for the preoperative management of patients who smoke vary considerably. Marrufo et al. surveyed 200 cardiothoracic surgeons who contribute to the STS General Thoracic Surgery Database to determine beliefs and practices regarding smoking cessation before lung resection [20]. Approximately half of the surgeons indicated that it is ethical to mandate smoking cessation prior to lung resection. However, 60% do not require cessation. The risk of disease progression was an important consideration when mandating smoking cessation prior to surgery. Of those who require smoking cessation, the duration of cessation most commonly required was at least 2 weeks. In our practice we strongly encourage every patient to stop or at least significantly reduce smoking before lung resection, but do not require cessation.

References

1. Garces YI, Yang P, Parkinson J, Zhao X, Wampfler JA, Ebbert JO, et al. The relationship between cigarette smoking and quality of life after lung cancer diagnosis. Chest. 2004;126(6):1733–41.
2. Dresler CM, Bailey M, Roper CR, Patterson GA, Cooper JD. Smoking cessation and lung cancer resection. Chest. 1996;110(5):1199–202.
3. Cataldo JK, Dubey S, Prochaska JJ. Smoking cessation: an integral part of lung cancer treatment. Oncology. 2010;78(5–6):289–301.
4. Hawn MT, Houston TK, Campagna EJ, Graham LA, Singh J, Bishop M, et al. The attributable risk of smoking on surgical complications. Ann Surg. 2011;254(6):914–20.
5. Schmid M, Sood A, Campbell L, Kapoor V, Dalela D, Klett DE, et al. Impact of smoking on perioperative outcomes after major surgery. Am J Surg. 2015;210(2):221–229.e6.
6. Samson P, Patel A, Garrett T, Crabtree T, Kreisel D, Krupnick AS, et al. Effects of delayed surgical resection on short-term and long-term outcomes in clinical stage I non-small cell lung cancer. Ann Thorac Surg. 2015;99(6):1906–13.
7. Yang CFJ, Wang H, Kumar A, Wang X, Hartwig MG, D'Amico TA, et al. Impact of timing of lobectomy on survival for clinical stage IA lung squamous cell carcinoma. Chest. 2017;152(6):1239–50.
8. Nakagawa M, Tanaka H, Tsukuma H, Kishi Y. Relationship between the duration of the preoperative smoke-free period and the incidence of postoperative pulmonary complications after pulmonary surgery. Chest. 2001;120(3):705–10.

9. Vaporciyan AA, Merriman KW, Ece F, Roth JA, Smythe WR, Swisher SG, et al. Incidence of major pulmonary morbidity after pneumonectomy: association with timing of smoking cessation. Ann Thorac Surg. 2002;73(2):420–6.
10. Fukui M, Suzuki K, Matsunaga T, Oh S, Takamochi K. Importance of smoking cessation on surgical outcome in primary lung cancer. Ann Thorac Surg. 2019;107(4):1005–9.
11. Groth SS, Whitson BA, Kuskowski MA, Holmstrom AM, Rubins JB, Kelly RF. Impact of preoperative smoking status on postoperative complication rates and pulmonary function test results 1-year following pulmonary resection for non-small cell lung cancer. Lung Cancer. 2009;64(3):352–7.
12. Seok Y, Hong N, Lee E. Impact of smoking history on postoperative pulmonary complications: a review of recent lung cancer patients. Ann Thorac Cardiovasc Surg. 2014;20(2):123–8.
13. Rodriguez M, Gómez-Hernandez MT, Novoa N, Jiménez MF, Aranda JL, Varela G. Refraining from smoking shortly before lobectomy has no influence on the risk of pulmonary complications: a case-control study on a matched population. Eur J Cardiothorac Surg. 2017;51(3):498–503.
14. Mason DP, Subramanian S, Nowicki ER, Grab JD, Murthy SC, Rice TW, et al. Impact of smoking cessation before resection of lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database study. Ann Thorac Surg. 2009;88(2):362–71.
15. Barrera R, Shi W, Amar D, Thaler HT, Gabovich N, Bains MS, et al. Smoking and timing of cessation: Impact on pulmonary complications after thoracotomy. Chest. 2005;127(6):1977–83.
16. Lugg ST, Tikka T, Agostini PJ, Kerr A, Adams K, Kalkat MS, et al. Smoking and timing of cessation on postoperative pulmonary complications after curative-intent lung cancer surgery. J Cardiothorac Surg. 2017;12(1):52.
17. Wolvers PJD, Bruin SC, Mairuhu WM, de Leeuw-Terwijn M, Hutten BA, Brandjes DPM, et al. Self-reported smoking compared to serum cotinine in bariatric surgery patients: smoking is underreported before the operation. Obes Surg. 2020;30(1):23–37.
18. Shields PG, Herbst RS, Arenberg D, Benowitz NL, Bierut L, Luckart JB, et al. Smoking cessation, Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2016;14(11):1430–68.
19. Leone FT, Evers-Casey S, Toll BA, Vachani A. Treatment of tobacco use in lung cancer. Chest. 2013;143(5):e61S–77S.
20. Marrufo AS, Kozower BD, Tancredi DJ, Nuño M, Cooke DT, Pollock BH, et al. Thoracic surgeons' beliefs and practices on smoking cessation before lung resection. Ann Thorac Surg. 2019;107:1494–9.

8 Is Low Tech as Good as High Tech Exercise Testing in Assessing Healthy Candidates for Lung Resection?

Michael Gooseman and Alessandro Brunelli

Introduction

For early stage non small cell lung cancer (NSCLC), surgery is widely recognised as the best treatment modality. However, even for the 'healthy patient' proceeding with surgery, a resection can cause variable functional impairment with associated morbidity and mortality. Exercise testing has a role in assessing the entire oxygen transport system with a view to detection of deficits that may present as postoperative complications. The aim of this chapter is to review the most relevant evidence relating to options for exercise testing which is now recognised as a critical component of the pre-operative functional assessment in patients undergoing lung resection.

Search Strategy

A literature search of English language publications from 1984 to 2019 was used to identify published data on exercise testing and its role in functional assessment and risk stratification in lung resection. The date range was extended deliberately to capture earlier studies relating to low tech assessment. Databases searched included PubMed, Embase and Cochrane Evidence Based Medicine. Terms used in the search included "low tech exercise testing lung resection," "high tech exercise testing lung resection," "cardiopulmonary exercise test," "shuttle walk test," "6 min walk test" and "stair climbing test" (Table 8.1). Additionally, searches were made using "functional assessment lung resection," "preoperative assessment lung

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Table 8.1 PICO formatted terms for literature search

Population	Intervention	Comparison	Outcomes
Candidates for lung resection	Shuttle walk test 6 min walking test Stair climbing test	Cardiopulmonary exercise test	Morbidity Mortality Complications

Bagg LR The 12-min walking distance; its use in the pre-operative assessment of patients with bronchial carcinoma before lung resection. Respiration 1984; 46: 342-34

resection". Articles that were related to surgery other than lung cancer resection were deliberately excluded. The data was classified using the GRADE system.

Results

The outcome of these searches demonstrates a significant body of literature specifically related to the pre-operative assessment and evaluation, including exercise assessment, of patients being considered for lung cancer resection surgery. In 2009 and 2010 evidence-based clinical guidelines focusing on functional evaluation of lung resection candidates were published by the European Respiratory Society/ European Society of Thoracic Surgeons (ERS/ESTS) and the British Thoracic Society/ Society for Cardiothoracic Surgeons (BTS/ SCTS) respectively [1, 2]. In 2013, Brunelli and colleagues produced clinical practice guidelines on behalf of the American College of Chest Physicians (ACCP) [3]. This work included a rigorous review of the available literature at the time with the production of an algorithm for the preoperative physiological assessment of this group of patients.

The result of these guidelines has been the general consensus that the formal cardiopulmonary exercise test (CPET) is the gold standard for functional assessment and risk stratification in patients proceeding to lung resection. However, CPET is not always an easily accessible test—an ERS/ ESTS web based survey from 2009 showed that the technology was available in 75% of hospitals. This survey also showed that only 10–30% of patients have a CPET prior to lung resection [4]. Brunelli and colleagues in a 2010 review suggested that the discrepancy between accessibility and utilisation may be related to the uncertainty around indications for CPET and its role in assessing the apparently healthy patient pre-operatively [5]. The ERS/ESTS survey showed that 18% of respondents used low tech exercise testing routinely for all patients [4].

Analysis of the available literature is made for the 6 min walk test, stair climbing test, shuttle test and the cardiopulmonary exercise test.

6 Min Walk Test (6MWT)

The walking test was first developed in the 1960s and should be performed as described in the American Thoracic Society guidelines [6]. This test was evaluated in thoracic surgery as long ago as the 1980s. Bagg, with a small series of 22 patients, was not able to demonstrate any difference between complicated and non-complicated patients in walking a distance over 12 min [7]. Similarly, in the same decade, Markos and colleagues with a series of 55 patients found that the distance walked over 12 min was not predictive of postoperative morbidity and mortality [8].

Pierce and colleagues showed that a 6 min walk test distance could predict post-operative respiratory failure but not other morbidity or mortality [9]. Conversely, Marjanski and colleagues were able to show that patients walking less than 500 m during this test had an increased risk of postoperative morbidity and increased length of hospital stay [10]. Current clinical guidance, reflecting this conflicting scientific evidence, recommends that the 6 min walk test should not be used in selecting patients for operation [1].

Shuttle Walk Test (SWT)

The incremental shuttle walk test was first designed with the aim of assessing the exercise capacity of patients suffering with chronic obstructive pulmonary disease (COPD). In 1994, Singh and colleagues found the SWT produced results that correlated more closely with the VO_2max than the 6MWT [11]. Regression analysis estimated that 25 shuttles indicated a VO_2max of 10 ml/kg/min [12]—a figure below which patients should not be considered for surgical resection. Indeed, ACCP guidelines recommend patients with a VO_2max below 10 ml/kg/min are counselled about sub-lobar resections or non-operative treatment options for their lung cancer [3].

Winn and colleagues did not find any statistically significant difference in the distance walked on the shuttle test between patients who did and did not develop post-operative complications following lung resection [13]. They showed that those patients who walked more than 400 m during a SWT had a VO_2max measured at a later CPET of greater than 15 ml/kg/min. Of those patients who failed to walk 400 m, less than half had a VO_2max below 15 ml/kg/min [14]. These findings led to the conclusion that SWT may underestimate exercise capacity.

Benzo and colleagues found a high correlation between each shuttle on the SWT and VO_2 consumption [15]. 25 shuttles had positive predictive value for predicting a VO_2peak >15 mlkg/min of 90%. Fennelly and colleagues, in 2017, showed that patients walking further than 400 m experienced a very low incidence of complications [16]. Current guidelines suggest that patients who can complete 400 m on the SWT are fit to undergo surgical resection [3].

Stair Climbing Test

The stair climbing test is now frequently used as a screening test as part of patient selection after first being studied several decades ago. One of the issues remains a lack of standardization in how the test is performed. Factors such as number of steps per flight, height of each individual step, and speed of ascent mean that results need to be interpreted with this in mind. For the 'healthy patient' proceeding with surgery, the ability of an exercise test to predict postoperative complications is important. Olsen and colleagues were the first group to raise the possibility of this test being formally adopted in the preoperative assessment. In a small study of 54 patients undergoing thoracotomy they showed that patients who could not climb three flights of stairs had greater rate of complications and longer hospital stay [17]. Information from this study has to be interpreted with caution given the small sample size and inconsistency of the surgical procedures undertaken. Many of the other studies looking at stair climbing as an exercise tool have examined patients known to have co-morbidity including significant history of cardiac disease and COPD.

Brunelli and colleagues, in a series of 109 patients, measured oxygen consumption during stair climbing using a portable gas analyser. Ninety-eight percent of patients climbing more than 22 m had a positive predictive value of 86% to predict a VO_2peak of 15 ml/kg/min [18]. Current clinical guidance suggests that patients able to ascend greater than 22 m can proceed to surgery without the need for further assessment with CPET [3].

Cardiopulmonary Exercise Test

While the scientific evidence for the low-tech exercise testing began to build during the 1980s, the first work regarding the CPET was published in the nineties. Bollinger and colleagues, with a series of 80 patients submitted to lung resection, showed that VO_2max less than 60% had a higher risk of postoperative adverse events [19]. This data was confirmed by prospective trial that was conducted during the nineties [20].

The more recent evidence has demonstrated that the absolute value of the maximal oxygen consumption measured in ml/kg/min (VO_2max) is the optimal ergometric measurement in quantifying risk in patients undergoing major anatomical lung resection. The important studies are summarised in Table 8.2.

The VO_2max obtained during CPET is now considered in international published guidelines, supported by the scientific evidence, as the most important and reliable parameter in assessing operative risk in patients going ahead with lung cancer resection. When the VO_2max is less than 10 ml/kg/min the risk for major lung resection is high and the patient should be considered for minor surgical resection or alternative nonsurgical therapy [3].

Table 8.2 Demonstration of VO_2max as a predictor of operative outcome

Author (year)	N	Surgery type	Study type (quality of evidence)	Outcome	Evidence quality
Loewen et al. (2007) [21]	346	Thoracotomy ± lung resection	Prospective observational study	VO_2max < 15 ml/kg/min—increased risk of complications	Moderate
Bayram et al. (2007) [22]	55	Major lung resection	Prospective observational study	VO_2max < 15 ml/kg/min—increased risk of complications	Low
Brunelli et al. (2009) [23]	204	Major lung resection	Retrospective observational study	VO_2max < 12 ml/kg/min—increased risk of complications	Moderate
Licker et al. (2011) [24]	210	Lung resection	Retrospective observational study	VO_2max < 10 ml/kg/min—increased risk of complications	Moderate

Conclusions and Recommendations

Available scientific evidence suggests that the SWT and stair climbing low technology exercise tests are reliable tools in detecting major cardiopulmonary deficits in the otherwise healthy candidate for surgery. However, they are limited in being able to accurately identify deficits in the oxygen transport system. It is therefore unlikely that high technology cardiopulmonary exercise tests that can directly and accurately measure expired gases will be fully replaced. CPET is the gold standard in precisely detecting and then quantifying aerobic reserve deficits.

Recommendations

- Low tech testing should be used as a first line screening test in apparently healthy candidates for lung resection (evidence quality moderate; strong recommendation).
- Any patient who fails to meet exercise thresholds of a low tech test should be referred for a formal CPET (evidence quality moderate; strong recommendation).

A Personal View of the Data

Pre-operative functional assessment prior to proceeding with lung resection is important. Even the apparently healthy patient can have significant underlying cardio-respiratory impairment putting them at high peri-operative risk. Identifying the highest risk patients allows for an open and informed discussion with the patient and ongoing care to be tailored to their needs. In every day practice the use of both low tech and high-tech exercise testing is important and can be used to complement each other. They are substantially different types of exercise: for instance, CPET is an incremental maximal test, while stair climb test is a constant work rate test. The muscles used to perform these tests may also vary, as stair climb for instance utilizes larger muscle mass including the back and gluteus. Therefore, the performance at each of these tests may be difficult to compare, taking into account that exercise performance is very exercise specific. In general, however, it is the opinion of the authors that low technology tests should not be used alone to exclude a patient from surgery without a formal CPET evaluation in case of poor performance. Nevertheless, they can obviate the use of more sophisticated tests in case of optimal results (i.e. >400 m at shuttle walk test or >22 m at stair climb test).

References

1. Brunelli A, Charloux A, Bollinger CT, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J. 2009;34:17–41.
2. Lim E, Baldwin D, Beckles M, et al. Guidelines on the radical management of patients with lung cancer. Thorax. 2010;65:iii1–iii27.
3. Brunelli A, Kim AW, Berger KI, et al. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e166S–90S.
4. Charlous A, Brunelli A, Bollinger CT, et al. European Respiratory Society and European Society of Thoracic Surgeons Joint Task Force on Fitness for Radical Therapy. Lung function evaluation before surgery in lung cancer patients: how are recent advances put into practice? A survey among members of the European Society of Thoracic Surgeons (ESTS) and of the Thoracic Oncology Section of the European Respiratory Society (ERS). Interact Cardiovasc Thorac Surg. 2009;9:925–31.
5. Brunelli A, Pompili C, Salati M. Low-technology exercise test in the preoperative evaluation of lung resection candidates. Monaldi Arch Chest Dis. 2010;73:72–8.
6. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111–7.
7. Bagg LR. The 12-min walking distance; its use in the pre-operative assessment of patients with bronchial carcinoma before lung resection. Respiration. 1984;46:342–5.
8. Markos J, Mullan BP, Hillman DR, et al. Preoperative assessment as a predictor of mortality and morbidity after lung resection. Am Rev Respir Dis. 1989;139:902–10.
9. Pierce RJ, Copland JM, Sharpe K, Barter CE. Preoperative risk evaluation for lung cancer resection. Chest. 1992;102:1774–9.
10. Marjanski T, Wnuk D, Bosakowski D, et al. Patients who do not reach a distance of 500 m during the 6-min walk test have an increased risk of postoperative complications and prolonged hospital stay after lobectomy. Eur J Cardiothorac Surg. 2015;47:213–9.

11. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax. 1992;47:1019–24.
12. Singh SJ, Morgan MD, Hardman AE, Rowe C, Bardsley PA. Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test in chronic airflow limitation. Eur Respir J. 1994;7:2016–20.
13. Win T, Jackson A, Groves AM, et al. Relationship of shuttle walk test and lung cancer surgical outcome. Eur J Cardiothorac Surg. 2004;26:1216–9.
14. Win T, Jackson A, Groves AM, Sharples LD, Charman SC, Laroche CM. Comparison of shuttle walk with measured peak oxygen consumption in patients with operable lung cancer. Thorax. 2006;61:57–60.
15. Benzo RP, Sciurba FC. Oxygen consumption, shuttle walking test and the evaluation of lung resection. Respiration. 2010;80(1):19–23.
16. Fennelly J, Potter L, Pompili C, Brunelli A. Performance in the shuttle walk test is associated with cardiopulmonary complications after lung resections. J Thorac Dis. 2017;9(3):789–95.
17. Olsen GN, Bolton JWR, Weiman DS, et al. Stair climbing as an exercise test to predict the postoperative complications of lung resection: two years experience. Chest. 1991;99:587–90.
18. Brunelli A, Xiume F, Refai M, Salati M, Di Nunzio L, Pompili C, Sabbatini A. Peak oxygen consumption measured during the stair-climbing test in lung resection candidates. Respiration. 2010;80(3):207–11.
19. Bollinger CT, Jordan P, Soler M, Stulz P, Gradel E, Skarvan K, Elsasser S, Gonon M, Wyser C, Tamm M. Exercise capacity as a predictor of postoperative complications in lung resection candidates. Am J Respir Crit Care Med. 1995;151:1472–80.
20. Brutsche MH, Spiliopoulos A, Bollinger CT, Licker M, Frey JG, Tschopp JM. Exercise capacity and extent of resection as predictors of surgical risk in lung cancer. Eur Respir J. 2000;15:828–32.
21. Loewen GM, Watson D, Kohman L, Herndon JE II, Shennib H, Kernstine K, Olak J, Mador MJ, Harpole D, Sugarbaker D, Green M. Preoperative exercise VO2 measurement for lung resection candidates: results of Cancer and Leukaemia Group B Protocol 9238. J Thorac Oncol. 2007;2:619–25.
22. Bayram AS, Candan T, Gebitekin C. Preoperative maximal exercise oxygen consumption test predicts postoperative pulmonary morbidity following major lung resection. Respirology. 2007;12:505–10.
23. Brunelli A, Belardinelli R, Refai M, Salati M, Socci L, Pompili C, Sabbatini A. Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. Chest. 2009;135:1260–7.
24. Licker M, Schnyder JM, Frey JG, Diaper J, Cartier V, Inan C, Robert J, Bridevaux PO, Tschopp JM. Impact of aerobic exercise capacity and procedure-related factors in lung cancer surgery. Eur Respir J. 2011;37:1189–98.

9 Does Assessment of Frailty and Sarcopenia in Lung Resection Candidates Affect Patient Selection?

Megan Huisingh-Scheetz and Michelle Martinchek

Introduction

Frailty and sarcopenia have been important concepts in aging research for decades to aid in identifying vulnerability to morbidity and mortality among older adults [1–6]. Approximately one in six community-dwelling older adults are estimated to be frail [7], and higher rates are projected among lung resection candidates [8]. As increasingly older patients are being considered for surgery, frailty and sarcopenia have been studied in surgical patient populations to help with risk stratification [9, 10]. Frailty identifies a syndrome indicating global physiologic vulnerability while sarcopenia refers specifically to low muscle volume and function. Sarcopenia can be, and often is, a component of frailty but it is not required.

Frailty. At least four consensus panels have assembled to operationalize a modern frailty definition and measurement approach [11–14]. One such panel, convened in 2012, successfully defined frailty as "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death," particularly in the face of a stressor [13]. However, there remains disagreement about how to best *measure* frailty. As such, a number of tools exist in the literature [15, 16]. Most tools stem from two theoretical constructs: the biologic physical frailty phenotype [1] and the accumulation of deficits theories [17]. The physical frailty phenotype, based on a proposed biologic pathway, is composed of five criteria: weak grip strength, slow gait speed, low physical activity, unintentional weight loss, and exhaustion or fatigability. Patients exhibiting 1–2 criteria are deemed pre-frail and ≥3 criteria are deemed frail.

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The accumulated deficits index combines a group of unique 'deficits', generally 30–70 items, from multiple domains (symptoms, physical exam signs, abnormal lab values, diseases, and disabilities) summed and divided by the total deficits assessment creating a score ranging from zero to one.

Sarcopenia. A number of consensus panels and task forces have defined and revised the definition of sarcopenia over the last several decades [18–27]. Groups agree that sarcopenia should be identified using a combination of low muscle mass and low muscle function (strength or performance). Low muscle mass can be identified using bioimpedance analysis, dual energy X-ray absorptiometry, total or partial body potassium per fat-free soft tissue, ultrasound, CT or MRI. Creatinine dilution is a much newer method [28]. Suggested cut points for low muscle mass vary significantly among expert groups, highlighting both a gap in literature as well as the relevance of ethnic-specific cut-points [19, 21, 25]. Muscle dysfunction can be identified using measures such as grip strength, knee flexion/extension, usual gait speed, chair stands, Timed Up and Go, 400-m walk, peak expiratory flow, the Short Physical Performance Battery, or stair climb power test. Some have advocated the use of sarcopenia screeners to case find [24].

Frailty and sarcopenia have shown predictive value in numerous surgical and procedural patient groups [9, 29–37]. Such efforts resulted in the 2012 American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society "best practices" guideline for the pre-operative care of the older adult which included a recommendation to assess frailty in all pre-operative older surgical candidates [38]. Despite the growing frailty and sarcopenia surgery literature base, few studies have explored frailty and sarcopenia in lung resection.

Search Strategy

A literature search of primary, human subject research articles published between 1999 and 2019 in the English language was conducted in September 2019 to identify studies reporting the relationship between pre-operative frailty or sarcopenia and post-operative lung resection outcomes (Table 9.1). Databases searched included Pubmed, MEDLINE (EBSCO), Cochrane Library, and CINAHL Plus with Full Text [*Search Term*: (lobectomy OR lobectomies OR pneumonectomy OR "pneumonectomy" [Mesh] OR pneumonectomies OR "lung resection" OR "lung surgery" OR "pulmonary surgical procedures" [Mesh]) AND ("Frail Elderly" [Mesh] OR "Frailty" [Mesh] OR frailty OR sarcopenia OR "sarcopenia" [Mesh])];

Table 9.1 PICO formatted terms for literature search

Patient/population	Intervention(s)	Comparison	Outcome
Patients, including adults ≥65 years, undergoing major/ lung resection	Pre-operative frailty or sarcopenia evaluation	Standard of care preoperative evaluation	Prediction of major surgical morbidity or mortality, length of stay, discharge location, postoperative quality of life, or cancer recurrence

Web of Science, Science Direct and Scopus [*Search Term*: (lobectomy OR lobectomies OR pneumonectomy OR pneumonectomies OR "lung resection" OR "lung surgery" OR "pulmonary surgical procedures") AND ("Frail Elderly" OR Frailty OR frailty OR sarcopenia)]; and MEDLINE (Ovid) [*Search Term*: (lobectomy OR lobectomies OR pneumonectomy OR pneumonectomies OR lung resection OR lung surgery OR pulmonary surgical procedures) AND (Frail Elderly OR Frailty OR frailty OR sarcopenia)].

To be eligible for inclusion, studies had to analyze or sub-analyze thoracic surgery candidates undergoing lung resection only (e.g., esophageal, lung transplant studies excluded). Studies including only medically managed (e.g., chemotherapy or radiation) lung cancer patients were excluded. Study samples had to include older adults (≥65 years) but not exclusively. Studies were only eligible if they included a pre-operative measure of frailty or sarcopenia that aligned with the modern definitions. Studies solely using age, body mass index, inflammatory markers, or disability of (instrumental) activities of daily living as the frailty or sarcopenia measure were excluded. One exception was the sole use of measured gait (e.g., 6-min walk test alone) which was allowed due to the recognition of gait speed as a single measure of frailty [39]. While experts recommend sarcopenia be captured with both muscle quantity and muscle quality, we allowed studies using only muscle quantity due to the lack of studies including both, noting this as a major gap in the literature. We excluded findings reported only in abstracts, conference papers, or unpublished data.

Results

A total of 121 unique article matches were identified using the pre-specified database search terms. Two independent reviewers identified 13 primary research articles that met inclusion criteria. An additional 36 relevant reviews, editorials, comments, or letters were also identified. Reference list review yielded an additional four primary research articles meeting inclusion criteria and an additional five related review articles. Reference list review yielded two additional unique eligible primary research articles for inclusion. Altogether 19 studies met criteria for inclusion: four addressing frailty and 15 addressing sarcopenia. Only results from lung resection-specific analyses or sub-analyses are reported. Multivariate analyses were preferentially reported when available. If multivariate analyses were not available, other analyses were reported.

Frailty and Lung Resection Outcomes (Table 9.2)

Pre-operative frailty assessment in lung resection was the focus of four retrospective articles. Three studies analyzed data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) dataset [40–42]. The remaining study analyzed data from three different hospitals [43].

Table 9.2 Frailty in lung resection

Author (year)	N (lung resection candidates only)	Age (years)	Data source and/or location	Frailty measurement (∗indicates use of validated frailty tool)	Surgery type	Outcomes	Study type (quality of evidence)
Mosquera 2016 [40]	~4,647.04 or 2% of total sample 232,352 of patients undergoing high-risk procedures that are linked to surgeon and hospital volume	Mean 63.9 for total sample (Not available for lung resection candidates only)	ACS-NSQIP[a] 2005–2012	11-item NSQIP Frailty Index[b] (adapted from CSHA-FI) [42]: non-frail = 0 points; mildly frail = 1 point; moderately frail = 2 points; severely frail ≥3 points (range 0–11 points)	Lung surgeries coded as "pulmonary resection"	Unadjusted Frailty Index and 30-day mortality by procedure type (only pulmonary resection shown): non-frail 0.8%, mildly frail ~2%, moderately frail ~3%, severely frail 6.4%, p = N/A	Retrospective (low)
Tsiouris 2013 [41]	1940	Mean 66 ± 11, range 19–90	ACS-NSQIP[a] 2005–2010	11-item NSQIP Modified Frailty Index[c] (adapted from CSHA-FI) [42]: (range 0–1)	Lobectomies coded as Current Procedure Terminology code 32480. Did not include VATS	Multivariate logistic regression on post-operative mortality: mFI > 0.27 OR 9.3 (95% CI 9.1–270), p = 0.002 Multivariate logistic regression on Clavien 4 complications: mFI > 0.27 OR 4.8 (95% CI 1.3–230), p = 0.027	Retrospective (low)

Velanovich 2013 [42]	4648 out of total sample 971,434 all surgical patients	Mean 55.3 ± 17.2, range 16–90+ for total sample (not available for thoracic surgery candidates only)	ACS-NSQIP[a] 2005–2009	11-item NSQIP Frailty Index[c] (adapted from CSHA-FI) [42]: (range 0–1, used ordinal variable 0.09, 0.18, 0.36, 0.45, 0.45, 0.63, 0.72, 0.81, 1.0)	General thoracic surgery NOS	Unadjusted Frailty Index and 30-day mortality by surgical complexity: OR for each frailty unit increase on ordinal scale: =1.8 (95% CI 1.18–2.73), trend p = 0.006 for low complexity; 1.84 (95% CI 1.57–2.14), trend p < 0.001 for moderate complexity; 1.57 (95% CI 1.28–1.93), trend p < 0.001 for high complexity Unadjusted Frailty Index and 30-day morbidity by surgical complexity: OR for each frailty unit increase on ordinal scale: =1.24 (95% CI 1.06–1.45), trend p=0.006 for low complexity; 1.53 (95% CI 1.38–1.69), trend p < 0.001 for moderate complexity; 1.25 (95% CI 1.15–1.37), trend p < 0.001 for high complexity	Retrospective (low)

(continued)

Table 9.2 (continued)

Author (year)	N (lung resection candidates only)	Age (years)	Data source and/or location	Frailty measurement (∗indicates use of validated frailty tool)	Surgery type	Outcomes	Study type (quality of evidence)
Handy 2002 [43]	139	Mean 62.05 ± 10.62, range, 31–86	Patients referred for lung cancer resection to three hospitals (academic hospital, Veteran's Affairs hospital, and community tertiary care center)	6-min walk test (>1000 ft. versus <1000 ft.)	Surgeon dictated, included lobectomy, pneumonectomy, and less-than lobectomy	Unspecified analysis: authors' note 6-min walk test was not associated with post-operative SF-36[d] or Ferrans and Powers' quality-of-life index scores. Actual data N/A	Prospective (very low)

[a]American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP)

[b]**11-Item NSQIP Frailty Index**: Functional health status totally dependent (1 point), Insulin-dependent diabetes (1 point); History of severe chronic obstructive lung disease or current pneumonia (1 point); Congestive heart failure within 30 days of operation (1 point), Myocardial infarction within 6 months of operation (1 point); Previous percutaneous coronary intervention, cardiac surgery or angina within 1 month of operation (1 point); Hypertension requiring medication (1 point); History of revascularization/amputation for peripheral vascular disease, or rest pain / gangrene (1 point); History of transient ischemic attack (1 point); Cerebrovascular accident with deficit (1 point); Impaired sensorium (1 point)

[c]**11-Item NSQIP (Modified) Frailty Index**: Functional health status partially or totally dependent (1 point), Non-insulin or insulin-dependent diabetes (1 point); History of severe chronic obstructive lung disease or current pneumonia (1 point); Congestive heart failure within 30 days of operation (1 point), Myocardial infarction within 6 months of operation (1 point); Previous percutaneous coronary intervention, cardiac surgery or angina within 1 month of operation (1 point); Hypertension requiring medication (1 point); History of revascularization / amputation for peripheral vascular disease, or rest pain / gangrene (1 point); History of transient ischemic attack (1 point); Cerebrovascular accident/stroke with neurologic deficit (1 point); Impaired sensorium (1 point)/11

[d]Short Form-36 Health Survey

The most commonly studied frailty tool was an adapted accumulated deficits frailty index (the 11-item NSQIP (Modified) Frailty Index (FI)) [40–42]. The remaining study used the 6-min walk test [43]. No studies included the physical frailty phenotype or related measures.

Outcomes included post-operative mortality [40–42], Clavien 4 complications [41], 30-day morbidity [42], post-operative SF-36 and Ferrans and Powers' quality-of-life index scores [43]. Two studies included only lung resection candidates undergoing lobectomy, pneumonectomy, or less-than lobectomy procedures [41, 43]. Two studies included all surgery types but conducted sub-analyses in "pulmonary resection" [40] and "general thoracic surgery" candidates [42].

Only one of the four studies included multivariate analyses in the target population. In an unadjusted analysis, Mosquera et al. found increasing frailty predicted increasing 30-day mortality risk among thoracic surgery candidates in the 2005–2012 NSQIP dataset (30-day mortality risk: non-frail 0.8%, mildly frail ~2%, moderately frail ~3%, severely frail 6.4%; p-value not available) [40]. After adjusting for age, American Society of Anesthesiologists (ASA) score, wound class, emergency operation, and functional status, Tsiouris et al. found the presence of frailty significantly predicted post-operative mortality among lobectomy patients though the 95% confidence intervals were wide (Modified FI > 0.27: OR 9.3, 95% CI 9.1–27, p = 0.002) [41]. In a similar model adjusting for age, ASA score, wound class, emergency operation, functional status, gender, and race, presence of frailty also significantly predicted post-operative Clavien 4 complications although the 95% confidence intervals were again wide (Modified FI > 0.27: OR 4.7, 95% CI 1.3–230, p = 0.027) [41]. In unadjusted analyses in 2005–2009 NSQIP surgery patients, Velanovich et al. found increasing frailty was significantly associated with worse 30-day mortality (1 frailty index unit increase: OR 1.8, 95% CI 1.18–2.73, trend p = 0.006 for low complexity surgery; OR 1.84, 95% CI 1.57–2.14, trend p < 0.001 for moderate complexity surgery; OR 1.57, 95% CI 1.28–1.93, trend p > 0.001 for high complexity surgery) and 30-day morbidity (1 frailty index unit increase: OR 1.24, 95% CI 1.06–1.45, trend p = 0.006 for low complexity surgery; OR 1.53, 95% CI 1.38–1.69, trend p < 0.001 for moderate complexity surgery; OR 1.25, 95% CI 1.15–1.37, trend p < 0.001 for high complexity surgery) regardless of surgical complexity [42]. Finally, Handy et al. reported that poor pre-operative performance on a 6-min walk test (<1000 ft.) did not predict post-operative function (Short Form-36 Health Survey) or quality of life (Ferrans and Powers' quality-of-life index) trajectories but did not show results in the manuscript [43].

Sarcopenia and Lung Resection Outcomes (Table 9.3)

Sarcopenia assessment in lung resection surgery was the focus of 15 retrospective, single center articles analyzing data from 1 to 12 years. Follow-up ranged from 23.6 to 61 months among the ten studies reporting this. Fourteen studies included patients with primary lung cancer, and 11 studies exclusively included patients with non-small cell lung cancer (NSCLC) of various stages. The remaining study included

Table 9.3 Sarcopenia in lung resection

Author (year)	N	Age (years)	Data source and/or location	Sarcopenia measurement: skeletal mass	Sarcopenia measurement: dynapenia	Surgery type and exclusion criteria	Outcome	Study type (quality of evidence)
Kawaguchi 2019 [45]	173 patients >75 years old with NSCLC stage 0–3	Mean 78.8	Shiga University of Medical Science, January 2005–December 2017	CT-measured total psoas area (TPA) at L3. Psoas muscle index (PMI) = TPA/height (cm^2/m^2) Sarcopenia cut-off: PMI < 3.70 cm^2/m^2 in men and <2.50 cm^2/m^2 in women	None	Lobectomy	Median follow-up 33.3 months Multivariate Cox proportional hazard model on survival: Low PMI OR 0.263 (95% CI 0.138–0.499), p < 0.001	Retrospective (low)
Nakada 2019 [58]	173 patients with clinical stage 1 NSCLC	Median 68, range 31–89	The Jikei University School of Medicine, April 2013–March 2018	CT-measured total psoas area (TPA) at L3. Psoas muscle index (PMI) = TPA/height (cm^2/m^2) Sarcopenia cut-off: PMI median value—1 standard deviation, which was <4.61 cm^2/m^2 for men and <3.26 cm^2/m^2 for women	None	Curative complete single-lobe thoracoscopic lobectomy Excluded if clinical stage II or III cancer, incomplete video-assisted thoracotomy, incomplete resection, bilobectomy, incomplete data, and no CT image at L3	Median follow-up 31 months Univariate analysis of sarcopenia and any postoperative complication: Spearman's rank correlation coefficient r = 0.03, p = 0.734 Univariate analysis of sarcopenia and disease-free survival: n = 58 (33.5%), p = 0.932	Retrospective (very low)

Sun 2019 [52]	274 patients with pathological stage 1–2 lung cancer	Mean 68.1 ± 10.6	University of Tokyo Hospital, January 2009–December 2013	CT-measured truncal mass index at L1 (area/height^2) Sarcopenia: <38 cm^2/m^2 for men and <29.6 cm^2/m^2 for women	None	Lobectomy with mediastinal lymph node dissection Excluded if CT >90 days pre-operatively, incomplete data	Median follow-up not reported Multivariate Cox survival regression on overall survival: sarcopenia HR 1.84 (95% CI 1.12–3.05), p = 0.017 Multivariate Cox survival regression on recurrence-free survival: sarcopenia HR 1.42 (95% CI 0.80–2.520, p = 0.23	Retrospective (low)
Troschel 2019 [46]	128 patients with pathologically confirmed lung cancer	Mean 61.02 ± 10.63	Society of Thoracic Surgeons General Thoracic Surgery Database, Massachusetts General Hospital, 1 January 2005 to 30 June 2017	CT-measured muscle cross-sectional area at T8 Sarcopenia cut-off: none (continuous variable)	None	Pneumonectomy for lung cancer Excluded if <18 years, CT >90 days prior to surgery, CT unavailable or missing muscle data, incomplete clinical data, extrapleural pneumonectomy	Median follow-up 23.6 months Multivariate Cox proportional hazards regression on overall survival: sarcopenia (continuous variable) HR 0.80 (95% CI 0.67–0.98), p = 0.02	Retrospective (low)

(continued)

Table 9.3 (continued)

Author (year)	N	Age (years)	Data source and/or location	Sarcopenia measurement: skeletal mass	Sarcopenia measurement: dynapenia	Surgery type and exclusion criteria	Outcome	Study type (quality of evidence)
Fintelmann 2018 [55]	135 patients with primary lung cancer, stage 0–2 (all except 1 patient were stage 0–1)	Mean 69	Massachusetts General Hospital, July 2015–June 2016	CT-measured muscle cross-sectional area at T5 Sarcopenia: defined with sex-specific muscle CSA median which is <181.2 cm^2 in men and <129.4 cm^2 in women	None	Lobectomy or bilobectomy Excluded if no imaging within 90 days of surgery, inadequate muscle visualization, no PFT within 12 mo of surgery	Median follow-up not reported Multivariate logistic regression on any postoperative complication (composite): high T5 muscle cross sectional area HR 0.86 (0.75–0.995), p = 0.04; postoperative respiratory complications: high T5 muscle cross sectional area HR OR 0.8 (95% CI 0.65–0.98), p = 0.04; postoperative ICU admission: high T5 muscle cross sectional area HR OR 0.73 (95% CI 0.56–0.95), p = 0.02; hospital LOS (in quartiles): high T5 muscle cross sectional area HR OR 0.87 (95% CI 0.78–0.98), p = 0.02) and 30-day hospital readmission: high T5 muscle cross sectional area OR 0.58 (95% CI 0.37–0.91), p = 0.02	Retrospective (low)

Kim 2018 [57]	272 patients with newly diagnosed pathologically proven NSCLC, all stages	Mean 62.9 ± 9.6, range 33–81	Gachon University Gil Medical Center, January 2011–December 2016	CT-measured muscle index at L3, normalized for height Sarcopenia cut-off: L3 muscle index of <55 cm^2/m^2 for men and <39 cm^2/m^2 for women	None	Lobectomy, bilobectomy, sleeve resection, pneumonectomy with systematic lymph node dissection. Surgery done for curative intent Excluded if baseline PET/CT images unavailable	Median follow-up 26.3 months Univariate analysis on overall postoperative complications: low L3 muscle index OR 1.59 (95% CI 0.84–3.02), p = 0.158 Univariate analysis on disease-free survival: low L3 muscle index 0.619 (0.315–1.216), p = 0.160	Retrospective (very low)

(continued)

Table 9.3 (continued)

Author (year)	N	Age (years)	Data source and/or location	Sarcopenia measurement: skeletal mass	Sarcopenia measurement: dynapenia	Surgery type and exclusion criteria	Outcome	Study type (quality of evidence)
Miller 2018 [44]	299 patients, all but 2 with malignant pathology (94.6% lung cancers)	Mean 67.5 ± 10.6	Roswell Park Cancer Institute, January 2014–December 2015	CT-measured cross sectional area of erector spinae muscle (ESM) and pectoralis muscles (PM) at T12 and within 1 cm of sterno-clavicular joint. Adjusted for height (cm^2/m^2): HA-ESM and HA-PM Sarcopenia cut-off: none (continuous variable)	None	Lobectomy or bilobectomy	Median follow-up not reported Multivariate logistic regression on any complication: HA-ESM (1 cm^2/m^2 increase) OR 0.96 (95% CI 0.91–1.02), p = 0.192. HA-PM OR 1.02 (95% CI 0.98–1.06), p = 0.397 Multivariate logistic regression on 30-day mortality: HA-ESM (1 cm^2/m^2 increase) OR 0.77 (95% CI 0.60–0.98). HA-PM OR 1.11 (95% CI 0.96–1.28) Multivariate logistic regression on any complication, pneumonia, readmission, and ICU stay. Not significant for HA-ESA and HA-PM Multivariate analysis on length of stay (log) : HA-ESM (1 cm^2/m^2 increase) β −0.024 (SE 0.010), p = 0.019. HA-PM β −0.008 (SE 0.008), p = 0.297	Retrospective (very low)

Nakamura 2018 [47]	328 patients with pathologically confirmed NSCLC, stage 0–3	Mean 69.8 Median 71.0, range 38–87	Mito Medical Center, January 2005–April 2017	CT-measured psoas muscle at caudal end of third lumbar vertebra. PMI=cross sectional area bilateral psoas muscle/height^2 (cm^2/m^2) Sarcopenia cut-off: <6.36 cm^2/m^2 for men and <3.92 cm^2/m^2 for women	None	Lung resection with curative intent Excluded if CT scan not evaluated at third lumbar vertebrae level	Median follow-up 35.5 months Multivariate Cox hazard model of overall survival: Low PMI HR 1.943 (95% CR 1.113–3.390), p = 0.019	Retrospective (low)
Takamori 2018 [48]	101 patients with primary pathologic stage 1 NSCLC	No mean reported Median 68, range 34–93	Kyushu University Hospital, January 2005–December 2010	CT-measured T12 paravertebral skeletal muscle index (cm^2/m^2) Sarcopenia post/pre ratio PPR) = post-operative/pre-operative normalized Sarcopenia cut-off: <0.9	None	Complete lung resection Excluded if no CT within 1 month of surgery and 10–14 months post-surgery, outside hospital CT, sublobar resection	Median follow-up not reported Multivariate proportional hazards model on disease-free survival: PPR <0.9 HR 2.88 (95% CI 1.29–6.43), p = 0.010 Multivariate proportional hazards model on overall survival: PPR <0.9 HR 3.82 (95% CI 1.44–10.55), p = 0.0072	Retrospective (low)

(continued)

Table 9.3 (continued)

Author (year)	N	Age (years)	Data source and/or location	Sarcopenia measurement: skeletal mass	Sarcopenia measurement: dynapenia	Surgery type and exclusion criteria	Outcome	Study type (quality of evidence)
Tsukioka 2018 (A) [56]	47 male patients with completely resected N2-positive NSCLC	Mean 68, range 35–84	Osaka City University Hospital, January 2003 – December 2012	CT-measured L3 muscle index [skeletal muscle area at the L3 (cm^2) for males = 126.9 × Body Surface Area − 66.2]/ height^2 Sarcopenia cut-off: <52.4 cm^2/m^2 in men	None	Definitive pulmonary resection with mediastinal lymph node dissection Excluded patients who had preoperative treatments, incompletely removed disease, pneumonectomy, pulmonary segmentectomy, or partial resection. Patients deemed ineligible for surgery also excluded (e.g., distant metastasis, mediastinal lymph node metastases a more than two stations, bulky mediastinal lymph node metastases, contralateral mediastinal lymph nodes, FEV_1 <40%)	Median follow-up 37 months Multivariate logistic regression on early recurrence (detected within 1 year of surgery): low L3 muscle index HR 0.1 (95% CI 0.01, 0.5), p = 0.004	Retrospective (low)

Tsukioka 2018 (B) [49]	69 patients with stage IIIA (N2) NSCLC	Mean 65.9 ± 9.8	Osaka City University Hospital, January 2003–December 2012	CT-measured L3 muscle index [skeletal muscle area at the L3 (cm^2) for males = 126.9 × Body Surface Area − 66.2 or for females = 125.6 × BSA − 81.1]/ height^2 Sarcopenia cut-off: <52.4 cm^2/m^2 in men and <38.5 cm^2/m^2 in women	None	Definitive pulmonary resection with mediastinal lymph node dissection Excluded patients who had preoperative treatments, incompletely removed disease, pneumonectomy, pulmonary segmentectomy, or partial resection	Median follow-up 56 months Multivariate Cox proportional hazard model on overall survival: Low L3 muscle index HR 3.1 (95% CI 1.58–6.06), p = 0.001	Retrospective (low)
Hervochon 2017 [54]	161 patients with NSCLC, all stages	Mean 62.6 ± 10.3	Paris City University Hospitals, January 2007–June 2012	CT-measured total psoas area (TPA) at mid-L3 Sarcopenia cut-off: <33rd percentile of TPA (1601 mm^2 for men and 999 mm^2 for women)	None	Pneumonectomy Excluded if no pre-operative CT scan available	Median survival 28 months Multivariate Cox survival regression on survival: <33rd percentile TPA RR 1.57 (95% CI 1.01–2.45), p = 0.045 Multivariate Cox survival regression on survival model adding BMI, CRP: <33rd percentile TPA RR 1.17 (95% CI 0.66–2.08), p = 0.59	Retrospective (low)

(continued)

Table 9.3 (continued)

Author (year)	N	Age (years)	Data source and/or location	Sarcopenia measurement: skeletal mass	Sarcopenia measurement: dynapenia	Surgery type and exclusion criteria	Outcome	Study type (quality of evidence)
Shoji 2017 [50]	147 patients with pathological stage 1 NSCLC	No mean reported Median 68, range 42–86	Kyushu University, August 2005–August 2010	CT-measured skeletal muscle cross-sectional area at L3, normalized (cm^2/m^2) Sarcopenia cut-off: <43.75 cm^2/m^2 for men and 41.10 cm^2/m^2 for women		Complete resection including lobectomy, segmentectomy, wedge resection (12.9% underwent adjuvant chemotherapy)	Median follow-up 59 months Multivariate Cox proportional hazards regression on overall survival: low L3 muscle mass HR 5.138 (95% CI 2.305–11.676), $p < 0.0001$	Retrospective (low)
Tsukioka 2017 [51]	215 male patients with stage I NSCLC	Mean 68, range 46–93	Osaka City University Hospital, January 2003–December 2012	CT-measured L3 muscle index [skeletal muscle area at the L3 (cm^2) for males = 126.9 × Body Surface Area − 66.2]/ $height^2$ Sarcopenia cut-off: <49 cm^2/m^2	None	Lobectomy or Segmentectomy with mediastinal lymph node dissection Excluded if preoperative treatments were given, history of malignancy in other organs, disease not completely removed	Median follow-up 61 month Multivariate Cox proportional hazard model on overall survival: low L3 muscle mass HR 3.3 (95% CI 1.31–7.56), $p = 0.012$	Retrospective (low)

Suzuki 2016 [53]	90 patients with stage 1 NSCLC	Mean 68.7 ± 8.7	Kyushu University Hospital, January 2005–December 2008	CT-measured skeletal muscle cross-sectional area at L3, normalized (cm^2/m^2) Sarcopenia cut-off: <43.75 cm^2/m^2 for men and <41.10 cm^2/m^2 for women	None	Complete lung resection with curative intent Excluded if no CT available	Median follow-up not specified Multivariate Cox proportional hazards model on overall survival: low L3 muscle mass HR 7.09 (95% CI 2.30–23.20), p = 0.0008 Multivariate Cox proportional hazards model on overall survival by gender: low L3 muscle mass HR for males 8.39 (95% CI 2.49–30.92), p = 0.0007; low L3 muscle mass HR for females not significant	Retrospective (low)

lung resection patients of all types but 94.6% had lung cancers [44]. The types of included lung resection procedures included varied widely among the studies (e.g., lobectomy, bilobectomy, segmentectomy, pneumonectomy, and sleeve resection).

All 15 articles measured sarcopenia using cross-sectional muscle area on computed tomography (CT) scan, but at various spinal levels. All studies provided different sarcopenia cut points for men and women, and most studies adjusted muscle area for height. Notably, no study included measures of dynapenia.

Eleven studies reported multivariate analysis relating pre-operative sarcopenia to post-operative survival (disease free or overall) or mortality, 7 of which found sarcopenia significantly increased risk of mortality or reduced survival. In a multivariate analysis adjusting for clinical, demographic, and health characteristics, Kawaguchi et al. found sarcopenia predicted worse post-operative survival (L3 psoas muscle index <3.70 cm^2/m^2 in men or <2.50 cm^2/m^2 in women: OR 0.263, 95% CI 0.138–0.499, $p < 0.001$) [45]. Troschel et al. found increasing muscle mass reduced risk of death after adjusting for clinical, demographic, and health characteristics (Continuous T8 cross-sectional muscle area: HR 0.80, 95% CI 0.67–0.98, $p = 0.02$) [46]. Nakamura et al. found sarcopenia predicted increased risk of death after adjusting for age, gender, CEA, and tumor stage (Low psoas muscle index: HR 1.943, 95% CR 1.113–3.390, $p = 0.019$) [47]. An interesting study by Takamori et al. evaluated the effect of a post-/pre-operative ratio (PPR) in muscle mass at T12 on survival. In a multivariate model adjusting for age, BMI, vascular invasion, and histologic type, they found that a PPR <0.9 predicted increased risk of death (PPR <0.9: HR 3.82, 95% CI 1.44–10.55, $p = 0.0072$) and disease recurrence (PPR <0.9: HR 2.88, 95% CI 1.29–6.43, $p = 0.010$) [48]. Tsukioka et al. found sarcopenia increased risk of death after adjusting for performance status and cytokeratin 19 fragment (*Calculated* L3 muscle index <52.4 cm^2/m^2 in males and <38.5 cm^2/m^2 in females: HR 3.1, 95% CI 1.58–6.06, $p = 0.001$) [49]. Shoji et al. found sarcopenia increased risk of death after adjusting for demographic and clinical characteristics (L3 muscle area <43.75 cm^2/m^2 in men and <41.10 cm^2/m^2 in women: HR 5.138, 95% CI 2.305–11.676, $p < 0.0001$) [50]. Finally, Tsukioka et al. found sarcopenia increased risk of death after adjusting for age, BMI, and clinical characteristics (*Calculated* L3 muscle index <49 cm^2/m^2: HR 3.3, 95% CI 1.31–7.56, $p = 0.012$) [51].

The remaining four multivariate mortality studies had mixed results, finding sarcopenia predictive of mortality in certain models but not others. A study by Sun et al. found that pre-operative sarcopenia increased risk of overall death (Lowest quartile of truncal mass index: HR 1.84, 95% CI 1.12–3.05, $p = 0.017$) but did not predict recurrence-free survival (Lowest quartile of truncal mass index HR: 1.42, 95% CI 0.80–2.520, $p = 0.23$) [52]. A study by Suzuki et al. also found that pre-operative sarcopenia decreased overall survival (<43.75 cm^2/m^2 for men or <41.10 cm^2/m^2 for women: HR 7.09, 95% CI 2.30–23.20, $p = 0.0008$), but stratification by gender revealed sarcopenia only predicted poor survival in men [53]. After adjusting for various pre-operative measures, Miller et al. found increasing erector spinae muscle area reduced odds of 30-day mortality (For each 1 cm^2/m^2 increase: OR 0.77, 95% CI 0.60–0.98) while pectoralis muscle area did not (For each 1 cm^2/m^2 increase: OR 1.11, 95% CI 0.96–1.28) [44]. Finally, Hervochen et al. noted that

pre-operative sarcopenia significantly increased risk of death after adjusting for histologic type and pathologic stage (<33rd percentile for total psoas muscle area: RR 1.57, 95% CI 1.01–2.45, p = 0.045) but not after further adjusting for BMI and C-reactive protein (CRP) [54].

Three studies reported multivariate analyses relating sarcopenia to other outcomes of interest. After adjusting for sex, age, BMI, FEV1% predicted, and surgical approach, Fintelmann et al. found that having greater muscle mass lowered odds of composite post-operative complications (≥gender-specific median T5 muscle area: OR 0.86, 95% CI 0.75–0.995, p = 0.04); postoperative respiratory complications (≥gender-specific median T5 muscle area: OR 0.8, 95% CI 0.65–0.98, p = 0.04); postoperative intensive care unit (ICU) admission (≥gender-specific median T5 muscle area: OR 0.73, 95% CI 0.56–0.95, p = 0.02); decreased hospital length of stay (LOS) (≥gender-specific median T5 muscle area: OR 0.87, 95% CI 0.78–0.98, p = 0.02); and decreased 30-day hospital readmission (≥gender-specific median T5 muscle area: OR 0.58, 95% CI 0.37–0.91, p = 0.02) [55]. After adjusting for pre-operative demographic, clinical and health characteristics, Miller et al. found no association between muscle area (height-adjusted erector spinae or pectoralis muscle area) with any post-operative complication, pneumonia, readmission, or ICU stay [44]. However, in this same study, increasing height-adjusted erector spinae muscle area was associated with reduced LOS (For each 1 cm^2/m^2 unit increase: β −0.024, SE 0.010, p = 0.019), while pectoralis muscle area was not [44]. In a model adjusting for CEA, tumor size, and post-operative chemotherapy exposure, Tsukioka et al. found that high muscle mass reduced risk of early recurrence (≥52.4 calculated L3 muscle index m^2/cm^2: HR 0.1, 95% CI 0.01–0.5, p = 0.004) [56].

Two studies found no association between sarcopenia and overall postoperative complications or disease free survival in unadjusted analyses [57, 58].

Conclusions and Recommendations

We found a narrow body of work (15 studies) studying sarcopenia measures and frailty in lung resection. These studies are limited by their retrospective nature, small sample sizes, varying inclusion / exclusion criteria, varying frailty and sarcopenia measurement approaches, and underuse of multivariate analyses adjusting for important pre-operative measures. With these limitations in mind, there is weak evidence from low quality studies that increasing frailty as measured by accumulated deficit-like models is associated with increased post-operative mortality and possibly increased risk of post-operative complications in lung resection. There is also weak evidence from low quality studies that those with pre-operative sarcopenia as measured by cross-sectional muscle area on CT are at increased risk of post-operative death. A few studies have inconsistently found a relationship between pre-operative sarcopenia and post- or peri-operative complications and length of stay. Based on these early lung resection studies, we make a weak recommendation for screening for frailty and sarcopenia in the preoperative assessment to improve risk stratification among surgical candidates. Gaps in frailty and sarcopenia research

in lung resection would benefit from continued collaborations between surgeons, geriatricians, and aging researchers to advance our understanding of multisystem physiologic vulnerability and stress recovery potential.

Recommendations

- Preoperative frailty should be assessed in adults being considered for lung resection (quality of evidence low; weak recommendation).
- Preoperative sarcopenia should be assessed in adults being considered for lung resection (quality of evidence low; weak recommendation).

A Personal View of the Data

Frailty and sarcopenia are incredibly important aspects of the older adult assessment with great relevance to surgeons. Recent scientific advances in frailty and sarcopenia have led to numerous expert consensus panels to refine definitions and measurement guides, though continued deliberations are on-going and should be followed closely in the literature. The bulk of surgical research to date suggesting the value of frailty and sarcopenia to surgical preoperative risk assessment has been outside of lung resection candidates, leaving room for incredible scientific growth in this patient population. However, the large and expanding body of studies demonstrating the added value of these measures to risk stratification in other surgical groups motivated the establishment of clinical service programs to offer frailty and sarcopenia (currently muscle function only) routinely to referring providers at our institution. The referral pathways for these assessments have only been standardized in one surgical group at our institution to date (kidney transplant) with hope of offering these evaluations more broadly in the future. These assessments play a significant role in surgical risk assessment at our institution for these patients [59].

Frailty and sarcopenia research would benefit from continued collaborations between surgeons, geriatricians and aging researchers to continue to advance our understanding of multisystem physiologic vulnerability and stress recovery potential. Further work exploring alternative and novel frailty measures in prospective lung resection studies; prospective studies including both muscle quantity AND quality sarcopenia measures; studies designed to help understand and possibly differentiate the interplay between frailty, disability, comorbidity, cognitive function, sarcopenia versus cachexia versus weight loss, exhaustion / fatigability; studies exploring feasibility including the added value of screening tools to case find; studies exploring the role of pre-operative chemotherapy and radiation therapy on frailty and sarcopenia-related surgical risk; studies exploring racial/ethnic and gender differences in measurement; studies exploring interventions that can reduce preoperative and post-operative frailty and sarcopenia; and studies exploring important older adult outcomes including discharge location and functional recovery are greatly needed.

References

1. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–56.
2. Mitnitski AB, Mogilner AJ, MacKnight C, Rockwood K. The mortality rate as a function of accumulated deficits in a frailty index. Mech Ageing Dev. 2002;123(11):1457–60.
3. Buchner DM, Wagner EH. Preventing frail health. Clin Geriatr Med. 1992;8(1):1–17.
4. Bortz WM 2nd. The physics of frailty. J Am Geriatr Soc. 1993;41(9):1004–8.
5. Li Q, Wang S, Milot E, Bergeron P, Ferrucci L, Fried LP, et al. Homeostatic dysregulation proceeds in parallel in multiple physiological systems. Aging Cell. 2015;14:1103–12.
6. Lipsitz LA, Goldberger AL. Loss of 'complexity' and aging. Potential applications of fractals and chaos theory to senescence. JAMA. 1992;267(13):1806–9.
7. Bandeen-Roche K, Seplaki CL, Huang J, Buta B, Kalyani RR, Varadhan R, et al. Frailty in older adults: a nationally representative profile in the United States. J Gerontol A Biol Sci Med Sci. 2015;70(11):1427–34.
8. Beckert AK, Huisingh-Scheetz M, Thompson K, Celauro AD, Williams J, Pachwicewicz P, et al. Screening for frailty in thoracic surgical patients. Ann Thorac Surg. 2017;103(3):956–61.
9. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 2010;210(6):901–8.
10. Institute of Medicine (US) Committee on the Future Health Care Workforce for Older Americans. Retooling for an aging America: building the health care workforce. Washington, DC: National Academies Press; 2008.
11. Ferrucci L, Guralnik JM, Studenski S, Fried LP, Cutler GB Jr, Walston JD. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. J Am Geriatr Soc. 2004;52(4):625–34.
12. Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc. 2006;54(6):991–1001.
13. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14(6):392–7.
14. Rodriguez-Manas L, Feart C, Mann G, Vina J, Chatterji S, Chodzko-Zajko W, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci. 2013;68(1):62–7.
15. Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue QL, et al. Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. Ageing Res Rev. 2016;26:53–61.
16. Huisingh-Scheetz M, Walston J. How should older adults with cancer be evaluated for frailty? J Geriatr Oncol. 2016;8:8–15.
17. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal. 2001;1:323–36.
18. Dent E, Morley JE, Cruz-Jentoft AJ, Arai H, Kritchevsky SB, Guralnik J, et al. International Clinical Practice Guidelines for Sarcopenia (ICFSR): screening, diagnosis and management. J Nutr Health Aging. 2018;22(10):1148–61.
19. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc. 2011;12(4):249–56.
20. Cesari M, Fielding RA, Pahor M, Goodpaster B, Hellerstein M, van Kan GA, et al. Biomarkers of sarcopenia in clinical trials-recommendations from the International Working Group on Sarcopenia. J Cachexia Sarcopenia Muscle. 2012;3(3):181–90.

21. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412–23.
22. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48:16–31.
23. Bauer J, Morley JE, Schols A, Ferrucci L, Cruz-Jentoft AJ, Dent E, et al. Sarcopenia: a time for action. An SCWD position paper. J Cachexia Sarcopenia Muscle. 2019;10:956–61.
24. Morley JE, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, et al. Sarcopenia with limited mobility: an international consensus. J Am Med Dir Assoc. 2011;12(6):403–9.
25. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc. 2014;15(2):95–101.
26. Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr. 2010;29(2):154–9.
27. Dam TT, Peters KW, Fragala M, Cawthon PM, Harris TB, McLean R, et al. An evidence-based comparison of operational criteria for the presence of sarcopenia. J Gerontol A Biol Sci Med Sci. 2014;69(5):584–90.
28. Shankaran M, Czerwieniec G, Fessler C, Wong PA, Killion S, Turner SM, et al. Dilution of oral D3-Creatine to measure creatine pool size and estimate skeletal muscle mass: development of a correction algorithm. J Cachexia Sarcopenia Muscle. 2018;9(3):540–6.
29. Joseph B, Pandit V, Zangbar B, Kulvatunyou N, Hashmi A, Green DJ, et al. Superiority of frailty over age in predicting outcomes among geriatric trauma patients: a prospective analysis. JAMA Surg. 2014;149(8):766–72.
30. Joseph B, Pandit V, Zangbar B, Kulvatunyou N, Tang A, O'Keeffe T, et al. Validating trauma-specific frailty index for geriatric trauma patients: a prospective analysis. J Am Coll Surg. 2014;219(1):10–7.e1.
31. Adams P, Ghanem T, Stachler R, Hall F, Velanovich V, Rubinfeld I. Frailty as a predictor of morbidity and mortality in inpatient head and neck surgery. JAMA Otolaryngol Head Neck Surg. 2013;139(8):783–9.
32. Afilalo J, Eisenberg MJ, Morin JF, Bergman H, Monette J, Noiseux N, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. J Am Coll Cardiol. 2010;56(20):1668–76.
33. Buettner S, Wagner D, Kim Y, Margonis GA, Makary MA, Wilson A, et al. Inclusion of sarcopenia outperforms the Modified Frailty Index in predicting 1-year mortality among 1,326 patients undergoing gastrointestinal surgery for a malignant indication. J Am Coll Surg. 2015;222:397–407.e2.
34. Crozier-Shaw G, Joyce WP. Too frail for surgery? A frailty index in major colorectal surgery. ANZ J Surg. 2018;88:1302–5.
35. Courtney-Brooks M, Tellawi AR, Scalici J, Duska LR, Jazaeri AA, Modesitt SC, et al. Frailty: an outcome predictor for elderly gynecologic oncology patients. Gynecol Oncol. 2012;126(1):20–4.
36. Green P, Woglom AE, Genereux P, Daneault B, Paradis JM, Schnell S, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. JACC Cardiovasc Interv. 2012;5(9):974–81.
37. McAdams-DeMarco MA, Law A, King E, Orandi B, Salter M, Gupta N, et al. Frailty and mortality in kidney transplant recipients. Am J Transplant. 2015;15(1):149–54.
38. Chow W, Ko C, Rosenthal R, Esnaola N. ACS NSQIP/AGS best practice guidelines: optimal preoperative assessment of the geriatric surgical patient. 2012. https://www.facs.org/~/media/files/quality%20programs/nsqip/acsnsqipagsgeriatric2012guidelines.ashx Accessed 2 June 2020
39. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. JAMA. 2011;305(1):50–8.
40. Mosquera C, Spaniolas K, Fitzgerald TL. Impact of frailty on surgical outcomes: the right patient for the right procedure. Surgery. 2016;160(2):272–80.

41. Tsiouris A, Hammoud ZT, Velanovich V, Hodari A, Borgi J, Rubinfeld I. A modified frailty index to assess morbidity and mortality after lobectomy. J Surg Res. 2013;183(1):40–6.
42. Velanovich V, Antoine H, Swartz A, Peters D, Rubinfeld I. Accumulating deficits model of frailty and postoperative mortality and morbidity: its application to a national database. J Surg Res. 2013;183(1):104–10.
43. Handy JR Jr, Asaph JW, Skokan L, Reed CE, Koh S, Brooks G, et al. What happens to patients undergoing lung cancer surgery? Outcomes and quality of life before and after surgery. Chest. 2002;122(1):21–30.
44. Miller JA, Harris K, Roche C, Dhillon S, Battoo A, Demmy T, et al. Sarcopenia is a predictor of outcomes after lobectomy. J Thorac Dis. 2018;10(1):432–40.
45. Kawaguchi Y, Hanaoka J, Ohshio Y, Okamoto K, Kaku R, Hayashi K, et al. Sarcopenia predicts poor postoperative outcome in elderly patients with lung cancer. Gen Thorac Cardiovasc Surg. 2019;67:949–54.
46. Troschel FM, Kuklinski MW, Knoll SJ, Best TD, Muniappan A, Gaissert HA, et al. Preoperative thoracic muscle area on computed tomography predicts long-term survival following pneumonectomy for lung cancer. Interact Cardiovasc Thorac Surg. 2019;28(4):542–9.
47. Nakamura R, Inage Y, Tobita R, Yoneyama S, Numata T, Ota K, et al. Sarcopenia in resected NSCLC: effect on postoperative outcomes. J Thorac Oncol. 2018;13(7):895–903.
48. Takamori S, Toyokawa G, Okamoto T, Shimokawa M, Kinoshita F, Kozuma Y, et al. Clinical impact and risk factors for skeletal muscle loss after complete resection of early non-small cell lung cancer. Ann Surg Oncol. 2018;25(5):1229–36.
49. Tsukioka T, Izumi N, Mizuguchi S, Kyukwang C, Komatsu H, Toda M, et al. Positive correlation between sarcopenia and elevation of neutrophil/lymphocyte ratio in pathological stage IIIA (N2-positive) non-small cell lung cancer patients. Gen Thorac Cardiovasc Surg. 2018;66(12):716–22.
50. Shoji F, Matsubara T, Kozuma Y, Haratake N, Akamine T, Takamori S, et al. Relationship between preoperative sarcopenia status and immuno-nutritional parameters in patients with early-stage non-small cell lung cancer. Anticancer Res. 2017;37(12):6997–7003.
51. Tsukioka T, Nishiyama N, Izumi N, Mizuguchi S, Komatsu H, Okada S, et al. Sarcopenia is a novel poor prognostic factor in male patients with pathological Stage I non-small cell lung cancer. Jpn J Clin Oncol. 2017;47(4):363–8.
52. Sun C, Anraku M, Karasaki T, Kuwano H, Nagayama K, Nitadori JI, et al. Low truncal muscle area on chest computed tomography: a poor prognostic factor for the cure of early-stage non-small-cell lung cancer. Eur J Cardiothorac Surg. 2019;55(3):414–20.
53. Suzuki Y, Okamoto T, Fujishita T, Katsura M, Akamine T, Takamori S, et al. Clinical implications of sarcopenia in patients undergoing complete resection for early non-small cell lung cancer. Lung Cancer. 2016;101:92–7.
54. Hervochon R, Bobbio A, Guinet C, Mansuet-Lupo A, Rabbat A, Regnard JF, et al. Body Mass Index and total Psoas area affect outcomes in patients undergoing pneumonectomy for cancer. Ann Thorac Surg. 2017;103(1):287–95.
55. Fintelmann FJ, Troschel FM, Mario J, Chretien YR, Knoll SJ, Muniappan A, et al. Thoracic skeletal muscle is associated with adverse outcomes after lobectomy for lung cancer. Ann Thorac Surg. 2018;105(5):1507–15.
56. Tsukioka T, Izumi N, Kyukwang C, Komatsu H, Toda M, Hara K, et al. Loss of muscle mass is a novel predictor of postoperative early recurrence in N2-positive non-small-cell lung cancer. Ann Thorac Cardiovasc Surg. 2018;24(3):121–6.
57. Kim EY, Lee HY, Kim KW, Lee JI, Kim YS, Choi WJ, et al. Preoperative computed tomography-determined sarcopenia and postoperative outcome after surgery for non-small cell lung cancer. Scand J Surg. 2018;107(3):244–51.
58. Nakada T, Noda Y, Kato D, Shibasaki T, Mori S, Asano H, et al. Risk factors and cancer recurrence associated with postoperative complications after thoracoscopic lobectomy for clinical stage I non-small cell lung cancer. Thorac Cancer. 2019;10:1945–52.
59. Huisingh-Scheetz M, Martinchek M, Becker Y, Ferguson MK, Thompson K. Translating frailty research into clinical practice: insights from the successful aging and frailty evaluation clinic. J Am Med Dir Assoc. 2019;20:672–8.

Can Frailty and Sarcopenia Be Mitigated in Lung Resection Candidates?

10

Mark K. Ferguson

Introduction

Frailty is defined as an increased vulnerability to physiologic stressors and is increasingly common with advancing age. It is estimated that about 45% percent of individuals over the age of 65 can be classified as pre-frail. In addition, true frailty increases with age in this population, with an incidence of 10% in those 65–69 years of age climbing to more than 35% in individuals 85–90 years of age [1]. In the general population frailty is associated with an increase in the incidence of falls, disability, and mortality. In surgical populations frailty is associated with an increased risk of postoperative complications, prolonged hospital length of stay, an increased frequency of discharge to other than home, increased costs of care, and decreased long-term survival. In a thoracic surgery outpatient clinic nearly 70% of new patients referred for surgery are pre-frail or frail [2].

Sarcopenia is defined as an age-associated loss of skeletal muscle mass and function. It is present in 10% to 20% of people aged 65–69, and this incidence increases to nearly 30% in those >70 years of age [3]. Sarcopenia is often associated with frailty, and in the general population its presence predicts falls, disability, and mortality. Within the surgery realm, sarcopenic patients are more prone to postoperative complications, prolonged hospital length of stay, and discharge to other than home, and their hospitalizations are costlier than non-sarcopenic patients.

Given the typical age range of lung cancer patients, it is no surprise that the incidence of frailty and sarcopenia are high. Frailty is associated with increased risks of surgical complications after lung resection [4], worse toxicity from chemotherapy [5], and decreased survival after stereotactic body radiotherapy (SBRT) [6]. Sarcopenia is associated with decreased survival in patients after lung cancer

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resection [7], decreased survival in patients undergoing radiation therapy for early or regionally advanced lung cancer [8], and reduced benefits of immunotherapy [9, 10].

Understanding the impact that frailty and sarcopenia have on outcomes after major lung resection is important in patient selection for surgery. Whether that impact can be mitigated through interventions such as exercise and nutritional repletion is the subject of this chapter.

Search Strategy

Studies focused on frailty or sarcopenia are increasingly common, but few studies evaluate those conditions in the setting of exercise intervention for lung cancer. For purposes of this chapter (and much of the clinical research), exercise capacity and stamina are used as surrogates for frailty and sarcopenia. A literature search was conducted using the databases PubMed, Cochran Library, Embase, and SCOPUS for the period 2010 through 2019 for articles published in English. Search terms included combinations of: lung OR pulmonary; cancer OR malignancy; sarcopenia OR muscle OR frailty; exercise OR nutrition OR rehabilitation (Table 10.1). Articles were selected that included a randomized comparison of preoperative exercise interventions to an alternative strategy, that included more than 15 patients in an arm, and that provided metrics identifying performance outcomes and/or surgical outcomes. Review articles and meta-analysis articles were reviewed and also were scanned to ensure that all appropriate publications were included.

Results

A total of 9 articles were identified that met criteria for randomized trials (Table 10.2) [11–19]. Their evidence quality was low to moderate. The interventions included inspiratory muscle training, endurance training, and resistance training; most studies included more than one of these interventions. The endurance training was often characterized as high intensity training, and the duration of these interventions were often as short as 1 week. Those that were ultra-short were usually performed in an inpatient setting. Instruments for measuring performance improvement included the 6 min walk test (6MWT), spirometry or DLCO, VO_{2max} as measured by cardiopulmonary exercise testing, perceived exertion rating on the Borg scale [20], and quality of life (QOL) assessments. Clinical outcomes of interest were postoperative complications (particularly postoperative pulmonary complications (PPCs)), and hospital length of stay.

Table 10.1 PICO formatted terms for literature search

P (Patients)	I (Intervention	C (Comparator)	O (Outcomes)
Patients with lung cancer considered high risk for frailty/sarcopenia	Exercise or nutrition intervention	No specific intervention	Postoperative complications Survival

Table 10.2 Results of randomized trials of preoperative exercise for lung resection

Author (reference) Year	Patients	Intervention	Duration	Metric	Preoperative performance outcomes in intervention group	Clinical outcomes after lung resection	Quality of evidence
Pehlivan [11] 2011	60	30 IMT+HIT 30 control	1 week	FEV1 DLCO% 6MWT Borg scale	Increased ($p = 0.01$) Increased ($p < 0.001$) Increased ($p < 0.001$) No change	PPCs reduced in intervention group ($p = 0.04$) Hospital length of stay reduced in intervention group ($p < 0.001$)	Moderate
Stefanelli [12] 2013	40 high risk	20 IMT+HIT 20 control	3 weeks 15 sessions	FEV1 DLCO Borg scale VO_{2max}%	No change No change Improved ($p < 0.05$) Increased ($p < 0.01$)	N/A	Moderate
Gao [13] 2015	142 high risk	71 IMT+ET 71 control	3–7 days	N/A	N/A	PPCs reduced in intervention group ($p = 0.009$) Overall complications reduced in intervention group ($p < 0.001$) Shorter hospital stay for intervention group ($p = 0.03$) No difference in costs	Low
Licker [14] 2016	151	74 HIT 71 control	2–3 times per week	VO_{2max}% 6MWT	Increased ($p = 0.003$) Increased ($p < 0.001$)	No difference in overall complications ($p = 0.08$) PPCs reduced in intervention group ($p < 0.001$)	Moderate
Lai [15] 2017	60 aged ≥70 years	30 IMT+HIT 30 control	1 week	6MWT QOL	Better in intervention compared to control ($p = 0.029$) No difference	Shorter hospital stay for intervention group ($p = 0.010$) PPCs reduced in intervention group ($p = 0.037$)	Moderate

(continued)

Table 10.2 (continued)

Author (reference) Year	Patients	Intervention	Duration	Metric	Preoperative performance outcomes in intervention group	Clinical outcomes after lung resection	Quality of evidence
Huang [16] 2017	90	30 IMT+RT 30 IMT 30 control	1 week	6MWT FEV1 FVC DLCO QOL Borg	No difference for either No difference for either No difference for either No difference for either No difference for either No difference for either	PPCs reduced in IMT+RT group compared to control group ($p = 0.045$) Shorter hospital stay for IMT+RT group compared to control group ($P = 0.001$)	Moderate
Lai [17] 2017	101 aged >75 years, COPD	51 IMT+HIT 50 control	1 week	6MWT QOL	Greater improvement in intervention group ($p < 0.001$) No difference	PPCs reduced in intervention group ($p = 0.019$)	Moderate
Boujibar [18] 2018	34	19 RT+ET 15 control	14–20 sessions	N/A	N/A	Number and severity of overall complications reduced in intervention group ($p = 0.038$; $p = 0.025$)	Low
Bhatia [19] 2019	151 deconditioned patients	74 HIT 77 control	2.5 weeks 8 sessions	VO_{2max}% 6MWT	More increase in HIT compared to control ($p = 0.004$) More increase in HIT compared to control ($p = 0.001$)	N/A	Moderate

IMT inspiratory muscle training, *RT* resistance training, *ET* endurance training, *HIT* high intensity endurance training, *PPC* postoperative pulmonary complications, *N/A* not applicable, *6MWT* 6 min walk test, *FEV1* forced expiratory volume (ml) during the first second and expressed as a percent predicted, *DLCO* diffusing capacity of the lung for carbon monoxide (ml/min/mmHg) and expressed as a % predicted, VO_{2max}% peak oxygen consumption during exercise (ml/kg/min) expressed as a percent of predicted, *COPD* chronic obstructive pulmonary disease

For performance outcomes, most studies demonstrate a statistically significant improvement associated with the intervention, especially for 6MWT (5 of 6 studies) and VO_{2max} (3 of 3 studies). This was true either for intra-group comparisons or inter-group comparisons. Clinical outcomes were better for the intervention group in at least one domain in 7 of 7 studies, particularly for PPCs (6 of 6 studies) and shortened hospital length of stay (3 of 3 studies).

Reviews and meta-analyses also demonstrated advantages associated with preoperative exercise intervention (Table 10.3) [21–26]. These publications often

Table 10.3 Results of reviews and meta-analyses of studies of preoperative exercise for lung resection patients

Author (reference) Year	Type of study (number of studies included)	Performance outcomes associated with exercise	Clinical outcomes associated with exercise	Quality of evidence
Pouwels [21] 2015	Systematic review (11)	Improved stamina Improved physical fitness Improved quality of life	Reduced hospital length of stay Reduced incidence of complications	Low
Ni [22] 2016	Systematic review (4)	Improved 6MWT (+62.8 m) Reduced dyspnea score (−14.3 points)	Reduced hospital length of stay (MD −4.98 days) Reduced incidence of complications (OR 0.33)	Low
Sebio Garcia [23] 2016	Meta-analysis (14)	Improved FEV1 (MD 0.27 L) Improved FVC (MD 0.38 L)	Reduced hospital length of stay (MD −4.83 days) Reduced incidence of PPCs (RR 0.45)	Moderate
Steffens [24] 2018	Systematic review (8)	N/A	Reduced hospital length of stay (MD −2.86 days) Reduced incidence of complications (RR 0.52)	Low
Li [25] 2019	Meta-analysis (7)	Improved 6MWT Improved VO_{2max}	Reduced hospital length of stay (MD −4.23 days) Reduced incidence of PPCs (OR 0.44)	Moderate
Rosero [26] 2019	Meta-analysis (10)	Improved 6MWT (MD 0.27) Improved VO_{2max} (MD 0.78) Reduced dyspnea score (MD −0.30)	Reduced hospital length of stay (MD −0.58 days) Reduced incidence of PPCs (RR 0.50)	Moderate

PPC postoperative pulmonary complications, *N/A* not applicable, *6MWT* 6 min walk test, *FEV1* forced expiratory volume (ml) during the first second and expressed as a percent predicted, *FVC* forced vital capacity, *VO_{2max}%* peak oxygen consumption during exercise (ml/kg/min) expressed as a percent of predicted, *MD* mean difference, *OR* odds ratio, *RR* risk ratio

included the same original studies, so the fact that their findings were similar should not be interpreted as strengthening the conclusions regarding an exercise intervention, but can be interpreted as a quality measure for the systematic review or meta-analysis approaches used. The reviews consistently found that stamina (6MWT), exercise capacity (VO_{2max}), and dyspnea were improved after an exercise intervention. Clinical outcome findings were also consistent, with all publications reporting reduced hospital length of stay and reduced complications, especially pulmonary complications, associated with preoperative exercise.

Conclusions and Recommendations

Lung resection for cancer carries an attendant risk of morbidity and mortality and thus requires careful patient selection. Preoperative assessment of surgical risk in such patients typically includes pulmonary function testing and evaluation of cardiovascular status. Often some form of exercise testing is performed, and assessment of frailty is increasingly common in individuals thought to be at risk. Although most patients seen by surgeons for evaluation are reasonably fit for resection, owing at least in part to pre-selection by the referring physician, there is usually a substantial number of patients who are found to be at increased risk. Traditional options for those patients include forging ahead with the planned operation and accepting the increased risk, altering the extent of resection (parenchymal sparing rather than lobectomy, for example), changing the surgical approach (minimally invasive rather than open), or offering a different treatment altogether, such as stereotactic body radiotherapy. Although the risk profile of patients is changing over time as surgical practice improves with the advent of minimally invasive approaches and enhanced recovery programs, making recommendations for higher risk patients remains an important challenge.

We now have evidence that preoperative exercise interventions are effective in reducing risk associated with major lung resection, particularly with regards to postoperative complications including pulmonary complications, and these interventions result in a decreased duration of postoperative hospital stay. The benefits from these interventions are likely owing to improved exercise capacity and stamina. Interestingly, benefits are often evident with as little as 1 week of exercise, indicating that the intervention can be accomplished without delaying surgery. As a result, it is recommended that patients who are at increased risk for major lung resection related to performance status, identification of sarcopenia, or evidence for prefrailty or frailty should complete a preoperative exercise program.

As with many recommendations for perioperative care, the devil is in the details. Exercise interventions include both standard programs (2 to 3 exercise periods per week) and high intensity programs (1 or more exercise periods daily). Interventions can also be moderate in their intensity, aiming to achieve 50% of maximum effort, or more strenuous, aiming for 75% to 80% of maximum effort. Studies that included ultra-short and high intensity interventions were usually performed in an inpatient setting, which is not a feasible undertaking in most settings because of cost

considerations. In a similar vein, whether the exercise is performed under supervision or is self-directed may have an impact on outcomes. Not every patient is a candidate for exercise intervention. Pre-frail patients will be more likely to be able to participate than the frailest of the frail. Patients must have sufficient physiologic reserves to permit their participation. Some patients will be unable to participate owing to orthopedic problems, claudication, and other comorbidities that don't directly relate to cardiopulmonary fitness. How to best assess those patients remains a challenge.

Additional considerations pertain to the types of exercise that are recommended. Many studies included one or more of the following: inspiratory muscle training, strength (resistance) training, and endurance (aerobic) training. What combination of these interventions is best for mitigating surgical risk is not known. We also don't know whether there is benefit in nutritional repletion as part of the intervention or for how long the intervention should be carried out. Additional high quality studies are needed to ascertain the optimal exercise regimen, its frequency and duration, and any additional interventions (nutrition, balance training) that might be appropriate. Ideally these studies will help clinicians understand how to individualize prehabilitation programs to optimize benefits to surgical candidates.

Recommendation

- Patients who are at increased risk for major lung resection should complete a preoperative exercise program (evidence quality moderate, strong recommendation).

A Personal View of the Data

The science and clinical practice of risk evaluation for major lung resection have evolved considerably in the past few decades. Nevertheless, many surgeons are unaware of guidelines for preoperative evaluation or do not use them in their clinical practice. The reasons for the latter are unclear but the behavior reflects common findings in how we practice medicine—much of it is based on what we were taught rather being evidence-based. Hopefully information such as that contained in this chapter will help surgeons improve their perioperative care of patients.

I have long been a proponent of having every patient for whom I am considering lung surgery participate in a preoperative exercise prehabilitation program. Normally I prescribe walking exercise only, with a goal of one to two miles of vigorous walking daily. Often patients are requested to begin this on the day of their first visit to see me in the outpatient clinic. The overall success rate of this type of intervention is high with regards to participation; no formal testing of performance metrics is done. Patients at the highest risk because of severe pulmonary dysfunction are referred for a 4-week program of cardiopulmonary rehabilitation on an outpatient basis, which includes supervised sessions three times per week.

This approach is accompanied by a strong admonition against smoking, and my patients are informed that they risk not getting an operation unless they quit smoking for several weeks prior to surgery. Not surprisingly, this approach results in a smoking cessation rate of about 98%.

More sophisticated approaches to exercise intervention in my practice historically have been limited in use because of access to resources including venue, equipment, expert supervision, and patient-specific recommendations. However, with expanding knowledge regarding frailty and sarcopenia, it is now evident that screening and intervention are important in appropriate patients. We are doing routine frailty/sarcopenia screening with the following instruments: FRAIL questionnaire [27], measurement of grip strength, and measurement of gait speed. An abnormal FRAIL questionnaire, grip strength <30 Kg for men or <20kg for women, or a gait speed <0.8m/sec is an indication for a comprehensive geriatric assessment as well as exercise intervention. Good quality evidence and strong recommendations support the benefits of exercise and nutrition interventions for sarcopenia [28]. Our current intervention for most patients is 2 to 3 weeks of daily home-based exercise including resistance and endurance training, the latter consisting of walking or use of a stationary bicycle. We find that the vast majority of patients are not only able to participate vigorously in such a program, but such participation results in a substantial improvement in their outlook regarding the treatment of their disease.

References

1. Bandeen-Roche K, Seplaki CL, Huang J, Buta B, Kalyani RR, Varadhan R, Xue QL, Walston JD, Kasper JD. Frailty in older adults: a nationally representative profile in the United States. J Gerontol A Biol Sci Med Sci. 2015;70(11):1427–34.
2. Beckert AK, Huisingh-Scheetz M, Thompson K, Celauro AD, Williams J, Pachwicewicz P, Ferguson MK. Screening for frailty in thoracic surgical patients. Ann Thorac Surg. 2017;103(3):956–61.
3. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, Chen LK, Fielding RA, Martin FC, Michel JP, Sieber C, Stout JR, Studenski SA, Vellas B, Woo J, Zamboni M, Cederholm T. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing. 2014;43(6):748–59.
4. Tsiouris A, Hammoud ZT, Velanovich V, Hodari A, Borgi J, Rubinfeld I. A modified frailty index to assess morbidity and mortality after lobectomy. J Surg Res. 2013;183(1):40–6.
5. Ruiz J, Miller AA, Tooze JA, Crane S, Petty WJ, Gajra A, Klepin HD. Frailty assessment predicts toxicity during first cycle chemotherapy for advanced lung cancer regardless of chronologic age. J Geriatr Oncol. 2019;10(1):48–54.
6. Raghavan G, Shaverdian N, Chan S, Chu FI, Lee P. Comparing outcomes of patients with early-stage non-small-cell lung cancer treated with stereotactic body radiotherapy based on frailty status. Clin Lung Cancer. 2018;19(5):e759–66.
7. Nakamura R, Inage Y, Tobita R, Yoneyama S, Numata T, Ota K, Yanai H, Endo T, Inadome Y, Sakashita S, Satoh H, Yuzawa K, Terashima T. Sarcopenia in resected NSCLC: effect on postoperative outcomes. J Thorac Oncol. 2018;13(7):895–903.
8. Burtin C, Bezuidenhout J, Sanders KJC, Dingemans AC, Schols AMWJ, Peeters STH, Spruit MA, De Ruysscher DKM. Handgrip weakness, low fat-free mass, and overall survival in non-small cell lung cancer treated with curative-intent radiotherapy. J Cachexia Sarcopenia Muscle. 2020;11:424–31. https://doi.org/10.1002/jcsm.12526.

9. Cortellini A, Verna L, Porzio G, Bozzetti F, Palumbo P, Masciocchi C, Cannita K, Parisi A, Brocco D, Tinari N, Ficorella C. Predictive value of skeletal muscle mass for immunotherapy with nivolumab in non-small cell lung cancer patients: a "hypothesis-generator" preliminary report. Thorac Cancer. 2019;10(2):347–51.
10. Tsukagoshi M, Yokobori T, Yajima T, Maeno T, Shimizu K, Mogi A, Araki K, Harimoto N, Shirabe K, Kaira K. Skeletal muscle mass predicts the outcome of nivolumab treatment for non-small cell lung cancer. Medicine (Baltimore). 2020;99(7):e19059.
11. Pehlivan E, Turna A, Gurses A, Gurses HN. The effects of preoperative short-term intense physical therapy in lung cancer patients: a randomized controlled trial. Ann Thorac Cardiovasc Surg. 2011;17(5):461–8.
12. Stefanelli F, Meoli I, Cobuccio R, Curcio C, Amore D, Casazza D, Tracey M, Rocco G. High-intensity training and cardiopulmonary exercise testing in patients with chronic obstructive pulmonary disease and non-small-cell lung cancer undergoing lobectomy. Eur J Cardiothorac Surg. 2013;44(4):e260–5.
13. Gao K, Yu PM, Su JH, He CQ, Liu LX, Zhou YB, Pu Q, Che GW. Cardiopulmonary exercise testing screening and pre-operative pulmonary rehabilitation reduce postoperative complications and improve fast-track recovery after lung cancer surgery: a study for 342 cases. Thorac Cancer. 2015;6(4):443–9.
14. Licker M, Karenovics W, Diaper J, Frésard I, Triponez F, Ellenberger C, Schorer R, Kayser B, Bridevaux PO. Short-term preoperative high-intensity interval training in patients awaiting lung cancer surgery: a randomized controlled trial. J Thorac Oncol. 2017;12(2):323–33.
15. Lai Y, Huang J, Yang M, Su J, Liu J, Che G. Seven-day intensive preoperative rehabilitation for elderly patients with lung cancer: a randomized controlled trial. J Surg Res. 2017;209:30–6.
16. Huang J, Lai Y, Zhou X, Li S, Su J, Yang M, Che G. Short-term high-intensity rehabilitation in radically treated lung cancer: a three-armed randomized controlled trial. J Thorac Dis. 2017;9(7):1919–29.
17. Lai Y, Su J, Qiu P, Wang M, Zhou K, Tang Y, Che G. Systematic short-term pulmonary rehabilitation before lung cancer lobectomy: a randomized trial. Interact Cardiovasc Thorac Surg. 2017;25(3):476–83.
18. Boujibar F, Bonnevie T, Debeaumont D, Bubenheim M, Cuvellier A, Peillon C, Gravier FE, Baste JM. Impact of prehabilitation on morbidity and mortality after pulmonary lobectomy by minimally invasive surgery: a cohort study. J Thorac Dis. 2018;10(4):2240–8.
19. Bhatia C, Kayser B. Preoperative high-intensity interval training is effective and safe in deconditioned patients with lung cancer: a randomized clinical trial. J Rehabil Med. 2019;51(9):712–8.
20. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377–81.
21. Pouwels S, Fiddelaers J, Teijink JA, Woorst JF, Siebenga J, Smeenk FW. Preoperative exercise therapy in lung surgery patients: a systematic review. Respir Med. 2015;109(12):1495–504.
22. Ni HJ, Pudasaini B, Yuan XT, Li HF, Shi L, Yuan P. Exercise training for patients pre- and postsurgically treated for non-small cell lung cancer: a systematic review and meta-analysis. Integr Cancer Ther. 2017;16(1):63–73.
23. Sebio Garcia R, Yáñez Brage MI, Giménez Moolhuyzen E, Granger CL, Denehy L. Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg. 2016;23(3):486–97.
24. Steffens D, Beckenkamp PR, Hancock M, Solomon M, Young J. Preoperative exercise halves the postoperative complication rate in patients with lung cancer: a systematic review of the effect of exercise on complications, length of stay and quality of life in patients with cancer. Br J Sports Med. 2018;52(5):344.
25. Li X, Li S, Yan S, Wang Y, Wang X, Sihoe ADL, Yang Y, Wu N. Impact of preoperative exercise therapy on surgical outcomes in lung cancer patients with or without COPD: a systematic review and meta-analysis. Cancer Manag Res. 2019;11:1765–77.

26. Rosero ID, Ramírez-Vélez R, Lucia A, Martínez-Velilla N, Santos-Lozano A, Valenzuela PL, Morilla I, Izquierdo M. Systematic review and meta-analysis of randomized, controlled trials on preoperative physical exercise interventions in patients with non-small-cell lung cancer. Cancers. 2019;11:944.
27. Abellan van Kan G, Rolland Y, Bergman H, et al. The I.A.N.A. Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging. 2008;12:29–37.
28. Dent E, Morley JE, Cruz-Jentoft AJ, Arai H, Kritchevsky SB, Guralnik J, Bauer JM, Pahor M, Clark BC, Cesari M, Ruiz J, Sieber CC, Aubertin-Leheudre M, Waters DL, Visvanathan R, Landi F, Villareal DT, Fielding R, Won CW, Theou O, Martin FC, Dong B, Woo J, Flicker L, Ferrucci L, Merchant RA, Cao L, Cederholm T, SML R, Rodríguez-Mañas L, Anker SD, Lundy J, Gutiérrez Robledo LM, Bautmans I, Aprahamian I, JMGA S, Izquierdo M, Vellas B. International clinical practice guidelines for sarcopenia (ICFSR): screening, diagnosis and management. J Nutr Health Aging. 2018;22(10):1148–61.

Is Antibiotic Prophylaxis Necessary for Major Lung Resection?

11

Darren S. Bryan and Mark K. Ferguson

Introduction

Surgical resection is the standard of care treatment for early stage lung cancer, and a necessary component of curative intent therapy for patients with locally advanced disease [1, 2]. With more than 200,000 newly diagnosed cases of lung cancer in the United States in 2018, lung resections are some of the most commonly performed oncologic operations [3]. Post-operative pulmonary complications and infectious complications, such as surgical site infection (SSI), post-operative pneumonia (POP), and empyema, have historically represented a major source of morbidity and mortality for patients undergoing lung resection [4]. As a whole, patients with post-operative pulmonary complications have been found to have more frequent and longer admissions in the intensive care unit, increased lengths of stay in the hospital, and a greater rate of in-hospital deaths [5].

Administration of antibiotics before select surgical procedures emerged in the early 1990s as a standard strategy for prevention of post-operative infectious complications [6]. Since that time, the administration of pre-operative antibiotics and SSI rates have been used as a quality metric for multiple national, state, and institutional-level quality-improvement campaigns, and have been subsequently incorporated into societal clinical practice guidelines. While such guidelines have been published for cardiac surgery, no standardized recommendations exist for patients undergoing lung resection [7–9]. This chapter addresses the use of perioperative antibiotics in patients undergoing lung resection and evaluates the published literature examining infectious outcomes.

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Table 11.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients undergoing elective lung resection	Prophylactic antibiotics	Absence of antibiotics	Surgical site infection, pneumonia, empyema

Search Strategy

We queried the PubMed, Embase, and Cochrane Evidence Based Medicine databases for publications categorized with the terms "antibiotic prophylaxis," "preoperative care/methods," "bacterial infections/control," "surgical wound infection" AND "procedure, thoracic surgical" (Table 11.1). Results were limited to those written in the English language, studying humans, and published within the last 15 years. Articles were hand screened for relevancy and references examined for additional works falling outside the search parameters. Articles primarily related to cardiac surgery were excluded from analysis, as were studies comparing only different antibiotics, or duration of antibiotic treatment.

Results

Overall Risk Reduction

Lung resection and perioperative care for patients undergoing such operations has evolved substantially in the past three decades, leading to changing risk factors and thus a shifting incidence of post-operative infection. One of the most notable changes to the field has been the application of minimally invasive technique such as video or robotic assisted thoracoscopic surgery. In 2016 Yang and colleagues queried the National Cancer Database and reported that of approximately 30,000 lobectomies performed for early stage lung cancer between 2010 and 2012, almost one third utilized minimally invasive technique [10]. With changing operative technique comes changing risk profiles. A 2015 Dutch study aimed to identify risk factors for post-operative pneumonia in patients undergoing pulmonary resection for lung cancer. Of the more than 7000 patients identified, 268 (3.6%) were diagnosed with post-operative pneumonia, and patients with thoracoscopic operations experienced pneumonia at half the rate as those undergoing thoracotomy [11]. Other studies have also found decreased rates of surgical site infection in patients undergoing thoracoscopic operations [12].

Wound Infection

Normal skin and respiratory flora are the primary cause of post-operative wound infection. In pulmonary surgery, this includes *Staphylococcus Aureus (most common),* coagulase negative staphylococci, *Streptococcus Pneumoniae*, and

gram-negative bacilli [9]. Prophylactic regimens should be based on hospital and community antibiotograms, but usually include a cephalosporin (most commonly cefazolin), or vancomycin when antibiotic resistant species are suspected.

Several studies met search criteria and examined rates of wound infections after administration of prophylactic antibiotics, however all fell outside of the pre-specified time window of publication in the last 15 years (Table 11.2). While dated, and performed before the era of thoracoscopic surgery, these data deserve mention. In 1977, Kvale and colleagues published what would be the first of several double-blind randomized controlled trials studying the perioperative application of antibiotics. They randomized patients undergoing pulmonary resection to a 5-day course of intramuscular/oral cephalosporin or placebo. Patients in the treatment arm experienced fewer overall infectious complications than those receiving the placebo (19% versus 50%, $p < 0.005$), leading the authors to conclude that pre-operative antibiotics are indicated for patients undergoing pulmonary resection [13]. Two subsequent randomized trials also looked at incidence of wound infections following lung resection. In 1982, Frimodt-Moller enrolled 92 patients undergoing resections including lobectomy and pneumonectomy, randomizing to six perioperative doses of penicillin G or placebo. Again, those in the treatment arm experienced fewer post-operative wound infections (4.4% versus 19.2%, $P = 0.03$) [14]. A third trial, published by Aznar and colleagues in 1991 randomized 127 patients to cefazolin or placebo. For a third time, wound infection was significantly reduced in the treatment arm (1.5% versus 14%, $P < 0.01$) [15].

The data from these studies, while more than 30 years old, do suggest a decrease in superficial wound infection with the use of pre-operative antibiotics in non-cardiac thoracic surgery. They set the stage for a shift in practice, with subsequent trials studying antibiotic type and duration. Until the present era, most published works examining post-operative complications have included antibiotics in all study arms. The weakness of these studies obviously lies in the time since publication and the difficulty of applying their conclusions to a different era of surgical practice. In the modern era, pre-operative utilization of chlorhexidine-alcohol based prep solutions, along with other antisepsis practices, have drastically decreased the rates of wound infection [16]. Furthermore, these studies were performed prior to the thoracoscopic era, with all patients undergoing thoracotomies. Infection control practices and surgical technique have evolved to overall make lung resection less invasive and less prone to surgical site infection.

Pneumonia and Empyema

Post-operative pneumonia can be a particularly troublesome complication, with some groups reporting rates of associated mortality approaching 20% [4]. Responsible pathogens include most commonly *Streptococcus pneumonia* and *Hemophilus spp*, both of which are frequently seen in community acquired pneumonia and are known colonizers of the bronchial tree. With this information, a French group changed their prophylactic antibiotic protocol for patients undergoing

Table 11.2 Efficacy of antibiotic prophylaxis in patients undergoing lung resection

Author (year)	N	Operations included	Arms	Incidence of Infectious Complications		P value	Evidence quality
				Control (complication type, %)	Treatment (complication type, %)		
Kvale (1977) [13]	77	Open wedge Open lobectomy Open pneumonectomy	Cephalosporin Placebo	50%	19%	0.005	High
Truesdale (1979) [19]	57	Open thoracotomy Open wedge Open lobectomy Open pneumonectomy	Cephalosporin Placebo	Pneumonia, bronchopleural fistula 17.2%	Pneumonia 17.8%	>0.5	High
Frimodt-Moller (1982) [14]	92	Open thoracotomy Open segmental resection Open lobectomy Open pneumonectomy	Penicillin G Placebo	Empyema (4.3) Pneumonia (40.4) Wound infection (19.2)	Empyema (4.4) Pneumonia (33.3) Wound infection (4.4)	0.03 (wound infection)	High
Aznar (1991) [15]	127	Non-cardiac thoracic surgery	Cefazolin Placebo	Empyema [14] Pneumonia [9] Wound infection [14]	Empyema [7] Pneumonia [4] Wound infection (1.5)	<0.01 (wound infection)	High

lung resection from cefamandole (a second-generation cephalosporin with activity against bacteria commonly found in wound infection, but not necessarily against bacteria isolated in patients with post-operative pneumonia) to high dose amoxicillin-clavulanate [17]. After implementation of the new protocol, they reported a significant reduction in post-operative pneumonia from 25 to 13.7%, with bronchial sampling at the time of operation showing decreased bacterial colonization. The study was criticized for its high initial rate of pneumonia, and that the second group of patients may have been more optimized pre-operatively, leading to decreased bronchial colonization [18]. Furthermore, the antibiotic dose used was more in line with treatment rather than prophylactic dosing.

While results from historic trials demonstrated a decrease in wound infection with application of pre-operative antibiotics, the same decrease was not shown for post-operative pneumonia or empyema. In both the Frimodt-Moller and Aznar trials, rates of post-operative pneumonia and empyema were not significantly different in treatment arms. Another study by Truesdale et al. in 1979 compared outcomes in patients undergoing lung resection who had received either a cephalosporin for prophylaxis, or placebo. Again, there was no noted difference between the groups in terms of pneumonia, or bronchopleural fistula [19].

Existing Guideline Recommendations

Peri-operative infection control practices have changed dramatically in the last three decades, as has the field of thoracic surgery. Guidelines, however, are sparse (Table 11.3). A 2017 Center for Disease Control and Prevention Guideline published in JAMA Surgery detailed recommendations for the prevention of surgical site infection garnered from 170 individual studies [20]. They found support for pre-operative skin preparation with alcohol-based antiseptic scrub, as well as bathing/cleansing with antiseptic soap the day prior to the operation. Additionally, prophylactic antibiotics were addressed. The report states that, "antimicrobial

Table 11.3 Existing guidelines and clinical practice recommendations for the use of antibiotics in patients undergoing lung resection

Author (year)	Publication	Findings/recommendations
Berrios-Torres (2017) [20]	JAMA Surgery	"Antimicrobial prophylaxis should be administered only when indicated based on published clinical practice guidelines"
Bratzler (2013) [6]	American Society of Healthcare Pharmacists	In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended. Strength of evidence for prophylaxis for VATS = C (lowest level); strength of evidence for prophylaxis for open thoracic procedures = A (highest level)

prophylaxis should be administered only when indicated based on published clinical practice guidelines," and thus is not necessarily supportive of blanket prophylactic antibiotic use in surgery.

Prophylactic antibiotics are frequently employed for lung resection in everyday practice. Many enhanced recovery pathways for patients undergoing lung resection do include prophylactic antibiotics, a policy endorsed by the European Society for Thoracic Surgery [21, 22]. Such recommendations are based on data detailing post-operative infections, namely, wound infection, empyema, and pneumonia.

The American Society of Health-System Pharmacists, in conjunction with the Infectious Diseases Society of America (IDSA) and the Surgical Infection Society (SIS), released a policy position in 2013 detailing recommendations for antimicrobial agents for the prevention of surgical-site infections [6]. For patients undergoing non-cardiac thoracic surgery, the group recommends pre-operative cefazolin or ampicillin-sulbactam with an assigned A (highest) level of evidence, based predominantly on trials mentioned in this text, mostly from the pre-thoracoscopic era. Patients who are undergoing planned thoracoscopic surgery are also recommended to receive pre-operative cefazolin or ampicillin, however with an assigned C (lowest) level of evidence.

Conclusions and Recommendations

Patients undergoing lung resection are at risk for peri-operative infectious complications, including wound infection, empyema, and pneumonia. Post-operative pneumonia, in particular, is a main source of morbidity and mortality. While pre-operative antibiotic prophylaxis has been a successful strategy in other fields of surgery to reduce rates of SSI, there is a paucity of data in the current surgical era to show efficacy in patients undergoing lung resection. Nevertheless, most published data on post-operative infections from the last several decades was garnered from patients who did receive antibiotic prophylaxis. Historic studies showed pre-operative antibiotics to be successful in decreasing the rate of wound infection in patients undergoing lung resection, however superficial infections in the era of thoracoscopic surgery are more rare, and often benign in nature. Data have not consistently demonstrated a decrease in empyema or post-operative pneumonia. Therefore, those undergoing open lung resection or VATS resection with a high probability of conversion to open should receive pre-operative antibiotic prophylaxis against wound infection. No recommendation can be made for antibiotic prophylaxis against post-operative wound infection for patients undergoing planned VATS resection with low likelihood of conversion to thoracotomy. No recommendation can be made for antibiotic prophylaxis against post-operative pneumonia or empyema.

Recommendations

- For patients undergoing planned thoracoscopic lung, no recommendation can be made for pre-operative antibiotics (evidence quality low, weak recommendation).
- Patients undergoing open lung resection should receive prophylactic antibiotics against postoperative wound infection (evidence quality low, weak recommendation).
- For patients undergoing lung resection, no recommendation can be made for antibiotic prophylaxis against post-operative pneumonia or empyema (evidence quality low, weak recommendation).

A Personal View of the Data

The initial trials investigating the use of perioperative antibiotics reported high rates of post-operative infectious complications. Since their publication over 30 years ago, rates of infection have decreased as surgical approaches and infection control practices have evolved substantially. This has occurred alongside an increased focus on wound infection as a quality indicator. Modern series report rates of post-operative infection for patients undergoing lung resection to be low, a finding even more pronounced among those undergoing minimally invasive operations. We recommend consideration for prophylaxis against superficial surgical site infection in patients having open operations or thoracoscopic operations with a high likelihood of conversion to open, targeting skin flora and common pathogens identified in wound infections according to relevant hospital antibiograms. Patients undergoing straight forward VATS lung resection likely see minimal benefit with the addition of antibiotics, however prospective data demonstrating this has not yet emerged.

We view post-operative pneumonia to be a complication associated with bronchial colonization, and thus the best prophylaxis against infection to be pre-operative patient optimization with exercise, airway clearance, and smoking cessation, rather than pre-incisional antibiotics.

References

1. Donington JS, Kim YT, Tong B, et al. Progress in the management of early-stage non-small cell lung cancer in 2017. J Thorac Oncol. 2018;13(6):767–78.
2. Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of Stage III non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2013;143(5 Suppl):e314S–40S.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.

4. Schussler O, Alifano M, Dermine H, et al. Postoperative pneumonia after major lung resection. Am J Respir Crit Care. 2006;173(10):1161–9.
5. Agostini P, Cieslik H, Rathinam S, et al. Postoperative pulmonary complications following thoracic surgery: are there any modifiable risk factors? Thorax. 2010;65(9):815–8.
6. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt). 2013;14(1):73–156.
7. Edwards FH, Engelman RM, Houck P, et al. The Society of Thoracic Surgeons Practice Guideline Series: antibiotic prophylaxis in cardiac surgery, part I: duration. Ann Thorac Surg. 2006;81(1):397–404.
8. Engelman R, Shahian D, Shemin R, et al. The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, part II: antibiotic choice. Ann Thorac Surg. 2007;83(4):1569–76.
9. Chang SH, Krupnick AS. Perioperative antibiotics in thoracic surgery. Thorac Surg Clin. 2012;22(1):35.
10. Yang C-FJ, Sun Z, Speicher PJ, et al. Use and outcomes of minimally invasive lobectomy for stage I non-small cell lung cancer in the National Cancer Data Base. Ann Thorac Surg. 2016;101(3):1037–42.
11. Simonsen DF, Søgaard M, Bozi I, et al. Risk factors for postoperative pneumonia after lung cancer surgery and impact of pneumonia on survival. Respir Med. 2015;109(10):1340–6.
12. Imperatori A, Rovera F, Rotolo N, et al. Prospective study of infection risk factors in 988 lung resections. Surg Infect (Larchmt). 2006;7(Suppl 2):S57–60.
13. Kvale P, Ranga V, Kopacz M, et al. Pulmonary resection. South Med J. 1977;70:64–8.
14. Frimodt-Møller N, Ostri P, Pedersen IK, et al. Antibiotic prophylaxis in pulmonary surgery: a double-blind study of penicillin versus placebo. Ann Surg. 1982;195(4):444.
15. Aznar R, Mateu M, Miro JM, et al. Antibiotic prophylaxis in non-cardiac thoracic surgery: cefazolin versus placebo. Eur J Cardiothorac Surg. 1991;5(10):515–8.
16. Darouiche RO, Wall MJ, Itani KMF, et al. Chlorhexidine–alcohol versus povidone–iodine for surgical-site antisepsis. N Engl J Med. 2010;362(1):18–26.
17. Schussler O, Dermine H, Alifano M, et al. Should we change antibiotic prophylaxis for lung surgery? Postoperative pneumonia is the critical issue. Ann Thorac Surg. 2008;86(6):1727–33.
18. Stern J-B, Pean Y. Antibiotic Prophylaxis for lung surgery: bronchial colonization is the critical issue? Ann Thorac Surg. 2009;88(3):1051.
19. Truesdale R, D'Alessandri R, Manuel V, et al. Antimicrobial vs placebo prophylaxis in noncardiac thoracic surgery. JAMA. 1979;241(12):1254–6.
20. Berríos-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. JAMA Surg. 2017;152(8):784–91.
21. Batchelor TJ, Rasburn NJ, Abdelnour-Berchtold E, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg. 2018;55(1):91–115.
22. Dinic VD, Stojanovic MD, Markovic D, et al. Enhanced recovery in thoracic surgery: a review. Front Med. 2018;5:14.

Uniportal Versus Multiportal VATS Lobectomy

12

Alan D. L. Sihoe

Introduction

Video-Assisted Thoracic Surgery (VATS) is today established as the minimally invasive surgical approach of choice for performing lobectomy for lung cancer [1–4]. Since VATS lobectomy was first developed over a quarter of a century ago, a large volume of clinical evidence has been produced to demonstrate its safety, efficacy, and advantages over traditional open thoracotomy [2, 5]. However, it was also recognized that even with conventional VATS—typically using three ports, including a 'utility' port—there was room for improvement. A number of studies have reported that 'multiportal' VATS (mVATS) still resulted in a substantial proportion of patients experiencing pain or paresthesias after surgery [4, 6, 7].

Alongside the emergence of robot-assisted surgery, another perhaps even more popular direction of surgical progress has been in 'next generation' VATS approaches [4, 8]. These have included needlescopic VATS, two-port VATS, and single-port VATS. The latter, Uniportal VATS (uVATS) for lobectomy, was first reported in 2011, and has since been adopted by many thoracic surgeons around the world [8–10]. Conceptually, limiting surgical access trauma to only one incision at only one intercostal level should provide the least pain and morbidity to the patient.

Nevertheless, those thoracic surgeons who have yet to use the uVATS approach feel they are now facing a difficult decision: if I am already performing mVATS lobectomy well, should I switch over to uVATS? This chapter attempts to answer this question using the currently available clinical evidence.

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Table 12.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes
Adult patients undergoing lobectomy for lung cancer	uVATS approach	mVATS approach	Safety Surgical outcomes Oncologic efficacy

Search Strategy

A literature search was conducted to identify papers comparing uVATS) and mVATS for lobectomy with curative intent in adult lung cancer patients. The PICO terms used for this strategy are summarized in Table 12.1. Electronic searches were performed using the Ovid Medline from 1946 to September 20, 2019. Key words and MeSH terms searches were conducted for 2 groups: 1) 'uniport∗' or 'single port∗' or 'single incision∗'; and 2) 'VATS' or 'thoracoscop∗' or 'video assist∗'. The 2 groups were combined with the Boolean operator 'AND'.

Initial screening of all search results was based on abstracts and titles. Eligible studies were defined as those that included 15 or more adult patients with a confirmed or suspected diagnosis of lung cancer treated by lobectomy using a uniportal VATS approach. All studies were limited to human subjects only. Papers were excluded if the primary focus was on indications for surgery other than for lung malignancy (such as mediastinal tumors, pneumothorax and hyperhidrosis), variant techniques (such as subxiphoid or robotic uVATS), or anesthetic techniques (such as non-intubated or awake surgery). Case reports, surgical technique papers, reviews, editorials, expert opinions, commentaries, conference abstracts and letters were excluded. Following the initial screening, full texts of potentially relevant articles were obtained. The full text papers were then further selected according to relevance to the PICO terms above.

Results

The final selection of 24 papers comparing uVATS) and mVATS included for this review are displayed in Table 12.2 [11–34]. The individual studies include from 15 to 167 patients who received uVATS for lung cancer.

The overall quality of the available evidence is low to moderate according to the GRADE system. Only three are prospective studies, but one has been published in a non-English journal of unknown quality, and the results are conspicuously one-sided (in favor of uVATS) [29]. Another of these prospective studies is a randomized study [20]. However, this paper has been criticized previously for possibly being under-powered and for possibly having an inappropriate control group [35]. The remaining 21 papers are all retrospective studies. Many are published in lesser known journals. Eight of them used propensity-score matching to reduce bias in the comparison between uVATS and mVATS. However, in doing so, the compared

Table 12.2 Studies comparing uniportal VATS (uVATS) and multiportal VATS (mVATS) for lobectomy for lung cancer

Study first author	Reference	Year of publication	uVATS	mVATS	OT	Blood loss	Lymph nodes dissected	CDD	LOS	Morbidity	Pain	Paresthesia	QoL	Survival	Comment
Wang	11	2015	46	46	U	U	U		ND	ND					Retrospective—comparative (with PSM)
McElnay	12	2015	15	95							0				Prospective—comparative (non-randomized)
Chung	13	2015	90	60	ND		ND	ND	ND	ND					Retrospective—comparative
Zhu	14	2015	33	49	M	ND		ND	ND	ND	U				Retrospective—comparative
Mu	15	2015	47	47	ND	ND	ND	ND	M	ND					Retrospective—comparative (with PSM)
Liu	16	2016	100	342	U	U	U		U	ND					Retrospective—comparative
Hirai	17	2016	60	20	ND	ND	ND	ND	ND	ND	U	U			Retrospective—comparative
Chang	18	2016	29	57	ND	U	ND	ND	U	ND					Retrospective—comparative
Shen	19	2016	100	100	ND	ND	ND		ND	ND					Retrospective—comparative (with PSM)
Perna	20	2016	51	55				ND	ND	ND	ND				Prospective—comparative (randomized)
French	21	2016	50	50	ND			ND	ND	ND	ND				Retrospective—comparative (historical control)
Hao	22	2016	115	101	M	ND	ND	U	U	ND	U	U	U		Retrospective—comparative

(Continued)

Table 12.2 (Continued)

Study first author	Reference	Year of publication	uVATS	mVATS	OT	Blood loss	Lymph nodes dissected	CDD	LOS	Morbidity	Pain	Paresthesia	QoL	Survival	Comment
Dai	23	2016	63	63	ND	U	ND	ND	ND	ND	U				Retrospective—comparative (with PSM)
Han	24	2017	167	212			ND	U		ND				ND	Retrospective—comparative
Ke	25	2017	40	40	U	ND	ND	U	U	ND	U				Retrospective—comparative (with PSM)
Heo	26	2017	32	32	ND	ND	ND	ND	ND	ND					Retrospective—comparative (with PSM)
Song	27	2017	26	26	ND	ND	U	ND	ND	ND					Retrospective—comparative (with PSM)
Stamenovic	28	2018	24	24	ND		ND			ND	U				Retrospective—comparative (with PSM)
Xu	29	2018	60	60		U		U	U		U		U		Prospective—comparative (non-randomized)
Li	30	2018	131	101	ND	ND		ND	ND		U				Retrospective—comparative
Wang	31	2018	153	113	ND	U	ND	U	U		U				Retrospective—comparative
Liu	32	2019	166	162	ND	ND		U	U	ND	U				Retrospective – comparative
Ko	33	2019	39	36	M	M	ND	ND	ND	ND	ND				Retrospective – comparative
Zhao	34	2019	73	56	ND	ND		ND	ND	ND	U				Retrospective—comparative

OT time operation time, *CDD* chest drain duration, *LOS* length of stay, *QoL* quality of life, *PSM* propensity score matching
Key: *M* multiportal better, *U* uniportal better, *ND* no difference between approaches

study arms have become quite small in number, affecting statistical power. The remaining 13 are simply retrospective studies comparing uVATS with mVATS controls from either contemporary or historical cohorts but with no bias-reduction performed.

Safety and Feasibility

Operation times for uVATS) and mVATS were compared in 20 of the papers. In 3 papers, uVATS was found to take longer to perform. In 3 other papers, mVATS was found to take longer to perform. In the remaining 14 papers, no significant difference was found between the approaches. Overall, it appears that uVATS does not pose such a technical challenge over mVATS that it causes any notable increase in operation times. This result is especially noteworthy given that the papers published likely represented the early or learning curve experience of most of the authors with uVATS.

Eighteen of the papers compared blood loss during lobectomy with the uVATS and mVATS approaches. Six papers reported less blood loss with uVATS, one reported less with mVATS, and 11 reported no difference between the approaches. Again, it appears that the adoption of uVATS did not add to the risk of blood loss compared to mVATS.

It is difficult to gauge the safety of the uVATS approach from the selected comparative papers alone. However, this author previously conducted another systematic review published in 2018 which included 22 papers reporting the results for a total of 3129 patients who received anatomical lung resection by uVATS) [36]. In that review, the mortality rate for uVATS was 0% in 16 of the 17 individual studies reporting this statistic, and 3.3% in the remaining one study. The morbidity rate for uVATS lung resection in the 17 individual studies reporting this statistic ranged from 3% to 40%. The single study with the largest cohort of 731 anatomical lung resections reported a morbidity rate of 5.6% [37]. None of the 22 selected articles in that review identified any safety issues pertaining specifically to the use of the uVATS approach.

The only caveat when looking at the safety and feasibility of uVATS is that almost all of the reviewed papers have come from large or ultra-large volume centers with surgeons who are generally already well experienced with the mVATS approach. The published evidence should not be taken as a guarantee of the safety of uVATS in the hands of surgeons with less experience and specific uVATS training.

Surgical Outcomes

Of the 19 papers looking at chest drain durations, 6 found shorter durations with uVATS and 13 found no difference. It is unknown why the number of incisions used should have any influence on post-operative drainage duration.

Of the 21 papers reporting post-operative lengths of stay, 7 reported shorter stays after uVATS, 1 reported shorter stays after mVATS, and 13 reported no difference. Although this may be construed as an indicator of faster recovery after uVATS, it is also worth noting that most of these studies were retrospective and unblended—and hence bias cannot be excluded. With this in mind, it should be noted that virtually all studies have not set pre-defined criteria for drain removal or discharge from hospital after surgery.

Of the 15 paper reporting pain experiences after surgery, 11 report that uVATS patients had less pain at least at one time point after surgery. Only 2 papers reported on paresthesia post-operatively, and both found that uVATS gave less paresthesia. The apparent reduction in pain and paresthesia represents the greatest demonstrated advantage of uVATS compared with mVATS in this review. The key qualification to this is that almost all the included studies have not set pre-defined, consistent and equal pain management protocols for all patients. Hence, bias in analgesia provision between the study arms cannot be excluded.

Twenty papers reported on post-operative complications or morbidity, and none found any difference between uVATS and mVATS. One should perhaps not draw too many conclusions from this as different papers have included different individual complications for reporting, and may have defined each complication differently.

Oncological Efficacy

Lymph node dissection has become a common surrogate to gauge the 'thoroughness' of the lung cancer resection [2, 5]. Sixteen papers in this review reported on this, but have assessed nodal dissection in sometimes different ways: some report total nodes dissected, others report nodal stations explored, and so on. Overall, 3 papers reported superiority using uVATS and 13 reported no difference. It appears that the use of one port only instead of multiple ports does not compromise surgical thoroughness—at least for more experienced surgeons.

Only one of the comparative studies reported survival outcomes [24]. For patients with stage I disease, Han et al. reported that the 3-year overall survival was 93.2% (95% CI, 85.7% to 96.8%) with uVATS, 93.7% (95% CI, 77.2% to 98.4%) for two-port VATS, and 87.3% (95% CI, 78.1% to 92.8%) for three-port VATS (p=0.753) [24]. The recurrence-free survival at 3-years was 76.9% (95% CI, 64.6% to 85.5%) for uVATS, 87.5% (95% CI, 69.9% to 95.1%) for two-port VATS, and 79.9% (95% CI, 69.9% to 86.9%) for three-port VATS (p=0.656). No other comparative survival studies were identified. However, in a retrospective series of 307 patients receiving uVATS anatomical lung resection for lung cancer, Wu et al. reported that the 2-year disease-free survival and 2-year overall survival were 92.3% and 100% for IA1, 73.7% and 91.4% for IA2, 75.2% and 93.4% for IA3, 62.1% and 85.9% for IB,

55.6% and 72.7% for IIA, 47.1% and 64.2% for IIB and 42.1% and 60.3% for IIIA (staged according to the AJCC 8th classification) [38].

Overall, these results suggest that the treatment efficacy for lung cancer is not compromised by the use of uVATS. Again, the caveat remains that these results may possibly represent the experience of uVATS pioneers and 'experts' only.

Conclusions and Recommendations

If I Am Already Performing mVATS, Can I Safely Switch to uVATS?

Answer: YES. The available evidence shows that even early in the learning curve of uVATS lobectomy, experienced mVATS surgeons have achieved operating times and blood loss comparable with mVATS. At the same time, adequacy of nodal dissection and lung cancer survival do not appear to be compromised by uVATS) when compared with mVATS results. These suggest that it is possible to switch to uVATS without causing harm to the patient. However, given the low quality and quantity of the clinical evidence, this recommendation can only be a weak one. This recommendation also comes with a strict condition: anyone embarking on the path to uVATS must begin with proper training to prepare oneself to the standard of the uVATS pioneers as described in these reviewed papers. Effective training in uVATS is now widely available in workshops and courses around the world [39, 40], and it is inexcusable not to be trained by an expert before attempting one's first uVATS lobectomy.

If I Am Already Performing mVATS, Should I Switch to uVATS?

Answer: MAYBE NOT. The current literature shows a strong trend for uVATS to give less post-operative pain and paresthesias than mVATS. Although the quality of the data is compromised by a lack of consistency in analgesic provision and in standardizing the pain observations, pain is nonetheless the one outcome measure where the majority of studies have demonstrated a benefit from uVATS). However, the absolute difference in pain scores between uVATS and mVATS is typically 2-points or less on a 10-point scale. Whether this small benefit alone justifies switching to uVATS is uncertain—especially when other means to effectively control pain and expedite post-operative recovery are available [41–43]. In terms of chest drain duration, length of stay, and morbidity rates, uVATS has not been shown to consistently outperform mVATS.

In summary, the old cliché about uVATS remains valid: the evidence demonstrates that it *can* be performed, but does not yet support that it *should* be performed.

Recommendations

- For surgeons who are already performing multiportal VATS lobectomy, it is safe to switch to uniportal VATS lobectomy (evidence quality low, weak recommendation).
- For surgeons who are already performing multiportal VATS lobectomy, switching to uVATS is not necessary, as this approach offers little in overall benefit to patients (evidence quality very low, weak recommendation).

A Personal View of the Data

Since this author's previous systematic review of uVATS [36], a greater quantity of papers have been published presenting original clinical data. This is encouraging and commendable. However, as has been made clear above, the quality of the clinical evidence comparing uVATS) and mVATS lobectomy remains fairly poor. Many have been published in lesser known journals, reflecting that they may have been rejected by the more established journals due to insufficient quality. Almost all are retrospective series, often with small cohort sizes, with consequently weak reliability.

One way to overcome is to combine the data from all the studies to perform a meta-analysis. Indeed, there appears to have been almost as many meta-analyses published on uVATS) versus mVATS in the past year or 2 as there have been original articles on the same topic [44–47]. This is disappointing because these meta-analyses are repeatedly reviewing the same weak data without contributing any fresh data. In this review, this author has deliberately avoided performing any statistical meta-analysis. The reason is that any meta-analysis is only as good as the data being fed into it ("garbage in, garbage out"). The 24 individual papers in this study vary greatly in terms of: which mode of mVATS is studied (ranging from three-ports to two-ports to Needlescopic VATS); criteria for drain removal or hospital discharge; post-operative analgesic protocol (or lack of one); definitions of post-operative morbidity; and so on. To forcibly combine these disparate studies in an attempt to churn out a '$p<0.05$' result is meaningless. Instead, in this review, the author has chosen to simply count the frequency at which different papers have found a difference in outcome between uVATS and mVATS in a range of outcomes. In this way, at least the study arms are kept to the most similar circumstances possible within each study.

Looking towards the future, one would advise that it is premature to continue conducting meta-analyses in this topic until there is a better batch of clinical data to work with. Proponents of uVATS (including this author!) should refrain from writing reviews and commentaries only as an easy way to publish, but instead get down to the hard work of establishing good prospective database to collect reliable, consistent data on the use of uVATS (and any other surgical approach for that matter) [35]. The emergence of uVATS) interest groups in Europe and Asia raise hopes that co-ordinated, hi-quality, multicentric data collection may become feasible in the near future [48, 49].

References

1. Sihoe ADL, Yim APC. Video-assisted pulmonary resections. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AEMR, Luketich JD, Rice TW, Pearson FG, editors. Thoracic surgery. 3rd ed. Philadelphia: Elsevier; 2008. p. 970–88.
2. Sihoe ADL. The evolution of VATS lobectomy. In: Cardoso P, editor. Topics in thoracic surgery. Rijeka: Intech; 2011. p. 181–210.
3. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e278S–313S.
4. Sihoe ADL. The evolution of minimally invasive thoracic surgery: implications for the practice of uniportal thoracoscopic surgery. J Thorac Dis. 2014;6(Suppl 6):S604–17. https://doi.org/10.3978/j.issn.2072-1439.2014.08.52.
5. Sihoe DLA. Reasons not to perform uniportal VATS lobectomy. J Thorac Dis. 2016;8:S333–43.
6. Passlick B, Born C, Sienel W, Thetter O. Incidence of chronic pain after minimal invasive surgery for spontaneous pneumothorax. Eur J Cardiothorac Surg. 2001;19:355–9.
7. Sihoe ADL, Au SS, Cheung ML, Chow IK, Chu KM, Law CY, Wan M, Yim APC. Incidence of chest wall paresthesia after video-assisted thoracic surgery for primary spontaneous pneumothorax. Eur J Cardiothorac Surg. 2004;25:1054–8.
8. Sihoe DLA. Uniportal video-assisted thoracic surgery (VATS) lobectomy. Ann Cardiothorac Surg. 2016;5:133–44.
9. Gonzalez D, Paradela M, Garcia J, de la Torre M. Single-port video-assisted thoracoscopic lobectomy. Interact Cardiovasc Thorac Surg. 2011;12:514–5.
10. Gonzalez-Rivas D, Paradela M, Fernandez R, Delgado M, Fieira E, Mendez L, Velasco C, de la Torre M. Uniportal video-assisted thoracoscopic lobectomy: two years of experience. Ann Thorac Surg. 2013;95:426–32.
11. Wang BY, Liu CY, Hsu PK, Shih CS, Liu CC. Single incision versus multiple incision thoracoscopic lobectomy and segmentectomy: a propensity matched analysis. Ann Surg. 2015;261:793–9.
12. McElnay PJ, Molyneux M, Krishnadas R, Batchelor TJP, West D, Casali G. Pain and recovery are comparable after either uniportal and multiport video assisted thoracoscopic lobectomy: an observation study. Eur J Cardiothorac Surg. 2015;47:912–5.
13. Chung JH, Choi YS, Cho JH, Kim HK, Kim J, Zo JI, et al. Uniportal video-assisted thoracoscopic lobectomy: an alternative to conventional thoracoscopic lobectomy in lung cancer surgery? Interact Cardiovasc Thorac Surg. 2015;20:813–9.
14. Zhu Y, Liang M, Wu W, Zheng J, Zheng W, Guo Z, Zheng B, Xu G, Chen C. Preliminary results of single-port versus triple-port complete thoracoscopic lobectomy for non-small cell lung cancer. Ann Transl Med. 2015;3(7):92. https://doi.org/10.3978/j.issn.2305-5839.2015.03.47.
15. Mu JW, Gao SG, Xue Q, Zhao J, Li N, Yang K, Su K, Yuan ZY, He J. A matched comparison study of uniportal versus triportal thoracoscopic lobectomy and sublobectomy for early-stage nonsmall cell lung cancer. Chin Med J (Engl). 2015;128:2731–5.
16. Liu CC, Shih CS, Pennarun N, Cheng CT. Transition from a multiport technique to a single-port technique for lung cancer surgery: is lymph node dissection inferior using the single-port technique? Eur J Cardiothorac Surg. 2016;49:i64–72.
17. Hirai K, Takeuchi S, Usuda J. Single-incision thoracoscopic surgery and conventional video-assisted thoracoscopic surgery: a retrospective comparative study of perioperative clinical outcomes. Eur J Cardiothorac Surg. 2016;49:i37–41.
18. Chang JM, Kam KH, Yen YT, Huang WL, Chan W, Tseng YL, Wu MH, Lai WW, Gonzalez-Rivas D. From biportal to uniportal video-assisted thoracoscopic anatomical lung resection: a single-institute experience. Medicine. 2016;95(40):e5097.
19. Shen Y, Wang H, Feng M, Xi Y, Tan L, Wang Q. Single- versus multiple-port thoracoscopic lobectomy for lung cancer: a propensity-matched study. Eur J Cardiothorac Surg. 2016;49:i48–53.

20. Perna V, Carvajal AF, Torrecilla JA, Gigirey O. Uniportal video-assisted thoracoscopic lobectomy versus other video-assisted thoracoscopic lobectomy techniques: a randomized study. Eur J Cardiothorac Surg. 2016;50:411–5.
21. French DG, Thompson C, Gilbert S. Transition from multiple port to single port video-assisted thoracoscopic anatomic pulmonary resection: early experience and comparison of perioperative outcomes. Ann Cardiothorac Surg. 2016;5:92–9. https://doi.org/10.21037/acs.2016.03.03.
22. Hao Z, Cai Y, Fu S, Zhang N, Fu X. [Comparison study of post-operative pain and short-term quality of life between uniportal and three portal video-assisted thoracic surgery for radical lung cancer resection]. [Chinese] Chin J Lung Cancer. 2016;19:122–128.
23. Dai F, Meng S, Mei L, Guan C, Ma Z. Single-port video-assisted thoracic surgery in the treatment of non-small cell lung cancer: a propensity-matched comparative analysis. J Thorac Dis. 2016;8(10):2872–8. https://doi.org/10.21037/jtd.2016.10.27.
24. Han KN, Kim HK, Choi YH. Midterm outcomes of single port thoracoscopic surgery for major pulmonary resection. PLoS One. 2017;12:e0186857.
25. Ke H, Liu Y, Zhou X, Xue Q. Anterior fissureless uniport vs. posterior intra-fissure triple-port thoracoscopic right upper lobectomy: a propensity-matched study. J Thorac Dis. 2017;9(10):3866–74. https://doi.org/10.21037/jtd.2017.09.61.
26. Heo W, Kang DK, Min HK, Jun HJ, Hwang YH. Feasibility and safety of single-port video-assisted thoracic surgery for primary lung cancer. Korean J Thorac Cardiovasc Surg. 2017;50:190–6.
27. Song KS, Park CK, Kim JB. Efficacy of single-port video-assisted thoracoscopic surgery lobectomy compared with triple-port vats by propensity score matching. Korean J Thorac Cardiovasc Surg. 2017;50:339–45.
28. Stamenovic D, Messerschmidt A, Jahn T, Schneider T. Initial experience with uniportal video-assisted thoracoscopic surgery for anatomical lung resections: a propensity score study and an observational assessment of the learning curve. Zentralbl Chir. 2018;143:84–9.
29. Xu GW, Xiong R, Wu HR, Li CW, Xu SB, Xie MR. A prospective comparative study examining the impact of uniportal and three portal video-assisted thoracic surgery on short-term quality of life in lung cancer. Chin J Surg. 2018;56(6):452–7.
30. Li CW, Xu MQ, Xu GW, et al. A comparative study of acute and chronic pain between single port and triple port video-assisted thoracic surgery for lung cancer. Chin J Lung Cancer. 2018;21(4):279–84.
31. Wang GX, Xiong R, Wu HR, et al. Short-term outcome of uniportal and three portal video-assisted thoracic surgery for patients with non-small cell lung cancer. Chin J Lung Cancer. 2018;21(12):896–901.
32. Liu Z, Yang R, Shao F. Comparison of postoperative pain and recovery between single-port and two-port thoracoscopic lobectomy for lung cancer. Thorac Cardiovasc Surg. 2019;67:142–6.
33. Ko HJ, Chiang XH, Yang SM, Yang MC. Needlescopic-assisted thoracoscopic pulmonary anatomical lobectomy and segmentectomy for lung cancer: a bridge between multiportal and uniportal thoracoscopic surgery. Surg Today. 2019;49:49–55. https://doi.org/10.1007/s00595-018-1707-y.
34. Zhao R, Shi Z, Cheng S. Uniport video assisted thoracoscopic surgery (U-VATS) exhibits increased feasibility, non-inferior tolerance, and equal efficiency compared with multiport VATS and open thoracotomy in the elderly non-small cell lung cancer patients at early stage. Medicine. 2019;98(28):e16137. https://doi.org/10.1097/MD.0000000000016137.
35. Gonzalez-Rivas D, Damico TA, Jiang G, Sihoe A. Uniportal video-assisted thoracic surgery: a call for better evidence, not just more evidence. Eur J Cardiothorac Surg. 2016;50:416–7. https://doi.org/10.1093/ejcts/ezw187.
36. Sihoe ADL. Uniportal lung cancer surgery: state of the evidence. Ann Thorac Surg. 2019;107(3):962–72. https://doi.org/10.1016/j.athoracsur.2018.08.023.
37. Xie D, Wang HF, Fei K, Chen C, Zhao DP, Zhou X, Xie BX, Jiang L, Chen QK, Song N, Dai J, Jiang GN, Zhu YM. Single-port video-assisted thoracic surgery in 1063 cases: a single-institution experience. Eur J Cardiothorac Surg. 2016;49:i31–6.

38. Wu CF, Fernandez R, de la Torre M, Delgado M, Fieira E, Wu CY, et al. Mid-term survival outcome of single-port video-assisted thoracoscopic anatomical lung resection: a two-centre experience. Eur J Cardiothorac Surg. 2018;54:252–9.
39. Sandri A, Sihoe ADL, Salati M, Gonzalez-Rivas D, Brunelli A. Training in uniportal video-assisted thoracic surgery. Thorac Surg Clin. 2017;27(4):417–23. https://doi.org/10.1016/j.thorsurg.2017.06.010.
40. Sihoe ADL, Gonzalez-Rivas D, Yang TY, Zhu Y, Jiang G. High volume intensive training course: a new paradigm for video-assisted thoracoscopic surgery education. Interact Cardiovasc Thorac Surg. 2018;27(3):365–71. https://doi.org/10.1093/icvts/ivy038.
41. Sihoe AD, Lee TW, Wan IY, Thung KH, Yim AP. The use of gabapentin for post-operative and post-traumatic pain in thoracic surgery patients. Eur J Cardiothorac Surg. 2006;29:795–9.
42. Sihoe AD, Manlulu AV, Lee TW, Thung KH, Yim AP. Pre-emptive local anesthesia for needlescopic video-assisted thoracic surgery: a randomised controlled trial. Eur J Cardiothorac Surg. 2007;31:103–8.
43. Sihoe DLA, Yu SYP, Kam TH, Lee SY, Liu X. Adherence to a clinical pathway for video assisted thoracic surgery: predictors and clinical importance. Innovations. 2016;11:179–86.
44. Zhang X, Yu Q, Lv D. The single-incision versus multiple-incision video-assisted thoracoscopic surgery in the treatment of lung cancer: a systematic review and meta-analysis. Indian J Cancer. 2017;54:291–300.
45. Yang Z, Shen Z, Zhou Q, Huang Y. Single-incision versus multiport video-assisted thoracoscopic surgery in the treatment of lung cancer: a systematic review and meta-analysis. Acta Chir Belg. 2018;118(2):85–93. https://doi.org/10.1080/00015458.2017.1379800.
46. Abouarab AA, Rahouma M, Kamel M, Ghaly G, Mohamed A. Single versus multi-incisional video-assisted thoracic surgery: a systematic review and meta-analysis. J Laproendosc Adv Surg Techniques. 2018;28:174–85.
47. Ng CSH, MacDonald JK, Gilbert S, Khan AZ, Kim YT, Louie BE, Marshall BM, Santos RS, Scarci M, Shargal Y, Fernando HC. Optimal approach to lobectomy for non-small cell lung cancer: systemic review and meta-analysis. Innovations. 2019;14(2):90–116. https://doi.org/10.1177/1556984519837027.
48. Bertolaccini L, Batirel H, Brunelli A, Gonzalez-Rivas D, Ismail M, Ucar AM, Ng CSH, Scarci M, Sihoe ADL, et al. Uniportal video-assisted thoracic surgery lobectomy: a consensus report from the Uniportal VATS Interest Group (UVIG) of the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg. 2019;56(2):224–9. https://doi.org/10.1093/ejcts/ezz133.
49. Sihoe DLA. Opportunities and challenges for thoracic surgery collaborations in China: a commentary. J Thorac Dis. 2016;8:S414–26.

Robotic Versus Video-Assisted Thoracoscopic Surgery (VATS) Major Lung Resection for Early Stage NSCLC

13

Brian E. Louie and Jordan Wilkerson

Introduction

The mainstay of treatment in the management of early stage non-small cell lung cancer (NSCLC) is surgical resection; however, the optimal approach is debated given the ongoing evolution in technique. The traditional thoracotomy approach has been slowly supplanted by minimally invasive techniques, which now represent the most common approach. Of the minimally invasive approaches, multiport video-assisted thoracoscopic surgery (VATS) is the preferred modality based on its safety profile, oncologic outcomes, and cost effectiveness, which are well established when compared to thoracotomy.

Interest in the robotic approach began shortly after 2010, as it was marketed as being superior to VATS with wristed dexterity and improved visualization with 10× magnification. Many studies from those who embraced the robotic lobectomy technique early have demonstrated it to be both safe and feasible. This led to increasing acceptance and adoption of the robotic platform as a viable alternative minimally invasive technique. Nevertheless, its growth has been hindered by reported longer operative times, challenges in transitioning and developing proficiency, and higher costs compared to VATS.

We reviewed the best available literature comparing the two minimally invasive techniques in the treatment of early stage lung cancer to determine the optimal surgical approach.

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Table 13.1 PICO formatted terms for literature search

Patients	Intervention	Comparator	Outcomes
Patients with early stage NSCLC	Robotic lobectomy	VATS lobectomy	Complications, LOS, Oncologic outcome, cost

Search Strategy

A systematic search was performed using the PubMed and EBSCO databases. The PICO terms utilized to guide the search strategy are demonstrated in Table 13.1. Additional search terms included: "pulmonary resection," "lung resection," "lobectomy," "segmentectomy," "lung cancer," "robotic," and "robotic surgical procedures." The search was limited to articles published in English from 2015 through 2019. Case reports were excluded. Studies evaluating uniportal VATS and some papers including pathologies other than NSCLC were excluded.

Results

There remains a paucity of high-level evidence comparing the two minimally invasive techniques, as no randomized controlled trials comparing VATS to robotic lobectomy were identified. There was one systematic review and meta-analysis, sponsored by the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS), which evaluated the optimal lobectomy approach in treating patients with early stage NSCLC [1]. It included a total of 145 studies in the synthesis seeking to identify which minimally invasive surgical approach to lobectomy was superior. Additionally, our literature search identified multiple case control studies and case series, which we limited to studies from the past 5 years as this represented more relevant data in regards to robotic resections given increasing experience with the approach. In total, we included 12 case control studies (Table 13.2).

Safety

The safety and feasibility of robotic lung resections was demonstrated by multiple case series during its early adoption. Although there were conflicting results in respect to perioperative outcomes in the initial cohort studies that followed, nearly all of the reviewed articles in our literature search demonstrated no significant difference in morbidity between VATS and robotic lung resection (Table 13.2). These findings are in line with the results of the ISMICS meta-analysis [1], which pooled six studies including 999 patients and showed no statistically significant difference in the rate of complications between the two modalities (OR 1.28; 95% CI, 0.75–2.17; P = 0.37). Within these pooled studies, 25% (138/545) of VATS patients

Table 13.2 Robotic vs. VATS lobectomy/segmentectomy outcomes

Study	Study arms	Operative time (min)	LOS (days)	Lymph nodes	Morbidity	Mortality (30 day)	Survival	Conversion rate	Cost	Quality of evidence
Lee (2015) [2]	Robotic 53	161	3	17	6	0	95%	1.9%	–	
	VATS 158	123	3	11	38	3	88%	3.2%	–	2a
	P-value	*0.02*	*0.25*	*<0.001*	*0.05*	*0.57*	*0.48 (2 year)*	–		
Bao (2016) [3]	Robotic 69	136	7.6	17.9	42	0	–	2.8%	$12,067	
	VATS 69	111	6.4	17.4	30	1	–	4.4%	$8328	2a
	P-value	*<0.001*	*0.078*	*0.660*	*0.157*	–		*0.84*	*<0.001*	
Louie (2016) [4]	Robotic 1,220	186	4	–	–	0.6	–	–	–	
	VATS 12,378	173	4	–	–	0.8	–	–	–	2a
	P-value	*<0.001*	–			*0.42*				
Rinieri (2016) [5]	Robotic	140	4	–	11.7%	–	–	1	–	
	VATS	150	5	–	20.6%	–	–	3	–	2a
	P-value	*0.5*	*0.633*							
Yang (2016) [6]	Robotic 1,938	–	5	8	–	1.3%	85%	10.3%	–	
	VATS 1,938	–	5	9	–	1.5%	86%	17.5%	–	2a
	P-value		*0.34*	*0.01*		*0.96*	*0.9* (2 year)	<0.01		
Gonde (2017) [7]	Robotic 57	183	5	–	37%	0	–	2%	$12,083	
	VATS 55	180	6	–	53%	2	–	16%	$10,613	2a
	P-value	*0.51*	*0.13*		*0.09*	–		*0.008*	*0.007*	
Oh (2017) [8]	Robotic 2951	275.1	6.9	–	37.3	1.2%	–	6.3%	–	
	VATS 2951	247.6	7.3	–	40.5	1.4%	–	13.1%	–	2a
	P-value	*<0.001*	*0.006*		*0.013*	*0.642*		*<0.001*		

(continued)

Table 13.2 (continued)

Study	Study arms	Operative time (min)	LOS (days)	Lymph nodes	Morbidity	Mortality (30 day)	Survival	Conversion rate	Cost	Quality of evidence
Rajaram (2017) [9]	Robotic 3,689	–	6.1	9.9	–	1.7%	–	–	–	
	VATS 3,689	–	5.9	10.9	–	1.4%	–	–	–	2a
	P-value		*0.019*	*0.001*		*0.545*				
Yang (2017) [10]	Robotic 172	–	4	5[a]	29.7%	0	77.6%	9%	–	
	VATS 141	–	4	3[a]	24.8%	1	73.5%	6%	–	2a
	P-value		–	*<0.001*	*0.55*	*0.30*	*0.10* (5 year)	*0.32*		
Kaur (2018) [11]	Robotic 42	324	5.09	–	64.3%	0%	–	7.1%	$15,274	
	VATS 96	211	5.03	–	50%	2.1%	–	10.4%	$12,131	2a
	P-value	*<0.001*	*0.358*		*0.123*	–		*0.548*	*<0.001*	
Li (2019) [12]	Robotic 230	90.84	4.95	9.70	–	0	–	1.27%	$13,182	
	VATS 230	92.25	5.59	8.45	–	0	–	1.07%	$9453	2a
	P-value	*0.208*	*<0.001*	*<0.001*		–		*0.733*	*<0.001*	
Merritt (2019) [13]	Robotic 114	203.6	4.9	14.21	–	0	–	5	–	
	VATS 114	301.2	5.5	10.39	–	0	–	4	–	2a
	P-value	*<0.001*	*0.265*	*<0.001*		–		*0.733*		

VATS video-assisted thoracoscopic surgery, *LOS* length of stay
[a]Number of lymph node stations evaluated

experienced complications compared to 24% (108/454) of patients in the robotic group, and there was no significant difference in 30-day mortality.

Notably, one study [8] retrospectively compared robotic, VATS, and open lobectomies from the Premier national database utilizing propensity matching and found a lower overall post-operative complication rate associated with robotic resection (P = 0.0061) relative to VATS, as well as a lower conversion rate to thoracotomy (6.3% vs. 13.1%; P < 0.001). However, a similar study using the Society of Thoracic Surgery (STS) database showed no difference in post-operative complications or 30-day mortality [4]. The decreased rate of conversion to thoracotomy with robotic lobectomy relative to VATS was further demonstrated in several other studies [6, 7].

Length of Stay

Analysis of the reviewed cohort studies predominately demonstrate a similar post-operative length of stay between the two minimally invasive modalities (Table 13.2), as no statistically significant difference was identified in many of the studies. In the STS database study [4], a similar median length of stay of 4 days was shown between robotic and VATS lobectomy, but a higher proportion of robotic patients were discharged in less than 4 days (48% vs. 39%; P < 0.001). Furthermore, a pooled analysis of five studies including 7752 patients in the ISMICS meta-analysis [1] showed no difference in length of hospital stay between VATS and robotic lobectomy (95% CI, −0.81 to 0.48; P = 0.62).

Oncologic Effectiveness

The oncologic effectiveness can be evaluated by looking at quality metrics such as lymph node harvest, nodal upstaging, disease free survival, and overall survival. In evaluating which technique offers a superior approach to lymph node harvest, the results of the evaluated cohort studies are mixed (Table 13.2) with one study showing no significant difference [3], several studies favoring VATS [6, 9], and others supporting a robotic approach [2, 10, 12, 13].

Taken together, these results do not clearly demonstrate superiority of either approach, which is further supported by the ISMICS meta-analysis [1], in which a pooled analysis of five studies including 7814 patients showed no statistically significant difference in the mean number of dissected lymph nodes between VATS and robotic surgery (mean difference [MD] −0.82; 95% CI, −2.69 to 1.04; P = 0.39). Similarly, a pooled analysis of two studies including 179 patients showed no significant difference in the mean number of lymph node stations sampled (MD −0.20; 95% CI, −1.07 to 0.68; P = 0.66). Significant heterogeneity was detected for both of these comparisons.

Nodal upstaging has long been used as a surrogate measure for a thorough lymph node dissection and hence a quality cancer operation, but no significant difference was identified between the robotic and VATS approach in three separate case control

studies [2, 4, 6], nor in the ISMICS [1] pooled analysis of six studies which included 18,216 patients. After lymph node sampling/dissection, 8% (1258/14,724) of VATS patients were upstaged compared to 10% (355/3492) of robotic patients (OR 1.02; 95% CI, 0.85–1.22; P = 0.87).

Only two studies reported on the rate of margin positivity associated with minimally invasive lobectomy. A retrospective National Cancer Database study [9] evaluated over 60,000 lobectomies for Stage I–IIIA NSCLC performed by either open, VATS, or robotic approaches. A comparison of outcomes in a propensity-matched group containing 3689 patients in each arm demonstrated no significant difference in the percent of positive surgical margins, where both robotic and VATS lobectomy were found to have a rate of 3.4% (P = 0.948). Similar outcomes were reported in another study [6], where positive surgical margins occurred in 2.4% of both arms (P = 0.32).

Survival

One of the first studies to address survival was a cohort comparison of 2-year survival data in early stage NSCLC treated by robotic or VATS resection [2]. The results of the study demonstrated similar overall survival (88% vs. 95%; P = 0.4) and disease-free survival (83% vs. 93%; P = 0.48). These findings were supported by a propensity-matched analysis which retrospectively evaluated the short-term survival of VATS and robotic lung resection [6]. The matched groups contained 924 patients each and demonstrated no significant difference between the two modalities at 2-years of follow up (VATS 86% vs. Robotic 85.3%; P = 0.9).

Only one comparative study [10] reported on the 5-year survival rates of VATS and robotic lobectomy. In propensity matched cohorts, the 5-year overall survival for the robotic group was 77.6% compared to 73.5% for VATS, which was not statistically significant (P = 0.10). The robotic group was notable for having a better disease free survival (DFS) compared to VATS on univariate analysis (72.7% vs. 65.5%; p = 0.047); however, this result was not confirmed on multivariate analysis. The long-term survival of robotic lobectomy patients was also evaluated in a multi-institutional retrospective review case series of 1339 patients where 5-year stage specific survival was: 83% for stage IA (n = 672), 77% for stage IB (n = 281), 68% for stage IIA (n = 118), and 70% for stage IIB (n = 99) [14].

Cost

A commonly cited drawback to the robotic platform has been an elevated cost compared to other techniques. Among the reviewed articles, four of the comparative studies [3, 7, 11, 12] evaluated the cost difference between the two minimally invasive modalities and all of them demonstrated a statistically significant higher cost associated with the robotic platform (Table 13.2). The ISMICS meta-analysis [1] identified only two studies including a total of 4268 patients that reported on the

total cost of surgery in US dollars. The total cost for VATS was significantly less than robotic surgery (MD −4238.03; 95% CI, −5507.27 to 2968.79; P < 0.0001).

A French single-center prospective cost study evaluated all patients undergoing minimally invasive lobectomy or segmentectomy [7]. Overall, the micro-cost analysis showed a statistically significant difference in total cost between VATS and robotic surgery (P = 0.007), with the robot costing an additional €1335 ($1491). Notably, most of these additional costs were attributed to medical expenses, consumables, and capital depreciation, as the operative times between the two groups were identical and, thus, not a contributing factor in cost discrepancy.

A Canadian single-institution retrospective cohort study [11] compared robotic and VATS resections for early stage lung cancer with respect to healthcare utilization during the first year of their developing robotic surgery program. Overall, the median total hospital cost per patient was $15,247 for robotic vs. $12,131 in the VATS cohort (P < 0.001), a difference of $3116. Longer operating times in the robotic group were cited as the main driver of the higher hospital costs, as the difference was rather significant (robotic 324 min vs. VATS 211 min; P < 0.001). Post-hoc analysis of the mean operating room time for the first 20 robotic procedures compared to the remaining 22 robotic procedures found an average improvement of 71 min, which resulted in a lower intra-operative cost difference of $883. A retrospective cohort study comparing the cost of robotic, VATS and open lobectomy for all lung cancer subtypes reiterated this finding, as improvement in operative time is necessary to make robotic lobectomy cost neutral compared to VATS lobectomy [15].

Conclusions and Recommendations

After thorough analysis of the described literature, the two minimally invasive lobectomy approaches can be considered equivalent in regard to safety, oncologic effectiveness, and overall survival. While cost is a variable that can potentially be neutralized with increased proficiency, VATS resections continue to be the least expensive modality. Thus, patients with early stage non-small cell lung cancer can safely undergo either robotic or VATS resection with no compromise in morbidity or oncologic outcome; albeit at an increased cost with the robotic platform (evidence quality moderate; weak recommendation).

Recommendations

- Patients with early stage non-small cell lung cancer can safely undergo either robotic or VATS resection with no compromise in morbidity or oncologic outcome, albeit at an increased cost with the robotic platform (evidence quality moderate; weak recommendation).

A Personal View of the Data

The optimal surgical approach to lobectomy for early stage NSCLC is likely to remain an ongoing debate for years to come. It seems clear that a minimally invasive approach is most optimal regardless of whether one chooses a VATS, robotic, or now the uniportal platform. It is unlikely that major outcome differences between any of the minimally invasive approaches will be uncovered and sway surgeons in one direction or another. Surgeons will prefer a certain modality because of a personal attraction to various elements of the approach. As experience with robotic lung resections continues to expand, growing evidence continues to demonstrate equivalent perioperative outcomes and oncologic effectiveness. The cost difference between the two modalities is a crucial issue as hospitals are being asked to do more with less. The key for robotic surgeons is to focus on the concept of operative proficiency and reduced variability so that operative times are reduced, which may bring robotic costs in line with VATS and nullify the question of cost [16].

References

1. Ng CSH, MacDonald JK, Gilbert S, Khan AZ, Kim YT, Louie BE, Fernando HC. Optimal approach to lobectomy for non-small cell lung cancer: systemic review and meta-analysis. Innovations. 2019;14(2):90–116.
2. Lee BE, Shapiro M, Rutledge JR, Korst RJ. Nodal upstaging in robotic and video-assisted thoracic surgery lobectomy for clinical N0 lung cancer. Ann Thorac Surg. 2015;100(1):229–34.
3. Bao F, Zhang C, Yang Y, He Z, Wang L, Hu J. Comparison of robotic and video-assisted thoracic surgery for lung cancer: a propensity-matched analysis. J Thorac Dis. 2016;8(7):1798–803.
4. Louie BE, Wilson JL, Kim S, Cerfolio RJ, Park BJ, Farivar AS, Vallières E, Aye RW, Burfeind WR, Block MI. Comparison of video-assisted thoracoscopic surgery and robotic approaches for clinical stage I and stage II non-small cell lung cancer using the Society of Thoracic Surgeons database. Ann Thorac Surg. 2016;102(3):917–24.
5. Rinieri P, Peillon C, Salaün M, Mahieu J, Bubenheim M, Baste J-M. Perioperative outcomes of video- and robot-assisted segmentectomies. Asian Cardiovasc Thorac Ann. 2016;24(2):145–51.
6. Yang C-FJ, Sun Z, Speicher PJ, Saud SM, Gulack BC, Hartwig MG, Harpole DH, Onaitis MW, Tong BC, D'Amico TA. Use and outcomes of minimally invasive lobectomy for stage I non-small cell lung cancer in the National Cancer Database. Ann Thorac Surg. 2016;101(3):1037–42.
7. Gondé H, Laurent M, Gillibert A, Sarsam O-M, Varin R, Grimandi G, Peillon C, Baste J-M. The affordability of minimally invasive procedures in major lung resection: a prospective study. Interact Cardiovasc Thorac Surg. 2017;25(3):469–75.
8. Oh DS, Reddy RM, Gorrepati ML, Mehendale S, Reed MF. Robotic-assisted, video-assisted thoracoscopic and open lobectomy: propensity-matched analysis of recent Premier data. Ann Thorac Surg. 2017;104(5):1733–40.
9. Rajaram R, Mohanty S, Bentrem DJ, Pavey ES, Odell DD, Bharat A, Bilimoria KY, DeCamp MM. Nationwide assessment of robotic lobectomy for non-small cell lung cancer. Ann Thorac Surg. 2017;103(4):1092–100.
10. Yang H-X, Woo KM, Sima CS, Bains MS, Adusumilli PS, Huang J, Finley DJ, Rizk NP, Rusch VW, Jones DR. Long-term survival based on the surgical approach to lobectomy for clinical stage I non-small cell lung cancer: comparison of robotic, video-assisted thoracic surgery, and thoracotomy lobectomy. Ann Surg. 2017;265(2):431–7.

11. Kaur MN, Xie F, Shiwcharan A, Patterson L, Shargall Y, Finley C, Schieman C, Hanna WC. Robotic versus video-assisted thoracoscopic lung resection during early program development. Ann Thorac Surg. 2018;105:1050–7.
12. Li JT, Liu PY, Huang J, Lu PJ, Lin H, Zhou QJ, Luo QQ. Perioperative outcomes of radical lobectomies using robotic-assisted thoracoscopic technique vs. video-assisted thoracoscopic technique: retrospective study of 1,075 consecutive p-stage I non-small cell lung cancer cases. J Thorac Dis. 2019;11(3):882–91.
13. Merritt RE, Kneuertz PJ, D'Souza DM. Successful transition to robotic-assisted lobectomy with previous proficiency in thoracoscopic lobectomy. Innovations. 2019;14(3):263–71.
14. Cerfolio RJ, Ghanim AF, Dylewski M, Veronesi G, Spaggiari L, Park BJ. The long-term survival of robotic lobectomy for non-small cell lung cancer: a multi-institutional study. J Thorac Cardiovasc Surg. 2018;155(2):778–86.
15. Deen SA, Wilson JL, Wilshire CL, Vallières E, Farivar AS, Aye RW, Ely RE, Louie BE. Defining the cost of care for lobectomy and segmentectomy: a comparison of open, video-assisted thoracoscopic, and robotic approaches. Ann Thorac Surg. 2014;97(3):1000–7.
16. Feczko AF, Wang H, Nishimura K, Farivar AS, Bograd AJ, Vallières E, Aye RW, Louie BE. Proficiency of robotic lobectomy based on prior surgical technique in the Society of Thoracic Surgeons General Thoracic Database. Ann Thorac Surg. 2019;108(4):1013–20.

14 Does Blood Patch for Persistent Postoperative Air Leak Reduce Air Leak Duration

Adam Lam and Mark K. Ferguson

Introduction

Persistent air leak plagues thoracic surgeons following pulmonary resection. A number of studies have examined both patient and operative risk factors that increase the propensity of developing persistent air leak [1–4]. However, despite advances in surgical techniques and technologies, persistent air leak remains a common complication associated with increased hospitalization costs and morbidity [5]. The American College of Chest Physicians currently recommends surgical management with thoracoscopy or thoracotomy for persistent air leaks that have not resolved following 4 days of drainage via tube thoracostomy [6]. The British Thoracic Society echoes similar recommendations for operative management after 3–5 days of persistent air leak following resection [7].

For patients with persistent air leaks who are not operative candidates, the consensus treatment from the American College of Chest Physicians is chemical pleurodesis with doxycycline or talc. A reported alternative to traditional chemical pleurodesis is blood patch pleurodesis. Robinson first described blood patch pleurodesis in 1987 as a method to prevent recurrence of a chronic air leak after it had sealed [8]. Shortly thereafter, Dumire and colleagues applied blood patch pleurodesis to actively seal a persistent air leak that had previously been refractory to tetracycline pleurodesis [9]. Since that time, multiple case series as well as randomized controlled studies have studied the efficacy of blood patch pleurodesis for persistent air leak. In this chapter, we review the published literature on blood patch pleurodesis for persistent air leak following pulmonary resection.

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Table 14.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with persistent air leak after major lung resection	Blood patch pleurodesis	Conservative management	Duration of air leak, complications, costs

Search Strategy

A Pubmed search was performed for articles between 1990 and 2019 reporting outcomes of blood patch pleurodesis. Search terms used were "blood patch air leak," "pneumothorax blood patch," "pulmonary resection blood patch," and "blood patch pleurodesis." We additionally reviewed publications referenced by articles found within our initial search. Article titles were initially screened for relevance, and then abstracts were further reviewed. We included only articles published in English. We initially included all studies in which patients underwent blood patch pleurodesis. This was subdivided into patients who had persistent air leak from either underlying lung disease (spontaneous pneumothorax) or pulmonary resection. Our final formal analysis includes only studies from patients who had a pulmonary resection (Table 14.1).

Results

Blood Patch Pleurodesis for Persistent Air Leak Following Pulmonary Resection

We found nine case series and two randomized controlled trials assessing the efficacy of blood patch pleurodesis for persistent air leak following pulmonary resection (Tables 14.2 and 14.3). The most common operation performed in studies was lobectomy. In some studies, patient cohorts were heterogeneous and consisted of persistent air leak from both pulmonary resection and spontaneous pneumothorax. There was institutional variability in definition of persistent air leak (ranging from 4 to 10 days) as well as variability in intervention (volume of autologous blood used and addition of supplemental factors).

Time to Resolution of Air Leak and Length of Stay

Overall the results of the studies were favorable for blood patch pleurodesis in managing persistent air leak following pulmonary resection. The rates of sealing following autologous blood patch pleurodesis ranged from 83 to 100%, with some studies reporting a proportion of air leaks closing almost immediately following pleurodesis [10–18]. When aggregating the case series data specifically for post-surgical patients, 81% of persistent air leaks ceased within 48 h of pleurodesis, and ultimately only 2% of air leaks failed to close following blood patch pleurodesis (Table 14.4). Again, it is important to note that these values represent average time

Table 14.2 Demographics and design of studies evaluating the efficacy of autologous blood patch for post-operative persistent air leak (PAL)

Study and year	Study design	Case definition	PAL duration (days)	Intervention
Yokomise et al. (1998)	Case Series	Patients with PAL following lobectomy for lung cancer; n = 10	7	50 cc ABP with 5.0KE of OK432; unclamped CT to −15 mm suction suspended 60 cm above patient
Rivas de Andres et al. (2000)	Case Series	Patients with PAL following pulmonary resection; n = 6 (4 lobectomy, 1 wedge resection, 1 segmentectomy)	10	50–250 cc ABP; unclamped CT suspended 60 cm above patient for 24 h
Lang-Lazdunski et al. (2004)	Case Series	Patients with PAL following pulmonary resection with forced expiratory air leak; n = 11	7	50 cc ABP, clamped CT for 30 min, then unclamped CT to water seal
Droghetti et al. (2006)	Case Series	Patients with PAL following pulmonary resection; n = 21 (13 lobectomy, 1 bilobectomy, 2 decortication, 5 lung volume reduction)	10	50–150 cc ABP; unclamped suspended above patient for 1 h
Korasidis et al. (2009)	Case Series	Patients with PAL following major resection for lung cancer; n = 39 (17 upper lobectomy, 5 sleeve lobectomy, 6 upper bilobectomy, 11 lower lobectomy	3	Pneumoperitoneum on POD3; 100 cc blood patch on POD4; unclamped CT to water seal suspended 60 cm above patient
Athanassiadi et al. (2009)	Case Series	Patient with PAL, majority following surgery; n = 20 (10 lobectomy, 3 wedge resection, 3 lung volume reduction, 3 secondary PTX)	7	60 cc ABP; unclamped CT to water seal suspended 6 h over patient
Oliveira et al. (2010)	Case Series	Patients with PAL, majority (16/27) following surgery (10 lobectomy, 4 bullectomy, 2 decortication); remainder of patients with primary or secondary PTX	5	24–200 cc ABP; unclamped CT suspended above patient for 30 min
Özpolat (2010)	Case Series	Patients with PAL; n = 24, minority (7/24) following pulmonary hydatid cyst operation	7	2 cc/kg ABP; unclamped suspended above patient for 2 h

(continued)

Table 14.2 (continued)

Study and year	Study design	Case definition	PAL duration (days)	Intervention
Lillegard et al. (2013)	Case Series	Patients under 18 years with PAL following thoracic procedure; n = 8 (4 VATS, 3TT, 1 Lung Biopsy)	5	1–2.5 cc/kg ABP, clamped CT for 3 h, then unclamped CT to water seal
Shackcloth et al. (2006)	RTC	Patients with PAL following pulmonary lobectomy; n = 20	5	120 cc ABP vs. conservative management; unclamped CT suspended above patient for 2 h; repeat ABP q48h as needed. Group size: study (n = 10) vs. control (n = 10) Crossover from control to study arm if no resolution of by POD10
Andreetti et al. (2007)	RTC	Patients with PAL following pulmonary lobectomy; n = 25 + 15 retrospective	6	50 cc ABP vs. 100 cc ABP vs. Control Group size: 50 cc (n = 12) vs. 100 cc (n = 13) vs. control (n = 15)

PAL Persistent air leak, *ABP* autologous blood patch, *VATS* video assisted thoracic surgery, *TT* tube thoracostomy, *PTX* pneumothorax, *CT* chest tube, *POD* postoperative day

to resolution for all the studies, many of which differed on type of resection performed, volume of blood instilled, and addition of supplemental factors (e.g. OK432).

The quicker time to resolution was also evident in the two randomized trials included in our review. Shackcloth et al. reported median air leak duration of 5 days (including the 5 days of persistent air leak) for autologous blood patch pleurodesis vs. 11 days in their control group [19]. Even more convincing, 8 out of the 10 patients in their control group crossed over into the blood patch pleurodesis arm for failure to seal air leak at 10 days, and all air leaks in the control group resolved by postoperative day 15. Andreeti et al. subsequently compared two groups undergoing blood patch pleurodesis (50 vs. 100 cc) with a retrospective cohort of patients that was conservatively managed with continued tube thoracostomy and drainage. They found the mean time to resolution of air leak was significantly shorter for the blood patch pleurodesis groups (2.3 days for 50 cc and 1.5 days for 100 cc, $p < 0.001$ for both groups) when compared to conservative management (6.3 days) [20].

Of note, in multiple studies, certain patients had to undergo repeat instillations of autologous blood patch in order to completely resolve the air leaks (Table 14.3). The timing for repeat pleurodesis varied, but typically occurred within 2 days of initial instillation.

While most studies reviewed did not report exact length of stay following blood patch pleurodesis, many stated that patients were discharged within 24–48 h

Table 14.3 Results of studies evaluating the efficacy of autologous blood patch for post-operative persistent air leak (PAL)

Study and year	Results (resolution, complications)	Quality of evidence
Yokomise et al. (1998)	All PALs sealed Number needing >1 dose ABP: 4/10 (40%) Timing to seal: mean 3.8 days Complications: None	Low
Rivas de Andres et al. (2000)	All PALs sealed Number needing >1 dose ABP: 0/6 (0%) Timing to seal: mean closure 16 days Complications: None	Low
Lang-Lazdunski et al. (2004)	All PALs sealed Number needing >1 dose ABP: 0/11 (0%) Timing to seal: 8/11 (72.7%) within 12 h and 3/11 (27.3%) within 48 h Complications: 1/11 (9%) with PNA; 2/11 (18%) with empyema	Low
Droghetti et al. (2006)	All PALs sealed Number needing >1 dose ABP: 4/21 (19%) Timing to seal: 15/21 (71%) within 12 h, 2/21 (10%) within 24 h, 4/21 (19%) within 60 h Complications: None	Low
Korasidis et al. (2009)	All PALs sealed Number needing >1 dose ABP: 2/39 (5%) Timing to seal: all within 48 h of blood patch Mean hospital stay: 8 days Complications: None	Low
Athanassiadi et al. (2009)	19/20 (95%) PALs sealed Number needing >1 dose ABP: 2/20 (10%) Timing to seal: 14/20 (70%) within 12 h, 3/20(15%) within 24 h, 2/20 (10%) within 48 h Complications: None	Low
Oliveira et al. (2010)	23/27 (85%) PALs sealed and 14/16 (87.5%) postsurgical sealed Number needing >1 dose ABP: 7/27 (26%) Timing to seal: mean closure 1.5 days Complications: 1/27 (4%) empyema	Low
Özpolat (2010)	21/24 (87.5%) PALs sealed overall and 7/7 (100%) postsurgical sealed Number needing >1 dose ABP: 4/24 (17%) Timing to seal: 20/24 (83%) within 24 h; 1/24 (4%) within 48 h Complications: None	Low
Lillegard et al. (2013)	All PALs sealed Number needing >1 dose ABP: 3/8 (37.5%) Timing to seal: 2/8(25%) immediately, 1/8 (12.5%) within 1 day 2/8(25%) within 2 days, 3/8 (37.5%) after 2 days Complications: 1/8 (12.5%) asymptomatic PTX	Low

(continued)

Table 14.3 (continued)

Study and year	Results (resolution, complications)	Quality of evidence
Shackcloth et al. (2006)	Treatment arm: All PALs sealed Number needing >1 dose ABP: 3/10 (30%) Timing to seal: Median within 24 h Complications: 1/10 (10%) with empyema Control arm: 2/10 (20%) sealed by POD10 Timing to seal: Median within 6 days Complication: None	Moderate
Andreetti et al. (2007)	50 cc ABP arm: All PALs sealed Number needing >1 dose ABP: 0/12 (0%) Timing to seal: mean 2.3 days Complications: none 100 cc ABP arm: Number needing >1 dose ABP: 0/13 (0%) All PALs sealed Timing to seal: mean 1.5 days Complications: none Control arm: All PALs sealed Timing to seal: mean 6.3 days Complications: 1/15 (7%) pneumonia	Moderate

following resolution of air leak. Therefore, since the blood patch pleurodesis decreased duration of persistent air leak, it also appeared to decrease the duration of hospital stay for these patients. Additionally, as costs are associated with length of hospitalization, it is likely that blood patch pleurodesis decreased overall costs for patients. Overall, blood patch pleurodesis can shorten time to resolution of air leak and overall hospital length of stay following pulmonary resection.

Complications

The most common side effect following blood patch pleurodesis was mild fever. The most feared complication seen following blood patch pleurodesis is tension pneumothorax [21]. However, this complication is rare, and most likely secondary to clamping the chest tube following instillation of autologous blood or blood clotting the tube itself. To reduce the risk of this complication, most institutions report irrigating the chest tubes with normal saline and maintaining the chest tube to water seal and suspending the drainage system above the patient to prevent backflow of the blood patch. The other major complication seen in studies was empyema, but rates of empyema were low, occurring only in 2 patients within the case series [13]. Otherwise, no other major complications were reported in our review.

Table 14.4 Timing to seal for persistent air leak for resection patients from case series

		Time to seal					
		Immediately	12 h	24 h	48 h	>48 h	No seal
Study	Lillegard et al. (2013)	2/8 (25%)	–	1/8 (12.5%)	2/8 (25.5%)	3/8 (37.5%)	–
	Korasidis et al. (2009)	–	–	–	39/39 (100%)	–	–
	Yokomise et al. (1998)	–	–	1/10 (10%)	2/10 (20%)	7/10 (70%)	–
	Lang-Lazdunski et al. (2004)	–	8/11 (73%)	–	3/11 (27%)	–	–
	Athanassiadi et al. (2009)	–	14/20 (70%)	3/20 (15%)	2/20 (10%)	–	1/20 (5%)
	Rivas de Andres et al. (2000)	–	–	–	–	6/6 (100%)	–
	Oliveira et al. (2010)	–	–	8/16 (50%)	4/16 (25%)	2/16 (12.5%)	2/16 (12.5%)
	Özpolat (2010)[a]	–	–	6/7 (86%)	1/7 (14%)	–	–
	Droghetti et al. (2006)	–	15/21 (71%)	2/21 (10%)		4/21 (19%)	–
	Overall frequency	2/138 (1%)	37/138 (27%)	21/138 (15%)	53/138 (38%)	22/138 (16%)	3/138 (2%)

[a]In studies with heterogeneous populations (resection and non-resection patients), only resection patients were included in analysis if timing to air leak closure was reported for individual cases

Limitations

These studies are not without limitations. First the risk of publication bias exists given the majority of the studies (including those with small sample sizes) demonstrated only a favorable effect. Second, some studies did not report the grade of the patients' air leaks, which questions the efficacy of blood patch pleurodesis with large continuous air leaks. Third, there was significant heterogeneity in the intervention applied and timing of application, limiting the generalizability of the aggregate studies. Finally, the overall sample sizes for all studies were small, and large sample studies should be initiated to delineate the true magnitude of effect association, as well as uncover atypical complications that may arise from the procedure. Addressing these issues in future studies would assist in standardization of autologous blood patch pleurodesis, as well as increase the strength of the overall recommendation for blood patch pleurodesis in persistent air leak.

Blood Patch Pleurodesis for Persistent Air Leak Following Spontaneous Pneumothorax

There have been case series, case control studies, and randomized control trials published defining the efficacy of blood patch pleurodesis for persistent air leak

from primary and secondary spontaneous pneumothorax. Given this chapter pertains to persistent air leak following pulmonary resection, these studies fall outside its scope, but are relevant in fleshing out the topic and will be briefly summarized.

Case reports and case series generally demonstrate efficacy of blood patch pleurodesis in resolution of air leaks from primary and secondary spontaneous, with most studies reporting resolution rates between 27 and 100% [22–26]. Two case control studies were reviewed. The first compared autologous blood patch vs. continued tube thoracostomy for ventilated patients with acute respiratory distress syndrome and persistent air leak: This study showed the autologous blood patch group had decreased mortality, time dependent on ventilator, and duration of stay in intensive care [27]. The second compared autologous blood patch to chemical (talc or tetracycline) pleurodesis. Talc had higher success for sealing air leak (84% vs. 75%), but autologous blood patch had quicker time to resolution of air leak (27 vs. 51 h) [28]. These rates of resolution were comparable to a retrospective cohort study by Aihara et al. (73% autologous blood patch vs. 79% chemical) [29].

Finally, two randomized controlled trials have directly compared the efficacy of blood patch pleurodesis to conservative management with tube thoracostomy for persistent air leak in patients with secondary spontaneous pneumothorax. Cao et al. compared the effects of increasing doses of autologous blood pleurodesis (0 vs. 0.5 vs. 1.0 vs. 2.0 mL/kg) in patients with persistent air leak (>7 days) secondary to chronic obstructive pulmonary disease [30]. In their cohort of 44 patients (11 per group), success rates for blood patch were 9%, 27%, 82%, and 82%, respectively, showing that the efficacy of blood patch pleurodesis peaks at approximately 1.0 mL/kg. Ibrahim et al. performed an additional study in 2019 that compared 50 cc autologous blood pleurodesis (n = 23) to continued conservative management (n = 24) for patients with persistent air leak (>3 days) from secondary spontaneous pneumothorax [31]. They showed a significant decrease in air leak duration (5.4 vs. 10.5 days, $p < 0.001$) for the autologous blood pleurodesis group, as well as significant decrease in time to drain removal (7.9 vs. 12.8 days, $p < 0.001$) and overall length of hospital stay (10.0 vs. 15.0 days, $p < 0.001$).

Overall, these results show promise for blood patch pleurodesis for persistent air leak from spontaneous pneumothorax.

Conclusions and Recommendations

While the majority of studies cited in this chapter are case series, there have been two small sample randomized controlled trials assessing the efficacy of blood patch pleurodesis for persistent air leak following pulmonary resection. Overall, the results from these studies are favorable. Autologous blood patch pleurodesis has a high efficacy of sealing persistent postoperative air leak, even in cases refractory to prolonged conservative management with tube thoracostomy and drainage. Complications from the procedure are minimal. Based on the available evidence, we recommend that blood patch pleurodesis should be considered for sealing persistent air leak following lung resection, and that repeated instillations of blood patch pleurodesis should be performed if air leak persists following first application.

Recommendations

- Blood patch pleurodesis is recommended for sealing persistent air leak following lung resection (Evidence quality moderate; weak recommendation)
- Repeated instillations of blood patch pleurodesis is recommended if air leak persists following first instillation (Evidence quality moderate; weak recommendation)

A Personal View of the Data

For patients with continued persistent air leak post-operatively, our default management is to continue drainage with tube thoracostomy and discharge patients to home if their air leak persists into the fourth postoperative day. The data in the studies included in this chapter are convincing, and suggest that autologous blood patch should be utilized more often in our patients with persistent air leak.

References

1. Cerfolio RJ, Bass CS, Pask AH, Katholi CR. Predictors and treatment of persistent air leaks. Ann Thorac Surg. 2002;73(6):1727–30.
2. Brunelli A, Monteverde M, Borri A, Salati M, Marasco RD, Fianchini A. Predictors of prolonged air leak after pulmonary lobectomy. Ann Thorac Surg. 2004;77(4):1205–10.
3. Okereke I, Murthy SC, Alster JM, Blackstone EH, Rice TW. Characterization and importance of air leak after lobectomy. Ann Thorac Surg. 2005;79(4):1167–73.
4. Pompili C, Falcoz PE, Salati M, Szanto Z, Brunelli A. A risk score to predict the incidence of prolonged air leak after video-assisted thoracoscopic lobectomy: an analysis from the European Society of Thoracic Surgeons database. J Thorac Cardiovasc Surg. 2017;153(4):957–65.
5. Varela G, Jimenez MF, Novoa N, Aranda JL. Estimating hospital costs attributable to prolonged air leak in pulmonary lobectomy. Eur J Cardiothorac Surg. 2005;27(2):329–33.
6. Baumann MH, Strange C, Heffner JE, Light R, Kirby TJ, Klein J, et al. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. Chest. 2001;119(2):590–602.
7. Havelock T, Teoh R, Laws D, Gleeson F. Group BTSPDG. Pleural procedures and thoracic ultrasound: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65(Suppl 2):ii61–76.
8. Robinson CL. Autologous blood for pleurodesis in recurrent and chronic spontaneous pneumothorax. Can J Surg. 1987;30(6):428–9.
9. Dumire R, Crabbe MM, Mappin FG, Fontenelle LJ. Autologous "blood patch" pleurodesis for persistent pulmonary air leak. Chest. 1992;101(1):64–6.
10. Athanassiadi K, Bagaev E, Haverich A. Autologous blood pleurodesis for persistent air leak. Thorac Cardiovasc Surg. 2009;57(8):476–9.
11. Droghetti A, Schiavini A, Muriana P, Comel A, De Donno G, Beccaria M, et al. Autologous blood patch in persistent air leaks after pulmonary resection. J Thorac Cardiovasc Surg. 2006;132(3):556–9.

12. Korasidis S, Andreetti C, D'Andrilli A, Ibrahim M, Ciccone A, Poggi C, et al. Management of residual pleural space and air leaks after major pulmonary resection. Interact Cardiovasc Thorac Surg. 2010;10(6):923–5.
13. Lang-Lazdunski L, Coonar AS. A prospective study of autologous 'blood patch' pleurodesis for persistent air leak after pulmonary resection. Eur J Cardiothorac Surg. 2004;26(5):897–900.
14. Lillegard JB, Kennedy RD, Ishitani MB, Zarroug AE, Feltis B. Autologous blood patch for persistent air leak in children. J Pediatr Surg. 2013;48(9):1862–6.
15. Oliveira FH, Cataneo DC, Ruiz RL Jr, Cataneo AJ. Persistent pleuropulmonary air leak treated with autologous blood: results from a university hospital and review of literature. Respiration. 2010;79(4):302–6.
16. Ozpolat B. Autologous blood patch pleurodesis in the management of prolonged air leak. Thorac Cardiovasc Surg. 2010;58(1):52–4.
17. Rivas de Andres JJ, Blanco S, de la Torre M. Postsurgical pleurodesis with autologous blood in patients with persistent air leak. Ann Thorac Surg. 2000;70(1):270–2.
18. Yokomise H, Satoh K, Ohno N, Tamura K. Autoblood plus OK432 pleurodesis with open drainage for persistent air leak after lobectomy. Ann Thorac Surg. 1998;65(2):563–5.
19. Shackcloth MJ, Poullis M, Jackson M, Soorae A, Page RD. Intrapleural instillation of autologous blood in the treatment of prolonged air leak after lobectomy: a prospective randomized controlled trial. Ann Thorac Surg. 2006;82(3):1052–6.
20. Andreetti C, Venuta F, Anile M, De Giacomo T, Diso D, Di Stasio M, et al. Pleurodesis with an autologous blood patch to prevent persistent air leaks after lobectomy. J Thorac Cardiovasc Surg. 2007;133(3):759–62.
21. Williams P, Laing R. Tension pneumothorax complicating autologous "blood patch" pleurodesis. Thorax. 2005;60(12):1066–7.
22. Ando M, Yamamoto M, Kitagawa C, Kumazawa A, Sato M, Shima K, et al. Autologous blood-patch pleurodesis for secondary spontaneous pneumothorax with persistent air leak. Respir Med. 1999;93(6):432–4.
23. Cagirici U, Sahin B, Cakan A, Kayabas H, Buduneli T. Autologous blood patch pleurodesis in spontaneous pneumothorax with persistent air leak. Scand Cardiovasc J. 1998;32(2):75–8.
24. Evman S, Alpay L, Metin S, Kiral H, Demir M, Yalcinsoy M, et al. The efficacy and economical benefits of blood patch pleurodesis in secondary spontaneous pneumothorax patients. Kardiochir Torakochirurgia Pol. 2016;13(1):21–5.
25. Kagohashi K, Ohara G, Shiozawa T, Tamura T, Miyazaki K, Kurishima K, et al. Blood-patch pleurodesis for pneumothorax in lung fibrosis due to progressive systemic sclerosis: a case report. Exp Ther Med. 2014;8(6):1919–21.
26. Karangelis D, Tagarakis GI, Daskalopoulos M, Skoumis G, Desimonas N, Saleptsis V, et al. Intrapleural instillation of autologous blood for persistent air leak in spontaneous pneumothorax-is it as effective as it is safe? J Cardiothorac Surg. 2010;5:61.
27. Martinez-Escobar S, Ruiz-Bailen M, Lorente-Acosta MJ, Vicente-Rull JR, Martinez-Coronel JF, Rodriguez-Cuartero A. Pleurodesis using autologous blood: a new concept in the management of persistent air leak in acute respiratory distress syndrome. J Crit Care. 2006;21(2):209–16.
28. Cobanoglu U, Melek M, Edirne Y. Autologous blood pleurodesis: a good choice in patients with persistent air leak. Ann Thorac Med. 2009;4(4):182–6.
29. Aihara K, Handa T, Nagai S, Tanizawa K, Watanabe K, Harada Y, et al. Efficacy of blood-patch pleurodesis for secondary spontaneous pneumothorax in interstitial lung disease. Intern Med. 2011;50(11):1157–62.
30. Cao G, Kang J, Wang F, Wang H. Intrapleural instillation of autologous blood for persistent air leak in spontaneous pneumothorax in patients with advanced chronic obstructive pulmonary disease. Ann Thorac Surg. 2012;93(5):1652–7.
31. Ibrahim IM, Elaziz MEA, El-Hag-Aly MA. Early autologous blood-patch pleurodesis versus conservative management for treatment of secondary spontaneous pneumothorax. Thorac Cardiovasc Surg. 2019;67(3):222–6.

Is Resection of Persistent N2 Disease After Induction Therapy Effective?

15

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Introduction

Stage III non-small cell lung cancer (NSCLC) encompasses a heterogeneous group of tumors, with patients in the subset due to N2 (stage IIIA [T1-2N2M0] and stage IIIB [T3-T4N2M0]) lymph node metastases representing approximately 10% of all NSCLC patients [1, 2]. The National Comprehensive Cancer Network (NCCN) recommends definitive concurrent chemoradiation for stage IIIB(N2) patients, while recommended treatment for patients with stage IIIA(N2) NSCLC is multimodality with some combination of surgical resection, chemotherapy, and radiation therapy [3]. The optimal management strategy, and in particular the benefit of surgery over chemoradiation for stage IIIA(N2), disease has not been definitively established by randomized controlled data, but induction chemotherapy with or without radiation therapy followed by surgery is generally accepted as appropriate for selected patients [4–12]. Guidelines, however, do not really make specific recommendations regarding definitive chemotherapy and radiation over neoadjuvant therapy and resection, and the definition of "potentially resectable N2" varies among centers and surgeons.

Whether to pursue surgery for patients with N2 disease is one of the most controversial topics in the spectrum of non-small cell lung cancer treatment and should always be considered with multidisciplinary input [13, 14]. The degree of lymph node involvement at the time of diagnosis (single versus multi-station disease, bulky versus non-bulky disease, or macroscopic versus microscopic disease) and the extent of pulmonary resection necessary (lobectomy versus pneumonectomy) are important considerations as to whether surgery should be pursued [15, 16]. The

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importance of induction therapy over primary surgery is widely accepted, though there is much less agreement as to whether that induction therapy should be chemotherapy alone or combined chemoradiation [17–21]. Opinions regarding the role of surgery also vary widely among both medical oncologists and thoracic surgeons [22, 23]. For example, 82% of thoracic surgeons would consider surgery for multistation macroscopic N2 disease compared with only 48% of medical oncologists. The response to induction therapy (to both the primary tumor and the involved lymph nodes) is an additional important factor that influences the decision to proceed with surgery after induction therapy for N2 disease. This chapter reviews published studies of outcomes of major lung resection for non-small cell lung cancer when N2 disease persists after induction therapy.

Search Strategy

The studies reviewed were identified by a search of Pubmed (www.pubmed.gov) with the search terms "(induction OR neoadjuvant) AND (N2 OR IIIA) AND lung AND resection" limited to the English language (Table 15.1). The Pubmed search covered the years 1992–2019 and was limited to the English language. The reviewed articles were selected based on the nature of the study and the number of patients involved. Only studies that provided detailed treatment specifics, perioperative outcomes, and long-term survival were included. For studies that included a heterogeneous group of stages including IIIA(N2), only those where the outcomes specific to the N2 subset were separately distinguishable were included.

Results

Multimodality therapy is fundamentally important to optimizing the oncologic outcome of patients with NSCLC and N2 disease [3, 24]. The majority of patients with N2 disease die of recurrent systemic disease despite apparently complete resection. Induction therapy may optimize disease control by clearing local mediastinal disease and perhaps even clinically non-detectable micro-metastatic disease, with the additional advantage of better patient tolerance and compliance for neoadjuvant

Table 15.1 PICO formatted terms for literature search

Patients	Intervention	Comparator	Outcomes
Pts with persistent N2 disease after induction therapy	Surgical resection	Observation	Treatment morbidity Mortality Long-term survival

therapy compared to adjuvant treatment [25]. However, an additional critically important consideration is the potential peri-operative morbidity of major lung resection after induction therapy [26, 27]. The potential oncologic benefits of surgery must be weighed against the short-term risks in patients with N2 disease, and the decision as to whether surgery is potentially feasible should generally be made before starting induction therapy [13, 14].

Evidence for Multimodality Therapy

Two prospective trials, both now performed several decades ago, demonstrated the importance of multimodality therapy for NSCLC patients with mediastinal nodal disease by showing dramatically better outcomes when resectable patients with clinically positive N2 disease received induction chemotherapy rather than proceeding with upfront surgical resection [5, 6, 28, 29]. Randomized studies have also shown the benefit of adjuvant chemotherapy after primary resection of patients with N2 disease [7, 8, 30–33]. Strong evidence therefore supports the use of surgery combined with chemotherapy in this situation, and clinical practice guidelines recommend induction therapy prior to resection when surgery is utilized [3, 13].

Oncologic Outcomes of Surgery for N2 Disease

Although the above described studies showed the importance of combining systemic therapy with surgery, the need for surgery as local therapy beyond definitive chemoradiation is unclear. A 21% complete pathologic response to chemoradiation in the Southwest Oncology Group (SWOG) Trial 8805 that assessed the feasibility of chemoradiation followed by surgery for stage III NSCLC led to performance of the North American Intergroup Trial 0139 that evaluated whether surgery added more to the risk or to the benefit of chemoradiation [12, 34]. This phase III study showed no significant difference in 5-year overall survival between induction (cisplatin/etoposide/45 Gy radiation) versus definitive chemoradiation (61 Gy radiation) [12]. Subsequent randomized trials have also failed to demonstrate a benefit to multimodality therapy with surgery over definitive chemoradiation [11, 35]. Not surprisingly, several meta-analyses of this topic do not provide strong evidence for pursuing surgery for N2 disease [36–39].

These important study findings, however, have failed to clearly define clinical practice. The Intergroup results were very heavily influenced by surgery related deaths, with a somewhat remarkably high 17.6% mortality after pneumonectomy—lobectomy had a mortality of only 1.1% [12]. A post hoc subgroup analysis showed that induction patients who underwent lobectomy had a significantly better prognosis than definitive chemoradiation patients. The study also found significantly better

prognosis for patients with nodal downstaging after resection over those with residual mediastinal nodal disease (41% 5-year survival versus 24%). Based on these findings, surgical resection after induction therapy is generally felt to have a role for patients with N2 disease in the setting of nodal downstaging and when lobectomy is feasible to achieve complete resection [4, 40].

Impact of Mediastinal Downstaging on Outcomes

As described above, the Intergroup study demonstrated significantly better survival for mediastinal nodal downstaging when surgery was performed after induction therapy [12]. SWOG trial 8805 had shown a similar prognostic value for the sterilization of mediastinal lymph nodes; 3-year survival was 44% in patients with eradication of mediastinal nodal disease but only 18% in those with persistent N2 disease [34]. Multiple other studies have had consistent findings that persistent N2 disease after induction therapy independently predicts worse outcomes [21, 41–43]. Patients with complete nodal clearance (ypN0) had the lowest recurrence risk in one study, while the risk of disease recurrence and death were similar in patients who had persistent N1 or N2 disease [44].

Nodal downstaging not surprisingly factors into the decision to perform resection, with only a minority of surgeons favoring surgery in the absence of nodal downstaging [22]. These consistent findings have led to a common practice of mediastinal restaging after induction therapy prior to surgery [45–47]. Considering the prognostic importance of nodal downstaging, performing pathologic restaging after induction therapy not surprisingly was found in one study to be a predictor of improved long-term survival, where patients who had pathologic mediastinal restaging following induction therapy but prior to resection had an improved 5-year survival of 45.2% compared with 13.9% for patients who did not undergo pathologic mediastinal restaging [48].

Outcomes for Persistent Mediastinal Disease

Unfortunately, restaging after induction therapy will demonstrate that a significant number of patients have persistent nodal disease. Downstaging after chemotherapy for pathologically proven N2 nodes is 20–40% and downstaging after chemoradiation is 46–68% [12, 18, 42, 49–56]. Therefore, surgeons commonly will need to decide on whether to operate when patients have persistent N2 disease after induction therapy.

Table 15.2 lists studies that have evaluated survival of patients who underwent resection with persistent N2 disease after induction therapy. Most studies were retrospective, but two were prospective phase II studies, and one was a prospective randomized trial. The induction therapy was chemotherapy in four studies and

Table 15.2 Survival of patients who undergo resection of persistent N2 disease

Reference	Study design	Number of patients treated with complete resection	Induction therapy	Survival of patients with residual N2 disease[a]	Survival of patients with ypN0-1 nodal disease[a]	Level of evidence
Cerfolio et al. [67]	Retrospective	113/149	CRT	42%	49–53%	Low
Decaluwe et al. [49]	Retrospective	63/92	CT	27%	49%	Low
Friedel et al. [50]	Prospective phase II	58/62	CRT	30.8%	38.5–53.3%	Moderate
Higgins et al. [58]	Retrospective	22	CT	34%	Not studied	Low
Shintani et al. [42]	Retrospective	NR/52	CRT	0 (n = 23)	58% (n = 29)	Very low
Stefani et al. [61]	Retrospective	164/175	CT	22%	45%	Low
Paul et al. [43]	Retrospective	131/136	CT (n = 119) and CRT (n = 17)	20%	45%	Low
Albain et al. [12]	Prospective/ Randomized	144/164	CRT	24%	41%	High
Jaklitsch et al. [53]	Prospective phase II	21/42	CT	16.9 months	47.8 months	Moderate
Port et al. [57]	Retrospective	47/52	CT	19%	30%	Low

CT chemotherapy, *CRT* chemoradiation, *NR* not reported
[a]Median survival in months or 5-year survival %

chemoradiation in four studies; one study included both types of induction therapy. All studies showed findings of worse survival for persistent N2 disease. The 5-year survival with patients with persistent N2 disease ranged from 22% to 34% for the induction chemotherapy patients and 0–42% for the chemoradiation patients. Only one study showed a 5-year survival of less than 20% for patients with persistent disease.

Other Considerations

Nodal downstaging has been consistently shown to have a positive association with survival [18, 29, 42, 52, 56, 59, 60]. Patients, however, may still have a reasonable prognosis even if their mediastinal nodes are not completely cleared of disease.

Having some response to pre-operative therapy may provide a similar prognostic benefit to mediastinal nodal clearance [18, 61, 62]. One study that assessed response based on pre- and post-induction imaging found significantly better survival even when patients had persistent hypermetabolic activity on positron emission tomography (PET) scans of up to 40% of the pre-treatment values [62]. Another study of 73 patients treated with induction chemoradiation and then resection showed that involved lymph node volume on imaging after preoperative chemoradiation was associated with both increased locoregional recurrence and decreased overall survival [63].

The number of involved stations also significantly impacts survival. Decaluwe found 5-year survival was significantly better for persistent single station disease compared to persistent disease at multiple stations (37% vs. 7%) [49]. These authors also found lower 5-year survival (17% vs. 39%; $p < 0.005$) for multi-station involvement compared to single level positive nodes prior to therapy.

An additional important factor for patients treated with surgery for persistent N2 disease is considering additional adjuvant therapy [21]. A National Cancer Database study of patients treated with induction chemotherapy and then surgery for cN2 NSCLC found survival benefits to both post-operative chemotherapy (3-year survival 49.3% vs. 58.3%) and post-operative radiation for patients (48.8% vs. 53.5%) with persistent N2 disease [64]. Another retrospective study also found that additional post-operative chemotherapy was associated with fewer distant disease failures in patients who had persistent N2 disease after induction chemotherapy and then surgical resection [65]. Interestingly, Billiet et al. did not find a similar survival benefit to post-operative radiation therapy for patients with residual N2 disease after chemotherapy and then resection [66].

Alternatives to Surgery

The multiple factors that influence the selection process for surgery makes comparison of what happens to patients who undergo resection for persistent N2 disease with non-surgical patients very difficult. One study found that over 50% of patients for whom surgery was initially considered for surgery did not ultimately undergo resection, likely due to inability to tolerate or progression on induction therapy [67]. Although prognosis might be expected to be dismal in that situation, 5-year survival has been reported to be as high as 17% [12, 67]. Non-surgical patients likely will get further chemotherapy or radiation. However, definitive chemoradiation for IIIA(N2) NSCLC is also not a benign treatment, with one study reporting 74% morbidity and 2.3% mortality [68].

Resection Extent: Is Pneumonectomy Acceptable?

The surgical procedure required for complete resection after induction therapy for N2 disease is an important consideration. Peri-operative mortality of

pneumonectomy after induction therapy was 17.6% in the Intergroup trial and 18% in another smaller retrospective study [69]. Another smaller study of 39 patients treated with induction chemotherapy had a 1-year mortality of 26% after pneumonectomy and 11% after lobectomy [70]. Five-year survival after surgery in this study was 43% after lobectomy and 16% pneumonectomy. Very careful patient selection may improve outcomes of pneumonectomy, as small single center studies have reported minimal mortality in this situation [71]. However, the potential for major morbidity must be carefully evaluated if a patient requires pneumonectomy after induction therapy for N2 disease.

Impact of Induction Therapy Choice

Another controversial topic when considering surgery for N2 is whether induction therapy should include radiation in addition to chemotherapy. The NCCN supports both strategies [3]. Combined chemoradiation is the strategy used by most United States centers and is generally associated with a better response, but has not been shown in randomized trials to improve survival over chemotherapy alone [12, 17, 18, 20, 21, 72–74]. A chemoradiation strategy may lead to undertreatment in cases where an induction dose of radiation is given but surgery is ultimately not performed, therefore leading to less than optimal local treatment. An advantage to induction chemotherapy alone is that a definitive radiation dose can subsequently be administered if surgery is deferred for any reason, therefore perhaps not compromising a patient's outcome with chemoradiation alone [19].

Risks of Major Pulmonary Resection After Induction Therapy

The potential oncologic benefits of surgery for persistent N2 disease after induction therapy that have been described must be weighed against the risks of surgery. Early reports found increased morbidity and mortality for lobectomy and pneumonectomy after induction therapy [75, 76]. Advances in surgical and anesthetic techniques, peri-operative care, and patient selection may have reduced the impact of induction therapy, as subsequent reports have found that induction therapy did not significantly increase the risk for mortality or morbidity [77–80]. Major lung surgery has been shown to be generally safe even after higher definitive doses of radiation [81]. Induction therapy, however, likely does confer some increased surgical risk and was a risk for a prolonged length of hospital stay, which was considered a surrogate for morbidity, in a Society of Thoracic Surgeons General Thoracic Surgery Database review of 4979 lobectomies performed between 2002 and 2006 [26]. Mortality was also significantly higher for pneumonectomy compared to lobectomy after induction therapy in several prospective and retrospective studies [12, 27, 74, 76, 82]. Table 15.3 lists the morbidity and mortality after induction therapy reported by multiple studies.

Table 15.3 Morbidity and mortality of major lung resection after induction therapy

Reference	Study design (n[a])	Induction treatment[b]	Summary of study findings	Level of evidence
Fowler et al. [76]	Retrospective (13)	CRT (60 Gy)	43% pneumonectomy mortality	Low
Bonomi et al. [75]	Retrospective (16)	CRT (40 Gy)	38% significant morbidity	Low
Deutsch et al. [82]	Retrospective (16)	CRT (60 Gy)	19% overall mortality, 33% pneumonectomy mortality	Low
Siegenthaler et al. [77]	Retrospective (76)	CT	1.3% mortality, 45% morbidity; similar outcomes for induction and non-induction patients	Low
Martin et al. [27]	Retrospective (470)	CT (all)/RT in 18% (50 Gy)	2.4% lobectomy mortality; right pneumonectomy had significantly higher mortality than left (23.9% vs. 0%)	Low
Albain et al. [12]	Prospective (202)	CRT (45 Gy)	Treatment-related mortality of 1% for lobectomy and 26% for pneumonectomy	Moderate
Evans et al. [80]	Retrospective (525)	CT (n = 153) RT (n = 23) CRT (n = 349)	2.3% overall mortality, 10.5% major morbidity	Moderate
Sonett et al. [81]	Retrospective (40)	CRT (62 Gy)	0% mortality	Low

CT chemotherapy, *RT* radiation therapy, *CRT* chemoradiation therapy
[a]Number of patients in the study that had received induction therapy prior to major lung resection
[b]Radiation dose shown is a median value

Conclusions and Recommendations

Published studies examining the role of surgery for N2 disease overall are a mixture of randomized trials and retrospective studies. Studies that address the topic of management when N2 disease persists after induction therapy are small, single-center, and retrospective in nature. Additional large-scale phase III trials in patients with N2 disease are unfortunately unlikely to be initiated to improve the current level of evidence, particularly for the specific situation of persistent N2 disease after induction therapy. More therapeutic options such as targeted therapies and immunotherapy will likely increase the complexity and variety of options [83]. The best option for specific patients will require careful evaluation by a multidisciplinary team that includes an experienced thoracic surgeon and relies on the evidence that has been discussed.

Patients with suspected N2 disease on initial staging studies should have pathologic mediastinal nodal evaluation and be treated with induction therapy prior to undergoing surgical resection. Surgical resection should only be considered for acceptable surgical candidates with single-station mediastinal nodal disease for

whom lobectomy is technically feasible; other patients should receive definitive chemoradiation. Induction therapy prior to surgery should be chemotherapy alone so that definitive radiation doses can be used if patients do not ultimately have resection. Patients for whom surgery was planned should be restaged after induction therapy and proceed to resection when nodal disease has been cleared. Patients for whom surgery was planned and have an imaging response but persistent mediastinal nodal disease after induction therapy should proceed with resection.

Recommendations

- Patients with suspected N2 disease on initial staging studies should have pathologic mediastinal nodal evaluation and be treated with induction therapy prior to undergoing surgical resection (high quality evidence, strong recommendation).
- Surgical resection should only be considered for acceptable surgical candidates with single-station mediastinal nodal disease for whom lobectomy is technically feasible; other patients should receive definitive chemoradiation (moderate quality evidence, strong recommendation).
- Induction therapy prior to surgery should be chemotherapy alone so that definitive radiation doses can be used if patients do not ultimately have resection (moderate quality evidence, weak recommendation).
- Patients for whom surgery was planned should be restaged after induction therapy and proceed to resection when nodal disease has been cleared (moderate quality evidence, strong recommendation).
- Patients for whom surgery was planned and have an imaging response but persistent mediastinal nodal disease after induction therapy should proceed with resection (low quality evidence, weak recommendation).

A Personal View of the Data

My approach to N2 disease closely follows the evidence and recommendations that have been described. Although the specific situation for all patients must be carefully considered individually, I would consider surgery to potentially have a role when patients have only one involved nodal station or only microscopic nodal disease if more than one station is involved and when lobectomy can be both tolerated and achieve complete resection. All patients should have pathologic confirmation of N2 disease and not proceed with treatment based on imaging studies only, to ensure those with false radiographic positives do not receive unnecessary induction therapy or are denied surgery at all. I prefer that the initial evaluation be done via endobronchial ultrasound guided biopsy, so that mediastinoscopy can be safely performed after therapy if needed to assess the response to induction therapy or to evaluate for N3 disease prior to

surgery. My preference for induction therapy is chemotherapy alone. If radiation is part of the induction therapy, I generally prefer a definitive dose be used if there is any question that the patient is likely to ultimately be an acceptable surgical candidate after the induction therapy. I would proceed with surgery if patients have some evidence of response without disease progression on restaging studies. I will generally attempt a minimally invasive approach to surgery if technically feasible when patients have received chemotherapy alone but would utilize a thoracotomy and cover the bronchial stump with an intercostal muscle flap when patients have received chemoradiation.

References

1. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(1):39–51.
2. Mountain CF. Revisions in the international system for staging lung cancer. Chest. 1997;111:1710–7.
3. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, et al. Non-small cell lung cancer, version 5.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw. 2017;15(4):504–35.
4. Robinson LA, Ruckdeschel JC, Wagner H Jr, et al. Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007;132:243S–65S.
5. Roth JA, Atkinson EN, Fossella F, et al. Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. Lung Cancer. 1998;21:1–6.
6. Rosell R, Gómez-Codina J, Camps C, et al. Preresectional chemotherapy in stage IIIA non-small-cell lung cancer: a 7-year assessment of a randomized controlled trial. Lung Cancer. 1999;26:7–14.
7. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006;7:719–27.
8. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med. 2004;350:351–60.
9. Johnstone DW, Byhardt RW, Ettinger D, et al. Phase III study comparing chemotherapy and radiotherapy with preoperative chemotherapy and surgical resection in patients with non-small-cell lung cancer with spread to mediastinal lymph nodes (N2); final report of RTOG 89-01. Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys. 2002;54:365–9.
10. Taylor NA, Liao ZX, Cox JD, et al. Equivalent outcome of patients with clinical Stage IIIA non-small-cell lung cancer treated with concurrent chemoradiation compared with induction chemotherapy followed by surgical resection. Int J Radiat Oncol Biol Phys. 2004;58:204–12.
11. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst. 2007;99:442–50.
12. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374:379–86.

13. Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of stage III non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e314S–40S.
14. Vansteenkiste J, Crino L, Dooms C, Douillard JY, Faivre-Finn C, Lim E, et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. Ann Oncol. 2014;25(8):1462–74.
15. Andre F, Grunenwald D, Pignon JP, et al. Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. J Clin Oncol. 2000;18:2981–9.
16. Ito M, Yamashita Y, Tsutani Y, et al. Classifications of N2 non-small-cell lung cancer based on the number and rate of metastatic mediastinal lymph nodes. Clin Lung Cancer. 2013;14:651–7.
17. Pless M, Stupp R, Ris HB, et al. SAKK Lung Cancer Project Group. Induction chemoradiation in stage IIIA/N2 nonsmall-cell lung cancer: a phase 3 randomised trial. Lancet. 2015;386:1049–56.
18. Katakami N, Tada H, Mitsudomi T, Kudoh S, Senba H, Matsui K, et al. A phase 3 study of induction treatment with concurrent chemoradiotherapy versus chemotherapy before surgery in patients with pathologically confirmed N2 stage IIIA nonsmall cell lung cancer (WJTOG9903). Cancer. 2012;118:6126–35.
19. Shah AA, Berry MF, Tzao C, Gandhi M, Worni M, Pietrobon R, D'Amico TA. Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer. Ann Thorac Surg. 2012;93(6):1807–12.
20. Yang CF, Gulack BC, Gu L, Speicher PJ, Wang X, Harpole DH, et al. Adding radiation to induction chemotherapy does not improve survival of patients with operable clinical N2 non-small cell lung cancer. J Thorac Cardiovasc Surg. 2015;150(6):1484–92.
21. Spicer JD, Shewale JB, Nelson DB, Mitchell KG, Bott MJ, Vallières E, et al. Multimodality therapy for N2 non-small cell lung cancer: an evolving paradigm. Ann Thorac Surg. 2019;107(1):277–84.
22. Veeramachaneni NK, Feins RH, Stephenson BJ, et al. Management of stage IIIA non-small cell lung cancer by thoracic surgeons in North America. Ann Thorac Surg. 2012;94:922–6.
23. Tanner NT, Gomez M, Rainwater C, et al. Physician preferences for management of patients with stage IIIA NSCLC: impact of bulk of nodal disease on therapy selection. J Thorac Oncol. 2012;7:365–9.
24. Berry MF, Worni M, Pietrobon R, D'Amico TA, Akushevich I. Variability in the treatment of elderly patients with stage IIIA (N2) non-small-cell lung cancer. J Thorac Oncol. 2013;8(6):744–52.
25. Farray D, Mirkovic N, Albain KS. Multimodality therapy for stage III non-small-cell lung cancer. J Clin Oncol. 2005;23:3257–69.
26. Wright CD, Gaissert HA, Grab JD, O'Brien SM, Peterson ED, Allen MS. Predictors of prolonged length of stay after lobectomy for lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk-adjustment model. Ann Thorac Surg. 2008;85:1857–65.
27. Martin J, Ginsberg RJ, Abolhoda A, Bains MS, Downey RJ, Korst RJ, et al. Morbidity and mortality after neoadjuvant therapy for lung cancer: the risks of right pneumonectomy. Ann Thorac Surg. 2001;72:1149–54.
28. Roth JA, Fossella F, Komaki R, Ryan MB, Putnam JB Jr, Lee JS, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. J Natl Cancer Inst. 1994;86:673–80.
29. Garrido P, González-Larriba JL, Insa A, Provencio M, Torres A, Isla D, et al. Long-term survival associated with complete resection after induction chemotherapy in stage IIIA (N2) and IIIB (T4N0-1) non small-cell lung cancer patients: the Spanish Lung Cancer Group Trial 9901. J Clin Oncol. 2007;25(30):4736–42.
30. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med. 2005;352:2589–97.
31. Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer

and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol. 2008;26:5043–51.
32. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26:3552–9.
33. Arriagada R, Auperin A, Burdett S, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet. 2010;375:1267–77.
34. Albain KS, Rusch VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol. 1995;13:1880–92.
35. Eberhardt WE, Pottgen C, Gauler TC, et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and selected IIIB non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). J Clin Oncol. 2015;33:4194–201.
36. McElnay PJ, Choong A, Jordan E, Song F, Lim E. Outcome of surgery versus radiotherapy after induction treatment in patients with N2 disease: systematic review and meta-analysis of randomised trials. Thorax. 2015;70(8):764–8.
37. Pottgen C, Eberhardt W, Stamatis G, Stuschke M. Definitive radiochemotherapy versus surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC) – a cumulative meta-analysis of the randomized evidence. Oncotarget. 2017;8(25):41670–8.
38. Ren Z, Zhou S, Liu Z, Xu S. Randomized controlled trials of induction treatment and surgery versus combined chemotherapy and radiotherapy in stages IIIA-N2 NSCLC: a systematic review and meta-analysis. J Thorac Dis. 2015;7(8):1414–22.
39. Xu YP, Li B, Xu XL, Mao WM. Is there a survival benefit in patients with stage IIIA (N2) non-small cell lung cancer receiving neo-adjuvant chemotherapy and/or radiotherapy prior to surgical resection: a systematic review and meta-analysis. Medicine (Baltimore). 2015;94:e879.
40. Postmus PE, Kerr KM, Oudkerk M, et al. ESMO Guidelines Committee. Early and locally advanced nonsmall-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(Suppl_4):iv1–iv21.
41. Yang H, Yao F, Zhao Y, Zhao H. Clinical outcomes of surgery after induction treatment in patients with pathologically proven N2-positive stage III non-small cell lung cancer. J Thorac Dis. 2015;7(9):1616–23.
42. Shintani Y, Funakoshi Y, Inoue M, Takeuchi Y, Okumura M, Maeda H, Ohta M. Pathological status of mediastinal lymph nodes after preoperative concurrent chemoradiotherapy determines prognosis in patients with non-small cell lung cancer. Ann Thorac Cardiovasc Surg. 2012;18(6):530–5.
43. Paul S, Mirza F, Port JL, Lee PC, Stiles BM, Kansler AL, Altorki NK. Survival of patients with clinical stage IIIA non-small cell lung cancer after induction therapy: age, mediastinal downstaging, and extent of pulmonary resection as independent predictors. J Thorac Cardiovasc Surg. 2011;141(1):48–58.
44. Lee J, Kim HK, Park BJ, Cho JH, Choi YS, Zo JI, et al. Recurrence dynamics after trimodality therapy (Neoadjuvant concurrent chemoradiotherapy and surgery) in patients with stage IIIA (N2) lung cancer. Lung Cancer. 2018;115:89–96.
45. De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg. 2014;45(5):787–98.
46. Jaklitsch MT, Gu L, Demmy T, Harpole DH, D'Amico TA, McKenna RJ, et al. Prospective phase II trial of preresection thoracoscopic mediastinal restaging after neoadjuvant therapy for IIIA (N2) non-small cell lung cancer: results of CALGB Protocol 39803. J Thorac Cardiovasc Surg. 2013;146(1):9–16.
47. De Waele M, Hendriks J, Lauwers P, Hertoghs M, Carp L, Salgado R, et al. Restaging the mediastinum in non-small cell lung cancer after induction therapy: non-invasive versus invasive procedures. Acta Chir Belg. 2011;111(3):161–4.

48. Yang CF, Adil SM, Anderson KL, Meyerhoff RR, Turley RS, Hartwig MG, et al. Impact of patient selection and treatment strategies on outcomes after lobectomy for biopsy-proven stage IIIA pN2 non-small cell lung cancer. Eur J Cardiothorac Surg. 2016;49(6):1607–13.
49. Decaluwé H, De Leyn P, Vansteenkiste J, Dooms C, Van Raemdonck D, Nafteux P, et al. Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival. Eur J Cardiothorac Surg. 2009;36(3):433–9.
50. Friedel G, Budach W, Dippon J, Spengler W, Eschmann SM, Pfannenberg C, et al. Phase II trial of a trimodality regimen for stage III non-small-cell lung cancer using chemotherapy as induction treatment with concurrent hyperfractionated chemoradiation with carboplatin and paclitaxel followed by subsequent resection: a single-center study. J Clin Oncol. 2010;28(6):942–8.
51. Edelman MJ, Hu C, Le QT, Donington JS, D'Souza WD, Dicker AP, et al. Randomized phase II Study of preoperative chemoradiotherapy ± panitumumab followed by consolidation chemotherapy in potentially operable locally advanced (Stage IIIa, N2+) non-small cell lung cancer: NRG Oncology RTOG 0839. J Thorac Oncol. 2017;12(9):1413–20.
52. Suntharalingam M, Paulus R, Edelman MJ, Krasna M, Burrows W, Gore E, et al. Radiation therapy oncology group protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. Int J Radiat Oncol Biol Phys. 2012;84(2):456–63.
53. Jaklitsch MT, Herndon JE 2nd, DeCamp MM Jr, Richards WG, Kumar P, Krasna MJ, et al. Nodal downstaging predicts survival following induction chemotherapy for stage IIIA (N2) non-small cell lung cancer in CALGB protocol #8935. J Surg Oncol. 2006;94(7):599–606.
54. Spaggiari L, Casiraghi M, Guarize J, Brambilla D, Petrella F, Maisonneuve P, De Marinis F. Outcome of patients with pN2 "potentially resectable" nonsmall cell lung cancer who underwent surgery after induction chemotherapy. Semin Thorac Cardiovasc Surg. 2016;28(2):593–602.
55. Tanaka F, Yokomise H, Soejima T, Uramoto H, Yamanaka T, Nakagawa K, et al. Induction chemoradiotherapy (50 Gy), followed by resection, for stage IIIA-N2 non-small cell lung cancer. Ann Thorac Surg. 2018;106(4):1018–24.
56. Kamel MK, Rahouma M, Ghaly G, Nasar A, Port JL, Stiles BM, et al. Clinical predictors of persistent mediastinal nodal disease after induction therapy for stage IIIA N2 non-small cell lung cancer. Ann Thorac Surg. 2017;103(1):281–6.
57. Port JL, Korst RJ, Lee PC, Levin MA, Becker DE, Keresztes R, Altorki NK. Surgical resection for residual N2 disease after induction chemotherapy. Ann Thorac Surg. 2005;79(5):1686–90.
58. Higgins KA, Chino JP, Ready N, Onaitis MW, Berry MF, D'Amico TA, Kelsey CR. Persistent N2 disease after neoadjuvant chemotherapy for non-small-cell lung cancer. J Thorac Cardiovasc Surg. 2011;142(5):1175–9.
59. Kim HK, Cho JH, Choi YS, Zo JI, Shim YM, Park K, et al. Outcomes of neoadjuvant concurrent chemoradiotherapy followed by surgery for non-small-cell lung cancer with N2 disease. Lung Cancer. 2016;96:56–62.
60. Shumway D, Corbin K, Salgia R, Hoffman P, Villaflor V, Malik RM, et al. Pathologic response rates following definitive dose image-guided chemoradiotherapy and resection for locally advanced non-small cell lung cancer. Lung Cancer. 2011;74:446–50.
61. Stefani A, Alifano M, Bobbio A, Grigoroiu M, Jouni R, Magdeleinat P, Regnard JF. Which patients should be operated on after induction chemotherapy for N2 non-small cell lung cancer? Analysis of a 7-year experience in 175 patients. J Thorac Cardiovasc Surg. 2010;140(2):356–63.
62. Dooms C, Verbeken E, Stroobants S, Nackaerts K, De Leyn P, Vansteenkiste J. Prognostic stratification of stage IIIA-N2 non-small-cell lung cancer after induction chemotherapy: a model based on the combination of morphometric-pathologic response in mediastinal nodes and primary tumor response on serial 18-fluoro-2-deoxy-glucose positron emission tomography. J Clin Oncol. 2008;26(7):1128–34.

63. Agrawal V, Coroller TP, Hou Y, Lee SW, Romano JL, Baldini EH, et al. Lymph node volume predicts survival but not nodal clearance in stage IIIA-IIIB NSCLC. PLoS One. 2017;12(4):e0174268.
64. Shinde A, Horne ZD, Li R, Glaser S, Massarelli E, Koczywas M, et al. Optimal adjuvant therapy in clinically N2 non-small cell lung cancer patients undergoing neoadjuvant chemotherapy and surgery: the importance of pathological response and lymph node ratio. Lung Cancer. 2019;133:136–43.
65. Amini A, Correa AM, Komaki R, Chang JY, Tsao AS, Roth JA, et al. The role of consolidation therapy for stage III non-small cell lung cancer with persistent N2 disease after induction chemotherapy. Ann Thorac Surg. 2012;94(3):914–20.
66. Billiet C, Peeters S, Decaluwé H, Vansteenkiste J, Dooms C, Deroose CM, et al. Outcome after PORT in ypN2 or R1/R2 versus no PORT in ypN0 stage III-N2 NSCLC after induction chemotherapy and resection. J Thorac Oncol. 2016;11(11):1940–53.
67. Cerfolio RJ, Maniscalco L, Bryant AS. The treatment of patients with stage IIIA non-small cell lung cancer from N2 disease: who returns to the surgical arena and who survives. Ann Thorac Surg. 2008;86(3):912–20.
68. Seder CW, Allen MS, Cassivi SD, Deschamps C, Nichols FC, Olivier KR, et al. Stage IIIA non-small cell lung cancer: morbidity and mortality of three distinct multimodality regimens. Ann Thorac Surg. 2013;95(5):1708–16.
69. Shah AA, Worni M, Kelsey CR, Onaitis MW, D'Amico TA, Berry MF. Does pneumonectomy have a role in the treatment of stage IIIA non-small cell lung cancer? Ann Thorac Surg. 2013;95(5):1700–7.
70. Kappers I, van Sandick JW, Burgers SA, Belderbos JS, van Zandwijk N, Klomp HM. Surgery after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer: why pneumonectomy should be avoided. Lung Cancer. 2010;68(2):222–7.
71. Yamaguchi M, Shimamatsu S, Edagawa M, Hirai F, Toyozawa R, Nosaki K, et al. Pneumonectomy after induction chemoradiotherapy for locally advanced non-small cell lung cancer: should curative intent pulmonary resection be avoided? Surg Today. 2019;49(3):197–205.
72. Rusch VW, Albain KS, Crowley JJ, Rice TW, Lonchyna V, McKenna R Jr, Livingston RB, Griffin BR, Benfield JR. Surgical resection of stage IIIA and stage IIIB non-small-cell lung cancer after concurrent induction chemoradiotherapy. A Southwest Oncology Group trial. J Thorac Cardiovasc Surg. 1993;105:97–104.
73. Chen Y, Peng X, Zhou Y, Xia K, Zhuang W. Comparing the benefits of chemoradiotherapy and chemotherapy for resectable stage III A/N2 non-small cell lung cancer: a meta-analysis. World J Surg Oncol. 2018;16(1):8.
74. Thomas M, Rübe C, Hoffknecht P, Macha HN, Freitag L, Linder A, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. Lancet Oncol. 2008;9(7):636–48.
75. Bonomi P, Faber LP, Warren W, Lincoln S, LaFollette S, Sharma M, Recine D. Postoperative bronchopulmonary complications in stage III lung cancer patients treated with preoperative paclitaxel-containing chemotherapy and concurrent radiation. Semin Oncol. 1997;24:S12-123–S112-129.
76. Fowler WC, Langer CJ, Curran WJ Jr, Keller SM. Postoperative complications after combined neoadjuvant treatment of lung cancer. Ann Thorac Surg. 1993;55:986–9.
77. Siegenthaler MP, Pisters KM, Merriman KW, Roth JA, Swisher SG, Walsh GL, et al. Preoperative chemotherapy for lung cancer does not increase surgical morbidity. Ann Thorac Surg. 2001;71:1105–11.
78. Perrot E, Guibert B, Mulsant P, Blandin S, Arnaud I, Roy P, Geriniere L, Souquet PJ. Preoperative chemotherapy does not increase complications after nonsmall cell lung cancer resection. Ann Thorac Surg. 2005;80:423–7.
79. Gilligan D, Nicolson M, Smith I, Groen H, Dalesio O, Goldstraw P, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/

NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. Lancet. 2007;369:1929–37.
80. Evans NR 3rd, Li S, Wright CD, Allen MS, Gaissert HA. The impact of induction therapy on morbidity and operative mortality after resection of primary lung cancer. J Thorac Cardiovasc Surg. 2010;139(4):991-6.e1–2.
81. Sonett JR, Suntharalingam M, Edelman MJ, Patel AB, Gamliel Z, Doyle A, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small-cell lung cancer. Ann Thorac Surg. 2004;78:1200–5.
82. Deutsch M, Crawford J, Leopold K, Wolfe W, Foster W, Herndon J, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy with thoracotomy in the treatment of clinically staged IIIA non-small cell lung cancer. Cancer. 1994;74:1243–52.
83. Edelman MJ, Hu C, Le QT, Donington JS, D'Souza WD, Dicker AP, Loo BW, Gore EM, Videtic GMM, Evans NR, Leach JW, Diehn M, Feigenberg SJ, Chen Y, Paulus R, Bradley JD. Randomized phase II study of preoperative chemoradiotherapy ± panitumumab followed by consolidation chemotherapy in potentially operable locally advanced (Stage IIIa, N2+) non-small cell lung cancer: NRG Oncology RTOG 0839. J Thorac Oncol. 2017;12(9):1413–20.

N2 Disease Discovered at the Time of Vats Lung Resection: Resect or Abort?

16

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Introduction

Since the 1990s the introduction and development of minimally invasive surgery has substantially modified the management of surgical diseases, including lung cancer.

According to the published data, video-assisted thoracoscopic surgery (VATS) lobectomy is oncologically equivalent to open surgery with similar (or even better) survival rates [1, 2]. In addition, there is evidence that VATS lobectomy is suitable also for patients at high perioperative risk [3, 4], and is associated with lower complication rates [5–7], shorter chest tube duration and hospital length of stay [5], better preservation of pulmonary function [4], and better postoperative quality of life [8] when compared to open surgery.

On the basis of these results, several authors have proposed extending the indications for the VATS approach in the setting of non-small cell lung cancer (NSCLC) to include advanced stage diseases, including those with mediastinal lymph node involvement (N2 disease). The most recent American College of Chest Physicians (ACCP) guidelines [9] divide stage III(N2) NSCLC into three readily identifiable groups: (1) patients with infiltrative stage III(N2) tumors, (2) patients with discrete clinically evident (by CT or CT-PET scan) N2 involvement, and (3) patients with occult N2 node involvement despite thorough preoperative staging. While in the first two situations the therapeutic strategy is well-described [9], there is more uncertainty regarding the last category of stage III(N2) NSCLC, when unsuspected N2 nodal disease is encountered intraoperatively during a planned formal lung resection for clinical stage I or II NSCLC. The management options may include

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proceeding with resection with subsequent adjuvant therapy or aborting the planned resection to allow for neoadjuvant treatment or definitive chemo-radiotherapy. In addition, in the case of deciding to continue with the planned resection, the choice of the approach should be taken into account. In fact, the adequacy of lymphadenectomy through VATS, compared to thoracotomy, is another matter of debate.

In this chapter we assess evidence regarding whether to proceed with resection when unexpected N2 disease is identified intraoperatively at the time of planned lung resection for NSCLC. There is no direct comparison of the results of the different therapeutic choices to guide the decision-making process in this context, and the conclusions must be extrapolated from different data sets.

Search Strategy

We performed a literature search using PubMed, Ovid Medline, Embase, Cochrane Central Register of Controlled Trials, ACP Journal Club, Database of Abstract of Review of Effectiveness, and the Cochrane Database of Systematic Reviews. We combined the term "unexpected N2", "N2 disease", "lung resection", "VATS", "surgical treatment", "neoadjuvant chemotherapy", "adjuvant chemo-radiotherapy" as either keywords or MesH terms (Table 16.1). The research yielded 832 studies. Among all these studies, we selected original scientific publications in the English language. Abstracts, case reports, conference presentation, editorials and expert opinions were excluded. We only selected articles published from 2005 to 2019 to have up-to-date literature.

Results

Resection

In the current literature, only a few studies have reported outcomes of surgical resection in case of unexpected N2 disease discovered at the time of surgery (Table 16.2). In fact, the majority of papers that reported survival of patients undergoing resection for N2 involvement also included cases with clinical N2 involvement.

Cerfolio et al. published the first report of 148 patients who underwent surgery for unexpected N2 NSCLC [10]. Overall 2- and 5-years survival rates were 58% and 35%, respectively, in patients with single nodal station involvement, while in patients with multiple station involvement they were 40% and 25%. After resection, 93% of patients received adjuvant therapy.

Table 16.1 PICO formatted terms for literature search

P (patients)	I (intervention)	C (comparator)	O (outcomes)
N2 disease in NSCLC	VATS resection	Resection/abort VATS/open	Long term survival Disease free survival

Table 16.2 Resection in the setting of unexpected N2 NSCLC

Study	Year	Stage	Regimen	Number of patients with pN2	Median survival (months)	5-year survival (%)	P value	Evidence grade
Douillard [16]	2006	pIB-IIIA	Surg + CT vs. Surg	407 vs. 433	65.7 vs. 43.7	42% vs. 26% (stage IIIA)	NR	High
Cerfolio [10]	2008	pIIIA	Surg + Adj	148	NR	35% (single-station) 25% (multi-station)	0.02	Moderate
Watanabe [11]	2008	cI-pIIIA	Surg + Adj	69	NR	45.5 (VATS) 45.1 (thoracotomy)	0.71	Moderate
Kim [12]	2010	cI pIIB-IIIB	Surg + Adj	40	NR	89 (3-years)	NR	Moderate
Lee [13]	2013	cIA-pIIIA	Surg + Adj (43.9%)	46	NR	33.5	0.10	Moderate
Bille [14]	2017	cI-pIII	Surg + Adj	146	37.9	36.4	NR	Moderate

Surg surgery, *Adj* adjuvant treatment, *c* clinical, *p* pathologic, *CT* chemotherapy, *Obs* observation, *NR* not reported

In 2008, Watanabe et al. [11] analyzed 69 patients with pN2, comparing those who underwent surgery by VATS to those operated by thoracotomy. They found similar 3- and 5-year survival rates (67.6% vs. 57.7% and 45.4% vs. 41.1%, p = 0.833) with a 3- and 5-year recurrence-free survival respectively of 60.9% vs. 49.6% and 60.9% vs. 49.6% (p = 0.714). Kim et al. reported similar results in 2010 [12]: among forty patients with pathologic N2 disease, 3-year overall survival was 89%, while the 3-year disease-free survival was only 33%. However, in all the aforementioned studies, no specific data about adjuvant treatment administration in N2 subjects was available.

In 2013, Lee et al. [13] published data on long-term survival in 46 NSCLC patients with unsuspected N2 disease. The 5-year survival rate was 33% for patients with pN2 disease, which was significantly worse than for patients with pN0 and pN1 disease. Only 43.9% of patients in the study underwent adjuvant treatment. More recently, Bille [14] analyzed outcomes of 146 patients with occult pN2 disease; median survival was 37.9 months, with a 5-year survival rate of 36.4%. Again, median survival was significantly worse than for patients with pN0 or pN1 disease (83.7 months and 48 months, respectively). No specific data on adjuvant treatment was reported.

The importance of adjuvant treatment in surgically resected N2 patients is still a matter of debate, although, according to several studies, there seems to be a survival benefit in patients undergoing such treatment compared to patients managed by surgery alone. Berghmans et al. [15], in 2005, published a meta-analysis of 19 studies that evaluated the effect of adjuvant therapy in patients with resectable NSCLC. Although a greater survival benefit was evident in early stage patients, a trend towards improved survival was observed also in patients with stage IIIA disease who underwent chemotherapy (hazard-ratio of 0.85).

These data were confirmed in the randomized controlled trial published by Douillart et al., who assigned 840 patients with stage IB-IIIA NSCLC to either adjuvant chemotherapy (n = 407) or observation alone (n = 433) [16]. In a subgroup analysis of stage IIIA patients, 5-year survival was 42% in the chemotherapy group and 26% in the observation alone group. This survival difference, however, was not statistically significant.

Finally, concerning the more adequate approach to perform lymphadenectomy, several studies have compared the accuracy of lymph node dissection by VATS compared to open surgery, finding no differences in the accuracy of dissection and in number of lymph node dissected, also in cases of N2 involvement [17].

Neoadjuvant Treatments (Chemotherapy + Surgery or Chemoradiation Therapy + Surgery)

The current literature does not provide definitive evidence regarding the best curative-intent multimodality approach in patients affected by stage IIIA(N2) NSCLC. Induction therapies have several benefits: (1) the treatment of disseminated micro-metastases; (2) the downstaging of the disease with a subsequent

increase in surgical resectability; (3) a better selection of surgical candidates as a poor response may contraindicate surgery; and (4) the ability to evaluate the response to induction therapy as a prognostic factor.

Commonly adopted induction treatments for potentially resectable N2 disease include chemotherapy or combination chemoradiotherapy [18]; the optimal treatment is still a matter of debate, but some recent randomized controlled trials have compared these two approaches to establish the superiority of one regimen over the other (Table 16.3). Thomas and colleagues [19] published a randomized trial in 2008 in which 524 eligible patients with stage IIIA-IIIB NSCLC were randomly assigned to one of two groups before surgery: the intervention group received three cycles of cisplatin + etoposide followed by radiation, while the control group received chemotherapy alone. The authors concluded that pre-operative chemoradiation, compared to chemotherapy, increases pathological response and mediastinal downstaging but does not result in improved overall survival rates.

Girard et al. [20] conducted a phase II trial, including 46 patients, which compared standard induction therapy (arm A: cisplatin + gemcitabine) with two different regimens of induction chemoradiotherapy (radiotherapy total dose 46 Gy with cisplatin and vinorelbine [arm B] or with carboplatin and paclitaxel [arm C]). The feasibility rate did not statistically differ between the three treatment arms while the response rate was significantly higher in patients who underwent chemoradiotherapy compared to those who underwent chemotherapy alone (87% vs. 57%, $p = 0.049$).

Another randomized controlled trial (phase III) was recently published by Katakami et al. [21]. In this study, 60 patients were randomized to receive induction chemotherapy (docetaxel + carboplatin) plus radiation therapy (CRS arm) or induction chemotherapy alone (CS arm) before surgery. Median progression-free survival and median overall survival did not significantly differ between the two groups (12.4 months vs. 9.7 months, $p = 0.187$; and 39.6 months vs. 29.9 months, $p = 0.397$ in the CRS arm versus the CS arm, respectively). A notable finding was that multistation lymph node disease was more common in CS arm (52% vs. 35%), which could be explained by the local control of the radiation therapy, which implies a lower downstaging rate in the CS arm.

In 2015 Pless and colleagues [22] reported the results of their multicenter trial in which 232 patients were enrolled: 117 patients were allocated to the chemoradiotherapy group (cisplatin + docetaxel followed by radiation) while 115 patients received induction chemotherapy alone. Median overall survival was 37.1 months in the chemoradiotherapy group vs. 26.2 months in the chemotherapy group, and median event-free survival was similar in the two groups (12.8 months vs. 11.6 months, $p = 0.67$). The authors concluded that radiation therapy in addition to chemotherapy did not offer any advantages compared to the chemotherapy alone and, therefore, suggested that regimens containing platin and docetaxel followed by surgery could be an adequate option for patients with stage IIIA/N2 non small cell lung cancer (NSCLC).

R0 resection seems to be more achievable after chemoradiotherapy than chemotherapy alone, even though it is known that radiation may cause extensive adhesions

Table 16.3 Induction chemotherapy vs. chemoradiotherapy + surgery

Study	Year	Stage	CT regimens	CT + RT regimens	Patients		Median survival (mts)		5-year survival (%)		P value	Evidence grade
					CT	CT + RT	CT	CT + RT	CT	CT + RT		
Thomas [19]	2008	IIIA/B	Cis + Eto	CE + RT (45 Gy) + CV	260	264	21.3	19.6	42	45	0.64	High
Girard [20]	2010	IIIA	Gem + Cis	VP/PC + RT (46 Gy)	14	32	24.2	13	43 (3-year)	87	0.2	Moderate
Katakami [21]	2012	IIIA	Doc + Car	DC + RT (40 Gy)	28	28	29.9	39.6	39.3 (3-year)	51.7	0.397	Moderate
Pless [22]	2015	IIIA	Doc + Cis	DP + RT (44 Gy)	115	117	26.2	31.7	NR	NR	–	High

CT chemotherapy, *RT* radiotherapy, *c* clinical, *p* pathological, *Cis* cisplatin, *Eto* etoposide, *Gem* gemcitabine, *Car* carboplatin, *Doc* docetaxel, *DP* cisplatin + docetaxel, *DC* docetaxel + carboplatin, *PC* carboplatin + paclitaxel, *VP* cisplatin + vinorelbine, *CE* cisplatin + etoposide, *CV* cisplatin + vindesine, *Gy* Grey

that can make the surgical dissection more challenging, particularly in the mediastinal region. A recent study revealed that the number of lymph nodes dissected is reduced after induction radiotherapy, raising concerns regarding the risks of a less adequate lymph node harvesting and pathologic staging in these patients [23].

To date, the best induction regimen in potentially resectable N2 NSCLC is still a matter of debate. The association between induction chemotherapy and induction radiation therapy seems to provide benefits in term of tumor and lymph nodes response, which do not appear to translate into improvement in long-term survival [24].

Chemoradiotherapy Alone

When occult N2 disease is discovered at the time of surgery, another treatment option could be to abort the planned resection and to administer definitive chemoradiation. In 2009, Albain et al. [25] published the results of a randomized controlled trial that compared chemoradiotherapy alone with chemoradiotherapy followed by surgical resection in patients affected by potentially resectable N2 disease. Five-year progression-free survival was statistically different between the two groups in favor of surgery (22% vs. 11%), and the pattern of recurrence was different: patients who underwent surgery had a 10% local recurrence incidence versus 22% in the control arm. Overall survival at 5 years was also superior in the surgery group; however, this result was not statistically significant (27% vs. 20%).

Interestingly, the type of surgical resection significantly affected the survival rate. For patients who underwent lobectomy after chemoradiation there was a clear survival advantage compared with matched controls in the non-operative arm (median survival 34 months vs. 22 months, 5-year 36% vs. 18%, respectively). The same was not found for patients in whom the surgical resection consisted of a pneumonectomy (median survival 19 months vs. 29 months, 5-year 22% vs. 24%, respectively). Therefore, based on this study, it is possible to affirm that the risks and benefits associated with chemoradiotherapy and surgery should be carefully evaluated on a case-by-case basis, and the more correct treatment strategy should be decided by a multidisciplinary team of experts.

Conclusions and Recommendation

The use of the term “unexpected” N2 implies mediastinal nodal involvement discovered intraoperatively in the course of lung resection surgery despite accurate clinical and, if indicated, invasive mediastinal staging. These cases should be distinguished from those of patients with ignored N2 disease (enlarged lymph nodes at CT scan or PET-positive nodes but no biopsy specimen) and underappreciated N2 (known high risk of false negative CT or PET findings but no biopsy specimen).

According to this definition, the problem of unexpected N2 disease occurs in about 10% of surgical patients (5–16%) [10, 11]. The main therapeutic alternatives

that have been analyzed include the continuation of the surgical procedure compared to its interruption in favor of an induction treatment (chemotherapy or chemo-radiotherapy) or of definitive non-surgical treatment. As a corollary of this first decision option, an attempt was made to clarify, in the case of surgical continuation, by which approach (open surgery versus VATS) to complete the resection and to perform the lymphadenectomy. We found no studies in the literature that objectively compare these three alternative treatment strategies specifically for patients with unexpected N2 disease. Therefore, we can only infer our conclusions from studies that include patients with clinically evident N2 disease.

Leaving these limitations aside, the analysis of the papers seems to generally show that neoadjuvant therapy appears to offer a survival benefit compared to surgical resection alone. Even worse results are evident in the studies of definitive chemo-radiotherapy treatment, which should not be considered in the setting of the unexpected N2.

The same conclusion was reported by Ferguson et al. [26], who in 2003 performed a decision analytic study that modeled survival for patients who were treated by initial resection for clinically unexpected N2 nodal disease with survival for patients undergoing resection after neoadjuvant therapy for N2 nodal disease. The no-initial resection resulted in a better median survival (2.1 years vs. 1.7 years) and, therefore, the author concluded that when clinically unexpected N2 disease is discovered at time of surgery, delaying resection until after completion of neoadjuvant therapy is beneficial.

Some additional considerations, in this context, are provided by Detterbeck [27], who published a systematic review regarding the intraoperative management of patients with unexpected N2 disease. Among the main positive prognostic factors that influence the survival of these patients, complete resection (R0) and single-level lymph node involvement have emerged among the most important ones. The author also reiterated the fundamental importance of performing a complete lymphadenectomy and of associated adjuvant therapies in order to improve the survival of these patients. Unfortunately, according to the literature, adjuvant therapies are delivered only in approximately 65% of cases.

This assumption is also confirmed by some of the studies reported in Table 16.2: in the study of Lee [13] less than 50% of patients underwent post-operative chemotherapy while in the other retrospective series (excluding the study of Cerfolio [10]) it was not possible to extrapolate this data.

Presumably, one of the main reasons why adjuvant treatments are delivered only to a limited proportion of N2-positive patients is that surgery often is accompanied by additional morbidity, which results in patients being unfit for postoperative therapies. In this context, the role of the surgical approach is a further element to be considered. As mentioned above, there is now evidence that the VATS approach allows performance of a systematic lymphadenectomy equivalent to that achievable by thoracotomy [17], and allows at the same time reduced morbidity and faster post-operative recovery [3–8]. Therefore, in the near future, it is expected that, with the growing confidence and the expanding indications of VATS worldwide, a higher

proportion of patients will be able to undergo an adjuvant treatment for their N2 disease than the percentage reported by the literature so far.

In conclusion, in cases of intraoperative finding of mediastinal lymph node involvement, based on the results reported for the different therapeutic options, we believe it is appropriate to proceed with surgical resection at that time, provided that is possible to perform a complete resection and a systematic lymphadenectomy. This resection can be safely performed with a VATS approach since this technique is not inferior to the open procedure in guaranteeing the two fundamental assumptions previously discussed. The advantage of an earlier functional recovery of patients that is offered by thoracoscopy will translate into a greater ability of patients to undergo postoperative adjuvant therapy. The results of this therapeutic combination are comparable with those reported for patients treated by induction therapy and surgical resection, and, importantly, the morbidity and mortality associated with an exploratory surgical procedure are avoided.

Recommendation

- In case of unexpected N2 involvement identified during a thoracoscopic procedure the surgeon should proceed with a complete resection and systematic mediastinal lymphadenectomy with the same VATS approach (evidence quality moderate, strong recommendation).

A Personal View of the Data

The correct evaluation of mediastinal lymph node involvement is a very common issue in thoracic surgery. A thorough preoperative lymph node staging is mandatory to determine the clinical N2 cases that should be referred for pre-operative neoadjuvant treatment. For patients with negative mediastinal staging (cN0-N1), thoracoscopic surgical resection (VATS) has now become the standard approach. In our opinion, if N2 nodal involvement is found at the time of surgical resection and all the involved lymph nodes and the primary tumor are technically resectable, then the surgeon should proceed with the planned thoracoscopic lung resection along with a mediastinal lymphadenectomy. Post-operative adjuvant treatments should be added to the therapeutic management of these patients to improve long-term survival.

References

1. Berry MF, D'Amico TA, Onaitis MW, Kelsey CR. Thoracoscopic approach to lobectomy for lung cancer does not compromise oncologic efficacy. Ann Thorac Surg. 2014;98:197–202.
2. Hanna WC, de Valence M, Atenafu EG, Cypel M, Waddell TK, Yasufuku K, et al. Is video-assisted lobectomy for non-small-cell lung cancer oncologically equivalent to open lobectomy? Eur J Cardiothorac Surg. 2013;43:1121–5.

3. Oparka J, Yan TD, Ryan E, Dunning J. Does video-assisted thoracic surgery provide a safe alternative to conventional techniques in patients with limited pulmonary function who are otherwise suitable for lung resection? Interact Cardiovasc Thorac Surg. 2013;17:159–62.
4. Zhang R, Ferguson MK. Video-assisted versus open lobectomy in patients with compromised lung function: a literature review and meta-analysis. PLoS One. 2015;10:1–12.
5. Nwogu CE, D'Cunha J, Pang H, Gu L, Wang X, Richards WG, et al. VATS lobectomy has better perioperative outcomes than open lobectomy: CALGB 31001, an ancillary analysis of CALGB 140202 (Alliance). Ann Thorac Surg. 2015;99:399–405.
6. Paul S, Altorki NK, Sheng S, Lee PC, Harpole DH, Onaitis MW, et al. Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: a propensity-matched analysis from the STS database. J Thorac Cardiovasc Surg. 2010;139:366–78.
7. Swanson SJ, Meyers BF, Gunnarsson CL, Moore M, Howington JA, Maddaus MA, et al. Video-assisted thoracoscopic lobectomy is less costly and morbid than open lobectomy: a retrospective multiinstitutional database analysis. Ann Thorac Surg. 2012;93:1027–32.
8. Bendixen M, Jørgensen OD, Kronborg C, Andersen C, Licht PB. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomized controlled trial. Lancet Oncol. 2016;17:836–44.
9. Ramnath N, Dilling TJ, Harris LJ, Kim AW, Michaud GC, Balekian AA, Diekemper R, Detterbeck FC, Arenberg DA. Treatment of stage III non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e314S–40S.
10. Cerfolio RJ, Bryant AS. Survival of patients with unsuspected N2 (Stage IIIA) nonsmall-cell lung cancer. Ann Thorac Surg. 2008;86:362–7.
11. Watanabe A, Mishina T, Ohori S, et al. Is video-assisted thoracoscopic surgery a feasible approach for clinical N0 and postoperatively pathological N2 non-small cell lung cancer? Eur J Cardiothorac Surg. 2008;33:812–8.
12. Kim HK, Choi YS, Kim J, et al. Outcomes of unexpected pathologic N1 and N2 disease after video-assisted thoracic surgery lobectomy for clinical stage I non-small cell lung cancer. J Thorac Cardiovasc Surg. 2010;140:1288–93.
13. Lee DH, Kim JB, Keum DY, et al. Long term survival of patients with unsuspected N2 disease in non-small cell lung cancer. Korean J Thorac Cardiovasc Surg. 2013;46:49–55.
14. Bille A, Woo KM, Ahmad U, et al. Incidence of occult pN2 disease following resection and mediastinal lymph node dissection in clinical stage I lung resection. Eur J Cardiothorac Surg. 2017;51:674–9.
15. Berghmans T, Paesmans M, Meert AP, et al. Survival improvement in resectable non-small cell lung cancer with (neo) adjuvant chemotherapy: results of a meta-analysis of the literature. Lung Cancer. 2005;49:13–23.
16. Douillart JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006;7:719–27.
17. Zhang W, Wei Y, Jiang H, et al. Thoracotomy is better than thoracoscopic lobectomy in the lymph node dissection of lung cancer: a systematic review and meta-analysis. World J Surg Oncol. 2016;17:14–290.
18. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumors. J Thorac Oncol. 2017;12:1434–41.
19. Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomized trial in stage III non-small-cell lung cancer. Lancet Oncol. 2008;9:636–48.
20. Girard N, Mornex F, Douillard J, et al. Is neoadjuvant chemoradiotherapy a feasible strategy for stage IIIA-N2 non-small cell lung cancer? Mature results of the randomized IFCT-0101 phase II trial. Lung Cancer. 2010;69:86–93.

21. Katakami N, Tada H, Mitsudomi T, et al. A Phase 3 study of induction treatment with concurrent chemoradiotherapy versus chemotherapy before surgery in patients with pathologically confirmed N2 stage IIIA nonsmall cell lung cancer (WJTOG9903). Cancer. 2012;118:6126–35.
22. Pless M, Stupp R, Ris H, et al. Induction chemoradiation in stage IIIA/N2 non-small cell lung cancer: a phase 2 randomized trial. Lancet. 2015;386:1049–56.
23. Yang CJ, Gulack BC, Gu L, et al. Adding radiation to induction chemotherapy does not improved survival of patients with operable clinical N2 non-small cell lung cancer. J Thorac Cardiovasc Surg. 2015;150:1484–93.
24. Chen Y, Peng X, Zhou Y, et al. Comparing the benefits of chemoradiotherapy for resectable stage III A/N2 non-small cell lung cancer: a meta-analysis. World J Surg Oncol. 2018;16:8.
25. Albain KS, Swann RS, Rusch VR, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small cell lung cancer. Lancet. 2009;374(9687):379–86.
26. Ferguson MK. Optimal management when unsuspected N2 nodal disease is identified during thoracotomy for lung cancer: cost-effectiveness analysis. J Thorac Cardiovasc Surg. 2003;126:1935–42.
27. Detterbeck F. What to do with "surprise" N2? Intraoperative management of patients with non-small cell lung cancer. J Thorac Oncol. 2008;3:289–302.

Does Induction Immunotherapy Confer Increased Operative Risk for Lung Resection?

17

James G. Connolly, Matthew J. Bott, and David R. Jones

Introduction

Complete surgical resection is the primary treatment for patients with stage I and II non-small cell lung cancer (NSCLC) as well as for selected patients with stage III disease. Patients with larger tumors and locoregional node-positive disease are more likely to develop distant metastatic disease, even when an R0 resection is achieved. We recently showed that, even in patients with an R0 resection and pN0 disease, the likelihood of developing metastases increased significantly based on tumor size [1]. Multiple international randomized phase III trials, initiated in the 1990s and reported in the early 2000s, confirmed that platinum-based adjuvant chemotherapy following surgery confers an absolute overall survival benefit of 5% at 5 years [2–4]. Interestingly, in several phase II and phase III trials, outcomes were similar between neoadjuvant chemotherapy and chemoradiotherapy [5–7]. To improve long-term survival for patients with early-stage lung cancer beyond the marginal increases noted above, further investigations into potential therapeutic alternatives are required.

Immune checkpoints constitute a distinct pathway that is endogenous to a healthy immune system and serves to maintain self-tolerance. Although an endogenous immune response to cancer has been observed in some preclinical and clinical models, the response is often ineffective because neoplastic cells develop multiple escape mechanisms to avoid immune recognition, including immune suppression, induction of tolerance, and T-cell signal dysfunction [8]. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that were developed to enhance antitumor immunity. ICIs target negative regulators of T-cell function on the cancer cell

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surface and facilitate tumor antigen recognition and subsequent immune-mediated cytotoxicity [9]. Although there are potentially many receptor targets, ICIs have been developed to bind two main costimulatory T-cell surface receptors: programmed cell death protein 1 (PD-1) or its ligand (PD-L1) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4).

Results of several randomized phase III trials show a significant overall and disease-free survival advantage for single-agent ICIs compared with standard cisplatin-based doublet chemotherapy in certain subsets of patients with metastatic NSCLC [10–13]. More recently, results from the PACIFIC trial demonstrated progression-free survival of 16.8 months for sequential chemoradiotherapy and durvalumab, compared with 5.6 months for chemoradiotherapy and matching placebo, among patients with unresectable stage IIIA/B NSCLC [10]. Importantly, in these large randomized clinical trials, a durable response has been seen in approximately 20% of patients treated with ICIs either in combination with chemotherapy or as monotherapy [12, 14–17].

Following the promising results for ICI therapy in the metastatic and locoregionally advanced settings, it was logical to investigate the potential efficacy of ICIs in the neoadjuvant setting for resectable earlier stage NSCLC. Advantages of the neoadjuvant approach include patient tolerability, significant antigen load with the tumor *in situ*, and pathologic assessment of tumor response, most frequently measured as major pathologic response [18]. However, the safety of induction immunotherapy before pulmonary resection is not well-known, and concerns about an intense posttreatment desmoplastic response, resulting in technical challenges and patient safety issues, exist. Therefore, an assessment of perioperative risk in patients receiving induction immunotherapy followed by pulmonary resection for lung cancer is needed.

Search Strategy

A literature search of all English language publications from 2012 to 2019 was performed to identify published data on operative risk after induction immunotherapy (Table 17.1). The PubMed and Google Scholar databases were queried. Search terms included “induction immunotherapy,” “immune checkpoint inhibitors,” and “neoadjuvant immunotherapy” each combined with each of “thoracic surgery/perioperative risk,” “lung cancer resection/complications,” and “pulmonary resection/safety.” Owing to the low volume of published manuscripts on the subject, abstracts from ongoing prospective trials were included for our reference material.

Table 17.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with regionally advanced resectable non-small cell lung cancer	Standard induction therapy followed by pulmonary resection	Induction therapy including immunotherapy followed by pulmonary resection	Surgical feasibility Complications Mortality

Results

Published clinical trial data on operative risk after ICI therapy are limited to two prospective trials (NCT02259621 and TOP1201 [NCT01820754]). Results from the NCT02259621 trial on induction immunotherapy in patients with resectable lung cancer (n = 21) were published in 2018. Researchers from Memorial Sloan Kettering Cancer Center and Johns Hopkins University administered two doses of neoadjuvant nivolumab, a PD-1 inhibitor, before surgical resection for clinical stage IB-IIIA NSCLC, to assess safety and feasibility [19, 20]. The second study, by Yang et al., reported preliminary data from the TOP1201 (NCT01820754) study, an open-label phase II trial in patients with clinical stage II-IIIA NSCLC (n = 13) treated with neoadjuvant ipilimumab (a CTLA-4 inhibitor) and paclitaxel plus either cisplatin or carboplatin, compared with standard chemotherapy [21].

Bott et al. published a single-institution retrospective study of 19 patients who underwent 21 pulmonary resections between 2012 and 2016 for advanced NSCLC, previously unresectable NSCLC, and other tumor types with metastases to the lung [22]. The research team evaluated all patients treated with immunotherapy, including nivolumab, pembrolizumab, and ipilimumab as well as combination nivolumab/ipilimumab, who subsequently underwent definitive surgical resection. Fifty percent of resections were lobectomies or greater, and the average frequency of immunotherapy was 21 doses (range, 1–70 doses).

Hilar and Mediastinal Inflammatory/Fibrotic Disease

One of the putative side effects of immunotherapy is an enhanced desmoplastic and inflammatory response that is most notable around hilar structures, including lymph nodes, bronchi, and segmental pulmonary arteries. Thoracic surgeons are already aware of similar tissue responses when operating on patients who received induction chemotherapy, and perhaps even more so with patients who received chemoradiotherapy. The above-mentioned clinical trials and retrospective study included cases with dense, sometimes vascularized adhesions between the chest wall and the primary tumor, the lung hilum and the mediastinum [22, 23]. It could be hypothesized that this inflammatory process portends an improved pathologic response to immunotherapy, but there are no clear data to support this assertion. Increased inflammation, fibrosis, and loss of tissue planes can certainly make mediastinal and hilar dissections technically challenging. Unfortunately, preoperative imaging poorly predicts the extent or lack of extent of inflammation or fibrosis after immunotherapy. In fact, several studies, including the NCT02259621 trial, have suggested that posttreatment radiographic response significantly underestimates major pathologic response [19].

Operative duration, blood loss, and transfusion requirements in the described studies were not significantly different from values for historical cohorts of patients treated with neoadjuvant chemotherapy. Importantly, in the NCT02259621 (induction nivolumab) and TOP1201 (induction ipilimumab) trials, the complete resection

(R0) rates were 95% and 100%, respectively. There was, however, an increased need to convert from a minimally invasive to an open thoracotomy approach [20–22]. Although this is likely related to the higher T stage of the tumors and the greater prevalence of node-positive disease, it is also possible that some of the conversions were secondary to previously described postimmunotherapy inflammatory changes. However, neither study has strong data to support this assertion. Importantly, there was no operative mortality in any of the studies (Table 17.2).

It is worth noting that the nomenclature and classification describing the treatment response after immunotherapy are not well-defined. Although previous authors have used terms such as "fibrosis," it is unclear whether this process would take place over the several week duration from therapy to surgery [20]. Collectively, among thoracic surgeons, there is a need for better terminology to intraoperatively quantify induction immunotherapy tissue responses so that appropriate correlations can be made with pathologic response, need for conversions, and patient outcomes.

Complications

Most of the data regarding immunotherapy-related toxicities are derived from the literature on advanced and metastatic NSCLC [24, 25]. A wide range of systems can be affected—most commonly, the gastrointestinal tract, endocrine glands, and skin—however, no prospective trials have characterized treatment strategies for this diverse array of side effects. Immunotherapy-related adverse events (irAEs) range from rash and pruritus to life-threatening pneumonitis. The most common irAE is cutaneous rash: approximately 40–60% of patients treated across all ICIs report symptoms of rash [26]. In the two prospective trials mentioned above, most complications were minor, either grade 1 or grade 2. The TOP1201 trial used a single-center surgery database comprising 42 patients who received preoperative platinum doublet chemotherapy to informally compare side-effect profiles. The authors observed no detrimental effects with the addition of ipilimumab compared with standard-of-care neoadjuvant chemotherapy [21]. Nevertheless, there is ample evidence in the literature that significant adverse events occur after the use of ICIs.

Diarrhea-related colitis is commonly seen in patients treated with ICIs [25]. In the TOP1201 trial, two patients experienced a delay in surgery of up to 4 weeks and 5 weeks, respectively, due to ipilimumab-induced diarrhea [21]. Case reports have demonstrated the efficacy of steroid therapy or immunosuppressive medications, such as infliximab, for the treatment of immune-related colitis [27]. The reporting on the TOP1201 trial does not characterize the severity of colitis, nor does it report the choice of treatment regimen. Bott et al. and Ford et al. did not report diarrhea-related irAEs, and no delays in time to surgery were observed with neoadjuvant nivolumab in these studies [19, 22].

Pneumonitis is a rare but potentially life-threatening complication of ICI use, particularly in patients who receive combination immunotherapy. A large multicenter retrospective review identified a wide variation in the onset of symptoms (9 days to 19.2 months), with varying disease severity (grade 1–5) [28]. Ten percent

Table 17.2 Published data on operative safety and feasibility for patients undergoing lung resection following induction immunotherapy

Trial name	N	Patient stage	Neoadjuvant intervention	Delay in surgery (%)	Conversion rate (%)	R0 (%)	CPR/ MPR (%)	LOS (range), days	Morbidity (%)	Mortality (%)	2-year OS (%)	2-year PFS/DFS (%)	Study type (quality of evidence)
Forde et al. (2018) [19]	21	IB-IIIA	Nivolumab	0	54	95	45	4 (2–17)	50	0	NR	NR	Phase I clinical trial (low)
Yang et al. (2018) [21]	13	II-IIIA	Ipilimumab	15	23	100	15	5 (4–6)	69	0	73	NR	Phase II clinical trial (moderate)
Bott et al. (2018) [22]	19	IV, metastatic disease	Nivolumab, pembroli-zumab, ipilimumab	N/A[a]	20	95	NR	NR	32	0	77	42	Retrospec-tive cohort (low)
Chaft et al. (2017) [23]	5	IIIA-IV	Anti-PD1, anti-PD-L1, anti-PD1 + anti-CTLA-4	20	50	100	NR	NR	20	0	Not enough time to follow-up	Not enough time to follow-up	Case series (low)

R0, complete resection

CPR complete pathologic response, *MPR* major pathologic response, *LOS* length of stay, *OS* overall survival, *PFS* progression-free survival, *DFS* disease-free survival, *NR* not reported

[a]Patients were not surgical candidates prior to neoadjuvant therapy

of patients in the CheckMate 012 trial treated with combination ipilimumab and nivolumab and 4% of patients in the KEYNOTE-001 trial treated with pembrolizumab developed pneumonitis [13, 29]. This side effect is particularly concerning in patients with lung cancer who potentially require curative resection [30]. In the study from Bott et al., there was one case of postoperative pneumonitis in the contralateral lung, which required postoperative reintubation. The same patient was eventually extubated and made a full recovery, undergoing a subsequent completion lobectomy 3 months after the initial procedure [22]. One patient in the TOP1201 trial developed ipilimumab-induced pneumonitis [21].

ICI-induced endocrinopathies represent a wide range of irAEs that are inherently challenging to diagnose due to their nonspecific presenting symptoms, including fatigue, nausea, and headache. Hypothyroidism and hyperthyroidism are the most common endocrinopathies, with incidences reported as high as 10% [15]. Symptoms are often transient but can pose additional risks in the perioperative period. For this reason, thyroid function tests are monitored throughout treatment to ensure diagnosis before symptom presentation [31]. Adrenal insufficiency is also clinically relevant for this patient population because of the potential hazards associated with surgical intervention [32]. Of note, three patients from the TOP1201 trial who received ipilimumab went on to develop adrenal insufficiency [21].

There were no operative-related deaths at 30 and 90 days postoperatively in either prospective trial or the retrospective study. In fact, in TOP1201, there were no reported deaths at 2 years for patients treated with immunotherapy and surgical resection [21] (Table 17.2). Of note, one patient in the Bott et al. study died from an unrelated traumatic injury at 61 days [22].

Future Studies

There are currently three phase I trials, 26 phase II trials, and five phase III trials investigating induction immunotherapy regimens in patients with operable NSCLC. All trials are investigating locally advanced or early stage lung cancer, with the exclusion of stage IA disease. Some studies are evaluating ICI monotherapy (LCMC3, SAKK 16/14, NEOMUN, MK3475-223), whereas others are looking at dual-ICI therapy (J1414, NEOSTAR), based on findings reported for advanced NSCLC [33–38].

Although conclusive evidence is not yet available, some studies have released preliminary safety data, including two studies presented at the 2019 American Society of Clinical Oncology annual meeting [33, 35]. The interim analysis from the Lung Cancer Mutation Consortium (NCT02927301) study on 101 out of a planned 180 patients with stage IB-IIIB NSCLC receiving two cycles of induction atezolizumab monotherapy was presented. Immunotherapy was well-tolerated, with only two non-ICI–related deaths reported [35]. Similarly, early results from the NEOSTAR (NCT03158129) trial—a multiarm phase II study of 44 patients with stage I-IIIA (N2) NSCLC treated with induction nivolumab or combination

nivolumab and ipilimumab—were presented. Surgical complications included two postoperative bronchopleural fistulas (4.5%) and eight cases of prolonged air leak (18.2%). Importantly, eight patients (22%) had an unspecified delay to surgery beyond 42 days (three in the nivolumab arm and five in the nivolumab and ipilimumab arm). The authors categorized 40% of resections in the NEOSTAR trial as "more complex than usual," and this difficulty was not associated with increased pathologic response (i.e., better pathologic response to therapy) [33]. The Spanish NADIM trial (NCT03081689) reported no adverse events following carboplatin and paclitaxel chemotherapy and nivolumab prior to resection and had no delays in surgery in their preliminary report of 30 patients [34].

Conclusions and Recommendations

While the early results for ICI monotherapy are promising, there is inadequate evidence to determine whether ICIs confer increased operative risk compared with traditional chemotherapy or chemoradiotherapy induction regimens. With few published studies, ICIs before surgical resection remain a potentially feasible alternative or supplement to standard cytotoxic chemotherapy. These early findings, almost exclusively with ICI monotherapy, reveal a good pathologic response rate, with high rates of R0 resection [20, 21]. Within these selected studies, surgical resections may be more technically challenging because of increased inflammation, fibrosis, and loss of normal tissue planes, particularly in the hilum and perivascular regions. However, these early reports include few patients and are largely anecdotal. Moreover, no formal grading system for assessment or characterization of these changes after immunotherapy exists, which makes the problem even more challenging. Compared with current chemotherapy/radiotherapy induction therapies, immunotherapy regimens were not associated with an apparent increase in observed adverse surgical outcomes. Although the initial oncologic and patient safety studies are encouraging, we await the results of the ongoing large randomized controlled trials to give a more rigorous assessment of operative risk and perioperative irAEs.

Recommendations

- Induction immune checkpoint inhibitors, when administered as monotherapy, can be used without concern for undue morbidity and mortality or disproportionate treatment-related toxicity (evidence quality low; weak recommendation).
- Use of induction immunotherapy regimens should be performed in a multidisciplinary manner, preferably as part of a clinical trial, until sufficient evidence on surgical and overall oncologic outcomes becomes available (evidence quality low, weak recommendation).

A Personal View of the Data

Induction and adjuvant ICIs, either alone or, more likely, in combination with chemotherapy, are almost certainly going to be used for operable NSCLC in the future. Although the published data currently do not offer a definitive assessment of operative risk, multiple ongoing phase III trials of induction chemotherapy and immunotherapy will address this question. Operative risk assessments from these studies should be published by the mid-2020s, while efficacy and comparison studies versus standard regimens will take longer. Personally, I do not believe operative risk is increased with monotherapy immunotherapy. I have seen denser, fibrotic adhesions intraoperatively following combined CTLA-4 and PD-1/-L1 inhibitor therapy, but that is clearly anecdotal. Perioperative irAEs are highly relevant for thoracic surgeons, and ongoing education is critical to minimize perioperative toxicities.

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References

1. Brandt WS, Bouabdallah I, Tan KS, Park BJ, Adusumilli PS, Molena D, et al. Factors associated with distant recurrence following R0 lobectomy for pN0 lung adenocarcinoma. J Thorac Cardiovasc Surg. 2018;155(3):1212–24.
2. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26(21):3552–9.
3. International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non–small-cell lung cancer. New Engl J Med. 2004;350(4):351–60.
4. Waller D, Peake MD, Stephens RJ, Gower NH, Milroy R, Parmar MK, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. Eur J Cardio-Thorac. 2004;26(1):173–82.
5. Girard N, Mornex F, Douillard JY, Bossard N, Quoix E, Beckendorf V, et al. Is neoadjuvant chemoradiotherapy a feasible strategy for stage IIIA-N2 non-small cell lung cancer? Mature results of the randomized IFCT-0101 phase II trial. Lung Cancer. 2010;69(1):86–93.
6. Katakami N, Tada H, Mitsudomi T, Kudoh S, Senba H, Matsui K, et al. A phase 3 study of induction treatment with concurrent chemoradiotherapy versus chemotherapy before surgery in patients with pathologically confirmed N2 stage IIIA nonsmall cell lung cancer (WJTOG9903). Cancer. 2012;118(24):6126–35.
7. Pless M, Stupp R, Ris HB, Stahel RA, Weder W, Thierstein S, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. Lancet. 2015;386(9998):1049–56.
8. Bakos O, Lawson C, Rouleau S, Tai LH. Combining surgery and immunotherapy: turning an immunosuppressive effect into a therapeutic opportunity. J Immunother Cancer. 2018;6(1):1–1.
9. Drake CG, Jaffee E, Pardoll DM. Mechanisms of immune evasion by tumors. Adv Immunol. 2006;90:51–81.
10. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med. 2018;379(24):2342–50.

11. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med. 2015;373(17):1627–39.
12. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med. 2018;378(22):2078–92.
13. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540–50.
14. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443–54.
15. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non–small-cell lung cancer. N Engl J Med. 2015;372(21):2018–28.
16. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. N Engl J Med. 2015;373(2):123–35.
17. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med. 2016;375(19):1823–33.
18. Hellmann MD, Chaft JE, William WN Jr, Rusch V, Pisters KM, Kalhor N, et al. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. Lancet Oncol. 2014;15(1):e42–50.
19. Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med. 2018;378(21):1976–86.
20. Bott MJ, Yang SC, Park BJ, Adusumilli PS, Rusch VW, Isbell JM, et al. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non–small cell lung cancer. J Thorac Cardiovasc Surg. 2019;158(1):269–76.
21. Yang CF, McSherry F, Mayne NR, Wang X, Berry MF, Tong B, et al. Surgical outcomes after neoadjuvant chemotherapy and ipilimumab for non-small cell lung cancer. Ann Thorac Surg. 2018;105(3):924–9.
22. Bott MJ, Cools-Lartigue J, Tan KS, Dycoco J, Bains MS, Downey RJ, et al. Safety and feasibility of lung resection after immunotherapy for metastatic or unresectable tumors. Ann Thorac Surg. 2018;106(1):178–83.
23. Chaft JE, Hellmann MD, Velez MJ, Travis WD, Rusch VW. Initial experience with lung cancer resection after treatment with T-cell checkpoint inhibitors. Ann Thorac Surg. 2017;104(3):e217–8.
24. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378(2):158–68.
25. Arnaud-Coffin P, Maillet D, Gan HK, Stelmes JJ, You B, Dalle S, et al. A systematic review of adverse events in randomized trials assessing immune checkpoint inhibitors. Int J Cancer. 2019;145(3):639–48.
26. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. JAMA Oncol. 2016;2(10):1346–53.
27. Yanai S, Nakamura S, Matsumoto T. Nivolumab-induced colitis treated by infliximab. Clin Gastroenterol Hepatol. 2017;15(4):e80–1.
28. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. J Clin Oncol. 2017;35:709–17.
29. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017;18(1):31–41.

30. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of programmed cell death 1 inhibitor–related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. JAMA Oncol. 2016;2(12):1607–16.
31. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. Ann Oncol. 2017;28:583–9.
32. Abdel-Rahman O, El Halawani H, Fouad M. Risk of endocrine complications in cancer patients treated with immune check point inhibitors: a meta-analysis. Future Oncol. 2016;12:413–25.
33. Sepesi B, Cascone T, William W, Lin H, Leung C, Weissferdt A, et al. Surgical outcomes following neoadjuvant nivolumab or nivolumab plus ipilimumab in non-small cell lung cancer–NEOSTAR study. J Thorac Oncol. 2019;14(10):S241–2.
34. Provencio M, Nadal E, Insa A, Campelo RG, Casal J, Domine M, et al. NADIM study: updated clinical research and outcomes. J Thorac Oncol. 2019;14(10):S241.
35. Kwiatkowski DJ, Rusch VW, Chaft JE, Johnson BE, Nicholas A, Wistuba II, et al. Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): interim analysis and biomarker data from a multicenter study (LCMC3). J Thorac Oncol. 2019;37(15):S8503.
36. Eichhorn F, Klotz LV, Bischoff H, Thomas M, Lasitschka F, Winter H, et al. Neoadjuvant anti-programmed death-1 immunotherapy by pembrolizumab in resectable nodal positive stage II/IIIa non-small-cell lung cancer (NSCLC): the NEOMUN trial. BMC Cancer. 2019;19(1):413.
37. Shu CA, Grigg C, Chiuzan C, Garofano RF, Patel V, Hernandez S, et al. Neoadjuvant atezolizumab + chemotherapy in resectable non-small cell lung cancer (NSCLC). J Clin Oncol. 2018;36(Suppl 15):8532.
38. Bar J, Urban D, Ofek E, Ackerstein A, Redinsky I, Golan N, et al. Neoadjuvant pembrolizumab (pembro) for early stage non-small cell lung cancer (NSCLC): updated report of a phase I study, MK3475-223. J Clin Oncol. 2019;37(Suppl 15):8534.

Does an Enhanced Recovery Program for Lobectomy Improve Surgical Outcomes?

18

Linda W. Martin and Reza J. Mehran

Introduction

Pulmonary resection for bronchogenic carcinoma is a morbid procedure. Regardless of how the procedure is performed—via thoracotomy, muscle sparing thoracotomy, video assisted single port or multiple ports or robotic assisted—the risks of complications are high and potentially life threatening. The mission of the operation, which is complete resection of the tumor and all lymph node basins, carries risk regardless of the incision. Pain is a major contributor to post-operative complications. Traditional pain management strategies are based on the use of narcotics. The side effects of narcotics are a significant complicating factor in an uneventful postoperative recovery [1]. Any maneuvers that reduce the pain associated with pulmonary surgery will improve the postoperative outcome. Enhanced recovery after surgery is a set of modules designed for streamlining the perioperative course of the patient. It aims to reduce the psychological and physiological stress of surgery [2]. One aspect of enhanced recovery is intended to not only reduce pain but actually eliminate pain after surgery regardless of the size of the incision. The objective of this chapter is to review the practice of enhanced recovery pathways (ERP) after surgery, in particular the application of the pain module, and describe the effect of the latter on perioperative outcomes based on the latest evidence in the literature.

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Search Strategy

A literature search of English language publications was used to identity published data on enhanced recovery after lung resection from January 2016 to October 2019 (Table 18.1). The database searched was PubMed. Terms used in the search were "enhanced recovery"[Title/Abstract] OR "ERAS"[Title/Abstract] AND "thoracic" AND "english"[Language]. A total of 262 articles were identified. Articles were excluded if they specifically addressed cardiac surgery or esophageal surgery or did not involve lung resection (188 articles). Editorials and commentaries were also removed (20 articles), leaving 54 papers. Nine papers were excluded that did not specifically look at enhanced recovery programs as a whole. One paper was added that was in press (total of 46 articles). Abstracts of these 46 papers were reviewed; 28 papers were excluded due to (1) review or narrative descriptive article, (2) outcomes not pertinent to specified outcomes for this chapter, or (3) article quality not pertinent to North American standards. Two randomized controlled trials, nine before/after cohort studies, two prospective cohort studies, one retrospective cohort study, one guideline, one systematic review, and two review articles were included in our analysis. The data was classified using the GRADE system.

Results

Guidelines were recently published and delineate each component of ERP for thoracic surgery in detail, with levels of evidence and recommendations [3]. The results of the search described above are listed in Table 18.2.

Fast-track pathways have been in existence for 20–30 years. The goal of reducing variability in care delivery is intuitively useful. Enhanced recovery takes that concept a step further, with the overarching goal of reducing the psychological and

Table 18.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with cancer undergoing lung resection	Enhanced recovery pathway	Standard recovery pathway[a]	Mortality Morbidity readmission rate Patient reported outcomes Pain scores Opioid use Return to intended oncologic therapy Length of hospital stay Cost

LOS length of stay

[a]In some cases comparison was between interventions with both groups on an Enhanced Recovery Pathway

Table 18.2 Studies reviewed and graded on enhanced recovery in lung resection

Study	Design	Patients	Outcome classification	Typical risk for non-ERP or other factor	Relative risk for ERP or other factor	Quality of evidence
Ansari (2016) [19]	RCT, blinded	Elective lung resection all on ERP	Comparison of 6 min walk test with or without high flow oxygen	With standard oxygen: Hospital stay median 4 days	With high flow oxygen: shorter hospital stay (2.5 days median, p = 0.03); higher satisfaction reported	Low (does not look at an ERP component/ intervention)
Scarci (2016) [8]	Before/after comparison	ERP for elective lung resection	LOS, patient satisfaction	LOS 11.7 days ICU admission 12.9%	LOS 5.2 days ICU admission 5.8%	Low
Brunelli (2017) [12]	Before/after comparison	VATS segmentectomy or lobectomy before and after ERP	Postoperative outcomes	30 day mortality 90 day mortality LOS Readmission rates	Same	Low to (Note ERP intervention was minimal)
Paci (2017) [4]	Before/after comparison	Elective lung cancer resection with and without ERP	Complications and costs	52% overall complication 34% pulmonary complication	32% overall complication 16% pulmonary complication Societal costs $4396 less (Canadian)	Moderate
Gonzalez (2018) [6]	Before/after comparison	ERP for VATS segment or lobectomy for malignancy	LOS, readmissions, complications, total costs	7 day median LOS 38% pulmonary complication 48% Overall complication	4 day median LOS 16% pulmonary complication 24% Overall complication Mean saving of $3686 Swiss dollars	Moderate
Huang (2018) [10]	Before/after comparison	Before and after ERP for uniportal VATS lung resection	LOS, complications	LOS 8.7 days before ERP	LOS 6.6 days	Moderate

(continued)

Table 18.2 (continued)

Study	Design	Patients	Outcome classification	Typical risk for non-ERP or other factor	Relative risk for ERP or other factor	Quality of evidence
Khandhar (2018) [11]	Before/after comparison	VATS lobectomy on ERP	Compliance with postoperative ambulation; complication rate	Median LOS 2 days	Median LOS 1 day 61.5% achieved target early ambulation goal	Low
Kim (2018) [13]	Retrospective cohort	ERP VATS lung resection	Discharge with opioids	No comparator group	All went home on narcotics, but only 10% with schedule 2	Low
Martin (2018) [9]	Before/after comparison	pulmonary, mediastinal pleural surgery before and after ERP, VATS and Open	Surgical outcomes, costs, length of stay, opioid use	VATS MME 86 mg; Thoracotomy median 6 days; MME 130 mg	VATS MME 22 mg; LOS unchanged Thoracotomy median 4 days; MME 54 mg; fluid balance and total hospital cost improved for both VATS and open Complication rates unchanged for VATS and open; pain scores unchanged for both	Moderate
Rogers (2018) [7]	Prospective Cohort	ERP for lung cancer resection	Compliance with elements of ERP	50% morbidity with low compliance	20% morbidity with high compliance	Moderate
Van Haren (2018) [5]	Before/after comparison	Elective lung cancer resection before and after ERP	Outcomes, complications	28.7% pulmonary complications 18.1% cardiac complications LOS median (thoracotomy): 5	19.9% pulmonary complications 12.3% cardiac complications LOS median (thoracotomy): 4 No change in readmission rate	Moderate

Zejun (2018) [18]	RCT	Epidural compared to PCA on ERP for VATS lobectomy	Pain score, surgical outcomes, time to first flatus	PCA	Epidural Lower pain scores POD 0-2 Shorter time to flatus by 10 h No difference in LOS	Low
Krebs (2019) [20]	Prospective Cohort	ERP for lung cancer lobectomy comparing VATS and Open	LOS, opioids, pain scores, surgical outcomes	VATS: LOS 4 days MME 33.2 LN median: 9 0% had neoadjuvant therapy; Readmit 1.4% Transfusion 0%	Open: LOS 4 days MME 30.8 LN median: 13 22% had neoadjuvant therapy; higher stage cancers than VATS Readmit 17% Transfusion related to surgery 3.4%	Moderate
Nelson (2019) [21]	Before/after comparison	Stage I–II node positive or >5 cm NSCLC with upfront resection before and after ERP	Receipt of adjuvant chemotherapy on an ERP	40% received all prescribed adjuvant chemotherapy; average start time 60 days postop	62% received all prescribed adjuvant chemotherapy; average start time 40 days postop	Moderate

RCT randomized controlled trial, *VATS* video-assisted thoracoscopic surgery, *LOS* length of stay, *PCA* patient controlled analgesia, *NSCLC* nonsmall cell lung cancer, *ERP* enhanced recovery protocol, *ICU* intensive care unit, *MME* milligram morphine equivalents, *LN* lymph node, *POD* postoperative day

physiologic stress of surgery, achieving short-term homeostasis and mid-term return to normal functional status as soon as possible. It is more about the quality, rather than the speed, of recovery. More recent focus on use of opioid sparing regimens has galvanized interest in these pathways in light of the epidemic of opioid overdose. Secondary benefits of reducing length of stay (LOS), complication rates, cost, and readmission rates are further motivation to consider implementation of an ERP.

Complication Rates, LOS, Readmissions, Costs

Four papers have shown decreased complication rates, in the range of 30–50% reduction in overall and pulmonary and/or cardiac complications [4–7]. Six studies demonstrated a shortened LOS [5, 8, 9], including three looking only at VATS resections managed on an ERP [6, 10, 11]. One study showed no difference in LOS for VATS on or off ERP, however the ERP was minimally different than the comparator group [12]. There is more room for impact on LOS for thoracotomy patients, who have historically had longer stays than VATS patients; these data support that there is still benefit of an ERP in a VATS population to decrease duration of hospitalization. Three publications indicated no difference in readmission rates [5, 9, 12], which is important in ensuring that the enthusiasm for early discharge has not led to higher readmission rates. With continued refinement of these pathways, the hope is that readmission rates will actually decline even with shorter LOS.

Three studies showed reduced costs, either hospital related [6, 9] or societal costs [4]. Data for this is emerging and comes from three different countries. The main driver of cost reduction is likely shortened hospital stay. Initiating an ERP for the primary goal of cost reduction is uncertain at this time; tracking costs and comparing to historical numbers is advised within individual institutions.

Opioid Use Reduction

One study has shown substantial (60–75%) opioid use reduction with ERP while achieving similar pain scores compared to pre-ERP regimens that primarily used patient controlled analgesia and thoracic epidurals [9]; another paper without a comparator group showed a low rate of schedule II narcotic prescriptions (10%) in conjunction with an ERP [13]. Avoidance of opioids is beneficial for minimizing side effects such as somnolence, respiratory depression, nausea, and constipation—none of which is in line with principles of enhanced recovery. With the staggering death rates from drug overdose in the United States in recent years there is attention to how surgical pain is affecting patient addiction rates. As many as 14–24% of opioid naïve thoracic surgical patients are still filling narcotics prescriptions 90 days after surgery [14], compared to about 3% with most other types of elective surgery [15]. It is hoped that an opioid sparing ERP that successfully treats perioperative pain will lower the development of opioid dependent patients; so far there are no publications available to assess this. Finally, there is emerging data on adverse

effects of opioids on cancer outcomes [16], including the suggestion that opioids may have a mitogenic effect on cancer cells [17]. This is yet another reason to focus on opioid-sparing strategies for thoracic cancer surgery.

Other Outcomes

A few studies have looked at specific outcomes comparing subgroups of patients already on an ERP. One study [18] compared use of patient-controlled analgesia to epidural and found epidural to be better. However this was not an opioid sparing approach, and the other components of the ERP were not well described in this study. Another paper looked at use of high flow oxygen in the setting of an ERP [19] and noted a shorter length of stay but no change in 6 min walk test, which was the primary endpoint of the study. Two papers [5, 20] have addressed the question of how ERP may remove differences between VATS and open lobectomy based on the idea that pain is the source of outcome differences, and if pain is well managed with an ERP, perhaps the two approaches are more similar in this setting. Both showed LOS of 4 days regardless of incision type and similar outcomes, even with inherent selection bias of more complex case/advanced stage and higher receipt of neoadjuvant therapy in the thoracotomy group.

Other ways ERP may impact cancer outcomes includes the concept of RIOT—return to intended oncologic therapy. A patient who has quickly and fully recovered from cancer surgery is more likely to proceed with prescribed chemotherapy and/or radiation compared to a patient who struggles with their recovery and has a poor performance status after surgery. It is logical that a patient who receives the full treatment recommended (e.g. four cycles of chemotherapy within 4–12 weeks of resection) and in a timely fashion will have a better cancer outcome than one who gets only one or two doses of chemotherapy in a delayed fashion [21]. Nelson and colleagues [22] found a >50% increase in the rate of delivering all prescribed adjuvant chemotherapy in the setting of pulmonary resection on an ERP (62% received full dose compared to 40%), and it was given about 2 weeks earlier than before full implementation of ERP. In addition, the readiness for adjuvant therapy was equal between minimally invasive and open surgery.

Limitations

There are important limitations in evaluating the quality of evidence for ERP interventions. Enhanced recovery program implementation requires buy-in across the institution because it affects patients at all phases of the surgical journey. Because nearly every provider who interfaces with the patient is involved, it is nearly impossible to randomize the intervention. Due to the inherent challenges described, most comparative studies on ERP are a before/after implementation. While this influences the traditional strength of data assessment, it is the best we have and there is no good way to isolate the intervention.

There is also huge variability in the components of an ERP from one institution to the next. Several ERPs in this literature review don't focus at all on opioid reduction. Patient teaching is optional in some studies. Rogers and colleagues [7] suggest the number of elements that are included and complied with influences the impact of ERP on outcomes. Despite efforts, it has not been possible to single out which components of an ERP have the most impact or cost-effectiveness.

Finally, when patient outcomes are under a quality microscope with development of an ERP, there may be a Hawthorne effect in play. Any attention on quality and outcomes may improve those outcomes just by virtue of being the subject of study, rather than due to the ERP intervention itself. In our opinion, one should not argue with success if this occurs.

Conclusions and Recommendations

Implementation of a thoracic ERP is recommended. Comprehensive ERPs allow for opioid reduction, return to oncologic therapy, potentially shorter LOS, and lower costs. Several papers have shown lower complication rates. They facilitate minimizing variability in patient care. Risks to patients of employing an ERP are low and chances of improving outcomes, costs, and opioid use are moderate to high. A thorough review of existing guidelines and established programs should be used to tailor an ERP to an individual institution; multidisciplinary teams are needed to successfully establish an ERP. The presence or absence of ERP should be incorporated into outcomes databases such as STS and NSQIP as this is a currently unmeasured factor that can affect outcomes.

Recommendation

- Implementation of a thoracic ERP is recommended (evidence quality moderate, strong recommendation).

A Personal View of the Data

ERP is the most important development in recent years in how we practice thoracic surgery. ERPs improve short term outcomes after major pulmonary surgery and decrease costs. They may also influence cancer outcomes by improving RIOT and by diminishing opioid exposure.

To start an ERP takes concerted effort and cannot be done solely by surgeons. It is strongly suggested to incorporate data collection and automatically flag charts (which is possible with many electronic medical records) to allow for tracking of standard outcomes, pain scores, fluid balance, opioid use, and costs. ERP is an iterative process and should be reviewed every 3–6 months; the need for changes in protocol and re-education of providers should be expected. It is very challenging to adjust the protocol if outcomes are not tracked. It is financially beneficial to invest

in the personnel and materials needed to develop an ERP, given the extensive cost savings to the institution. At University of Virginia, enrolling just over 5600 patients on nine specialty-specific ERPs in a 5-year period generated $9.6 M in additional hospital revenue relative to a $1.53 M investment in personnel and resources.

A last word on methods of pain control—this is not the primary focus of this chapter but is a critical consideration in designing an ERP. Many publications suggest use of epidural catheters for pain management as part of an ERP. At our institutions, we agree that regional anesthesia is favored but have completely done away with epidural use and moved to long-acting posterior intercostal nerve blocks. We have experience now with thousands of patients with this approach between our two institutions. Avoidance of epidurals facilitates early removal of urinary catheters and arterial lines (if used at all), makes it easier to minimize intravenous fluids as the hypotension that occurs with epidural use is not an issue, and takes away yet another tube tethering the patient to their hospital bed. There is convincing data on the efficacy of nerve blocks with liposomal bupivacaine compared to epidural use [23, 24]. We feel strongly that the timing and method of nerve block is critical for efficacy [24] and the negative studies on liposomal bupivacaine rib blocks have not used a consistent or effective technique.

References

1. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. BMJ. 2014;348:g1251.
2. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. JAMA Surg. 2017;152(3):292–8.
3. Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS(R)) Society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg. 2019;55(1):91–115.
4. Paci P, Madani A, Lee L, et al. Economic impact of an enhanced recovery pathway for lung resection. Ann Thorac Surg. 2017;104(3):950–7.
5. Van Haren RM, Mehran RJ, Mena GE, et al. Enhanced recovery decreases pulmonary and cardiac complications after thoracotomy for lung cancer. Ann Thorac Surg. 2018;106(1):272–9.
6. Gonzalez M, Abdelnour-Berchtold E, Perentes JY, et al. An enhanced recovery after surgery program for video-assisted thoracoscopic surgery anatomical lung resections is cost-effective. J Thorac Dis. 2018;10(10):5879–88.
7. Rogers LJ, Bleetman D, Messenger DE, et al. The impact of enhanced recovery after surgery (ERAS) protocol compliance on morbidity from resection for primary lung cancer. J Thorac Cardiovasc Surg. 2018;155(4):1843–52.
8. Scarci M, Solli P, Bedetti B. Enhanced recovery pathway for thoracic surgery in the UK. J Thorac Dis. 2016;8(Suppl 1):S78–83.
9. Martin LW, Sarosiek BM, Harrison MA, et al. Implementing a thoracic enhanced recovery program: lessons learned in the first year. Ann Thorac Surg. 2018;105(6):1597–604.
10. Huang H, Ma H, Chen S. Enhanced recovery after surgery using uniportal video-assisted thoracic surgery for lung cancer: a preliminary study. Thorac Cancer. 2018;9(1):83–7.
11. Khandhar SJ, Schatz CL, Collins DT, et al. Thoracic enhanced recovery with ambulation after surgery: a 6-year experience. Eur J Cardiothorac Surg. 2018;53(6):1192–8.

12. Brunelli A, Thomas C, Dinesh P, Lumb A. Enhanced recovery pathway versus standard care in patients undergoing video-assisted thoracoscopic lobectomy. J Thorac Cardiovasc Surg. 2017;154(6):2084–90.
13. Kim MP, Chan EY, Meisenbach LM, Dumitru R, Brown JK, Masud FN. Enhanced recovery after thoracic surgery reduces discharge on highly dependent narcotics. J Thorac Dis. 2018;10(2):984–90.
14. Brescia AA, Harrington CA, Mazurek AA, et al. Factors associated with new persistent opioid usage after lung resection. Ann Thorac Surg. 2019;107(2):363–8.
15. Brummett CM, Waljee JF, Goesling J, et al. New persistent opioid use after minor and major surgical procedures in US adults. JAMA Surg. 2017;152(6):e170504.
16. Nelson DB, Cata JP, Niu J, et al. Persistent opioid use is associated with worse survival after lobectomy for stage I non-small cell lung cancer. Pain. 2019;160(10):2365–73.
17. Lennon FE, Mirzapoiazova T, Mambetsariev B, et al. The Mu opioid receptor promotes opioid and growth factor-induced proliferation, migration and Epithelial Mesenchymal Transition (EMT) in human lung cancer. PLoS One. 2014;9(3):e91577.
18. Zejun N, Wei F, Lin L, He D, Haichen C. Improvement of recovery parameters using patient-controlled epidural analgesia for video-assisted thoracoscopic surgery lobectomy in enhanced recovery after surgery: A prospective, randomized single center study. Thorac Cancer. 2018;9(9):1174–9.
19. Ansari BM, Hogan MP, Collier TJ, et al. A randomized controlled trial of high-flow nasal oxygen (Optiflow) as part of an enhanced recovery program after lung resection surgery. Ann Thorac Surg. 2016;101(2):459–64.
20. Krebs ED, Mehaffey JH, Sarosiek BM, Blank RS, Lau CL, Martin LW. Is less really more? Reexamining video-assisted thoracoscopic versus open lobectomy in the setting of an enhanced recovery protocol. J Thorac Cardiovasc Surg. 2019;
21. Nelson DB, Mehran RJ, Mitchell KG, et al. Enhanced recovery after thoracic surgery is associated with improved adjuvant chemotherapy completion for non-small cell lung cancer. J Thorac Cardiovasc Surg. 2019;158(1):279–286.e271.
22. Aloia TA, Zimmitti G, Conrad C, Gottumukalla V, Kopetz S, Vauthey JN. Return to intended oncologic treatment (RIOT): a novel metric for evaluating the quality of oncosurgical therapy for malignancy. J Surg Oncol. 2014;110(2):107–14.
23. Rice DC, Cata JP, Mena GE, Rodriguez-Restrepo A, Correa AM, Mehran RJ. Posterior intercostal nerve block with liposomal bupivacaine: an alternative to thoracic epidural analgesia. Ann Thorac Surg. 2015;99(6):1953–60.
24. Martin LW, Mehran RJ. Intercostal nerve blockade for thoracic surgery with liposomal bupivacaine: the devil is in the details. J Thorac Dis. 2019;11(Suppl 9):S1202–5.

Resection vs. SBRT for Stage I NSCLC in Patients with Good Pulmonary Function

19

Chase Corvin and Mark K. Ferguson

Introduction

Although lung cancer remains the leading cause of cancer death in the United States, the increase in low-dose CT screening after the publication of the National Lung Screening Trial has provided the opportunity to diagnose patients in earlier, more curable stages. Furthermore, an estimated 52% increase in lung cancer incidence in the aging US population is anticipated between 2010 and 2030. Providing effective and affordable care for early stage lung cancer is a paramount concern [1]. There is uncertainty over which treatments are best for these patients, who often have important medical and cardiopulmonary comorbidities. For surgical candidates, lobectomy is the gold standard for treatment of Stage I non-small cell lung cancer (NSCLC). Alternatively, in those who are not surgical candidates due to poor cardiopulmonary function or comorbidities, stereotactic body radiation therapy (SBRT) provides a useful alternative with adequate local control rates. In patients with adequate pulmonary function, however, the choice between resection and SBRT remains unclear. This chapter addresses the question of whether surgical resection or SBRT provides the best long term outcomes for operable patients with stage I NSCLC.

Search Strategy

A literature search was completed using OVID Medline. MESH keyword terms included carcinoma, non-small-cell lung AND thoracic surgery, video-assisted OR thoracotomy OR resection AND radiosurgery (Table 19.1). The search was limited

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Table 19.1 PICO formatted terms for literature search

P (Population)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with resectable stage I NSCLC	SBRT	Segmentectomy/ lobectomy	Overall survival Cancer specific survival

to the period between August 2009 and August 2019 and to publications in the English language. We identified 141 articles, which were then screened for studies comparing SBRT to surgical resection for stage I NSCLC, resulting in 27 appropriate articles for this review. These articles and their references were thoroughly reviewed and pertinent studies referenced were also extracted for inclusion in the assessment.

Results

Surgical Resection

Surgical resection is a standard of care for patients with early stage NSCLC; 5 year survival rates after lobectomy are greater than 80% with recurrence rates of 0.07 per patient year [2, 3]. Historically, oncologic and overall survival outcomes were felt to be better after lobectomy for patients with T1-2N0 NSCLC compared to limited resection based upon the Lung Cancer Study Group [4]. More recent studies, however, have questioned these results and attempted to determine in which patients segmental or lobar resection may be appropriate. In a multicenter nonrandomized study in Japan, Okada et al. demonstrated that for T1N0M0 NSCLC's less than 2 cm, sublobar resection demonstrated similar disease free and 5 year overall survival rates compared to lobectomy, although the study was not designed or powered to be a non-inferiority study. Sublobar resection was also associated with better post-operative pulmonary function [5]. Two more recent retrospective analyses by Nakamura and Zhao also suggested that VATS segmentectomy was not associated with worse overall survival or recurrence free survival compared with VATS lobectomy in stage I NSCLC [2, 6]. Currently, there are two randomized trials that have completed enrollment and are in the follow up phase of comparing lobar versus sub-lobar resection. CALGB 14053 is a multicenter randomized non-inferiority trial expected to be completed in March 2021 and compares segmentectomy and wedge resection to lobectomy for small (≤2 cm) peripheral NSCLC [7]. In an early analysis, this study found no difference in perioperative morbidity and mortality and is awaiting long term follow up [8]. JCOG0802/WJOG4607L is also an ongoing phase III randomized non-inferiority trial in Japan comparing lobectomy with segmentectomy for small (≤2 cm) peripheral NSCLC, and its last expected follow up is in August 2020 [9]. Finally, the STEPS trial began recruiting in January 2016 in China and is a phase III multicenter randomized trial comparing sublobar resection versus lobectomy in patients ≥70 years old with stage I peripheral NSCLC [10].

Although lobectomy remains the standard of care for operable patients with stage I NSCLC, these ongoing trials may find that segmentectomy provides a good alternative with similar outcomes, while sparing lung parenchyma and improving postoperative pulmonary function. Wedge resection, on the other hand, has been associated with worse oncologic and overall outcomes, but may be appropriate in certain populations such as those with increased frailty or multiple comorbidities (Table 19.2) [11].

Radiotherapy

Prior to stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiation therapy (SABR), patients who were not operative candidates due to poor cardiopulmonary function or comorbidities had few treatment options. They were typically offered conventional radiotherapy or observation, but each of these is associated with poor outcomes. In a retrospective analysis for non-surgical candidates with stage I NSCLC, McGarry et al. found no significant difference in median survival for those undergoing observation only vs. radiotherapy [12]. Three year overall and cancer specific survival after conventional radiotherapy are only 34% and 39%, respectively [12, 13]. SBRT provides a smaller irradiated volume using hypofractionated therapy, leading to a significantly higher localized daily dose over a shorter treatment course [14]. As a result, it has emerged as a viable alternative to surgery, with improved control and survival rates for these patients (Table 19.3).

Several trials have demonstrated the success of SBRT for inoperable stage I NSCLC patients. Concurrent prospective studies in the Netherlands and United States found that 3 year overall survival after SBRT for inoperable patients with stage I NSCLC was 43–60%. Rates of major toxicity after SBRT range from 10% to 30%, with the higher rates being for more central tumors [14–18]. The subsequent Radiation Therapy Oncology Group (RTOG) 0236 trial therefore included only patients with tumors more than 2 cm away from the proximal bronchial tree, and found that 3 year OS was 56%. Although local control in this study was acceptable, 22% of patients experienced disseminated failure [19]. This high rate of distant failure has also been demonstrated in other SBRT trials, suggesting the possible need for other adjuvant therapy in these inoperable stage I NSCLC patients [14].

More recent studies have evaluated SBRT in patients with stage I NSCLC who are potentially operative candidates. In the Japan Clinical Oncology Group study 0403, 3 year overall survival was 77% for operative candidates compared with 60% for inoperable patients [14]. The RTOG 0618 multicenter prospective trial looked at the use of SBRT only in candidates suited for at least sublobar resection for peripheral stage I NSCLC, and found that 4 year overall and disease free survival were 56% and 57%, respectively, with a disseminated failure rate of only 12% [18]. Based on these studies, SBRT clearly provides benefit for inoperable patients and those who refuse surgery, with much higher survival compared to observation or conventional radiotherapy.

Table 19.2 Studies of surgical resection

Author	Period	Study type	Treatment	N	Overall survival	Cancer specific survival	Disease free survival	30 Day mortality	Recurrence	Median follow up (years)	Quality of evidence
Ginsberg [4]	1982–1988	Prospective randomized trial	Lobectomy	125	70% 5 year	–	–	1.6%	18% 5 year	4.5	Moderate
			Sublobar	122	61% 5 year	–	–	0.8%	31% 5 year		
Okada [5]	1992–2001	Nonrandomized prospective	Sublobar	305	90% 5 year	–	86% 5 year	0.3%		6.0	Low
			Lobectomy	262	90% 5 year	–	83% 5 year	0%		5.9	
Smith [11]	1998–2006	Retrospective multicenter database	Segmental wedge	704 2821	HR 0.80[a]	HR 0.72[a]	–			–	Low
Nakamura [2]	2000–2010	Retrospective single center	Lobectomy	289	82% 5 year	–	–	–	18% 5 year	4.5	Low
			Segmental	38	87% 5 year	–	–	–	8% 5 year	2.4	
			Wedge	84	55% 5 year	–	–	–	16% 5 year	2.2	
Zhao [6]	2009–2012	Retrospective single center	Lobectomy	138	–	100% 1 year	–	0%	4% 1 year	0.9	Low
			Segmental	36	–	100% 1 year	–	2.8%	3% 1 year	0.9	

[a]Favors segmental resection

Table 19.3 Studies of radiotherapy treatments

Author	Period	Study type	Treatment	N	Median survival (months)	Overall survival	Cancer specific survival	Disease/ progression free survival	Local control rate	Recurrence/ progression	Toxicity (severe)	Mean follow up (years)	Quality of evidence
McGarry [12]	1994–1999	Retrospective single center	RT	36	20	–	43%	–	–	–	–	–	Low
			Observation	49	14	–	53%	–	–	–	–	–	
Baumann [15]	2003–2005	Prospective phase II	SBRT	57	40.6	60% 3 year	88% 3 year	52% 3 year	92% 3 year	24% 3 year	30%	2.9	Moderate
Timmerman RTOG 0236 [16]	2004–2006	Prospective phase II	SBRT	55	48.1	56% 3 year	–	48% 3 year	98% 3 year	26% 3 year	16%	2.9	Moderate
Nagata JCOG 0403 [14]	2004–2008	Prospective phase II	SBRT—operable	64	–	77% 3 year	–	55% 3 year	85% 3 year	38% 3 year	8%	5.6	Moderate
			SBRT—inoperable	100	–	60% 3 year	–	50% 3 year	87% 3 year	31% 3 year	12%	3.9	
Fakiris [17]	2008	Prospective phase II	SBRT	70	32.4	43% 3 year	82% 3 year	–	88% 3 year	21% 3 year	16%	4.2	Moderate
Timmerman RTOG 0618 [18]	2007–2010	Prospective phase II	SBRT	31	55.2	56% 4 year	–	57% 4 year	96% 4 year	27% 4 year	12%	4.0	Moderate

Surgical Resection vs. Radiotherapy

Although surgical resection and radiotherapy are both good options for patients with stage I NSCLC, their relative efficacy remains unclear. Arguments in favor of SBRT include lower treatment related mortality and complications, outpatient treatment, minimal reduction in pulmonary function after SBRT, and reduced costs compared with surgical resection [20–23]. Treatment related mortality for SBRT is less than 0.5% compared to 1–2% for surgical resection [4, 24]. The rate of major toxicity (grade 3 or higher) for SBRT in peripheral tumors is 12–16% and is comparable to the 16% complication rate for VATS resections; however, resections via thoracotomy are associated with a 31% complication rate [17–19, 25]. On the other hand, benefits to surgery include upstaging in 16–33% of patients, allowing for better decision making for adjuvant therapy [26–29]. Lobectomy and segmentectomy also resect draining lymph node basins in addition to the primary tumor, which may lead to better loco-regional control than SBRT.

To determine which therapy provides better overall survival, cancer specific survival, and lower morbidity, three randomized controlled trials, STARS, ROSEL, and ACOSOG Z4099 began enrollment [30–32]. Unfortunately, all three trials closed early due to poor accrual. Multiple groups have analyzed the data from these trials, including Chang et al., who found from a pooled data of STARS and ROSEL that 3 year overall survival was significantly better for SBRT than surgical resection, 95% vs. 79%, but there was no significant difference in recurrence free survival, 86% vs. 80%. When analyzed separately, however, the difference in overall survival was significant only for STARS and not for ROSEL patients [33]. This analysis has received much criticism for suggesting that SBRT was equally effective and potentially superior to surgical resection in terms of overall survival. Critics highlighted the fact that the analysis was based on two non-inferiority studies that accrued only 4% (22/960 and 36/1030) of the patients expected to be needed to prove non-inferiority. The sample was not large enough to adequately detect adverse events or compare underlying differences in the two treatment arms and cannot be generalizable to a larger population. The validity of this and similar analyses should therefore be questioned and should not be used to guide clinical practice [30, 31, 33–35].

In the absence of any completed randomized trials, many authors have attempted to answer whether SBRT is equivalent to surgical resection via retrospective analyses. Historically, however, most SBRT patients are not surgical candidates due to comorbidities or poor cardiopulmonary function, which also lead to worse outcomes. To account for these differences, many studies utilize propensity score matching to find comparable surgical and SBRT patients. For example, Crabtree et al. utilized a matched comparison and found significant advantages in 3 year overall and disease free survival after surgery, regardless of resection type [26]. When examining outcomes of these studies, however, one key consideration is whether segmental and wedge resections are grouped together in the analysis, as their outcomes may differ. Smith et al. found retrospectively that segmentectomy is associated with better overall survival and cancer-specific survival than wedge resection, although overall survival was not significantly different for patients older

than 70 [11]. This may be related to parenchymal margin status, nodal upstaging, and nodal stations sampled [36]. Therefore, the focus of the current analyses is on comparisons between SBRT and specific surgical resections, including lobectomy, segmentectomy, and wedge resection.

Lobectomy for early stage NSCLC has been retrospectively compared with SBRT by several authors. For the most part these studies, including those by Bryant et al. and Hamaji et al., have found that lobectomy is associated with higher overall (69% vs. 37%) and cancer specific survival (84% vs. 57%) with greater all cause and cancer specific mortality for SBRT (HR 1.38, 1.45) [24, 37]. Robinson et al. also found a similar increase in overall survival for lobar resection, but no significant difference in cancer specific survival [28]. Based on available evidence, lobectomy for patients with stage I NSCLC leads to higher overall survival and likely cancer specific survival than SBRT.

For sublobar resection, outcomes are less clear. Unfortunately, many retrospective comparisons between SBRT and sublobar resections group segmental and wedge resections together even though their outcomes may differ [2, 6, 11, 36]. These studies include those by Matsuo et al., Bryant et al., and Chen et al., the results of which are included in Table 19.4. When segmental and wedge resection are individually compared with SBRT, however, researchers do in fact find better overall and cancer specific survival with segmentectomy for patients with stage I NSCLC. Analysis of the Surveillance, Epidemiology, and End Results Medicare registry demonstrated worse overall and cancer specific survival for SBRT compared with segmentectomy (HR 1.55), but no difference between SBRT and wedge resection [38].

For wedge resection, on the other hand, it is less clear that there is a survival benefit compared to SBRT. A retrospective analysis comparing SBRT and wedge resection found that, while overall survival was significantly different (87% for wedge vs. 72% for SBRT), there was no significant difference in cancer specific survival (94% vs. 93%). These groups, however, differed significantly in their comorbidity scores and ages, which could have biased overall survival in favor of wedge resection [39]. Port et al. found no difference in 3 year overall survival, but did find a difference in 3 year recurrence free survival in favor of wedge resection [27]. Further studies are need to determine if there are patients that may benefit more from SBRT than wedge resection.

For operable patients with stage I NSCLC, lobectomy and segmentectomy appear to provide superior outcomes compared to SBRT, while wedge resection may be equivalent. The benefit patients receive from surgery compared with SBRT may vary from patient to patient depending on comorbidities and overall life expectancy. Several studies have looked at elderly patients, who tend to be frail with a lower overall life expectancy. These studies have found higher mortality at 30 days and 6 months after surgery, but better survival and locoregional control after 6 months for the patients receiving surgery [40, 41]. The decision of whether to pursue resection or SBRT in these patients may also depend on the size of the tumor. Even in older patients with more comorbidities, surgical resection provides better outcomes for tumors larger than 2 cm in diameter [42]. Therefore, in patients who

Table 19.4 Studies of surgical resection versus SBRT

Author	Period	Study type	Treatment	N	Overall survival	Cancer specific survival	Disease/ progression free survival	Mean follow up (years)	Quality of evidence
Bryant [24]	2006–2015	Retrospective population study	Lobectomy Sublobar SBRT	2986 634 449	70% 5 year 56% 5 year 44% 5 year			2.9 2.6 1.5	Low
Chang [33]	2008–2013	Pooled analysis	Lobectomy SBRT	27 31	79% 3 year 95% 3 year		80% 3 year 86% 3 year	2.9 3.3	Low
Crabtree [26]	2004–2010	Retrospective single center	Surgery SBRT	458 151	68% 3 year 52% 3 year		65% 3 year 47% 3 year	2.8 2.0	Low
Grills [39]	2003–2008	Retrospective single center	Wedge SBRT	69 58	87% 2.5 year 72% 2.5 year	94% 2.5 year 93% 2.5 year		2.5 2.5	Low
Hamaji [37]	2003–2009	Retrospective single center	Lobectomy SBRT	413 104	69% 5 year 37% 5 year	84% 5 year 57% 5 year		4.8 3.6	Low
Matsuo [43]	2003–2009	Retrospective single center	Sublobar SBRT	65 115	56% 5 year 40% 5 year			5.3 6.7	Low
Nakagawa [42]	2001–2011	Retrospective multicenter database	Surgery SBRT	183 35	68% 5 year 44% 5 year			3.4 3.8	Low
Palma [40]	2005–2007	Retrospective population study	Surgery SBRT	60 60	60% 3 year 42% 3 year			3.6 3.6	Low
Port [27]	2001–2012	Retrospective study	Wedge SBRT	76 23	87% 3 year 75% 3 year		88% 3 year 72% 3 year	2.9 2.9	Low
Robinson [28]	2004–2008	Retrospective single center	Lobectomy SBRT	260 78	64% 4 year 30% 4 year	81% 4 year 75% 4 year		4.3 4.2	Low
Wang [44]	2002–2010	Retrospective population study	Surgery SBRT	104 74	77.5% 5 year 44.6% 5 year	73% 5 year 58% 5 year	58% 5 year 27% 5 year	5.2 5.2	Low

have a life expectancy of greater than 3 years, surgical resection remains the treatment of choice. For patients with tumors less than 2 cm who have less than 3 years of overall life expectancy due to comorbidities and frailty, it would be reasonable to consider SBRT over surgical resection.

Conclusions and Recommendations

In operative candidates, lobectomy should be offered over SBRT based on moderate quality evidence. There is weak evidence that segmental resection provides better overall and cancer specific survival compared with SBRT in borderline operable patients. There is likely no significant difference in survival outcomes between wedge resection and SBRT, although further evidence is needed. For patients with tumors less than 2 cm in diameter whose life expectancy is less than 3 years due to frailty or comorbidities, it would be reasonable to consider SBRT over surgical resection based on discussions with the patient. Morbidity is similar between VATS resections and SBRT, though SBRT has a higher morbidity with more central tumors and surgical resection has a higher morbidity if done via thoracotomy. SBRT can be completed in a few outpatient sessions whereas patients who undergo VATS often only require a few day hospital stay or can even be done as an outpatient with wedge resection. With better technique and post-operative care, procedure related mortality for surgical resection is approaching that of SBRT.

Recommendations

- For patients with medically operable stage I NSCLC, we recommend lobectomy as the standard treatment (evidence quality high; strong recommendation)
- For patients who are borderline operative candidates, we recommend segmentectomy over SBRT if feasible (evidence quality low, weak recommendation).
- In patients with a limited life expectancy due to frailty or comorbidities, we recommend considering both wedge resections and SBRT as treatment options, especially for peripheral tumors <2 cm in diameter (evidence quality low, weak recommendation).

A Personal View of the Data

When patients with early stage non-small cell lung cancer present to clinic, the proper treatment depends on the patient's level of frailty, comorbidities, and pulmonary function. If the patient is overall healthy with good pulmonary function, they should be offered a VATS lobectomy. If the patient has decreased pulmonary function or is at higher risk of a second primary NSCLC in their lifetime due to a prolonged smoking history or multiple nodules on imaging, we would consider

offering them a VATS segmental resection if the tumor location is amenable. Finally, for operative candidates who are higher risk for surgery and have a decreased life expectancy due to frailty or comorbidities, we would include both VATS wedge resection and SBRT in our discussion with them as possible treatment options in lieu of lobar or segmental resection. These patients are likely to not live long enough to experience the survival benefit associated with lobar and segmental resection, and are at increased risk of treatment related morbidity and mortality.

References

1. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol. 2009;27(17):2758–65.
2. Nakamura H, Taniguchi Y, Miwa K, et al. Comparison of the surgical outcomes of thoracoscopic lobectomy, segmentectomy, and wedge resection for clinical stage I non-small cell lung cancer. Thorac Cardiovasc Surg. 2011;59(3):137–41.
3. Thomas P, Rubinstein L. Cancer recurrence after resection: T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg. 1990;49(2):242–6.
4. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg. 1995;60(3):615–22.
5. Okada M, Koike T, Higashiyama M, et al. Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study. J Thorac Cardiovasc Surg. 2006;132(4):769–75.
6. Zhao X, Qian L, Luo Q, et al. Segmentectomy as a safe and equally effective surgical option under complete video-assisted thoracic surgery for patients of stage I non-small cell lung cancer. J Cardiothorac Surg. 2013;8:116. https://doi.org/10.1186/1749-8090-8-116.
7. ClinicalTrials.gov. Comparison of different types of surgery in treating patients with stage IA non-small cell lung cancer. Available at: https://clinicaltrials.gov/ct2/show/NCT00499330?term=CALGB+140503&draw=2&rank=1. Accessed 13 Jan 2020.
8. Altorki NK, Wang X, Wigle D, et al. Perioperative mortality and morbidity after sublobar versus lobar resection for early-stage non-small-cell lung cancer: post-hoc analysis of an international, randomised, phase 3 trial (CALGB/Alliance 140503). Lancet Respir Med. 2018;6(12):915–24.
9. UMIN-CTR Clinical Trial. A phase III randomised trial of lobectomy versus limited resection (segmentectomy) for small (2 cm or less) peripheral non-small cell lung cancer (JCOG0802/WJOG4607L) 2009. Available at: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000002300&type=summary&language=E. Accessed 13 Jan 2020.
10. ClinicalTrials.gov. Surgical treatment of elderly patients with cT1N0M0 non-small cell lung cancer comparison between sublobar resection and lobectomy (STEPS) NCT02360761 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02360761?term=NCT02360761&draw=2&rank=1. Accessed 13 Jan 2020.
11. Smith CB, Swanson SJ, Mhango G, et al. Survival after segmentectomy and wedge resection in stage I non-small-cell lung cancer. J Thorac Oncol. 2013;8(1):73–8.
12. McGarry RC, Song GB, des Rosiers P, et al. Observation-only management of early stage, medically inoperable lung cancer - poor outcome. Chest. 2002;121(4):1155–8.
13. Qiao XY, Tullgren O, Lax I, et al. The role of radiotherapy in treatment of stage I non-small cell lung cancer. Lung Cancer. 2003;41(1):1–11.
14. Nagata Y, Hiraoka M, Shibata T, et al. Prospective trial of stereotactic body radiation therapy for both operable and inoperable T1N0M0 non-small cell lung cancer: Japan Clinical Oncology Group Study JCOG0403. Int J Radiat Oncol Biol Phys. 2015;93(5):989–96.

15. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol. 2009;27(20):3290–6.
16. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol. 2006;24(30):4833–9.
17. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys. 2009;75(3):677–82.
18. Timmerman RD, Paulus R, Pass HI, et al. Stereotactic body radiation therapy for operable early-stage lung cancer: findings from the NRG Oncology RTOG 0618 trial. JAMA Oncol. 2018;4(9):1263–6.
19. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010;303(11):1070–6.
20. Bishawi M, Kim B, Moore WH, et al. Pulmonary function testing after stereotactic body radiotherapy to the lung. Int J Radiat Oncol Biol Phys. 2012;82(1):e107–w10.
21. Paix A, Noel G, Falcoz PE, et al. Cost-effectiveness analysis of stereotactic body radiotherapy and surgery for medically operable early stage non small cell lung cancer. Radiother Oncol. 2018;128(3):534–40.
22. Shah A, Hahn SM, Stetson RL, et al. Cost-effectiveness of stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. Cancer. 2013;119(17):3123–32.
23. Smith BD, Jiang J, Chang JY, et al. Cost-effectiveness of stereotactic radiation, sublobar resection, and lobectomy for early non-small cell lung cancers in older adults. J Geriatr Oncol. 2015;6(4):324–31.
24. Bryant AK, Mundt RC, Sandhu AP, et al. Stereotactic body radiation therapy versus surgery for early lung cancer among US veterans. Ann Thorac Surg. 2018;105(2):425–31.
25. Whitson BA, Groth SS, Duval SJ, et al. Surgery for early-stage non-small cell lung cancer: a systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. Ann Thorac Surg. 2008;86(6):2008–18.
26. Crabtree TD, Puri V, Robinson C, et al. Analysis of first recurrence and survival in patients with stage I non-small cell lung cancer treated with surgical resection or stereotactic radiation therapy. J Thorac Cardiovasc Surg. 2014;147(4):1183–91.
27. Port JL, Parashar B, Osakwe N, et al. A propensity-matched analysis of wedge resection and stereotactic body radiotherapy for early stage lung cancer. Ann Thorac Surg. 2014;98(4):1152–9.
28. Robinson CG, DeWees TA, El Naqa IM, et al. Patterns of failure after stereotactic body radiation therapy or lobar resection for clinical stage I non-small-cell lung cancer. J Thorac Oncol. 2013;8(2):192–201.
29. Chen H, Laba JM, Boldt RG, et al. Stereotactic ablative radiation therapy versus surgery in early lung cancer: a meta-analysis of propensity score studies. Int J Radiat Oncol Biol Phys. 2018;101(1):186–94.
30. Roth J. Randomized study to compare CyberKnife to surgical resection in stage I non-small cell lung cancer (STARS) 2009. Available at: https://clinicaltrials.gov/ct2/show/NCT00840749. Accessed Sep 2019.
31. Senan S, Smit E. Trial of either surgery or stereotactic radiotherapy for early stage (IA) lung cancer (ROSEL) 2008. Available at: https://clinicaltrials.gov/ct2/show/NCT00687986. Accessed Sep 2019.
32. Fernando HC, Timmerman R. American College of Surgeons Oncology Group Z4099/Radiation Therapy Oncology Group 1021: a randomized study of sublobar resection compared with stereotactic body radiotherapy for high-risk stage I non-small cell lung cancer. J Thorac Cardiovasc Surg. 2012;144(3):S35–8.
33. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2015;16(6):630–7.

34. Meyers BF, Puri V, Broderick SR, et al. Lobectomy versus stereotactic body radiotherapy for stage I non-small cell lung cancer: post hoc analysis dressed up as level-1 evidence? J Thorac Cardiovasc Surg. 2015;150(3):468–71.
35. Jones DR. Do we know bad science when we see it? J Thorac Cardiovasc Surg. 2015;150(3):472–3.
36. Kent M, Landreneau R, Mandrekar S, et al. Segmentectomy versus wedge resection for non-small cell lung cancer in high-risk operable patients. Ann Thorac Surg. 2013;96(5):1747–55.
37. Hamaji M, Chen F, Matsuo Y, et al. Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer. Ann Thorac Surg. 2015;99(4):1122–9.
38. Ezer N, Veluswamy RR, Mhango G, et al. Outcomes after stereotactic body radiotherapy versus limited resection in older patients with early-stage lung cancer. J Thorac Oncol. 2015;10(8):1201–6.
39. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol. 2010;28(6):928–35.
40. Palma D, Visser O, Lagerwaard FJ, et al. Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery. Radiother Oncol. 2011;101(2):240–4.
41. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. JAMA Surg. 2014;149(12):1244–53.
42. Nakagawa T, Negoro Y, Matsuoka T, et al. Comparison of the outcomes of stereotactic body radiotherapy and surgery in elderly patients with cT1-2N0M0 non-small cell lung cancer. Respir Investig. 2014;52(4):221–6.
43. Matsuo Y, Chen F, Hamaji M, et al. Comparison of long-term survival outcomes between stereotactic body radiotherapy and sublobar resection for stage I non-small-cell lung cancer in patients at high risk for lobectomy: a propensity score matching analysis. Eur J Cancer. 2014;50(17):2932–8.
44. Wang P, Zhang D, Guo XG, Li XM, Du LH, Sun BJ, Fang XQ, Guo YH, Guo J, An L, Qu GP, Liu CT. A propensity-matched analysis of surgery and stereotactic body radiotherapy for early stage non-small cell lung cancer in the elderly. Medicine (Baltimore). 2016;95(52):e5723.

Do Endobronchial Valves Assist in Resolution of Postoperative Persistent Air Leak?

20

Laura Frye and Sean Stoy

Introduction

An alveolar-pleural fistula (APF) is a communication between the alveoli and the pleural space which results in an air leak by allowing the free passage of air into the pleural space. An air leak lasting greater than 5–7 days, despite adequate conservative management, is classified as a persistent air leak (PAL). Persistent air leaks are common complications of thoracic surgery, most notably in patients undergoing lung volume reduction surgery (LVRS) or pulmonary resection [1]. In patients undergoing lobectomy the incidence of PAL is as high as 26% [1–3]. For those undergoing LVRS, DeCamp et al. found a 46% incidence of PAL after 7 days [4]. Patients with postoperative persistent air leaks incur significant morbidity, prolonged hospital stays, and associated increased costs [5].

Currently accepted management strategies for PAL include prolonged drainage via tube thoracostomy, occasionally utilizing ambulatory drainage valves, nonsurgical pleurodesis via chemical or autologous blood patch instillation, and surgical repair employing a variety of techniques. Although reoperative surgery may help resolve an ongoing air leak, the procedures carry significant morbidity, driving the push for a less invasive effective management approach.

Recently and increasingly, a range of bronchoscopic maneuvers to isolate and treat the source of leak are being utilized. Anecdotal success has been described with the use of sealants, Watanabe spigots, metal coils, and airway stents [6–8]. Most recently, bronchoscopically placed one-way valves to temporarily occlude the

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communicating airways have been successful [9]. These endobronchial valves (EBV) are appealing as they allow for continued clearance of bronchial secretions, reducing the risk of post-obstructive pneumonia, and are removable. This chapter will briefly outline the clinical relevance of postoperative air leaks and the risk factors for the development of PAL, and reviews the data evaluating the use of endobronchial valves in the management of PAL.

Search Strategy

A literature search was conducted in PubMed, EMbase, and Cochrane library for original studies published from 2004 to July 2019 on the use of endobronchial or intrabronchial one-way valves for treatment of postoperative persistent air leaks (Table 20.1). The search used the keyword of "valve" in conjunction with "air leak" or "postoperative air leak" or "bronchopleural fistula" or "alveolar-pleural fistula". Articles were excluded if the patient demographics did not include postoperative thoracic patients. Nine retrospective case series, three prospective case series, one systematic review, and four review articles were included in our analysis. The data was classified using the GRADE system.

Results

One of the earliest reports of the successful use of endobronchial valves for air leaks of various etiologies was published by Travaline and colleagues in 2009 [9]. They described the experience at 17 centers in 40 patients with persistent air leaks over a 4-year period. In this retrospective review, 93% of patients had improvement in air leak following valve placement with 48% having complete cessation of the leak. The mean time from valve insertion to chest tube removal was 21 days (median 7.5; interquartile range 3–29 days) and time from valve placement to hospital discharge was 19 ± 28 days (median 11 days; interquartile range 4–27 days). Of the 40 patients, six experienced adverse events: one patient developed pneumonia, one valve had bacterial colonization, two patients had issues with valve placement itself (malpositioning and expectoration), and the remaining developed moderate hypoxemia.

The largest studies on endobronchial valves for PAL to date are two retrospective multicenter studies, one by Gilbert and colleagues in 2016 and the other by Fiorelli and colleagues in 2018. The studies included 75 and 74 patients respectively. In the

Table 20.1 PICO formatted terms for literature search

P (Population)	I (Intervention)	C (Comparison)	O (Outcomes)
Patients with a prolonged postoperative air leak	Endobronchial or intrabronchial valve placement	Conservative management or operative repair	Reduction in air leak Cessation of air leak

Gilbert study, nearly three quarters of patients underwent valve placement for off-label use (53 of 75) [10].

The more recent study by Fiorelli evaluated a heterogeneous cohort of patients with persistent air leak as well, but 57% had specifically postoperative air leaks [11]. All patients in the study failed to improve with standard therapy. Endobronchial valves were placed in 67 patients following which a complete resolution of air leak was seen in 59 patients (88%), a reduction in six patients (9%), and no benefit in two patients (3%). Seven patients did not undergo valve placement due to an inability to isolate the source of the air leak. The comparison of data before and after valve treatment demonstrated a significant reduction in air leak duration (16.2 ± 8.8 days vs. 5.0 ± 1.7 days, $p < 0.0001$), time to successful chest tube removal (16.2 ± 8.8 days vs. 7.3 ± 2.7 days, $p < 0.0001$), and hospital length of stay (16.2 ± 8.8 days vs. 9.7 ± 2.8 days, $p = 0.004$).

To better understand which patients are likely to respond successfully to balloon isolation and valve placement for persistent air leak, Majid and colleagues recently evaluated the role of collateral ventilation in IBV placement [12]. They utilized chest computed tomography to assess collateral ventilation. Collateral ventilation (CV) was considered present if the treated lobe was adjacent to a fissure that was <90% complete. They noted that the procedure was more likely to be successful in patients without collateral ventilation and those who had a shorter median time to air leak resolution. Endobronchial PAL treatment was most successful in patients without CV who achieved complete lobar occlusion with valve placement.

A more invasive approach to assessing fissure integrity and to quantify collateral ventilation is a catheter-based measurement using the Chartis Pulmonary Assessment System (Pulmonx Inc., Redwood, CA, USA). This system allows sealing of a lung compartment and measurement of air pressure and flow from the sealed compartment. Based on this data, the Chartis system classifies collateral ventilation in a target lobe [13].

Additional less invasive CT correlates have been explored as the market for endobronchial valves has expanded with bronchoscopic lung volume reduction surgery. If a degree of fissure integrity is necessary to trigger atelectasis and avoid significant interlobar collateral ventilation, additional quantitative CT correlates may provide complementary data comparable to that obtained by Chartis. Two such predictors are low attenuation clusters (LAC) and vascular volumetric percentage of patient's detected smallest vessels/small vessel volume proportion (SVPVV). LAC is an index of terminal airspace enlargement and is a surrogate for intralobar collateral ventilation. In a study by Schuhmann et al. they demonstrated that FI, LAC and SVPVV led to comparable results to Chartis [14]. This is particularly important given prior studies showing that up to 16% of subjects may not be able to be evaluated with invasive approaches such as Chartis [15].

These non-invasive (fissure integrity, low attenuation clusters, and small vessel volume proportion) and invasive (Chartis) techniques provide insights into which patients are most likely to have a reduction or cessation in their air leaks following valve placement. In patients at increased risk for peri-operative complications the quantitative CT predictors may be preferred in an attempt to avoid administering

sedating medications or positive pressure ventilation if a therapeutic target cannot be identified.

A summary of case series of IBV and EBV use for a variety of indications as well as one summary report, including patient characteristics and procedural outcomes, is listed in Tables 20.2 (9, 10, 16–24) and 20.3 (9–12, 16–23). Overall success for valve use in postoperative patients does not appear to be related to the duration of air leak or which prior interventions were performed. The success rate for valve use is high, and the complication rate is low.

Conclusions and Recommendations

Based on these case series as well as multiple case reports, the placement of IBVs and EBVs is a reasonable option for patients in whom conservative treatment has failed or who are poor surgical candidates for operative repair. The cost of endobronchial valves can be justified in selected patients, those with evidence suggesting the lack of interlobar collateral ventilation, particularly if a reduction in hospital length of stay is achieved. To better understand cost-effectiveness, direct comparisons with other interventions is needed.

Recommendation

- Placement of IBVs and EBVs is recommended for patients with persistent postoperative air leak in whom conservative treatment has failed or who are poor surgical candidates for operative repair (evidence quality low, weak recommendation).

A Personal View of the Data

Prolonged air leaks are a significant clinical problem in the postoperative patient. Alternatives to surgical correction utilizing less invasive management strategies have provided inconsistent results, however the development of endobronchial valves offers a new treatment option. There have now been multiple reports of successful management of persistent air leaks in on-label and off-label indications but the scope of this role, indications, and efficacy require further investigation. In patients without collateral ventilation, valves offer a promising minimally invasive approach to ameliorating persistent air leak. In patients with evidence of collateral ventilation, valve placement may be unsuccessful due to the inability to induce atelectasis at the site of the fistula and multiple segments may require occlusion for therapeutic success. Needed are prospectively conducted, randomized controlled clinical trials wherein valve treatment is compared to other modalities including non-surgical pleurodesis, other bronchoscopic techniques, surgical procedures, or a combination of these options.

Table 20.2 Summary of findings

Author (Year) [Reference]	Publication type (quality of evidence)	Pts	Age	Underlying disease, etiology of leak (n)	Previous interventions (n)	Duration of air leak before valve placement	Number of valves used
Travaline (2009) [9]	Retrospective (low)	40	Mean 60 ± 14	Recurrent PTX[a] (21) Postoperative (7) Iatrogenic (6) First spontaneous PTX (4)	Chest tube (39) Eloesser flap (1) Blood patch (3) Wedge resection (1) Pleurodesis (1)	Median 20 days IQR[b] 15–45 days	Mean ± SD 2.9 ± 1.9
Conforti (2010) [16]	Retrospective (low)	4	Mean 52	Postoperative (3) First pneumothorax (1)	Glue slurry (1)	Not specified	Mean 1.5
Gillespie (2011) [17]	Retrospective (low)	7	Median 58	Emphysema (5) Malignancy (3) Radiation fibrosis (1) Thoracic infection (2)	Pleurodesis or pleurectomy (4) Surgical interventions (6)	Median ~4 weeks, range ~2 weeks to 5 months	Median 3.5
Fillinger (2013) [18]	Prospective (low)	13	Not specified	Lung cancer (2) Pneumothorax (2) Empyema (4) Pulmonary metastasis (1) Mesothelioma (3) Bronchiectasis (1)	Chest tube (4) Pleurodesis (1) Lobectomy (3) Decortication (2) Pleurectomy (3)	Median 17 days	Mean ± SD 1.4 ± 0.7
Hance (2015) [19]	Retrospective (low)	14	Mean 60	Postoperative (8) Pneumothorax (2) Ruptured bleb (2) Pneumonia (1) Chest tube injury (1)	Chest tube (14)	Mean 21.6 days Median 18 days	Median 2

(continued)

Table 20.2 (continued)

Author (Year) [Reference]	Publication type (quality of evidence)	Pts	Age	Underlying disease, etiology of leak (n)	Previous interventions (n)	Duration of air leak before valve placement	Number of valves used
Reed (2015) [20]	Retrospective (low)	21	Range 16 months to 70 years	Postoperative (8) Pneumothorax (11) Cavitary lung infection (3) Postpneumonectomy BPF (2)	Chest tube (18) Pleurodesis (1) Muscle flap coverage (2) Decortication (1)	Mean 26 days Median 8 days	Mean 3.6 Median 3 Range 1–12
Cordovilla (2015) [21]	Prospective (low)	8	Mean 68.5	Pneumothorax (7) Postoperative (1)	Chest tube (8)	Median 15.5 days	Median 2 Range 1–4
Podgaetz (2015) [22]	Retrospective (low)	19	Median 60	Pneumothorax (16) Postoperative (3)	Chest tube (19) Chemical pleurodesis (2) Blood patch (1)	Median 9 days Mean 12.8 days	Median 4 Range 2–6
Gilbert (2016) [10]	Retrospective (low)	75	Mean 61.1 Median 64	Postoperative (28) Pneumothorax (84)	Chest tube (112) Thoracoscopy with parenchyma stapling (3) Blood patch (1) Fibrin glue (1)	Median: 9 days IQR: 7–14	Mean: 2.6 Range 1–8
Podgaetz (2016) [23]	Prospective (low)	13	Median 60	Postoperative (2) Iatrogenic (4) COPD (7)	Chest tube (13)	Median 9 days Mean 14.9 days	Median 4 Range 2–6
Ding (2017) [24]	Systematic review (low)	52	Mean 57	Postoperative (12) Pneumothorax (35) Fistula (8) Empyema (9)	Not specified	Median 15 days	Median 2 Range 1–8

SD standard deviation, *Pts* patients
[a]PTX-pneumothorax
[b]IQR-interquartile range

Table 20.3 Outcomes of one-way valve deployment in case series

First author	Pts	Complete resolution	Reduction	No change	Recurrence	Complications related to one-way valves	Removal of one-way valves	Days to one-way valve removal
Travaline (2009) [9]	40	19	18	2		6; moderate desaturation, pneumonia, bacterial colonization, valve expectoration, malpositioning requiring replacement, unspecified	8	Mean ± SD 66 ± 53
Conforti (2010) [16]	4	4					1	6 months
Gillespie (2011) [17]	7	5	2		1		5	Mean 37 days
Fillinger (2013) [18]	13	13			3		7	
Hance (2015) [19]	14	14			4	6; persistent air leak (4), death (2—not related to deployment)	3	Mean ± SD 138 ± 84
Reed (2015) [20]	21	4 postop pts	4 postop pts	0 postop pts	0 postop pts		17	Mean 57 Range 1–177 days
Cordovilla (2015) [21]	8	6		2	1		8	Median 49 Range 8–720

(continued)

Table 20.3 (continued)

First author	Pts	Complete resolution	Reduction	No change	Recurrence	Complications related to one-way valves	Removal of one-way valves	Days to one-way valve removal
Podgaetz (2015) [22]	19	18		1			16	Range 4–6 weeks
Gilbert (2016) [10]	59	59				2; empyema, contralateral pneumothorax		
Podgaetz (2016) [23]	13	13					9	Range 4–6 weeks
Fiorelli (2018) [11]	67	67	67	67			55	Mean 134 ± 83 days
Majid (2019) [12]	26	26				2; pneumonia		

References

1. Liberman M, Muzihansky A, Wright CD, et al. Incidence and risk factors of persistent air leak after major pulmonary resection and use of chemical pleurodesis. Ann Thorac Surg. 2010;89(3):891–7.
2. Stolz AJ, Schutzner J, Lischke R, et al. Predictors of prolonged air leak following pulmonary lobectomy. Eur J Cardiothorac Surg. 2005;27(2):3340336.
3. Brunelli A, Monteverde M, Borri A, et al. Predictors of prolonged air leak after pulmonary lobectomy. Ann Thorac Surg. 2004;77(4):1205–10.
4. DeCamp MM, Blackstone EH, Naunheim KS, et al. Patient and surgical factors influencing air leak after lung volume reduction surgery: lessons learned from the National Emphysema Treatment Trial. Ann Thorac Surg. 2006;82(1):197–206.
5. Shrager JB, DeCamp MM, Murthy SC. Intraoperative and postoperative management of air leaks in patients with emphysema. Thorac Surg Clin. 2009;19:223–31.
6. Watanabe S, Watanabe T, Urayama H. Endobronchial occlusion method of bronchopleural fistula with metallic coils and glue. Thorac Cardiovasc Surg. 2003;51(2):106–8.
7. Watanabe Y, Matsuo K, Tamaoki A, et al. Bronchial occlusion with endobronchial Watanabe spigot. J Bronchol. 2003;10(4):264–7.
8. Mehta HJ, Malhotra P, Begnaud A, et al. Treatment of alveolar-pleural fistula with application of synthetic hydrogel. Chest. 2015;154(3):695–9.
9. Travaline JM, McKenna RJ, De Giacomo T. Treatment of persistent pulmonary air leaks using endobronchial valves. Chest. 2009;136(2):355–60.
10. Gilbert CR, Casal R, Lee HL, et al. Use of one-way intrabronchial valves in air leak management after tube thoracostomy drainage. Ann Thorac Surg. 2016;101:1891–986.
11. Fiorelli A, D'Andrili A, Cascone R, et al. Unidirectional endobronchial valves for management of persistent air-leaks: results of a multicenter study. J Thorac Dis. 2018;10(11):6158–67.
12. Majid A, Kheir F, Sierra-Ruiz M, et al. Assessment of fissure integrity in patients with intrabronchial valves for treatment of prolonged air leak. Ann Thorac Surg. 2019;107:407–11.
13. Mantri S, Macaraeg C, Shetty S, et al. Measurement of collateral flow in the lung with a dedicated endobronchial catheter system. J Bronchol Intervent Pulmonol. 2009;16:141–33.
14. Schuhmann M, Raffy P, Yin Y, et al. Computed tomography predictors of response to endobronchial valve reduction treatment: comparison with Chartis. Am J Respir Crit Care Med. 2015;191(7):767–74.
15. Gompelmann D, Eberhardt R, Michaud G, et al. Predicting atelectasis by assessment of collateral ventilation prior to endobronchial lung volume reduction: a feasibility study. Respiration. 2010;80:419–25.
16. Conforti S, Torre M, Fieschi S, et al. Successful treatment of persistent post-operative air leaks following the placement of an endobronchial one-way valve. Monaldi Arch Chest Dis. 2010;73(2):88–91.
17. Gillespie CT, Sterman DH, Cerfolio RJ, et al. Endobronchial valve treatment for prolonged air leaks of the lung: a case series. Ann Thorac Surg. 2011;91:270–3.
18. Fillinger I, Stubenberger E, Muller MR, et al. Endoscopic one-way valve implantation in patients with prolonged air leak and the use of digital air leak monitoring. Ann Thorac Surg. 2013;95(4):1243–9.
19. Hance JM, Martin JT, Mullett TW. Endobronchial valves in the treatment of persistent air leaks. Ann Thorac Surg. 2015;100:1780–6.
20. Reed MF, Gilbert CR, Taylor MD, Toth JW. Endobronchial valves for challenging air leaks. Ann Thorac Surg. 2015;100:1181–7.
21. Cordovilla R, Torracchi AM, Novoa N, et al. Endobronchial valves in the treatment of persistent air leak, an alternative to surgery. Arch Bronconeumol. 2015;51(1):10–5.
22. Podgaetz E, Andrade RS, Zamora F, et al. Endobronchial treatment of bronchopleural fistulas by using intrabronchial valve system: a case series. Semin Thorac Surg. 2015;27:218–22.
23. Podgaetz E, Zamora F, Gibson H, et al. Intrabronchial valve treatment for prolonged air leak: can we justify the cost? Can Respir J. 2016;2016:2867547.
24. Ding M, Gao Y, Zeng X, et al. Endobronchial one-way valves for treatment of persistent air leaks: a systematic review. Respir Res. 2017;18:186–95.

21 Is Long-Term Surveillance Effective After Resection of Stage I Non-small Cell Lung Cancer?

Seth T. Sankary and Mark K. Ferguson

Introduction

Surveillance is an important component in the management of lung cancer survivorship, but the optimal imaging strategy following resection of early stage NSCLC has not been well characterized. This topic is of growing importance as there are over 450,000 Americans living with NSCLC and that number is expected to increase 22% by 2030 [1, 2]. With improvements in lung cancer screening, more patients are identified with early stage disease and undergo definitive surgical treatment [1, 3]. This results in a growing cohort of patients that have completed potentially curative therapy and become candidates for formal surveillance.

Clinicians utilize imaging surveillance with the goals of early recognition of asymptomatic locoregional recurrent disease, detection of a second primary lung cancer (SPLC), and management of patient fear and anxiety [4]. The risk of locoregional recurrence can be high depending on patient and tumor characteristics. Estimates vary widely with a range of 6–10% per year, which is highest in the first 2 years. The risk of a SPLC ranges from 3% to 6% per year [5, 6]. A bimodal pattern of disease has been described with increased risk of recurrence at peaking at 2 years and the increased incidence of SPLC peaking at 6 years [7]. Despite the theoretical advantages of early surveillance, studies have failed to demonstrate a survival benefit with frequent imaging [6–8]. In this chapter we review the literature to analyze the impact of surveillance imaging protocols on overall survival, early detection of locoregional recurrence or SPLC, and cost.

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Search Strategy

A literature search of English language publications from 2010 to 2019 was used to identify published data on CT surveillance following surgical resection of Stage I NSCLC. Databases searched were PubMed, Google Scholar, Cochrane Evidence Based Medicine. MESH search terms included: "carcinoma, non-small cell lung/surgery," "neoplasm recurrence," "metachronous second primary neoplasms," "population surveillance," "computed tomography," "survival," "mortality," "cost" (Table 21.1). Articles were excluded if they included primary non-surgical treatment of disease. We identified three comparative retrospective cohort studies, two retrospective analyses, one prospective cohort study, one meta-analysis review, and five guidelines that addressed components of our patient population, interventions, comparators, and outcomes. We additionally reviewed publications referenced by articles found in our initial search. The data was classified using the GRADE system.

Results

Overall Survival

Multiple studies in our search compare CT scan to no imaging or CXR alone (Table 21.2). Backhus et al. studied a large Medicare cohort of 4421 patients who underwent resection for Stage I or II NSCLC and found no survival benefit whether CT scan or no imaging occurred at the initial episode of surveillance. In subgroup analysis of Stage I patients they describe a 15% reduced risk of death HR 0.85 [95% CI 0.74–0.98] compared to no imaging, however there was no difference in lung cancer specific survival (HR 1.03 [95% CI 0.85–1.26]) [9]. Crabtree et al. demonstrated that among patients with a subsequent malignancy, time to diagnosis was shorter for those who received CT surveillance vs. CXR (1.93 years vs. 2.56 years; $p = 0.046$). Despite the improved time to diagnosis, 5 year cancer-specific survival was not significantly different (39.1% for CT vs. 50.7% for CXR; mean 4.47 years vs. 6.51 years; $p = 0.353$) [6].

Studies in our search also attempted to discern whether more intensive surveillance frequency would improve survival. McMurry et al. used the robust SEER database to compare survival in patients who were followed every 3 months vs. 6 months vs. 12 months and found no difference in survival between any groups (6 months relative to 3 months HR 1.12 CI: 0.98–1.29 $p = 0.09$; 12 months relative

Table 21.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with stage I NSCLC following definitive surgical resection	Regular CT surveillance	No CT surveillance	Survival, diagnosis of recurrent disease, diagnosis of SPLC, cost, quality of life

Table 21.2 Studies evaluating the efficacy of CT surveillance for improving outcomes following surgical resection for stage 1 NSCLC

Study (year)	Study design (quality of evidence)	Population	Intervention	Control/ comparison (n)	Cost/QOL	Oncologic outcomes, survival
Backhus [9] (2016)	Comparative retrospective cohort design (low) Database study from SEER records Comparison of patients with CT follow-up vs. no imaging	AJCC 6 Stage I–II NSCLC who underwent surgical resection n = 18,406	Initial post-operative CT scan within 4–8 mo n = 4421	No imaging n = 2293 CXR n = 11,047 PET/CT n = 645	NR	Initial CT was not associated with a significant difference in 5-year survival (61.4%) compared to no imaging (60.4%) p = 0.11. CT was not associated with reduced risk of death HR (1.04 (95% CI 0.96–1.14)). 32% received secondary intervention following resection, rates did not significantly vary based on initial imaging modality
Bille [11] (2016)	Retrospective analysis (low) Database study from single institution's hospital records Retrospective analysis of Stage I NSCLC patients who underwent wedge resection	AJCC 7 Stage I NSCLC who underwent wedge resection n = 446	CT surveillance (q3mo n = 14, q4mo n = 44, q6mo n = 367, q8–12 mo n = 21) n = 446	NR	NR	8% diagnosed with SPLC, 34% with recurrence. 82% of recurrence was locoregional OS for SPLC was 68 mo; OS for recurrence depends on site of recurrence: 40.5 mo, 16.9 mo, 13.3 mo (local, regional, distant)
Calman [8] (2011)	Retrospective review and meta-analysis (low) Meta-analysis comparing intensive vs. non-intensive follow-up	Stage I–III NSCLC who underwent resection from eight studies. n = 1669	Intensive surveillance, Nurse driven follow-up	Standard CT surveillance, Conventional specialist led follow-up	Nurse driven FU at 12 mo with better emotional functioning and less neuropathy (p = .05)	Survival was not significantly improved with intensive follow-up HR: 0.83 (0.66–1.05 p = 0.13) Asymptomatic recurrence was associated with significantly longer survival HR 0.61 (0.5–0.7 p < 0.01)

(continued)

Table 21.2 (continued)

Study (year)	Study design (quality of evidence)	Population	Intervention	Control/ comparison (n)	Cost/QOL	Oncologic outcomes, survival
Crabtree [6] 2015	Comparative retrospective cohort design (low) Database study from single institution's hospital records Comparison of patients who underwent CT surveillance vs. CXR	AJCC 7 Stage I NSCLC who underwent surgical resection n = 544	CT surveillance (avg 1.56/year) n = 232	CXR surveillance (avg 1.58/year) n = 322	CT group had a 4% false-positive rate resulting in unnecessary diagnostic procedures vs. 1% in CXR	Imaging modality (CT vs. CXR) not associated with survival (p = 0.958) CT surveillance patients less likely to be symptomatic at time of detection (51% vs. 81% p = 0.001) Successive malignancies more likely to be detected during scheduled surveillance with CT than CXR (73% vs. 46% p = 0.001) CT vs. CXR had no difference in whether successive malignancies were treated with curative intent (41% vs. 40% p = 0.639)
Hanna [12] (2014)	Comparative prospective cohort design (moderate) Single institution Following lung cancer resections patients underwent prospective surveillance with minimal-dose CT thorax (MnDCT) and CXR with images interpreted by different blinded radiologists	AJCC 7 Stage I–IV NSCLC who underwent surgical resection n = 271 Stage I (79%) Stage II (12.5%) Stage III (6.6%) Stage IV (1.1%)	MnDCT q3mo until 2 years post op then q6mo until 5 years post-op	Control = same study populations CXR q3mo until 2 years post op then q6mo until 5 years post-op	PPV of MnDCT is 25.1% vs. 91.7% for CXR	Sensitivity of MnDCT for diagnosis of new or recurrent lung cancer was 94.2% vs. 21.2% (p < 0.0001) New or recurrent cancer in 23.2% of patients, 77.8% were detected with asymptomatic disease. 75% of asymptomatic patients were candidates for curative treatment with surgery or radiation and had OS of median 69 mo (12–76 mo) All who presented with symptomatic disease were ineligible for curative surgery.

Lou [5] (2013)	Retrospective analysis (low) Database study from single institution's hospital records Observational study looking at patterns of recurrence/SPLC in patients undergoing surveillance	AJCC 7 Stage I–II NSCLC who underwent surgical resection n = 1294	CT surveillance every 6–12 mo (avg 1.5/year)	NR	25% had abnormal CT scans, 21% underwent interval CT scan, 5% underwent invasive procedure, 0.3% suffered complications	20% of patients developed recurrence. Sixty-one percent of recurrences were detected on surveillance CT scan (82% locoregional only, 46% distant-only recurrences). SPLC was seen in 7% of pts and detected 93% by surveillance CT scan. Ninety-six percent of SPLC diagnosed at Stage I–II and >60% of these patients had surgery.
McMurry [10] (2019)	Comparative retrospective cohort design (low) Database study from NCDB records Comparison of more vs. less frequent CT surveillance	AJCC 7 Stage I–III NSCLC who underwent surgical resection n = 4463	CT surveillance frequency 3 mo vs. 6 mo vs. 12 mo	Parallel regression to compare subgroups	NR	More frequent imaging showed no survival benefit (6 mo relative to 3 mo HR 1.12 CI: 0.98–1.29 p = 0.09; 12 mo relative to 3 mo HR 1.06 CI: 0.86–1.31) More recent pre recurrence imaging not associated with post recurrence survival (HR 1.02/mo since imaging; CI: 0.99–1.04)

mo month, *NR* not reported, *OS* overall survival, *PPV* positive predictive value, *HR* hazard ratio, *CI* confidence interval, *FU* follow-up

to 3 months HR 1.06 CI: 0.86–1.31) [10]. In a meta-analysis of eight largely retrospective cohort studies, Calman et al. used aggregate survival data and found no significant improvement in intensive follow-up vs. standard surveillance (HR 0.83 (0.66–1.05) p = 0.13) [8].

Recurrence

Many authors found that CT scan was a superior tool to diagnose asymptomatic locoregional disease recurrence. Recurrence risk in early stage NSCLC can be defined by location and extent, including local, locoregional, and distant recurrence, with each portending a worse median overall survival [11]. Hypothetically, early detection of recurrent disease at a locoregional stage would positively impact survival. In a novel study comparing CT vs. CXR, Hanna et al. prospectively analyzed a cohort of 271 patients staged I–III who underwent definitive resection and had surveillance with both low dose CT and CXR at 3 months for the first 2 years and 6 months until 5 years. In their cohort 23.2% developed locoregional disease recurrence or SPLC. Pairs of CXR and minimal dose CT were analyzed and CT was significantly more sensitive than CXR for the diagnosis of new or recurrent cancer (94% vs. 21.2%). This allowed for 77.8% of cases to be detected while the patient was asymptomatic—75% of these were candidates for curative treatment. Crabtree et al. also showed that CT scan was superior to CXR in detecting asymptomatic recurrence, 81% vs. 51% (p = 0.001) [6]. Calman et al. demonstrated, and multiple other observational studies similarly concluded, that asymptomatic recurrence was associated with significantly longer survival (HR 0.61 (0.5–0.70) p < 0.01) [5, 8, 11, 12]. Despite this, Crabtree showed no difference between CT and CXR in whether subsequent malignancies were treated with curative or palliative intent (41% vs. 40% p = 0.639) and McMurry showed that timing of pre-recurrence imaging was not associated with post-recurrence survival (HR 1.02/months since imaging; CI 0.99–1.04) [6, 10].

Metachronous Second Primary Lung Cancer

Another potential advantage of imaging surveillance is early detection of SPLC. In patients with previously resected lung cancer, curative surgery for second cancer is associated with 5 year survival of 60% [13]. Early tumor stage is the only significant determinant of survival following surgical treatment of metachronous lung cancer [14]. The National Lung Screening Trial demonstrated a survival benefit in screening high-risk patients with low-dose CT scan vs. CXR, and patients with personal history of lung cancer are at even higher annual risk of 3–6% per year of developing a second lung cancer [5, 11, 15]. Two studies showed that CT was more effective than CXR in the diagnosis of asymptomatic SPLC [6, 12]. No study comparing frequency of surveillance found any advantage of more frequent surveillance in improving early diagnosis of SPLC.

Cost

While many studies mention cost, there is scant data regarding modeling of cost-effectiveness of CT surveillance. Kent et al. created a decision analysis model comparing a hypothetical cohort of patients who underwent resection with curative intent and underwent annual chest CT to a similar group that had no surveillance. They found that patients who entered the surveillance program under age 65, had a CT cost <$700, had an incidence of SPLC greater than 1.6% per patient per year of follow-up, and a false positive rate of surveillance CT less than 14%, were likely to meet a cost effective threshold of $60,000 per quality-adjusted life-year. In the case of previously resected Stage I NSCLC, CT would be deemed a cost-effective intervention in most patients; however older patients or lower volume centers with higher rates of false positive surveillance CT scan may be associated with higher costs per quality adjusted life year [16]. In addition to upfront costs, patients undergoing CT surveillance are subject to increased (4% vs. 1% in CXR) false positive findings, invasive procedures, and subsequent complications [5, 6]. Adjunct measures such as low dose CT had a positive predictive value of only 25.1% compared to 91.7% for CXR [12].

Summary of Clinical Guidelines

Despite the weak evidence, many international guidelines advocate for routine surveillance following surgical resection for NSCLC; however, there are inconsistencies with regards to frequency and imaging modality (Table 21.3) [17–19]. In the US, practice guidelines from the American College of Chest Physicians, The International Association for the Study of Lung Cancer, and the National

Table 21.3 Summary of international guidelines for surveillance following resection for NSCLC

Guidelines	Frequency	Methodology
ACCP [7]	6 months for 2 years then annually	History, physical examination, CT
ESMO [17]	6 months for first 2–3 years and every 12 months thereafter. CT at 12 months, 24 months, and annually	History, physical examination, CT contrast enhanced for first 2 years, then without
NCCN [18]	6 months for first 2–3 years, then annually	History, physical examination, CT contrast enhanced for first 2 years, then without
NICE [19]	Follow-up with specialist within 6 weeks, regular appointments thereafter	Off protocol driven follow-up led by a lung cancer clinical nurse specialist
ASCO [20]	6 months for the first 2 years then annually	History, physical examination, CT contrast enhanced for the first 2 years then low dose CT thereafter

ACCP American College of Chest Physicians, *ESMO* European Society of Medical Oncology, *NCCN* National Comprehensive Cancer Center Network, *NICE* National Institute for Health and Clinical Excellence, *ASCO* American Society of Clinical Oncology

Comprehensive Cancer Center Network each recommend different surveillance intensities and imaging modalities ranging from CXR to CT and at intervals from 3 months to annually [7, 8]. These guidelines continue to be shaped by expert opinion, as the body of evidence is largely comprised of retrospective studies that show that surveillance is associated with earlier diagnosis of locoregional recurrence and SPLC [6, 9, 10].

Conclusions and Recommendations

Most of the studies cited in this chapter are database studies limited by retrospective analysis, heterogeneous study populations, and diverse surveillance protocols. Given these limitations, no study found improved overall or cancer specific survival for either CT surveillance vs. no imaging or increased frequency of surveillance. Multiple studies show that CT is more useful for identifying recurrent disease or SPLC at early stage. Other studies have shown that identification of early recurrence of SPLC is associated with increased second lung interventions and improved survival. Based on this, and the hope that additional larger studies will demonstrate a survival benefit for appropriate surveillance intervals, we recommend regular CT surveillance for patients who have had successful resection of a stage I NSCLC.

Recommendation

- Following surgical excision for Stage I NSCLC patients should undergo annual CT surveillance to identify locoregional disease recurrence or SPLC (evidence quality low; weak recommendation).

A Personal View of the Data

Our approach to post-resection surveillance includes history, physical examination, and CT imaging every 6 months for the first 2 years and annually thereafter. Standard CT scans are performed until year 2, and low dose scans are performed thereafter. This is in accordance with new recommendations made by the American Society for Clinical Oncology [20]. This allows us to detect asymptomatic locoregional disease or new second primary lung cancers at an early enough stage to allow for curative intent intervention. In the absence of high quality prospective data proving a lack of benefit of more frequent screening, we feel comfortable that our approach weighs the costs and false positives of over screening with the benefits stated above. As new therapies to treat recurrent disease develop, earlier recognition of recurrence has the potential to result in survival improvement. More studies will need to be performed to inform optimal surveillance strategies.

References

1. American Cancer Society. Cancer prevalence: how many people have cancer? http://www.cancer.org/cancer/cancerbasics/cancer-prevalence. Updated 2017. Accessed Sep 2019.
2. SEER. https://seer.cancer.gov/archive/csr/1975_2015/results_merged/sect_15_lung_bronchus.pdf. Updated 2015. Accessed Sep 2019.
3. Howington JA, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):278S–e313S.
4. National Cancer Institute. Survivorship. http://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-treatment-and-survivorship-facts-and-figures/cancer-treatment-and-survivorship-facts-and-figures-2019-2021.pdf. Updated 2019. Accessed Sep 2019.
5. Lou F, Huang J, Sima CS, Dycoco J, Rusch V, Bach PB. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg. 2013;145(1):75–82.
6. Crabtree TD, Puri V, Chen SB, Gierada DS, Bell JM, Broderick S, Krupnick AS, Kreisel D, Patterson GA, Meyers BF. Does the method of radiologic surveillance affect survival after resection of stage I non-small cell lung cancer? J Thorac Cardiovasc Surg. 2015;149(1):45–52. 53.e1-3.
7. Colt HG, Murgu SD, Korst RJ, Slatore CG, Unger M, Quadrelli S. Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e437S–54S.
8. Calman L, Beaver K, Hind D, Lorigan P, Roberts C, Lloyd-Jones M. Survival benefits from follow-up of patients with lung cancer: a systematic review and meta-analysis. J Thorac Oncol. 2011;6(12):1993–2004.
9. Backhus LM, Farjah F, Liang CK, He H, Varghese TKJR, Au DH, Flum DR, Zeliadt SB. Imaging surveillance and survival for surgically resected non-small-cell lung cancer. J Surg Res. 2016;200(1):171–6.
10. McMurry TL, Stukenborg GJ, Kessler LG, Colditz GA, Wong ML, Francescatti AB, Jones DR, Schumacher JR, Greenberg CC, Chang GJ, Winchester DP, McKellar DP, Kozower BD. More frequent surveillance following lung cancer resection is not associated with improved survival: a nationally representative cohort study. Ann Surg. 2018;268(4):632–9.
11. Billè A, Ahmad U, Woo KM, Suzuki K, Adusumilli P, Huang J, Jones DR, Rizk NP. Detection of recurrence patterns after wedge resection for early stage lung cancer: rationale for radiologic follow-up. Ann Thorac Surg. 2016;102(4):1067–73.
12. Hanna WC, Paul NS, Darling GE, Moshonov H, Allison F, Waddell TK, Cypel M, de Perrot ME, Yasufuku K, Keshaviee S, Pierre AF. Minimal-dose computed tomography is superior to chest x-ray for the follow-up and treatment of patients with resected lung cancer. J Thorac Cardiovasc Surg. 2014;147:30–3.
13. Hamaji M, Matsuo Y, Chen-Yoshikawa TF, Mizowaki T, Date H. Surgery and stereotactic body radiotherapy for early stage non-small cell lung cancer: review of meta-analyses. J Thorac Dis. 2019;11(Suppl 13):S1646–52.
14. Lamont JP, Kakuda JT, Smith D, Wagman LD, Grannis FW. Systematic postoperative radiologic follow-up in patients with non-small cell lung cancer for detecting second primary lung cancer in stage IA. Arch Surg. 2002;137(8):935–8. Discussion 938–40.
15. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD, Team NR. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395–409.
16. Kent MS, Korn P, Port JL, Lee PC, Altorki NK, Korst RJ. Cost effectiveness of chest computed tomography after lung cancer resection: a decision analysis model. Ann Thorac Surg. 2005;80(4):1215–22. Discussion 1222–3.

17. Vansteenkiste J, De Ruysscher D, Eberhardt WE, Lim E, Senan S, Felip E, Peters S, Group EGW. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi89–98.
18. National Comprehensive Cancer Network. NSCLC (Version 7.2019). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed Sep 2019.
19. National Institute for Health and Care Excellence. Lung cancer: diagnosis and management [Version NG122]. https://www.nice.org.uk/guidance/ng122/chapter/Recommendations. Accessed Sep 2019.
20. Schneider BJ, Ismaila N, Aerts J, Chiles C, Daly ME, Detterbeck FC, Hearn JWD, Katz SI, Leighl NB, Levy B, Meyers B, Murgu S, Nekhlyudov L, Santos ES, Singh N, Tashbar J, Yankelevitz D, Altorki N. Lung cancer surveillance after definitive curative-intent therapy: ASCO Guideline. J Clin Oncol. 2020;38(7):753–66.

Does ECMO for Lung Failure in ICU Patients Improve Survival?

22

Ben Dunne and Marc de Perrot

Introduction

The role of extracorporeal membrane oxygenation (ECMO) for acute lung failure has been debated for decades. However, as ECMO is increasingly being used for the management of patients with acute lung failure, particularly in acute respiratory distress syndrome (ARDS), there has been an increased focus on the evidence to support its use. In this chapter we detail the best available evidence for the use of ECMO for acute lung failure in three distinct patient populations: primarily hypoxic respiratory failure; primarily hypercarbic respiratory failure; decompensated pre-capillary pulmonary hypertension. We believe that these three subgroups represent very different patient populations, are managed with different modes of extracorporeal support, and have different levels of evidence to support their use. As such, we analysed the three subgroups independently.

Search Strategy

A systematic literature search was performed with the assistance of a Medical Information Specialist. Databases searched were OVID Medline, OVID Epub Ahead of Print, Cochrane CENTRAL, Embase (Table 22.1). The search was limited to articles published from 2000 through 2019, in English, and including only adult human subjects. The search terms used were 'Acute Lung Injury', 'Acute Respiratory Distress Syndrome', 'Hypercarbia', 'Hypercapnoea', 'Pulmonary Hypertension', 'Mortality', 'Prognosis', AND 'Extracorporeal Membrane Oxygenation',

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Table 22.1 PICO formatted terms for literature search

Population	Intervention	Control	Outcome
Hypoxic lung failure	ECMO	Conventional mechanical ventilation	Mortality Treatment failure
Hypercarbic lung failure	ECCOR	Conventional mechanical ventilation	Mortality Avoidance of intubation
Decompensated pre-capillary pulmonary hypertension	ECMO	NA	Mortality

'Extracorporeal Life Support', 'Extracorporeal CO_2 Removal', 'Extracorporeal Carbon Dioxide Removal', 'Extracorporeal Decarboxylation'. Case reports, editorials, review articles, conference abstracts and letters to the editor were excluded. Articles presenting original research data were reviewed, as were systematic reviews, and meta-analyses.

For the subgroup of patients with primarily hypoxic respiratory failure we limited our review to randomised controlled trials (RCTs), observational studies with matched control cohorts, and meta-analyses. We included three observational studies with matched controls, two randomised trials and one meta-analysis (the most recent and thus most relevant meta-analysis). For the subgroup of patients with primarily hypercarbic respiratory failure we limited our review to observational studies with matched control groups. We included three observational studies with matched control groups. For the subgroup of patients with decompensated pre-capillary pulmonary hypertension there were no articles comparing venoarterial (VA) ECMO or other modes of ECMO support with alternative treatment strategies for decompensated right heart failure.

Results

Hypoxaemic Lung Failure

Our search strategy produced six papers of note comparing venovenous (VV) ECMO in the care of patients with primarily hypoxaemic lung failure to conventional mechanical ventilation. There have been three observational studies with matched comparison groups on this topic, two randomised controlled trials and one high-quality meta-analysis that included the results of all five of the above studies (Table 22.2).

The first RCT included was the CESAR trial [1]. This was essentially a randomised trial of referral to an ECMO centre compared to management in a non-ECMO centre. The primary outcome was death or severe disability at 6 months. The ECMO group was statistically superior: 37% vs. 53% ($p = 0.03$, Hazard ratio (HR) 0.69; 95% confidence interval (CI) 0.05–0.97). The secondary outcome of death at 6 months showed a strong trend in favour of ECMO: 37% vs. 50% ($p = 0.07$ HR

Table 22.2 Hypoxaemic lung failure studies

Author	Year	Design	Intervention (n)	Control (n)	Outcome	Intervention	Control	p	Quality of evidence
Munshi [6]	2019	Meta-analysis	429 (2 RCTs)	429	60 day mortality	RR 0.73 (0.58–0.92)			High
			773 (2 RCTs, 3 Observational)	773	30 day mortality	RR 0.69 (0.5–0.95)			High
			429 (2 RCTs)	429	Treatment Failure	RR 0.58 (0.39–0.85)			High
			429 (2 RCTs)	429	Mortality at longest FU	RR 0.76 (0.6–0.95)			
Combes [2] (EOLIA)	2018	RCT	124	125	60 day mortality	35%	46%	P = 0.07 RR 0.76 0.55–1.04	Moderate
			124	125	Treatment Failure	35%	58%	p = 0.001 RR 0.62 0.47–0.82	High
Peek [1] (CESAR)	2009	RCT	90	90	6 month mortality or severe disability	37%	53%	p = 0.03 HR 0.69 0.05–0.97	Moderate
			90	90	6 month mortality	37%	50%	p = 0.07 HR 0.73 0.52–1.03	Moderate

(continued)

Table 22.2 (continued)

Author	Year	Design	Intervention (n)	Control (n)	Outcome	Intervention	Control	p	Quality of evidence
Tsai [5]	2015	Observational	45	45	Hospital mortality	49%	75%	p = 0.009	Low
			45	45	6 month mortality	lower		P = 0.001	Low
Pham [4]	2013	Observational	52	52	ICU mortality	50%	40%	p = 0.32 HR 1.48 0.68–3.23	Low
Noah [3]	2011	Observational	59	59	Hospital mortality	24%	52%	p = 0.006 RR 0.45 0.26–0.79	Low

RR relative risk (95% CI), *RCT* randomized controlled trial, *FU* follow-up, *HR* hazard ratio (95% CI)

0.73; 95% CI 0.52–1.03). There has been significant criticism of this trial as only 75% of the 'ECMO' patients received ECMO and the control group patients were not all managed with ARDSNet best-practice low-pressure ventilation. This may have skewed the results in favour of ECMO. However, the opposite effect may be exerted by the fact that no patients were transferred on ECMO so five of the 90 patients died in the original hospital after being referred for ECMO but were too sick to transport. Thus, these sickest patients may have been salvaged by mobile ECMO and their deaths falsely elevate the mortality rate of the 'ECMO' group as they never actually reached the ECMO hospital or received ECMO.

These criticisms informed the design of the EOLIA trial [2]. This trial compared 124 recipients of VV ECMO to 125 patients managed with conventional mechanical ventilation using best-practice strategies. The study was designed to show a 20% difference in mortality but regrettably was stopped early for futility after recruiting 249 patients. This decision has been criticized. The primary endpoint was death at 60 days. There was a trend towards superiority in the ECMO group 35% vs. 46% ($p = 0.09$; relative risk (RR) 0.76; 95% CI 0.55–1.04) and many feel that significance would have been achieved if the trial had run its course. The key secondary endpoint of treatment failure, defined as death in the ECMO group or death/crossover to ECMO in the ventilation group, showed a distinct advantage for ECMO of 35% vs. 58% ($p = 0.001$; RR 0.62; 95% CI 0.47–0.82). This was largely powered by a 28% crossover to ECMO in the conventional ventilation group. This trial was essentially a trial of early vs. rescue ECMO in severe ARDS. The data showed a high rate of treatment failure with conventional ventilation and poor outcomes in those referred late for ECMO, as the mortality in this group was 57%.

The first matched observational study by Noah et al. [3] was performed in the UK in the wake of the 2009 influenza outbreak. Similar to the CESAR trial, this examined referral to an ECMO centre rather than ECMO specifically. There were 80 patients referred to four ECMO centres in the UK and 83% of these received ECMO. These patients were matched to control groups using a number of techniques. Hospital mortality was the primary endpoint. Outcomes for individually matched patients (59 pairs) were superior for the ECMO group (24% vs. 52%; RR 0.45; 95% CI 0.26–0.79; $p = 0.006$). For propensity matched (75 pairs) the outcomes also favored the ECMO group (24% vs. 47%; RR 0.51; 95% CI 0.31–0.81; $p = 0.008$). Finally, among generally matched (75 pairs) results were similar (24% vs. 51%; RR 0.47; 95% CI 0.31–0.72; $p = 0.001$). Thus, regardless of the matching technique, referral for ECMO was superior for hospital mortality.

A further matched observational study by Pham et al. [4] was published in 2013 using data from the 2009–2010 influenza outbreak across 30 centres in France. There were 103 ECMO patients and 157 non-ECMO patients. These groups produced 52 matched pairs. There was no significant difference is ICU mortality between the two groups: 50% vs. 40% ($p = 0.32$; HR 1.48; 95% CI 0.68–3.23). A secondary analysis matched all 103 ECMO patients to 58 non-ECMO patients and showed a significant advantage for ECMO (OR 0.45; 95% CI 0.25–0.78; $p = 0.01$).

The third observational study was from a single centre in Taiwan by Tsai et al. [5]. There were 216 patients with severe ARDS; 81 were managed with ECMO, 135

were managed without. The authors were clear that the non-ECMO group were managed with appropriate ARDSNet low-pressure ventilation. Hospital mortality was the primary endpoint, and 6-month mortality was a secondary endpoint. Matching produced 45 pairs. Hospital mortality was 49% in the ECMO group and 75% in the non-ECMO group (p = 0.009). Mortality at 6 months was statistically lower in the ECMO group (p = 0.001) although the percentage survival in each group was not stated in the manuscript. The criticisms of this paper were the high rate of VA ECMO use in the ECMO group (18%) and the high mortality in the non-ECMO group.

These papers were all included in a meta-analysis by Munshi et al. [6]. Their primary analysis was 60-day mortality using the two existing RCTs. These two RCTs were also analysed for mortality at longest follow-up (6 months) and treatment failure. All five studies were analysed for the 30-day mortality endpoint. ECMO was superior for 60-day mortality: RR 0.73 (95% CI 0.58–0.92). On the secondary analyses ECMO was also superior for 30-day mortality (RR 0.69; 95% CI 0.5–0.95), 6-month mortality (RR 0.76; 95% CI 0.6–0.95), and treatment failure (RR 0.58; 95% CI 0.39–0.85).

Hypercarbic Lung Failure

Our search strategy produced three papers comparing low-flow ECMO/extracorporeal carbon dioxide removal (ECCOR) to conventional ventilation in patients with primarily hypercarbic lung failure due to COPD (Table 22.3). These were all observational studies with historical control groups. There were no RCTs or meta-analyses.

Braune et al. [7] compared 25 patients with exacerbations of COPD managed with ECCOR in an attempt to avoid mechanical ventilation to 25 matched historical controls. ECCOR was delivered in a VV configuration using a pump-driven Novalung membrane. All 25 control patients were ventilated at baseline. Ventilation was required in 44% of the ECCOR group. The primary endpoint was 28-day mortality, which was equivalent: 16% vs. 12% (p = 0.68). Mortality at 90 days was also equivalent: 28% vs. 28% (p = 1.0).

Kluge et al. [8], similarly matched 21 patients with exacerbations of COPD treated with ECCOR and NIV to 21 historical controls who were all ventilated. The ECCOR was delivered using a pumpless femoral VA Novalung device. Only 10% of the ECCOR group required ventilation. Mortality at 28 days (24% vs. 19%, p = 0.84) and 6 months (33% vs. 33%, p = 0.89) was not different.

Del Sorbo et al. [9] compared 25 patients with COPD exacerbation managed with NIV and ECCOR to 21 historical controls managed with NIV alone. ECCOR was delivered using a modified CVVHD circuit via a 14 Fr dual-lumen femoral venous cannula. The primary endpoint was avoidance of intubation. The strategy of NIV with ECCOR was superior to NIV alone: 12% vs. 33% intubation (HR 0.27; 95% CI 0.07–0.9; p = 0.047). Hospital mortality was also significantly lower at 8% vs. 33% (p = 0.034). Although they reported that 13 patients (52%) had adverse

Table 22.3 Hypercarbic lung failure studies

Author	Year	Design	Intervention (n)	Control (n)	Outcome	Intervention	Control	p	Quality of evidence
Braune [7]	2016	Observational	25	25	28 day mortality	16%	12%	p = 0.68	Low
			25	25	90 day mortality	28%	28%	p = 1.0	Low
Del Sorbo [9]	2015	Observational	25	21	Avoidance of intubation	12%	33%	p = 0.04 HR 0.27 (0.07–0.9)	Low
			25	21	Hospital mortality	8%	33%	p = 0.03	Low
Kluge [8]	2012	Observational	21	21	28 day mortality	24%	19%	p = 0.84	Low
			21	21	6 month mortality	33%	33%	p = 0.89	Low

HR hazard ratio (95% CI)

events related to the ECCOR, nine of these patients had clot formation in the ECCOR circuit alone as their adverse event, three had bleeding from the femoral venous cannulation site, and one had a retroperitoneal haematoma, resulting in a 5% major complication rate.

Lung Failure Due to Refractory/Decompensated Pre-capillary Pulmonary Hypertension

No studies with comparative data were available for the use of VA ECMO or PA-LA Novalung in decompensated pre-capillary pulmonary hypertension. This is a result of the lack of acceptable treatment alternatives. VA ECMO remains the most commonly used treatment option for pulmonary hypertension refractory to medical management as a bridge to definitive therapy such as transplantation or pulmonary endarterectomy.

Conclusions and Recommendations

Severe hypoxic acute lung failure continues to have a significant mortality. There is now sufficient evidence to support the use of venovenous ECMO to improve short-term survival in these patients. There is also strong evidence that VV ECMO improves 6-month survival, although longer-term outcomes have not been examined. We make a strong recommendation for the use of VV ECMO in patients with severe hypoxic respiratory failure.

There is weak evidence to support the use of ECCOR to avoid intubation in patients with hypercarbic respiratory failure on NIV. There is weak evidence that this may translate into a survival benefit for these patients. We make a weak recommendation to consider its use in this patient subset.

Recommendations

- VV ECMO is recommended for patients with severe primarily hypoxic respiratory failure (evidence quality high, strong recommendation).
- ECCOR is recommended for patients with primarily hypercarbic respiratory failure (evidence quality low, weak recommendation).

A Personal View of the Data

The evidence is increasingly supportive of the use of VV ECMO for severe hypoxic lung failure. Those of us involved in the provision of ECMO for this patient population have seen dramatic recoveries in patients that would not have been salvaged with conventional ventilation and the evidence now supports the inclusion of ECMO

as standard of care for severe ARDS. However, ongoing efforts must continue to reduce the morbidity and cost associated with this significant undertaking.

References

1. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374(9698):1351–63. PubMed PMID: 19762075.
2. Combes A, Hajage D, Capellier G, Demoule A, Lavoue S, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med. 2018;378(21):1965–75. PubMed PMID: 29791822.
3. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA. 2011;306(15):1659–68. PubMed PMID: 21976615.
4. Pham T, Combes A, Roze H, Chevret S, Mercat A, Roch A, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. Am J Respir Crit Care Med. 2013;187(3):276–85. PubMed PMID: 23155145.
5. Tsai HC, Chang CH, Tsai FC, Fan PC, Juan KC, Lin CY, et al. Acute respiratory distress syndrome with and without extracorporeal membrane oxygenation: a score matched study. Ann Thorac Surg. 2015;100(2):458–64. PubMed PMID: 26116481.
6. Munshi L, Walkey A, Goligher E, Pham T, Uleryk EM, Fan E. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. Lancet Respir Med. 2019;7(2):163–72. PubMed PMID: 30642776.
7. Braune S, Sieweke A, Brettner F, Staudinger T, Joannidis M, Verbrugge S, et al. The feasibility and safety of extracorporeal carbon dioxide removal to avoid intubation in patients with COPD unresponsive to noninvasive ventilation for acute hypercapnic respiratory failure (ECLAIR study): multicentre case-control study. Intensive Care Med. 2016;42(9):1437–44. PubMed PMID: 27456703.
8. Kluge S, Braune SA, Engel M, Nierhaus A, Frings D, Ebelt H, et al. Avoiding invasive mechanical ventilation by extracorporeal carbon dioxide removal in patients failing noninvasive ventilation. Intensive Care Med. 2012;38(10):1632–9. PubMed PMID: 22836139.
9. Del Sorbo L, Pisani L, Filippini C, Fanelli V, Fasano L, Terragni P, et al. Extracorporeal Co2 removal in hypercapnic patients at risk of noninvasive ventilation failure: a matched cohort study with historical control. Crit Care Med. 2015;43(1):120–7. PubMed PMID: 25230375.

Does Local Therapy for Oligometastatic Disease in Lung Cancer Patients Improve Survival?

23

Jessica S. Donington

Introduction

The concept of oligometastases was introduced in 1995 by Hellman and Weichselbaum, who hypothesized that metastatic disease occurs in a step-wise manner, initially with limited metastases followed by progression to widespread disease [1]. Early on, metastases were thought to be limited in number and location based on interaction of tumor cells with target organs in a "seed and soil" pattern [1, 2]. Imaging advancements, including high resolution CT, PET/CT and MRI, have increased the identification of isolated and small volume metastatic deposits. A significantly greater proportion of patients are now being identified early in the metastatic spectrum, and with the potential to benefit from curative local treatment, this is creating new paradigms in the management of metastatic cancer. Grouping of all patients with metastatic solid tumors into a single clinical cohort with a uniform treatment approach is no longer adequate. There exist subsets of patients with oligometastatic disease who have improved survival and the potential to benefit from a more aggressive treatment approach.

Approximately 50–60% of all non-small cell lung cancer (NSCLC) patients present with stage IV disease. Traditionally, systemic therapy has been the treatment of choice for these patients, but the majority will fail at original sites of gross disease [3]. The introduction of targeted therapies in the form of tyrosine kinase inhibitors and check point inhibitors has led to survival improvements compared to cytotoxic chemotherapy alone, but the earliest failures continue to most frequently occur in original sites of gross disease. There remains a great need for improvement in clinical management that improves median survival. It is estimated that more than half of stage IV NSCLC patients have lesions potentially amenable to local

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consolidative treatment (LCT) in the form of surgery or stereotactic body radiotherapy (SBRT) [3]. Survival is prolonged in these patients compared to those with more widespread disease, and the eighth edition of the American Joint Committee on Cancer (AJCC) Lung Cancer staging system now includes a M1b category for oligometastatic disease [4]. The M1b category is defined by a single metastatic lesion in a distant organ. Clinical evidence to support improved treatment outcomes in the oligometastatic NSCLC has generally been limited to non-randomized observational studies. Many of these studies suggest that local treatment of oligometastatic disease can lead to better-than-expected survival compared with a general population of patients with metastatic disease [5]. There exists a clear rationale to consider whether local therapies add value to systemic therapy in patients with limited metastatic NSCLC by enhancing control and survival endpoints.

Search Strategy

Table 23.1 lists the PICO terms used in search of English language publications listed on Pubmed from 1960 to 2019. Key words used included a combination of "and" or "or" for non-small cell lung cancer, oligometastasis, isolated metastasis, radiation therapy, stereotactic radiotherapy, surgery, local consolidative therapy, prognosis, progression free survival, and overall survival. Overall, 684 references were identified and a total of 45 were reviewed for this chapter.

Results

Local Consolidative Therapy

Local consolidative therapy is term used for definitive therapies directed at sites of known disease following systemic therapy. Surgery or curative doses of radiation therapy, either external beam or stereotactic body radiotherapy (SBRT), are the most common LCTs used in NSCLC. Much of the recent literature, retrospective series, and even some prospective trials combine these modalities together under this single umbrella term [5–8]. To date, there are no head-to-head comparisons between surgery and radiation of outcomes in the oligometastatic setting. The closest thing to a comparison of local modalities is in a recent meta-analysis of oligometastatic NSCLC from Ashworth et al. [5]. They examined individual patient data from 757 patients, mostly with ≤3 metastatic lesions, treated with surgery or

Table 23.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with oligometastatic NSCLC	Systemic therapy + local consolidative therapy, surgery, or definitive radiotherapy therapy	Systemic therapy alone	Overall survival Progression-free survival

radiation. The median overall survival (OS) was 26 months, and surgical treatment of the primary tumor was associated with improved progression-free survival (PFS).

The oldest series using LCT in oligometastatic NSCLC were all surgical. Surgery has been used in oligometastatic NSCLC for >40 years with 5-year survivals of 15–55%, but broad adoption has been hampered by several factors: (1) the supporting data is all retrospective; (2) the experience is limited to patients with a single metastatic site; and (3) many attribute the survival advantage to selection bias alone. There has been considerable excitement generated around LCT in oligometastatic NSCLC in recent years as a result of a series prospective trials from radiation oncologists. The "Oligomez trial" was a small prospective phase II trial which closed early due to the significant progression free survival (PFS) improvement with the addition of LCT to chemotherapy alone [9, 10]. The trial's design was a key aspect of its success: it was open to patients with ≤3 metastasis who did not progress during standard first line chemotherapy, thereby excluding patients with unfavorable tumor biology. Seventy four patients were randomized to aggressive LCT to all disease sites or standard care. The addition of LCT significantly improved PFS (14.2 months vs. 4.4 months) [9] and overall survival (OS) (41.2 months vs. 17.0 months) [10]. The time to progression of a new site of disease was also prolonged in the LCT arm. Surgery was part of LCT in 25% of patients, the remainder received radiation (external beam or SBRT).

Iyengar et al. reported similar results in a second small prospective phase II trial with a similar design. This trial used only SBRT—surgery and external beam radiation were not allowed—and included up to six sites of disease [11]. This trial was also closed early when the interim analysis noted a significant improvement in PFS (9.7 months vs. 3.5 months) with LCT. No patients failed at a treated site of disease, shifting expected patterns of failure.

Palma et al. recently reported results from the SABR-COMET study, a phase II randomized trial of SBRT vs. maintenance therapy for patients with five or fewer metastatic lesions and no progression following first line therapy [12]. The trial was open to all sites and histologies, and 18 of the 99 participants had NSCLC. There were three treatment-related deaths in the SBRT arm, but the trial met its primary end point with an improvement in median OS from 28 to 41 months [12].

These prospective trials have caught the attention of medical oncologists and brought the consideration of LCT after chemotherapy to the forefront of care for patients with oligometastatic NSCLC. It is difficult to address the role of surgery in oligometastatic NSCLC without consideration of this data.

Surgery

The oldest series reporting the use of surgery for stage IV NSCLC relate to treatment of isolated brain metastasis [13, 14]. Early series provided evidence for prolonged survival following resection of the primary tumor and brain radiation over chemotherapy alone [15, 16]. Results from larger contemporary series are outlined in Table 23.2 and report 5-year overall survivals of 23–38% following complete

Table 23.2 Retrospective series of surgery in the treatment of oligometastatic non-small cell lung cancer

Author	Year	N	Metastatic site	5-year survival	Median survival	Prognostic factors
Congedo [17]	2012	53	Brain 39 Adrenal 8 Bone 6 Other 2	23%	19 mos	Use of PET Completeness of lung resection
Collaud [18]	2012	29	Brain 19 Lung 8 Adrenal 2	36%	20.5 mos	T stage
Tonnies [19]	2014	99	Lung 57 Brain 21 Adrenal 6 Other 11	38%	41 mos	Metastasis to lung N stage Tumor grade

N number of patients, *mos* months, *PET* positron emission tomography

resection [17–19]. Prospective data on the use of surgery in oligometastatic NSCLC is sparse and results are not encouraging. In a prospective phase II trial performed by Downey et al., 23 patients enrolled on a protocol that included aggressive induction chemotherapy followed by resection of all sites of disease and consolidation chemotherapy. Only 12 patients successfully completed induction chemotherapy and the median OS was 11 months with two patients surviving to 5 years [20].

Despite the lack of prospective data supporting its use, surgery has been used in the treatment of metastatic NSCLC with increasing frequency. Metastasectomy for primary NSCLC is second in incidence only to colon cancers. An analysis from the National Inpatient Sample (NIS) uncovered a 5.8% average annual increase in resections of NSCLC metastases between 2000 and 2011 [21]. The increase was attributed to several factors, including more efficacious and better tolerated systemic therapies, including targeted agents, which have slowed the progression of metastatic spread and altered patterns of resistance. Simultaneously, there have been significant improvements in surgical techniques, with increased use of minimally invasive approaches, making resections better tolerated and negating long interruptions from systemic treatments. The majority of patients considered for resection of metastatic NSCLC fall into three categories: isolated metastasis to the brain, adrenal glands, or contralateral lung. Occasional patients with isolated metastases to other sites are considered for such therapy, but evidence for prolonged survival following local therapy is sparse [22].

In evidence-based guidelines from the American College of Chest Physicians (ACCP) the recommendation for patients who present de novo with a single metastasis after full staging is aggressive curative intent treatment of the primary and metastatic site in those with good performance status and in whom both sites are amenable to complete resection or ablation [23]. Resection by lobectomy remains a standard treatment option for patients with oligometastatic disease, with better prognosis for node negative patients and those undergoing complete resection [23]. Curative intent local treatments should only be considered after a thorough search

for disease at other sites. Mediastinal lymph node involvement portends a poor prognosis [24–28], so consideration should be given to invasive mediastinal staging in any patient with oligometastatic disease being considered for resection.

Isolated Brain Metastasis

Up to one quarter of all patients with stage IV NSCLC harbor brain metastasis. Adenocarcinomas are associated with higher rates of brain metastasis, and in 10% of patients with metastatic adenocarcinoma the brain is the only site of involvement [23]. Brain MRI is recommended in addition to PET/CT because of increased sensitivity [29]. Treatment of the brain lesion can be by resection or stereotactic radiosurgery (SRS). Radiosurgery has the advantage of being able to be performed in almost any location, including the brain stem [30–32]. Multiple brain metastases are not a contraindication to an aggressive treatment approach. Three or fewer lesions was an old limit [23, 33] for what was reasonable to treat with SRS, but that has been expanded in recent years. Five year survival following definitive treatment of isolated brain metastasis and primary NSCLC ranges from 10% to 24%, and is not significantly impacted by synchronous or metachronous presentation [28, 34]. Results from surgical series with >20 patients are outlined in Table 23.3 [13, 24–26, 28, 30, 34, 35] and most of the series are quite old.

Modi et al. performed an evidence-based review of the value of thoracic resection in this setting, and concluded that, in the absence of mediastinal nodal involvement, complete resection of the primary tumor in patients with isolated brain metastasis improves survival [27]. Prognosis is improved in patients who are

Table 23.3 Retrospective series of surgery in the treatment of oligometastatic non-small cell lung cancer to the brain

Author	Year	N	5-year survival	Median survival	Prognostic factors
Bonnette [28]	2001	103	12%	11 mos	Histology
Billing [29]	2001	28	12%	24 mos	N stage
Granone [24]	2001	20	14%	23 mos	Histology, N stage
Getman [34]	2004	16 synchronous 16 metachronous	19% 19%	9 mos 16 mos	None detected
Furak [26]	2005	65	19%	19 mos	N/R
Girard [25]	2006	29	18%	22 mos	Performance status, histology, response to chemo
Flannery [30]	2008	42	21%	18 mos	Performance status
Cheufou [35]	2014	37	10%	14 mos	None detected

N number of patients, *mos* months, *N/R* not reported

younger, female, have lower T-stage, and good performance status [24, 25, 28]. There is no randomized data specifically addressing adjuvant chemotherapy for resected stage IV disease, but based on the evidence supporting adjuvant chemotherapy for completely resected stage II and III [36], it is also recommended in this scenario [23, 33]. A question for patients present with synchronous isolated brain metastasis is, which treatment should be undertaken first, the systemic or localized therapies?

Isolated Adrenal Metastasis

In well-selected patients with isolated adrenal metastasis from NSCLC, survival following complete resection of primary and metastasis ranges from 20% to 35% (Table 23.4) [37–42]. Similar to those with isolated brain metastasis, mediastinal lymph node involvement portends worse prognosis and therefor invasive mediastinal staging is encouraged [43]. Histology and laterality appear to have no impact on survival, and adjuvant chemotherapy is recommended. Operative mortality is extremely low in reported series, and local control and long-term survival are not compromised by a laparoscopic approach to adrenalectomy [38].

Isolated Lung Metastasis

In the eighth AJCC staging system oligometastatic spread within the lungs does not fall into the new M1b classification, but remains T3/4 disease if ipsilateral and M1a if contralateral. Bilateral NSCLC lesions with the same histology and that do not arise in the background of a ground glass opacity are a staging challenge. In the absence of other disease it is difficult to distinguish synchronous primary cancers and oligometastatic spread. Analysis of mutational status and genetic clonality differences are being investigated, but are not clinically reliable at this time [44]. The clinical judgment of an experienced multi-modality team is essential [23, 45], and the criteria described by Martini and Melamed in 1975 remain relevant [46]. Data on synchronous bilateral cancers is sparse, only four of 50 patients from Martini and Melamed met these criteria. As with isolated brain and adrenal metastasis, an

Table 23.4 Retrospective series of surgery in the treatment of oligometastatic non-small cell lung cancer to the adrenal glands

Author	Year	N	5-year survival	Median survival	Prognostic factors
Luketich [42]	1996	8	20%	31 mos	N/R
Porte [40]	2001	43	7%	11 mos	None
Mercier [39]	2005	23	23%	13 mos	DFI >6 mos
Strong [38]	2007	18 laparoscopic 21 open	21% 30%	13 mos 18 mos	N/R
Tanvetyanon [41]	2008	48 synchronous 66 metachronous	26% 25%	12 mos 31 mos	None
Raz [37]	2011	20	34%	N/R	N stage, ipsilateral

N number of patients, *mos* months, *N/R* not reported, *DFI* disease-free interval

exhaustive search for additional metastatic disease with PET/CT and invasive mediastinal staging is recommended prior to considering curative resection to both lesions. Parenchymal sparing resections are typically recommended when possible in this setting, with the site requiring the lesser resection being completed first to help facilitate the second resection. Overall survival following complete resection is ranges from 28% to 58% in most series [45], which is lower than one would expect for treatment of early stage NSCLC, but better than for other resected oligometastatic sites, suggesting a mix of metastatic and synchronous primaries.

Population-Based Analyses

There are several recent population-based analyses which suggest improved survival with surgical intervention in select sub-populations with stage IV NSCLC [47–50]. Inherent selection bias is a significant issue with any such analyses, but in two analyses the authors attempted to overcome that bias by only focusing on cohorts most commonly offered resection. David et al. examined the National Cancer Database (NCDB)and created a surgical selection score (SSS) using clinical factors most commonly associated with the use of surgery in advanced NSCLC including: histology, tumor size, clinical T status, clinical N status, clinical M status, Charlson comorbidity index, age, race, facility type, and insurance status. In stage IV patients with a high SSS (those most fit for resection), the risk for death was twofold higher in those patients with who did not undergo surgery compared to those who were resected [47]. Similarly, Yang et al. analyzed patients in the NCDB with cT1-2, N0, M1 and T3, N0, M1 disease and noted improved 5-year OS compared to those undergoing chemoradiation (25.1% vs. 5.8%) [49]. They also found that survival was impacted by local regional stage and the extent of resection, with those undergoing lobectomy having superior outcomes compared to those undergoing pneumonectomy or sublobar resection.

Conclusions and Recommendations

In patients with oligometastatic NSCLC with ≤3 metastatic sites amenable to resection or ablation, who do not progress on first line systemic therapy, LCT (either as surgery, external beam radiation therapy, or SBRT) to the primary tumor and all sites of disease is recommended. Patients with an N0/N1 resectable primary NSCLC and an isolated brain or adrenal metastasis should be evaluated for aggressive curative therapy following a thorough search for metastatic spread with mediastinal and extra-thoracic imaging and invasive mediational staging. If no other sites of metastases are detected, resection of the primary tumor and resection or ablation of the metastasis is recommended. Similarly, in patients with a no other sites of metastases and a previously completely resected primary NSCLC, who develop an isolated metastasis to the brain or adrenal gland (*metachronous* presentation), resection or ablation of an isolated brain or adrenal metastasis is recommended. Patients who

have undergone a curative resection of an isolated brain or adrenal metastasis and a primary NSCLC should be evaluated for adjuvant chemotherapy if they had not received chemotherapy prior to resection. Patients with a resectable N0/N1 primary NSCLC and a solitary lesion in the contralateral lung are a staging quandary (M1a disease versus multiple primary tumors); they should undergo extra-thoracic imaging (either whole-body PET or abdominal CT plus bone scan), invasive mediastinal staging, and multidisciplinary evaluation is recommended. In most cases these should be considered as synchronous secondary primary tumors and, if possible, treated with aggressively with curative intent.

Recommendations

- In patients with oligometastatic NSCLC with ≤3 metastatic sites amenable to resection or ablation, who do not progress on first line systemic therapy, LCT to the primary tumor and all sites of disease is recommended (evidence quality high, strong recommendation).
- In patients with a resectable N0/1 primary NSCLC and an isolated brain or adrenal metastasis and no other sites of metastases, resection of the primary tumor and resection or ablation of the metastasis is recommended (evidence quality moderate, strong recommendation).
- For patients with no other sites of metastases and a previously completely resected primary NSCLC, resection or ablation of a new isolated brain or adrenal metastasis (*metachronous* presentation) is recommended (evidence quality moderate, strong recommendation).
- Patients with a resectable N0/N1 primary NSCLC and a solitary lesion in the contralateral lung should be treated with curative intent for synchronous primary tumors (evidence quality moderate, strong recommendation).

A Personal View of the Data

There is a growing appreciation for the heterogeneity of stage IV NSCLC and expectation for improved outcomes in those with oligometastatic spread. This is most obvious by inclusion of the new M1b oligometastatic classification in the eighth edition of the AJCC lung cancer stating system. Most agree that favorable biology is the primary driver of prognosis in the oligometastatic setting, and the true impact of local interventions on prognosis is unclear. But in an era when local treatments carry minimal morbidity and mortality, the lack of clarity should not translate into a denial of intervention in well-selected oligometastatic patients. Recent phase II randomized studies demonstrate a near tripling of PFS with the addition of LCT in oligometastatic patients following first line chemotherapy [9, 11]. Treatment of

both the primary and metastatic lesions in these trials was predominately by radiotherapy. Consideration for resection should remain an important part of treatment of oligometastatic NSCLC. Surgery has been used in this setting for >40 years, and cure is the goal for these patients. Therefore local control, improved staging, and tissue acquisition afforded by resection validate its continued use. In the oligometastatic setting, the T and N stage carry prognostic significance. Therefore thorough staging is essential prior to embarking on an aggressive surgical approach, and invasive mediastinal staging carries increased importance. Similarly, resection by lobectomy appears to carry the best prognosis, and careful consideration should be made for more extensive resections. Ongoing questions of interest include: How many metastatic lesions can be included within the definition of oligometastasis? What is the best order of treatments? Which local therapies provide the greatest potential for cure?

References

1. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995;13(1):8–10.
2. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol. 2011;8(6):378–82.
3. Rusthoven KE, Hammerman SF, Kavanagh BD, Birtwhistle MJ, Stares M, Camidge DR. Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis. Acta Oncol. 2009;48(4):578–83.
4. Eberhardt WE, Mitchell A, Crowley J, Kondo H, Kim YT, Turrisi A 3rd, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the m descriptors in the forthcoming Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol. 2015;10(11):1515–22.
5. Ashworth AB, Senan S, Palma DA, Riquet M, Ahn YC, Ricardi U, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. Clin Lung Cancer. 2014;15(5):346–55.
6. Li D, Zhu X, Wang H, Qiu M, Li N. Should aggressive thoracic therapy be performed in patients with synchronous oligometastatic non-small cell lung cancer? A meta-analysis. J Thorac Dis. 2017;9(2):310–7.
7. Li S, Zhu R, Li D, Li N, Zhu X. Prognostic factors of oligometastatic non-small cell lung cancer: a meta-analysis. J Thorac Dis. 2018;10(6):3701–13.
8. Juan O, Popat S. Ablative therapy for oligometastatic non-small cell lung cancer. Clin Lung Cancer. 2017;18(6):595–606.
9. Gomez DR, Blumenschein GR Jr, Lee JJ, Hernandez M, Ye R, Camidge DR, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol. 2016;17(12):1672–82.
10. Gomez DR, Tang C, Zhang J, Blumenschein GR Jr, Hernandez M, Lee JJ, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, phase II, randomized study. J Clin Oncol. 2019;37(18):1558–65.
11. Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. JAMA Oncol. 2018;4(1):e173501.

12. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet. 2019;393(10185):2051–8.
13. Wronski M, Arbit E, Burt M, Galicich JH. Survival after surgical treatment of brain metastases from lung cancer: a follow-up study of 231 patients treated between 1976 and 1991. J Neurosurg. 1995;83(4):605–16.
14. Nakagawa H, Miyawaki Y, Fujita T, Kubo S, Tokiyoshi K, Tsuruzono K, et al. Surgical treatment of brain metastases of lung cancer: retrospective analysis of 89 cases. J Neurol Neurosurg Psychiatry. 1994;57(8):950–6.
15. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA. 1998;280(17):1485–9.
16. Burt M, Wronski M, Arbit E, Galicich JH. Resection of brain metastases from non-small-cell lung carcinoma. Results of therapy. J Thorac Cardiovasc Surg. 1992;103(3):399–411.
17. Congedo MT, Cesario A, Lococo F, De Waure C, Apolone G, Meacci E, et al. Surgery for oligometastatic non-small cell lung cancer: long-term results from a single center experience. J Thorac Cardiovasc Surg. 2012;144(2):444–52.
18. Collaud S, Stahel R, Inci I, Hillinger S, Schneiter D, Kestenholz P, et al. Survival of patients treated surgically for synchronous single-organ metastatic NSCLC and advanced pathologic TN stage. Lung Cancer. 2012;78(3):234–8.
19. Tonnies M, Pfannschmidt J, Bauer TT, Kollmeier J, Tonnies S, Kaiser D. Metastasectomy for synchronous solitary non-small cell lung cancer metastases. Ann Thorac Surg. 2014;98(1):249–56.
20. Downey RJ, Ng KK, Kris MG, Bains MS, Miller VA, Heelan R, et al. A phase II trial of chemotherapy and surgery for non-small cell lung cancer patients with a synchronous solitary metastasis. Lung Cancer. 2002;38(2):193–7.
21. Bartlett EK, Simmons KD, Wachtel H, Roses RE, Fraker DL, Kelz RR, et al. The rise in metastasectomy across cancer types over the past decade. Cancer. 2015;121(5):747–57.
22. Salah S, Tanvetyanon T, Abbasi S. Metastatectomy for extra-cranial extra-adrenal non-small cell lung cancer solitary metastases: systematic review and analysis of reported cases. Lung Cancer. 2012;75(1):9–14.
23. Kozower BD, Larner JM, Detterbeck FC, Jones DR. Special treatment issues in non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e369S–e99S.
24. Granone P, Margaritora S, D'Andrilli A, Cesario A, Kawamukai K, Meacci E. Non-small cell lung cancer with single brain metastasis: the role of surgical treatment. Eur J Cardiothorac Surg. 2001;20(2):361–6.
25. Girard N, Cottin V, Tronc F, Etienne-Mastroianni B, Thivolet-Bejui F, Honnorat J, et al. Chemotherapy is the cornerstone of the combined surgical treatment of lung cancer with synchronous brain metastases. Lung Cancer. 2006;53(1):51–8.
26. Furak J, Trojan I, Szoke T, Agocs L, Csekeo A, Kas J, et al. Lung cancer and its operable brain metastasis: survival rate and staging problems. Ann Thorac Surg. 2005;79(1):241–7.
27. Modi A, Vohra HA, Weeden DF. Does surgery for primary non-small cell lung cancer and cerebral metastasis have any impact on survival? Interact Cardiovasc Thorac Surg. 2009;8(4):467–73.
28. Bonnette P, Puyo P, Gabriel C, Giudicelli R, Regnard JF, Riquet M, et al. Surgical management of non-small cell lung cancer with synchronous brain metastases. Chest. 2001;119(5):1469–75.
29. Billing PS, Miller DL, Allen MS, Deschamps C, Trastek VF, Pairolero PC. Surgical treatment of primary lung cancer with synchronous brain metastases. J Thorac Cardiovasc Surg. 2001;122(3):548–53.
30. Flannery TW, Suntharalingam M, Regine WF, Chin LS, Krasna MJ, Shehata MK, et al. Long-term survival in patients with synchronous, solitary brain metastasis from non-small-cell lung cancer treated with radiosurgery. Int J Radiat Oncol Biol Phys. 2008;72(1):19–23.
31. Fuentes R, Bonfill X, Exposito J. Surgery versus radiosurgery for patients with a solitary brain metastasis from non-small cell lung cancer. Cochrane Database Syst Rev. 2006;1:CD004840.

32. Mariya Y, Sekizawa G, Matsuoka Y, Seki H, Sugawara T. Outcome of stereotactic radiosurgery for patients with non-small cell lung cancer metastatic to the brain. J Radiat Res. 2010;51(3):333–42.
33. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v1–v27.
34. Getman V, Devyatko E, Dunkler D, Eckersberger F, End A, Klepetko W, et al. Prognosis of patients with non-small cell lung cancer with isolated brain metastases undergoing combined surgical treatment. Eur J Cardiothorac Surg. 2004;25(6):1107–13.
35. Cheufou DH, Welter S, Chalvatzoulis E, Christof D, Theegarten D, Stamatis G. Surgery of primary lung cancer with oligometastatic m1b synchronous single brain metastasis: analysis of 37 cases. Thorac Cardiovasc Surg. 2014;62(7):612–5.
36. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26(21):3552–9.
37. Raz DJ, Lanuti M, Gaissert HC, Wright CD, Mathisen DJ, Wain JC. Outcomes of patients with isolated adrenal metastasis from non-small cell lung carcinoma. Ann Thorac Surg. 2011;92(5):1788–92. Discussion 93.
38. Strong VE, D'Angelica M, Tang L, Prete F, Gonen M, Coit D, et al. Laparoscopic adrenalectomy for isolated adrenal metastasis. Ann Surg Oncol. 2007;14(12):3392–400.
39. Mercier O, Fadel E, de Perrot M, Mussot S, Stella F, Chapelier A, et al. Surgical treatment of solitary adrenal metastasis from non-small cell lung cancer. J Thorac Cardiovasc Surg. 2005;130(1):136–40.
40. Porte H, Siat J, Guibert B, Lepimpec-Barthes F, Jancovici R, Bernard A, et al. Resection of adrenal metastases from non-small cell lung cancer: a multicenter study. Ann Thorac Surg. 2001;71(3):981–5.
41. Tanvetyanon T, Robinson LA, Schell MJ, Strong VE, Kapoor R, Coit DG, et al. Outcomes of adrenalectomy for isolated synchronous versus metachronous adrenal metastases in non-small-cell lung cancer: a systematic review and pooled analysis. J Clin Oncol. 2008;26(7):1142–7.
42. Luketich JD, Burt ME. Does resection of adrenal metastases from non-small cell lung cancer improve survival? Ann Thorac Surg. 1996;62(6):1614–6.
43. Aloia TA, Zimmitti G, Conrad C, Gottumukalla V, Kopetz S, Vauthey JN. Return to intended oncologic treatment (RIOT): a novel metric for evaluating the quality of oncosurgical therapy for malignancy. J Surg Oncol. 2014;110(2):107–14.
44. Wu CT, Lin MW, Hsieh MS, Kuo SW, Chang YL. New aspects of the clinicopathology and genetic profile of metachronous multiple lung cancers. Ann Surg. 2014;259(5):1018–24.
45. Detterbeck FC, Franklin WA, Nicholson AG, Girard N, Arenberg DA, Travis WD, et al. The IASLC Lung Cancer Staging Project: background data and proposed criteria to distinguish separate primary lung cancers from metastatic foci in patients with two lung tumors in the forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(5):651–65.
46. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg. 1975;70(4):606–12.
47. David EA, Andersen SW, Beckett LA, Melnikow J, Clark JM, Brown LM, et al. Survival benefits associated with surgery for advanced non-small cell lung cancer. J Thorac Cardiovasc Surg. 2019;157(4):1620–8.
48. David EA, Canter RJ, Chen Y, Cooke DT, Cress RD. Surgical management of advanced non-small cell lung cancer is decreasing but is associated with improved survival. Ann Thorac Surg. 2016;102(4):1101–9.
49. Yang CJ, Gu L, Shah SA, Yerokun BA, D'Amico TA, Hartwig MG, et al. Long-term outcomes of surgical resection for stage IV non-small-cell lung cancer: a national analysis. Lung Cancer. 2018;115:75–83.
50. Shen H, Cao Y, Li X, Tan Y, Chen J, Yang Z, et al. Surgical intervention improves survival for metastatic non-small cell lung cancer patients. Medicine (Baltimore). 2016;95(21):e3800.

Is Pulmonary Metastasectomy Effective in Prolonging Survival?

24

Erin M. Corsini and Mara B. Antonoff

Introduction

The lung is the most frequent site of metastatic disease spread among extrapulmonary primary malignancies, commonly seen among patients with colorectal cancer, sarcoma, renal cell carcinoma, and germ cell tumors [1]. While stage IV disease was once viewed as a state with few curative treatment options, surgical resection has been increasingly offered for select patient populations with limited metastatic disease burden [2, 3]. This has typically been defined by control of primary disease, absence of extrapulmonary metastases, and anatomically completely resectable pulmonary lesions [3]. Within this framework, such an intervention may afford patients with advanced disease a survival benefit with minimal associated surgical morbidity [1, 2, 4].

Despite this prevalent practice, however, investigations demonstrating its role among a variety of multimodality approaches remain notably absent from the literature to otherwise guide clinicians. Importantly, in considering metastasectomy for a patient or population of patients, one must weigh the survival benefits of such an intervention with the risks, albeit accepted to be minimal, of surgery. One must recognize that operative procedures are associated with inherent risks, as well as the concomitant need for a break from systemic therapy perioperatively, which may also be of consequence if residual disease persists postoperatively. This topic is further complicated, not only by advancements in chemotherapy, immunotherapy, and targeted agents for various molecular markers, but also by the diverse variety of primary oncologic processes which may be subject to this treatment approach [1, 5].

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Given that randomized clinical trials elucidating the optimal management of pulmonary metastatic disease are lacking, single-arm, retrospective reviews have been the primary source of data for multidisciplinary oncology care teams. However, prospective trials are presently underway for the treatment of colorectal metastatic disease, which may aid in guiding future practice, though early results are not yet available [6]. As such, a comprehensive review of the literature provides the best understanding of the current recommendations for practice.

Search Strategy

In order to characterize the outcomes of patients with resectable pulmonary metastatic disease, a Pubmed search was undertaken using the MeSH terms "lung" and "metastasectomy", and limited to the English language (Table 24.1). Additional searches were performed with keywords "lung," "pulmonary," "metastasectomy." Original articles, systematic reviews, and meta-analyses published from 2012 through 2019 were included. In total, this approach revealed 140 abstracts for review. Because no randomized data are yet available, and the outcomes of non-operatively managed patients are difficult to garner from the literature, systematic reviews and larger retrospective reports on adult patients were prioritized.

Description of Published Data

Survival

Perhaps the most prevalent histology among the literature for metastasectomy is colorectal carcinoma, as it is the most frequent tumor to metastasize to the lung, and it is estimated that 5–18% of patients will have pulmonary metastases diagnosed at some point during the disease course [7]. As such, several systematic reviews and meta-analyses are available which shed light on this topic.

Gonzalez et al. completed a meta-analysis of 25 retrospective investigations published from 2000 to 2011 which included 2925 patients treated with metastasectomy [8]. Of 24 studies which included only patients with R0 resection, the overall 5-year survival ranged from 27% to 68%. Median disease free interval (DFI) ranged from 19 to 39 months, and a shorter interval was associated with an increased

Table 24.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with anatomically resectable, lung-limited pulmonary metastatic disease	Pulmonary metastasectomy	Non-operative management, including chemotherapy, radiation therapy, radiofrequency ablation, and observation	Survival, morbidity

hazard of death (hazard ratio [HR], 1.59; 95% confidence interval [CI], 1.27–1.98). Additional factors found to be of prognostic importance were the presence of multiple metastases (HR, 2.04; 95% CI, 1.72–2.41); mediastinal or hilar nodal involvement (HR, 1.65; 95% CI, 1.38–2.02); and elevated carcinoembryonic antigen (CEA) (HR, 1.91; 95% CI, 1.57–2.32). Importantly, among seven studies which specifically evaluated a history of prior hepatic metastasectomy, this was not determined to correlate with survival outcomes (HR, 1.22; 95% CI, 0.91–1.64).

A meta-analysis by Zabaleta et al. more closely examined the prognostic significance of hepatic metastatic disease, and demonstrated an increased hazard of death for patients with prior liver metastases (HR, 1.37; 95% CI, 1.14–1.64) [9]. These results were based upon data collected from 3501 patients across 17 studies with low heterogeneity. Other factors associated with poorer survival included positive intrathoracic nodal disease, positive surgical margins, number and size of pulmonary metastases, preoperative CEA, DFI, and wedge resection (vs. lobectomy). Median overall survival among patients with a history of liver metastases (n = 744) was less than the overall cohort at 51.8 months (vs. 64 months), with 5-year survival of 44.5% (vs. 51.9%). Among patients with available data regarding timing of hepatic and pulmonary metastatic disease diagnoses (n = 273), patients presented with synchronous liver-lung metastases in equal proportion to metachronous lesions (138, 50.5% vs. 135, 49.5%); mean survival times did not differ between these two groups.

Similarly, a subsequent review by Lumachi et al. pooled data from 15 studies published between 2002 and 2015 which evaluated the outcomes of 1669 patients [7]. Included reports were those with at least 50 patients per study with reported 5-year survival rates, and multivariable analyses to determine factors associated with survival. Among this group, the median 5-year survival rate was 45% (range 25–72%). Factors associated with poorer survival on multivariable analysis were similar to Gonzalez's report, and included larger nodule size, bilateral nodules, elevated CEA, hilar or mediastinal LN involvement, shorter DFI, incomplete (R1) resection, poorly differentiated tumors, receipt of neoadjuvant chemotherapy, older age, and female sex. The authors further evaluated the relationship of colorectal mutational status to survival outcomes, and noted several reports which demonstrate KRAS- and BRAF-mutant patients to have higher incidences of pulmonary metastases and, additionally, poorer outcomes. These results are echoed by a more recent report by Corsini et al. which showed similar results for patients with RAS (KRAS or NRAS) or TP53 mutations following metastasectomy, though mutant APC was associated with prolonged survival [10].

While colorectal metastases remain the most common indication for pulmonary metastasectomy, several other primary malignancies frequently occur in the lung and have been the topic of investigations. Marulli et al. assessed 21 retrospective reports from 1996 to 2016 [11]. While the authors importantly note the heterogeneity within these investigations, particularly in terms of histologic classification (osteosarcoma versus soft-tissue sarcoma), 5-year survival rates between 15% and 51% were reported, with superior survival identified among those with osteosarcoma. Similar to other tumor types discussed herein, commonly identified

prognostic factors were age, DFI, number of metastases, and completeness of resection. The authors also discussed the association of grade with outcomes, although this is appears to be intimately related to the extent of pulmonary disease (high grade sarcoma associated with more pulmonary metastases). Traditionally chemoresistant, tumor responsiveness to (or nonprogression during) neoadjuvant treatment was cited as a favorable prognostic indicator as well. The relationship between number and size of metastases, as well as total tumor burden (bilateral versus unilateral), with outcomes is less clear for sarcoma, as compared to colorectal carcinoma, for example [11, 12]. Select groups of sarcoma patients have been known to undergo multiple metastasectomies over the course of the disease.

Astute understanding of prognostic factors for patients with soft-tissue sarcomas is made challenging by the wide variety of histologic variants, given that many investigations report on mixed histologies. Leiomyosarcoma appears to have a less aggressive biology, with some investigations reporting somewhat superior survival when compared to other histologic subtypes [11]. In their large, single center evaluation, Chudgar et al. evaluated 539 patients with soft-tissue sarcoma undergoing 760 metastasectomies, many of whom had leiomyosarcoma (n = 169, 39%) [13]. With the exception of fibrosarcoma, which was a relatively small proportion of the cohort (n = 33, 6%), those with leiomyosarcoma had the longest median overall survival at 42 months (HR, 0.66; 95% CI, 0.48–0.89). Among the entire cohort, the 5-year survival was 34%. Other prognostic factors determined by multivariable analysis included primary tumor size, DFI, number of metastases, response to neoadjuvant therapy, surgical approach, and presentation with synchronous metastatic sites of disease.

In considering metastasectomy for melanoma, surgical management of pulmonary metastatic disease positively correlated with a survival advantage when compared to nonsurgical management [14]. In addition to metastasectomy conferring a survival advantage, other prognostic indicators were histologic classification, extrathoracic metastatic disease, and number of lung lesions. Similar publications have also implicated responsiveness to systemic therapies (chemotherapy and immunotherapy), as well as DFI [2]. Survival rates at 5 years ranged from 4.5% to 38% [1, 14]. The authors also cited advancements in targeted agents which, when used in conjunction with surgical resection in appropriately selected candidates, may further confer survival advantages for this unique population. Additionally, using the Ontario Cancer Registry, Hanna et al. evaluated the outcomes of 99 patients following metastasectomy for melanoma and determined the 5-year survival to be 21% [15]. Tumor size and completeness of resection were deemed to be related to outcomes.

Renal cell carcinoma commonly presents as stage IV disease, and though this portends a poor prognosis, resection of limited pulmonary metastatic disease similarly appears to offer favorable outcomes with 5-year survival rates of 36–53% [14]. A review by Zhao et al. reported results of 16 studies published from 1997 to 2014 covering 1447 patients [16]. The median 5-year survival was 43%, and multivariable analysis revealed regional nodal involvement related to the primary tumor and/or metastases, completeness of resection, size and number of metastases, and DFI

to be associated with survival outcomes. Similar to melanoma, monoclonal antibodies and inhibitor molecules, such as bevacizumab and sorafenib, are changing the state of disease management [14].

Thoracic Nodal Dissection

Recommendations regarding intrathoracic lymph node dissection in the setting of metastasectomy have been less clear. In their review of prior investigations, Sihag et al. identified several works which demonstrated poorer durable survival benefit in patients with intrathoracic nodal disease [17]. Prior works have, furthermore, been unable to establish a differential survival based upon nodal sampling versus radical lymphadenectomy, or N1 versus N2 disease [18]. Nodal sampling or total lymphadenectomy, however, is not routine, and is often only undertaken in the setting of aggressive disease biology or concerning mediastinal or hilar nodal tissue. While these principles represent a selection bias, and therefore prevent any conclusive evidence to support this practice globally, performing nodal sampling/dissection may help to direct management in the adjuvant setting.

Extent of Resection

A parenchymal conserving approach should be emphasized for pulmonary metastasectomy, particularly when considering patients with multiple lesions or the anticipated need for future resections. A stapled segmental resection is most often employed, while more extensive anatomic resections are reserved for larger (or multiple) tumors [4, 19]. Such an approach also minimizes risks of postoperative morbidity. In comparison to a stapled wedge, segmentectomy may also have superior overall and disease-free survival according to some reports [19].

Several authors have suggested that pneumonectomy be a strong contraindication to metastasectomy, carrying up to a 19% perioperative mortality risk. However, rare indications for such an extensive procedure have been advocated by some, including for solitary, central tumors after a prolonged DFI [4]. For more peripheral disease, however, given the lack of evidence, completeness of resection continues to be cited as the most important consideration for any metastasectomy. Barring positive margins, a minimalist, lung-sparing approach has not been demonstrated to be inferior, and affords the patient the opportunity for future metastasectomies, if needed.

Lung-Directed Chemotherapy

Phillips et al. reviewed several factors in the management of patients with colorectal pulmonary metastases, including the use of systemic therapy directed at lung lesions [19]. The authors note that no consensus exists as to the use of neoadjuvant or

adjuvant chemotherapy related to treatment of pulmonary metastases. Among 354 patients evaluated as part of a multi-institutional study, neoadjuvant and adjuvant systemic therapy were used in 7.6% and 34.5% of cases, without observed differences in disease-free or overall survival [20]. An additional analysis in only patients with positive intrathoracic nodal disease was furthermore unable to identify a benefit to chemotherapy used in the adjuvant setting [21].

In a recent review by Guerrera et al., six studies including data pertaining to administration of perioperative chemotherapy were analyzed [22]. Overall, systemic therapy used in the perioperative period with respect to pulmonary metastasectomy did not demonstrate a survival benefit, however, all studies reported prolonged disease-free survival among patients who received chemotherapy. Although the authors concluded that the available evidence does not support a shift towards incorporation of lung-directed chemotherapy into the treatment paradigm overall, there may be select patients who are most likely to benefit. They note that such populations include patients with multiple or metachronous pulmonary metastases, low-risk patients, and those of certain molecular subtypes. While supporting data are limited to a single study, there many also be evidence to demonstrate superiority of oxaliplatin-based regimens in terms of long-term outcomes, particularly when compared to irinotecan.

Surgical Approach

Just as there is debate as to the optimal operation for resection of primary lung malignancies, so, too, are there investigations exploring this topic in the realm of metastasectomy. Although randomized controlled trials have not been completed in this arena, several reports have examined this topic. A review by Greenwood et al. offers reassuring, if guarded, evidence to support either thoracotomy or VATS as equivalent in terms of survival in their review [23]. Though high rates of complications, as well as longer hospital and chest tube durations, were observed in patients undergoing thoracotomy for a variety of histologies, differences in baseline characteristics suggest the possibility of selection bias, limiting extrapolation of these data. Furthermore, while surgical margins were narrower in patients undergoing VATS metastasectomy, this did not result in survival differences between groups.

In a unique prospective investigation by Eckardt et al., pulmonary metastases identified on computed tomography imaging were evaluated by both VATS and open thoracotomy [24]. This prospective observer-blinded study evaluated 89 patients in whom 140 pulmonary metastases were identified on computed tomography imaging, and included a variety of primary malignancies. Patients were taken to the operating room where they first underwent VATS during which digital palpation was attempted to identify the known nodule. Without resecting the metastasis, a new operating team completed a thoracotomy and similarly attempted to identify the nodules. VATS was successful in identifying 122 (87%) nodules; while thoracotomy was able to identify all radiographically-identified metastases, 67 additional nodules were found, comprised of 22 (33%) secondary metastases, 43 (64%) benign

lesions, and two (3%) primary lung malignancies. In contrast, no extra tumors were identified via VATS. Because a significant proportion of these additionally recognized tumors were of malignant etiology despite routine dedicated computed tomography imaging (3 mm slice thickness), the authors concluded that VATS is inadequate for the management of pulmonary metastatic disease. In a related review, Macherey et al. reported an increased detection of nodules by manual palpation when compared to helical computed tomography imaging, though nearly half (48.5%) of these lesions were of benign etiology [25]. Conclusions related to the superiority of one approach over another from Macherey's report, however, are limited by the fact that a majority of studies reviewed included scans with slice thickness greater than 5 mm, up to and including 10 mm. Despite the increased detection of additional nodules, resulting 5-year survival rates do not differ when considering patients undergoing thoracotomy versus VATS resections [14].

The selection of surgical approach should also be weighed with the risk of postoperative complications. Greenwood et al. found the length of both hospital stay and chest tube duration to be shorter among patients undergoing VATS resection, though the issue of selection bias affecting these outcomes limits extrapolation of these data [23]. The authors were unable to demonstrate survival differences between the two surgical groups, despite some individual studies showing closer surgical margins among patients undergoing VATS metastasectomy. Postoperative events were also more common among patients receiving thoracotomy.

Conclusions and Recommendations

Although the available data limit our ability to know the precise incremental benefit of surgery over nonsurgical management which is afforded to patients with lung-limited metastatic disease, it is evident that survival in this unique population can be improved via resection in selected patients. In particular, those patients with single, small nodules after a prolonged DFI have the most to gain. Metastasectomy for colorectal carcinoma and sarcoma are commonly undertaken and afford reasonable survival expectations to these patient populations, although the benefit is less clear for patients with melanoma, especially in the setting of poor prognosticators.

When considering an open or minimally invasive approach, it is important to consider that while a thoracotomy may aid in detecting additional nodules, such lesions may be benign, and, even in the setting of malignant lesions, a survival benefit has not been demonstrated in patients who have undergone more thorough resections. Nodal sampling, particularly for bulky or concerning adenopathy, may be clinically important to management decisions, though such resections have not been shown to improve outcomes. Finally, a parenchymal-sparing approach is paramount, particularly in this population with proven lung disease, and a propensity to require future resections.

In considering our recommendations, it is important to recall that we are unarmed with randomized data which would otherwise help us to best identify the ideal cohort of patients who may benefit from resection. Because of this lack of evidence,

the possibility of selection bias cannot be excluded, such that patients who appear to profit from metastasectomy in retrospective investigations may alternatively represent a unique, resectable group with favorable disease characteristics, who would be more likely to have fortunate prognoses, even in the absence of surgery.

Recommendations

- Resection is recommended for a single metastasis OR a limited number of metastases in the setting of a prolonged DFI (evidence quality low; weak recommendation).
- When a minimally invasive approach is technically feasible, either thoracotomy or video-assisted thoracoscopic surgical resections are acceptable (evidence quality low; weak recommendation).
- Surgery should be undertaken only if complete local control is achievable (evidence quality low; weak recommendation).
- A parenchymal-sparing approach should be employed (evidence quality low; weak recommendation)
- Intrathoracic nodal dissection is recommended if it will aid in guiding adjuvant therapeutic strategies (evidence quality low; weak recommendation).

A Personal View of the Data

With proper patient selection, pulmonary metastasectomy can substantially prolong survival, provide patients with a disease-free state, and release them from the interminable need for systemic therapy.

In general, we know that patients with fewer metastases, longer DFI, and less aggressive disease characteristics derive the greatest benefit from pulmonary resection (Table 24.2). However, as practicing clinicians, it is also not easy to deny operations to patients with greater numbers of lesions, metastases present at diagnosis, and aggressive tumor biology. This problem is particularly challenging given the frequency with which we see lung-limited colorectal and sarcoma metastases in patients who are young, otherwise healthy, and eager for aggressive therapy regardless of their relatively higher risk of subsequent pulmonary recurrence. Younger adults in these scenarios tend to have favorable performance status, reassuring spirometry values, and eagerness to "fight the odds." Thus, while data such as DFI and number of metastases help us render prognoses to our patients, they do not necessarily determine strict criteria for resection. Strict criteria for resection should include: absence of extrathoracic disease, control of the primary tumor, anatomic ability to resect all pulmonary disease, and adequate pulmonary function to tolerate the necessary resection to render the patient disease-free.

Table 24.2 Series on pulmonary resection for metastatic disease

Author (Year)	Patient group	Outcomes	Histology	5-Year survival	Prognostic factors of poorer survival
Gonzalez et al. (2013) [8]	25 studies published between 2000 and 2011	Overall survival Multivariable analysis of prognostic factors for survival	Colorectal carcinoma	27–68% (for 24 studies including only patients with R0 resection)	DFI, multiple lung metastases, positive hilar/mediastinal LN, CEA
Lumachi et al. (2016) [7]	15 studies published between 2002 and 2015	Overall survival Multivariable analysis of prognostic factors for survival	Colorectal carcinoma	25–72%	CEA, multiple or bilateral lung metastases, positive hilar/mediastinal LN, DFI, positive margins, use of neoadjuvant chemotherapy, age
Zabelata et al. (2018) [9]	17 studies published between 2007 and 2014	Overall survival Multivariable analysis of prognostic factors for survival	Colorectal carcinoma	51.9%	History of liver metastases, positive intrathoracic LN, positive margins, number of lung metastases, metastasis size, CEA, DFI, wedge resection
Marulli et al. (2017) [11]	21 studies published between 1996 and 2016	Overall survival Multivariable analysis of prognostic factors for survival	Sarcoma	15–51%	DFI, positive margins, number of lung metastases, age, histologic subtype; grade
Chudgar et al. (2017) [13]	Single center, 1991–2014, n = 539	Overall survival Disease-free survival Multivariable analysis	Soft-tissue sarcoma	34%	Histologic subtype, primary tumor size, DFI, number of metastases, response to neoadjuvant therapy, surgical approach, synchronous metastases
Zhao et al. (2017) [16]	16 studies published between 1997 and 2014	Overall survival Multivariable analysis of prognostic factors for survival	Renal cell carcinoma	18–58% (43% overall)	Primary tumor LN involvement, positive margins, number of lung metastases, metastasis size, positive hilar/mediastinal LN, synchronous metastases, DFI

(continued)

Table 24.2 (continued)

Author (Year)	Patient group	Outcomes	Histology	5-Year survival	Prognostic factors of poorer survival
Hanna et al. (2018) [15]	Registry, 2004–2012, n = 99	Overall survival Multivariable analysis of prognostic factors for survival	Melanoma	21%	Tumor size, positive margins Note: increasing tumor size correlated with positive surgical margins

DFI disease-free interval, *LN* lymph node, *CEA* carcinoembryonic antigen

We do not have adequate data to suggest any benefit to nodal sampling or dissection; however, it is a low morbidity adjunct that may provide prognostic information to the treating oncology team. Moreover, nodes that are grossly abnormal should be removed, despite unknown benefit, for diagnostic purposes.

With regard to operative approach, the authors tend to make individualized decisions based on each patient's situation. Patients with a single, solitary metastasis that has been present for an extended period of surveillance without development of other nodules might be easily removed thoracoscopically. On the other extreme, patients with five or greater metastases that are anatomically resectable may fare better with a small, muscle-sparing thoracotomy, given the higher likelihood of identifying additional lesions that were not anticipated on preoperative imaging and the increased range of motion for stapler angles to maximize sparing of parenchyma. Moreover, recent data have shown that the postoperative differences between VATS and open surgery are narrowed in an enhanced recovery environment. Thus, we would recommend tailoring the surgical approach to the patient and his/her disease state.

References

1. Cheung FP, Alam NZ, Wright GM. The past, present and future of pulmonary metastasectomy: a review article. Ann Thorac Cardiovasc Surg. 2019;25:129–41.
2. Petrella F, Diotti C, Rimessi A, Spaggiari L. Pulmonary metastasectomy: an overview. J Thorac Dis. 2017;9:S1291–s8.
3. Erhunmwunsee L, Tong BC. Preoperative evaluation and indications for pulmonary metastasectomy. Thorac Surg Clin. 2016;26:7–12.
4. Nichols FC. Pulmonary metastasectomy: role of pulmonary metastasectomy and type of surgery. Curr Treat Options in Oncol. 2014;15:465–75.
5. Schweiger T, Lang G, Klepetko W, Hoetzenecker K. Prognostic factors in pulmonary metastasectomy: spotlight on molecular and radiological markers. Eur J Cardiothorac Surg. 2014;45:408–16.
6. ClinicalTrials.gov. Chemotherapy and/or metastasectomy in treating patients with metastatic colorectal adenocarcinoma with lung metastases. Available at https://clinicaltrials.gov/ct2/show/NCT03599752. Accessed 10 Sep 2019.
7. Lumachi F, Chiara GB, Tozzoli R, Del Conte A, Basso SM. Factors affecting survival in patients with lung metastases from colorectal cancer. A short meta-analysis. Anticancer Res. 2016;36:13–9.

8. Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. Ann Surg Oncol. 2013;20:572–9.
9. Zabaleta J, Iida T, Falcoz PE, et al. Individual data meta-analysis for the study of survival after pulmonary metastasectomy in colorectal cancer patients: a history of resected liver metastases worsens the prognosis. Eur J Surg Oncol. 2018;44:1006–12.
10. Corsini EM, Mitchell KG, Mehran RJ, et al. Colorectal cancer mutations are associated with survival and recurrence after pulmonary metastasectomy. J Surg Oncol. 2019;120:729.
11. Marulli G, Mammana M, Comacchio G, Rea F. Survival and prognostic factors following pulmonary metastasectomy for sarcoma. J Thorac Dis. 2017;9:S1305–s15.
12. Digesu CS, Wiesel O, Vaporciyan AA, Colson YL. Management of sarcoma metastases to the lung. Surg Oncol Clin N Am. 2016;25:721–33.
13. Chudgar NP, Brennan MF, Munhoz RR, et al. Pulmonary metastasectomy with therapeutic intent for soft-tissue sarcoma. J Thorac Cardiovasc Surg. 2017;154:319–30.e1.
14. Ripley RT, Downey RJ. Pulmonary metastasectomy. J Surg Oncol. 2014;109:42–6.
15. Hanna TP, Chauvin C, Miao Q, et al. Clinical outcomes after pulmonary metastasectomy for melanoma: a population-based study. Ann Thorac Surg. 2018;106:1675–81.
16. Zhao Y, Li J, Li C, Fan J, Liu L. Prognostic factors for overall survival after lung metastasectomy in renal cell cancer patients: a systematic review and meta-analysis. Int J Surg. 2017;41:70–7.
17. Sihag S, Muniappan A. Lymph node dissection and pulmonary metastasectomy. Thorac Surg Clin. 2016;26:315–23.
18. Seebacher G, Decker S, Fischer JR, Held M, Schafers HJ, Graeter TP. Unexpected lymph node disease in resections for pulmonary metastases. Ann Thorac Surg. 2015;99:231–6.
19. Phillips JD, Hasson RM. Surgical management of colorectal lung metastases. J Surg Oncol. 2019;119:629–35.
20. Pages PB, Serayssol C, Brioude G, et al. Risk factors for survival and recurrence after lung metastasectomy. J Surg Res. 2016;203:293–300.
21. Hamaji M, Cassivi SD, Shen KR, et al. Is lymph node dissection required in pulmonary metastasectomy for colorectal adenocarcinoma? Ann Thorac Surg. 2012;94:1796–800.
22. Guerrera F, Falcoz PE, Renaud S, Massard G. Does perioperative chemotherapy improve survival in patients with resectable lung metastases of colorectal cancer? Interact Cardiovasc Thorac Surg. 2017;24:789–91.
23. Greenwood A, West D. Is a thoracotomy rather than thoracoscopic resection associated with improved survival after pulmonary metastasectomy? Interact Cardiovasc Thorac Surg. 2013;17:720–4.
24. Eckardt J, Licht PB. Thoracoscopic or open surgery for pulmonary metastasectomy: an observer blinded study. Ann Thorac Surg. 2014;98:466–70.
25. Macherey S, Doerr F, Heldwein M, Hekmat K. Is manual palpation of the lung necessary in patients undergoing pulmonary metastasectomy? Interact Cardiovasc Thorac Surg. 2016;22:351–9.

Part II

Esophagus

Surgical Resection Versus Endoscopic Therapy for T1bN0 Esophageal Adenocarcinoma

25

Bailey Su and Mark K. Ferguson

Introduction

Treatment for esophageal cancer has traditionally centered around removal of tumor burden, mainly by esophagectomy. However, with the improvement of endoscopic surveillance and early detection, more T1 cancers are being diagnosed, and due to the perceived safety of endoscopic therapy (ET), the rate of local treatment for T1 esophageal cancer has been steadily increasing from 8.1% in 1998 to 24.1% in 2008 [1]. Notably, the rate of ET specifically for T1b lesions has also increased, from 6.6% in 2004 to 20.9% in 2010 [2]. However, the inability to resect and thoroughly evaluate lymph nodes with ET remains a major concern, given the relatively high risk of lymph node involvement even in early stage esophageal carcinoma. Additionally, ET frequently requires multiple procedures to clear all disease as well as frequent long-term endoscopic surveillance [3]. The objective of this chapter is to compare the outcomes after ET versus esophagectomy for T1bN0 esophageal adenocarcinoma (EAC), taking into consideration the morbidity/mortality of each procedure along with the risk of lymph node metastasis (LNM) in clinical T1b disease.

Search Strategy

The PubMed database was searched for full text articles in English (from 2004 to 2019), utilizing any of the following terms: “early esophageal adenocarcinoma”, “T1”, “early-stage”, “submucosal adenocarcinoma”, “endoscopic resection”, “endoscopic mucosal resection”, “endoscopic submucosal dissection”, “esophagectomy”, “lymph node metastasis/metastases”, “outcomes”. The reference list of all

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Table 25.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Resectable patients with clinical T1bN0 esophageal cancer	Esophagectomy	Endoscopic therapy	Morbidity Mortality Oncologic outcomes (OS, DFS, CSS and recurrence)

OS overall survival, *DFS* disease-free survival, *CSS* cancer-specific survival

reviewed papers was also searched for applicable articles subsequently included in this chapter (Table 25.1).

Results

Outcomes of Endoscopic Therapy Versus Esophagectomy

Morbidity and Oncologic Outcomes After Endoscopic Therapy

Overall, ET for esophageal mucosal adenocarcinoma seems safe with moderately good oncologic outcomes (Table 25.2). The reported rates of bleeding after ET for early EAC lesions ranges from 0% to 6.5% and rates of perforation are similarly low at 0–2.2% [4–6]. Post-procedural stricture is the most common complication (0–22.2%), the risk of which increases if larger pieces of tissue must be resected. Treatment of strictures often requires multiple interventions, each of which carries a risk of perforation [6]. Probst et al. reported a 0% perforation incidence with the initial endoscopic resection, however they did have a subsequent dilation-related perforation for a patient who underwent ET and developed a stricture [5].

The oncologic outcomes after ET for T1b EAC are scarce and have been inconsistently reported, but appear promising. Rates of curative resection ranged from 56.3% to 87% and likely varied depending on endoscopist experience. Complete endoluminal remission required a mean of 2.6 ± 2.9 endoscopic procedures over a mean treatment period of 4.5 ± 5.3 months, and rates of local recurrence ranged from 0% to 2.4% [4–6]. Only one study reported an estimated 5-year survival (84%), but it's important to note that this was only for patients with low risk T1b lesions confined to sm1 (Manner) [4].

Taken together, these studies suggest that ESD is safe for submucosal EAC, however longer-term data with much larger sample sizes are necessary to determine the true impact of endoscopic therapy alone on local recurrence rates and overall survival.

Morbidity and Oncologic Outcomes After Esophagectomy

While esophagectomy has been generally considered a high-risk operation, more recent studies have reported excellent outcomes after esophagectomy, with in-hospital mortality as low as 1–2.82% for all-comers in high volume centers [7–9]. There are a handful of studies with relatively large sample sizes that have looked at outcomes after esophagectomy specifically for early EAC (Table 25.3) [10–15]. Again, the rate of in-hospital mortality is relatively low, ranging from 2.6% to 4.5% [10, 12–14]. The rate of overall morbidity is around 32%, with anastomotic leak rates ranging from 8% to 10.3% [10, 12].

Table 25.2 Procedural and oncologic outcomes after endoscopic therapy for early stage esophageal adenocarcinoma

Author [ref]	Year	N	T-stage	Curative resection	Bleeding	Perforation	Stricture	LN mets	Metachronous neoplasia	Local recurrence	5 Year survival	Mean follow-up	Grade
Manner [4]	2013	66	Low risk pT1b sm1	53/61 (87%)	0/66 (0%)	1/66 (1.5%)	0/66 (0%)	1/53 (1.9%)	10/53 (18.9%)	NR	84%	47 ± 29.1 months	Moderate
Probst [5]	2015	87	T1a, T1b	All EAC: 63/87 (72.4%) ≤M3: 46/60 (76.7%) >M3: 17/27 (63.0%)	>M3 1/27 (3.7%)	>M3 0/27 (0%)	6/27 (22.2%)	NR	NR	2/82 (2.4%)	NR	24.3 months	Low
Yang [6]	2017	46	HGD, T1a, T1b	EAC only: 18/32 (56.3%)	3/46 (6.5%)	1/46 (2.2%)	7/46 (15.2%)	NR	NR	0/32 (0%)	NR	11.3 months	Low

N sample size, *T-stage* tumor stage, *LN* lymph node, *GRADE* Grades of recommendation, Assessment, Development and Evaluation, *sm* submucosal, *NR* not reported, *EAC* esophageal adenocarcinoma, *m3* mucosal 3, *HGD* high grade dysplasia

Table 25.3 Oncologic outcomes after esophagectomy for early stage esophageal adenocarcinoma

Author Year [ref]	N	Study type	T-stages (N)	Surgery type (N)	Peri-operative morbidity	Survival	Follow up	Grade
Altorki et al 2008 [10]	75	Single center, retrospective	T1a (30) T1b (45) (60 EAC, 15 SCC)	Open transthoracic (49) Open transhiatal (26)	Overall: 24/75 (32%) Anastomotic leak: 6/75 (8%)	In-hospital mortality: 2/75 (2.6%) Median OS: 12.4 years 5-year OS: 78.6% T1a: 90%, T1b: 71% 5-year CSS: 86.5% T1a: 96.7%, T1b: 79.6%	Median: 4.4 years	Low
Pennathur et al 2009 [11]	100	Single center, retrospective	T1a (29) T1b (71)	Open McKeown (77) Open Ivor-Lewis (5) Transhiatal (18)	NR	30-day mortality: 0% Median OS: 84 months Median 3 year DFS: 80% Estimated 5-year OS (T1b only): 60%	Median: 66 months	Low
Grotenhuis et al 2010 [12]	222	Multi-center, retrospective	T1b (164 EAC, 58 SCC)	Open transthoracic (132) Transhiatal (90)	Anastomotic leak: TTE: 11/132 (8.3%) THE: 12/90 (13.3%) Bleeding: TTE: 2/132 (1.5%) THE: 2/90 (2.2%)	In-hospital mortality: 10/222 (4.5%) 5-year OS: 65.8% 5-year DFS: 77.5% 5-year DFS (EAC only): 76.7% Recurrence: 46/222 (20.7%)	At least 5 years	Moderate
Griffin et al 2011 [13]	119	Single center, retrospective	HGD (23) T1a (31) T1b (65)	Open Ivor-Lewis	NR	In-hospital mortality: 5/119 (4%) OS: 79% CSS (T1b): 88% Recurrence (T1b): 8/119 (7%)	Median: 1246 days	Moderate

Lorenz et al 2014 [14]	168	Single center, retrospective	T1a (42) T1b (126)	Open Ivor Lewis (130) Modified Merendino (30) Transhiatal (2) MIE McKeown (6)	NR	In-hospital: 5/168 (2.97%) 5-year OS: 79% sm1—83.5%, sm2—67.8%, sm3—70.4% 5-year CSS: sm1—92.3%, sm2—89.2%, sm3—81% 5-year recurrence: 13% sm1—6.9%, sm2—16.8%, sm3—21.9%[a]	Median: 64 months	Moderate
Dubecz et al 2015 [15]	589	SEER DB review	T1a (329) T1b (345)	NR	NR	5-year OS: T1a—86%, T1b 65%	Median: 27 months	Moderate

N sample size, *T-stage* tumor stage, *GRADE* Grades of recommendation, Assessment, Development and Evaluation, *NR* not reported, *OS* overall survival, *DFS* disease-free survival, *EAC* esophageal adenocarcinoma, *SCC* squamous cell carcinoma, *TTE* transthoracic esophagectomy, *THE* transhiatal esophagectomy, *HGD* high grade dysplasia, *MIE* minimally invasive esophagectomy, *CSS* cancer-specific survival, *sm* submucosal, *SEER DB* Surveillance, Epidemiology, and End Results database

[a]Five-year recurrence rate for patients with sm2/3 disease was significantly higher than those with m1-sm1 disease (20.3% vs. 5.7%; P = 0.021)

In regard to oncologic outcomes for patients with T1b EAC, 5-year overall survival rates after esophagectomy ranged from 65% to 79% [10, 12, 14, 15]. For patients specifically with sm1 disease, Lorenz et al. found a 5-year overall survival rate of 83.5% after esophagectomy, comparable to the estimated 5-year survival rate of 84% reported after endoscopic resection by Manner et al. [4, 14]. The median overall survival was 7–12.4 years and 5-year cancer specific survival ranged from 79.6% to 92.3% [10, 14]. Interestingly, Lorenz et al. examined 168 esophagectomy specimens, 124 of which had had a prior endoscopic resection. After surgery, it was found that 113 (91.2%) of the endoscopically resected specimens histologically corresponded exactly to the postoperative histology. For the other 11 patients, the final histology showed a deeper infiltration as compared to the endoscopically resected specimen, although none of these had a clear margin basally originally, so surgery was recommended regardless [14].

Overall Survival Comparison Between ET and Esophagectomy

In regards to overall survival, there are only a few studies that directly compare survival after endoscopic therapy (ET) to esophagectomy for T1b esophageal adenocarcinoma, and they all utilize the Surveillance Epidemiology and End Results (SEER) cancer database. Zeng et al. analyzed data from 1998 to 2013, and compared cancer-specific survival (CSS) and overall survival (OS) after treatment for T1b tumors (both adenocarcinoma and squamous cell carcinoma) [16]. They found no differences in treatment-related CSS (HR, 0.651; 95% CI 0.174–2.434; $P = 0.651$) or overall survival (HR, 1.950; 95% CI 0.770–4.942; $P = 0.159$) after ET versus surgery. Ngamruengphong and colleagues had similar findings when looking specifically at T1b adenocarcinoma from 1998 to 2009. They also found no difference in CSS (HR 0.46; 95% CI 0.16–1.28; $P = 0.14$) or OS (HR 0.97; 95% CI 0.53–1.77; $P = 0.93$) after ET versus surgery [17]. Similarly, Wani et al. used data from 1998 to 2009 and also found comparable 2- and 5-year cancer-related mortality rates when comparing ET to surgery for T1b EAC [18].

Lymph Node Metastasis

The main disadvantage of ET for T1b adenocarcinoma is the risk of leaving behind untreated nodal disease, particularly when the presence of LNM is the most important factor for prognosis [11, 14, 15, 19]. For patients with early EAC (both T1a and T1b), Lorenz at al. reported a 5-year survival rate of 87.1% for pN0 disease versus 56.0% for pN+ disease ($P < 0.001$), concluding that the presence of LNM was the strongest predictor for a cure [14]. In fact, LNM was an independent risk factor for overall survival, tumor-specific survival and tumor recurrence. Dubecz et al. also found that the overall 5-year survival rate for early EAC was significantly better for pN0 versus pN+ disease (78% vs. 51%, $P < 0.001$) [15]. These studies indicate that accurate nodal staging is critical to patient prognosis.

In order for ET to be considered a viable option for management of early EAC, the rates of LNM would need to be acceptably low or our ability to predict lymph node involvement would need to be exceedingly high. There are many studies which have reported the rates of LNM for T1a and T1b esophageal adenocarcinoma based on esophagectomy specimens (Table 25.4) [2, 3, 11, 13–15, 19–26]. The rate of

Table 25.4 Rates of lymph node metastasis in patients undergoing esophagectomy for T1 lesions

Author Year [ref]	Study type	Total N (N T1b)	T1a LNM	T1b LNM		Notes	GRADE
				Sm1	Sm2/3		
Bollschweiler et al. 2005 [20]	Retrospective, single center	36 (22)	0/14 (0%)	2/9 (22%)	7/13 (54%)	Sm3 vs. Sm1/2 ($P < 0.01$)	Low
Pennathur et al. 2009 [11]	Retrospective, single center	100 (71)	2/29 (7%)	19/71 (27%)			Moderate
Badreddine et al. 2010 [21]	Retrospective, single center	80 (80)	-	4/31 (12.9%)	10/49 (20.4%)	No significant difference in nodal prevalence among submucosal subclasses	Moderate
Sepesi et al. 2010 [22]	Retrospective, single center	54 (29)	0/25 (0%)	3/14 (21%)	6/15 (40%)	No significant difference in nodal prevalence among submucosal subclasses	Low
Griffin et al. 2011 [13]	Retrospective, single center	96 (65)	0/31 (0%)	5/22 (23%)	3/43 (7%)	No significant difference in nodal prevalence among submucosal subclasses	Low
Leers et al. 2011 [19]	Retrospective, single center	126 (51)	1/75 (1.3%)	11/51 (22%)			Moderate
Raja et al. 2011 [23]	Retrospective, single center	107 (107)	–	3/35 (8.6%)	23/72 (31.9%)	Invasion of the deep mucosa was an independent risk factor for LNM ($P < 0.001$)	Moderate
Lee et al. 2013 [24]	Retrospective, multi-center	258 (136)	9/122 (7.4%)	35/136 (25.7%)			Moderate
Lorenz et al. 2014 [14]	Prospective, single center (prospective cohort)	168 (126)	4/42 (9.5%)	3/37 (8%)	23/89 (25.8%)	Significant correlation between increasing tumor depth (m1 to sm3) and LNM ($P = 0.004$)	Moderate
Merkow et al 2014 [2]	NCDB review	3963 (2153)	90/1810 (5.0%)	358/2153 (16.6%)		EAC 89.4%, SCC 10.6%	Moderate

(continued)

Table 25.4 (continued)

Author Year [ref]	Study type	Total N (N T1b)	T1a LNM	T1b LNM		Notes	GRADE
				Sm1	Sm2/3		
Nentwich et al. 2014 [25]	Retrospective, single center	37 (37)	–	3/8 (37.5%)	7/29 (24.1%)	No significant difference in nodal prevalence among submucosal subclasses	Low
Dubecz et al. 2015 [15]	SEER database review	1127	6.4% If >23 LN removed: 8.1%	19.6% If >23 LN removed: 27.8%			Moderate
Scholvinck et al. 2016 [26]	Retrospective database review (Netherlands)	26	–	0/1 (0%)	5/25 (20%)		Low
Boys et al. 2016 [3]	Multi-center retrospective	42 (23)	0%	26%			Low

N sample size, *LNM* lymph node metastasis, *GRADE* Grades of recommendation, Assessment, Development and Evaluation, *sm* submucosal, *NCDB* National Cancer Database, *LN* lymph node, *EAC* esophageal adenocarcinoma, *SCC* squamous cell carcinoma

LNM for sm1 invasion ranged from 0% to 37.5%, whereas the rate for sm2/3 invasion ranged from 7% to 54%. Studies that did not report rates based on submucosal subdivision reported a rate for all T1b lesions of 19.6–27%.

Several studies have reported risk factors to help predict the likelihood of LNM for T1b EAC. Leers et al. found that poor tumor differentiation, the presence of lymphovascular invasion (LVI), and tumor size ≥2 cm to be significantly associated with LNM [19]. Boys et al. reported similar findings, with poor tumor differentiation, LVI, and invasion into the submucosa >500 μm to be associated with higher rates of LNM [3]. While no single risk factor was identified as being the most predictive, the more risk factors present, the higher the likelihood of nodal metastasis. A predictive scoring system reported by Lee et al. has also been proposed as an algorithm to determine the risk of LNM for early EAC [24]. The weighted system takes into account tumor size, depth of invasion, differentiation and LVI, but has been criticized for weighing certain criteria too heavily and others not enough. The c-index of the model was 0.82, suggesting utility in differentiating risk categories (low risk ≤2% incidence; moderate risk 3–6% incidence; high risk ≥7% incidence).

Conclusions and Recommendations

ET is an appealing alternative to esophagectomy for T1bN0 esophageal adenocarcinoma, but the reported rates of LNM remain high. ET often requires multiple procedures to eradicate disease and relegates a patient to frequent lifelong endoscopic surveillance. In contrast, while there have been improvements in outcomes after esophagectomy, it remains a high-risk procedure.

Current diagnostic modalities (e.g. PET/CT, EUS-FNA) are fairly good at evaluating tumor burden/depth and lymph node involvement, but the significant impact of missing LNM on patient prognosis is not acceptable. This is particularly true because adjuvant therapy has limited efficacy in improving long-term prognosis, so removal of all disease remains imperative. For patients who are good surgical candidates, esophagectomy should be considered the standard of care for T1bN0 esophageal adenocarcinoma. Even for sm1 tumors, the rate of LNM still remains high and these patients should be treated with esophagectomy. For poor surgical candidates, ET can be considered after careful discussion with the patient and weighing the risk of undertreating with endoscopic therapy relative to the morbidity/mortality of esophagectomy.

Recommendations

- For surgically fit patients, esophagectomy is recommended for T1bN0 esophageal adenocarcinoma (evidence quality moderate; weak recommendation).
- For patients who are not good surgical candidates, endoscopic therapy is recommended, particularly for superficial submucosal disease (sm1) with low risk features (evidence quality low; weak recommendation).

A Personal View of the Data

We frequently find that tumors have a higher T-stage than originally diagnosed on EUS, and the risk of leaving untreated lymph nodes is not acceptable. While EUS-FNA has become fairly good at detecting nodal disease, the poor prognosis associated with presence of lymph node disease is a strong motivator to ensure clearance of all disease burden and important for post-operative decision making. As a result, in our practice, we continue to perform esophagectomy in all qualified patients with T1bN0 EAC.

References

1. Berry MF, Zeyer-Brunner J, Castleberry AW, Martin JT, Gloor B, Pietrobon R, et al. Treatment modalities for T1N0 esophageal cancers: a comparative analysis of local therapy versus surgical resection. J Thorac Oncol. 2013;8:796–802.
2. Merkow RP, Bilimoria KY, Keswani RN, Chung J, Sherman KL, Knab LM, et al. Treatment trends, risk of lymph node metastasis, and outcomes for localized esophageal cancer. J Natl Cancer Inst. 2014;106(7)
3. Boys JA, Worrell SG, Chandrasoma P, Vallone JG, Maru DM, Zhang L, et al. Can the risk of lymph node metastases be gauged in endoscopically resected submucosal esophageal adenocarcinomas? A multi-center study. J Gastrointest Surg. 2016;20:6–12. Discussion 12.
4. Manner H, Pech O, Heldmann Y, May A, Pohl J, Behrens A, et al. Efficacy, safety, and long-term results of endoscopic treatment for early stage adenocarcinoma of the esophagus with low-risk sm1 invasion. Clin Gastroenterol Hepatol. 2013;11:630–5. quiz e45.
5. Probst A, Aust D, Märkl B, Anthuber M, Messmann H. Early esophageal cancer in Europe: endoscopic treatment by endoscopic submucosal dissection. Endoscopy. 2015;47:113–21.
6. Yang D, Coman RM, Kahaleh M, Waxman I, Wang AY, Sethi A, et al. Endoscopic submucosal dissection for Barrett's early neoplasia: a multicenter study in the United States. Gastrointest Endosc. 2017;86:600–7.
7. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med. 2011;364:2128–37.
8. Markar SR, Karthikesalingam A, Thrumurthy S, Low DE. Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000-2011. J Gastrointest Surg. 2012;16:1055–63.
9. Luketich JD, Pennathur A, Awais O, Levy RM, Keeley S, Shende M, et al. Outcomes after minimally invasive esophagectomy: review of over 1000 patients. Ann Surg. 2012;256:95–103.
10. Altorki NK, Lee PC, Liss Y, Meherally D, Korst RJ, Christos P, et al. Multifocal neoplasia and nodal metastases in T1 esophageal carcinoma: implications for endoscopic treatment. Ann Surg. 2008;247:434–9.
11. Pennathur A, Farkas A, Krasinskas AM, Ferson PF, Gooding WE, Gibson MK, et al. Esophagectomy for T1 esophageal cancer: outcomes in 100 patients and implications for endoscopic therapy. Ann Thorac Surg. 2009;87:1048–54. Discussion 1054.
12. Grotenhuis BA, van Heijl M, Zehetner J, Moons J, Wijnhoven BPL, van Berge Henegouwen MI, et al. Surgical management of submucosal esophageal cancer: extended or regional lymphadenectomy? Ann Surg. 2010;252:823–30.
13. Griffin SM, Burt AD, Jennings NA. Lymph node metastasis in early esophageal adenocarcinoma. Ann Surg. 2011;254:731–6. Discussion 736.
14. Lorenz D, Origer J, Pauthner M, Graupe F, Fisseler-Eckhoff A, Stolte M, et al. Prognostic risk factors of early esophageal adenocarcinomas. Ann Surg. 2014;259:469–76.

15. Dubecz A, Kern M, Solymosi N, Schweigert M, Stein HJ. Predictors of lymph node metastasis in surgically resected T1 esophageal cancer. Ann Thorac Surg. 2015;99:1879–85. Discussion 1886.
16. Zeng Y, Liang W, Liu J, He J. Endoscopic treatment versus esophagectomy for early-stage esophageal cancer: a population-based study using propensity score matching. J Gastrointest Surg. 2017;21:1977–83.
17. Ngamruengphong S, Wolfsen HC, Wallace MB. Survival of patients with superficial esophageal adenocarcinoma after endoscopic treatment vs surgery. Clin Gastroenterol Hepatol. 2013;11:1424–1429.e2. quiz e81.
18. Wani S, Drahos J, Cook MB, Rastogi A, Bansal A, Yen R, et al. Comparison of endoscopic therapies and surgical resection in patients with early esophageal cancer: a population-based study. Gastrointest Endosc. 2014;79:224–232.e1.
19. Leers JM, DeMeester SR, Oezcelik A, Klipfel N, Ayazi S, Abate E, et al. The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma a retrospective review of esophagectomy specimens. Ann Surg. 2011;253:271–8.
20. Bollschweiler E, Baldus SE, Schröder W, Prenzel K, Gutschow C, Schneider PM, et al. High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinomas and adenocarcinomas. Endoscopy. 2006;38:149–56.
21. Badreddine RJ, Prasad GA, Lewis JT, Lutzke LS, Borkenhagen LS, Dunagan KT, et al. Depth of submucosal invasion does not predict lymph node metastasis and survival of patients with esophageal carcinoma. Clin Gastroenterol Hepatol. 2010;8:248–53.
22. Sepesi B, Watson TJ, Zhou D, Polomsky M, Litle VR, Jones CE, et al. Are endoscopic therapies appropriate for superficial submucosal esophageal adenocarcinoma? An analysis of esophagectomy specimens. J Am Coll Surg. 2010;210:418–27.
23. Raja S, Rice TW, Goldblum JR, Rybicki LA, Murthy SC, Mason DP, et al. Esophageal submucosa: the watershed for esophageal cancer. J Thorac Cardiovasc Surg. 2011;142:1403–11.e1.
24. Lee L, Ronellenfitsch U, Hofstetter WL, Darling G, Gaiser T, Lippert C, et al. Predicting lymph node metastases in early esophageal adenocarcinoma using a simple scoring system. J Am Coll Surg. 2013;217:191–9.
25. Nentwich MF, von Loga K, Reeh M, Uzunoglu FG, Marx A, Izbicki JR, et al. Depth of submucosal tumor infiltration and its relevance in lymphatic metastasis formation for T1b squamous cell and adenocarcinomas of the esophagus. J Gastrointest Surg. 2014;18:242–9. Discussion 249.
26. Schölvinck D, Künzli H, Meijer S, Seldenrijk K, van Berge Henegouwen M, Bergman J, et al. Management of patients with T1b esophageal adenocarcinoma: a retrospective cohort study on patient management and risk of metastatic disease. Surg Endosc. 2016;30:4102–13.

Does Induction Therapy for T2N0 Esophageal Adenocarcinoma Patients Improve Survival?

26

Claire L. Donohoe and John V. Reynolds

Introduction

Neoadjuvant therapy, either combination chemotherapy and radiation therapy (NeoCRT), or pre- and postoperative chemotherapy, is currently the standard of care in the management of esophageal adenocarcinoma (EAC), with the CROSS [1] and FLOT [2] regimens, respectively, providing the best evidence for such regimens at this time [3]. However, the threshold for defining "locally advanced" is not standardised. Although clinically staged cT3 or cT4, and predicted nodal involvement ($cN \geq 1$), clearly represents locally advanced disease, most clinical trials of neoadjuvant approaches also include predicted node negative disease in combination with cT3 or cT2 stage. The biggest controversy relates to cT2N0 disease, where the theoretic premise for the local and systemic advantage of radiation and chemotherapy, respectively, prior to high quality en-bloc oncologic resection, is clearly debatable [1, 4–6]. No report from the key RCTs in locally advanced EAC has provided clear data that this cohort benefits, consequently there exists no clear randomised Grade A recommendation to inform practice. The main contemporary RCTs, comparing CROSS and FLOT or FLOT/MAGIC regimens, the ESOPEC [7] and NeoAEGIS [8] trials, respectively, also enrolled patients with cT2N0 disease, but are not

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stratified on this basis. These trials moreover are likely not to be reported fully for approximately 3 years.

One RCT, albeit where 70% of patients had squamous cell cancer, provides relevant points to this discussion. In this study, the French FFCD 9901 trial, 195 patients with cT1N0//N+, cT2N0/N+ or cT3N0 tumours were assigned to preoperative 5-FU and cisplatin and concurrent 45 Gy RT versus surgery alone [6]. The trial was stopped early as the planned enrolment would not show a significant benefit in favor of one arm over the other, with 5 year survival of 41.1% vs. 33.8% in the surgery vs. multimodal groups, respectively (p = 0.94). Importantly, neoCRT was associated with a near threefold increase in postoperative in-hospital mortality (11.4% vs. 3.4%).

A major confounder in making informed decisions on cT2N0 cases is the inaccuracy of clinical staging. Endoscopic ultrasound (EUS), the gold standard, is volume and experience-dependent [9]. CT-PET assessment of nodal disease has high specificity but low sensitivity, with nodal involvement in up to 50% of predicted node negative cases. Under-staging is a bigger clinical issue than over-staging in the context of this debate, at 37–62%, compared with approximately 20% of patients over-staged (Table 26.1). Accordingly, it a valid thesis that factors associated with under-staging may be factored into decision making at tumor boards outside of clinical trials. Where patients progress to surgery alone, and where significant nodal involvement is identified at pathology, adjuvant therapy will then be recommended but this decision is also limited by the lack of high quality randomized data demonstrating benefit, adding a further layer of complexity to this question. It is probable that some patients with pN1-3 disease after surgery alone receive inadequate or ineffective adjuvant treatment due to treatment intolerance, with the potential consequence of an inferior outcome to patients treated with neoadjuvant therapy. The heterogeneity of cT2N0, in concert with the fact that at best 50% of patients will have some response to neoadjuvant chemo and/or radiation therapy, suggests a very large cohort of patients would be required to show any treatment benefit in a randomized comparison, with significant implications in trial design.

Consequently, little quality data exists to inform management. In this chapter we summarise the available current evidence that may underpin decisions, and our interpretation of how this might be applied.

Search Strategy

Table 26.2 summarises the key PICO question for this chapter. The search strategy used the terms (((((((t2n0 esophageal cancer) OR t2n0 esophageal cancer) OR t2n0 esophageal adenocarcinoma) OR t2n0 esophageal adenocarcinoma) OR t2n0 esophageal adenocarcinoma) OR t2n0 oesophageal cancer) OR t2n0 oesophageal cancer) on PUBMED. This returned 131 papers. Of these, 95 papers were not relevant to the PICO question after reviewing the abstract. Full texts were obtained for the remaining papers (n = 36) and the references from these papers were reviewed for further relevant papers with two further relevant papers identified.

Table 26.1 Summary of relevant database and single centre cohort studies

Authors	Years	Data type	Country	# Patients included	Ratio of ac/scc (n)	Clinical overstaging rate (%)	Clinical understaging rate (%)	EUS use	CT use	PET use	Induction treatment	# Surgery only	# Induction	Overall survival at 5 years (surgery vs. induction group)	Comments
Markar	2000–2010	30 European centres	Francophone	355	171/184	18.9%	48.10%	Y	y	On demand	Various	285	70	Median: 43.4 (95% CI 36.1–50.5) vs. 39.2 (95% 19.6–58.7) months, p = 0.56	
Dolan	1999–2011	Single centre	USA	27	NR	38%	56%	Y	y	Some	NCRT			37% vs. 68.7%	Understaging in T2N0 group
Martin	1998–2008	Seer registry	USA	490	339/151	NR	NR	NR	NR	NR	Radiation used during treatment	267	223	38.6% vs. 42.3%	Not sure if chemotherapy also used for treatment; no data on pathological stage results
Rice	1987–2005	Single centre	USA	61	NR	63%	37%	Y	EUS for clinical stage	EUS used for clinical stage	NCRT	53	8	52% vs. 12%	
Speicher	1998–2011	Cancer database 70% of national population	USA	1559	NR	31.70%	41.60%	NR	NR	NR	NCRT (85%)	871	688	Median: 41.1 months vs. 41.9 months, p = 0.51	Equivalent inhospital mortality and R1/2 resection rates
Zhang	1989–2009	Single centre	USA	69	54/15	21.30%	50%	Some (65%)	y	Some	NCRT (5fu pt >4400 gy)	14	55	49.5% vs. 53.8%	Equivalent R1 resection rate

(continued)

Table 26.1 (continued)

Authors	Years	Data type	Country	# Patients included	Ratio of ac/scc (n)	Clinical overstaging rate (%)	Clinical understaging rate (%)	EUS use	CT use	PET use	Induction treatment	# Surgery only	# Induction	Overall survival at 5 years (surgery vs. induction group)	Comments
Crabtree	2002–2011	STS database		752	611/141	25.90%	46.70%	Assumed yes	Assumed yes	Assumed yes	NR	270	482	NR	No difference in peri-operative mortality
Hardacker	1990–2011	Single centre	USA	68	57/11	43.80%	48.50%	Y	y	No	NR	35	33	45.7% vs. 51.5%	
Malin	1990–2001	Single centre	USA	43	35/8	NR	NR		y	n	NCRT (5fu and pt)	23	20	34.8% vs. 35%	
Samson	2006–2012	Cancer database 70% of national population	USA	1785	1378/407		45.70%	NR	NR	NR	NR	932	853	Median survival induction group: 43.8 months ± 3 months versus surgery alone 20.8 ± 2.3 months ($p < 0.001$) versus surgery + adjuvant therapy: 34.6 ± 4.2 months ($p = 0.14$)	Overlap in the Speicher et al. database cohort
ECSGPC	2002–2012	15 Western centres	USA	767	673/133	45%	41%	377/548	y	329/500	195 CRT, 73 chemo	499	268	Median: 63 (95% CI 48–78) months versus 71 (95% CI 53–90) months, $p = 0.956$	
Goense	2005–2014	National database	Netherlands	533	277/76	0%	62%	NR	NR	NR	NCRT (CROSS)	180 (145)	353 (277)	36% vs. 48%, $p < 0.001$	

Table 26.2 PICO formatted terms for literature search

Patients	Intervention	Comparator	Outcomes
cT2N0 esophageal adenocarcinoma in resectable patients	Induction therapy then resection	Resection without induction	Oncologic outcomes

Results

Of 17 RCTs of induction therapy for locally advanced esophageal cancer [3], three trials included patients with cT2N0 disease [1, 4, 5]. No trial reported outcomes per clinical stage, hence no high quality RCT data exists to inform this question. The aforementioned French FFCD 9901 trial recruited from 2000 to 2009 [6], with 57 of 195 patients having adenocarcinoma. There was no breakdown of either the clinical stage or pathologic stage according to histologic subtype and therefore, it is unclear how many of these patients had cT2N0 disease and how many T3 or stage I cancers. The trial was stopped early for futility as the planned enrolment would not show a significant benefit in favour of one arm over the other.

There have been two systematic reviews which included meta-analyses of retrospective observational cohort studies. None include data from randomized trials. To date, there are seven studies (Table 26.1) from large population-based or multicentre data [10–16] and five studies from single centre cohorts [17–20]. Even the larger population-based database studies are prone to bias and thus the evidence base is of very low quality.

Mota et al. [21] in 2018 published a meta-analysis of ten cohort studies of cT2N0 cases including 5265 patients, 1171 with squamous histology, 1620 cases with unreported histology, and 490 cases which may have been duplicated studies. There was considerable heterogeneity in the results of the meta-analysis ($I^2 = 0.60$) for overall survival at 5 years, but no difference in survival (risk difference: 0.00; 95% CI: −0.09, 0.09), and recurrence (risk difference: 0.21; 95% CI: −0.03, 0.45). There was a lower probability of involved resection margins after neoadjuvant therapy (n = 3723 patients, risk difference 0.04 (0.02–0.06); $I^2 = 0\%$). Kidane et al. [22] in 2019 reported a meta-analysis of nine cohort studies containing 5433 patients including 962 cases with squamous histology and 1586 cases with unreported histology. There was no significant difference between the overall survival at 5 years (HR: 0.99, 95% CI 0.92–1.08, p = 0.17, $I^2 = 0\%$), nor was there an increased risk of mortality or major complications. Although both meta-analyses indicate no compelling benefit to neoadjuvant therapy in this clinical scenario, it is difficult to justify performing a meta-analysis of the various cohort studies given the degree of heterogeneity between the various studies, the large gaps in characterisation of the treated populations, and significant potential for bias in each study.

Sources of Bias in the Literature Base

- Mixture of histologic subtypes in all cohort studies, subtypes not reported separately to allow subgroup analysis. We know from the CROSS trial that squamous cell cancer (SCC) has at least a twofold enhanced sensitivity to chemoradiation

than adenocarcinomas, and from the broader literature that radical chemoradiation alone may be curative for SCC.
- Mixture of treatment paradigms including differing or unreported chemotherapy regimens within and between centres.
- Confounding bias due to the use of adjuvant therapy, which is not reported, especially within the upfront surgery cohort which may lead to overestimation of the results of surgery or underestimate the benefit of neoadjuvant therapy.
- Long time period represented in the studies (1990–2014), an era where changes in the patterns of care have evolved, as well as the treatment regimens.
- Staging modalities are not uniform between studies and are frequently not reported
- Variability in access to staging resources (EUS/CT-PET) which may influence staging accuracy
- Staging accuracy is highly user dependent for EUS
- Selection bias—there is variability according to centre in their approach to cT2N0 (e.g. all patients have induction therapy, no patients have induction therapy, fitter patients or younger patients only have induction therapy). Usual treatment algorithms are not reported. One multicentre study indicated that centres with more accurate staging (although staging accuracy was still only correct in 20% versus 14% in less accurate centres) were more likely to favour a straight to surgery approach [15]. In another, higher volume centres favoured an induction approach [13].

Notwithstanding, to date the majority of both database and single centre cohort studies do not show a difference in the overall survival or disease specific survival at 5 years in patients with cT2N0 tumours who receive induction therapy compared with those who have surgery upfront. The major caveats, as listed above, are that these are biased studies including both adenocarcinoma and SCC, and a variety of treatment modalities including adjuvant therapy in the surgery upfront group and variability in the induction treatments delivered.

There is one recent report that is an exception, however. A study from the Netherlands on cT2N0 patients, not included in the above meta-analyses [16], included data acquired from the Dutch Cancer Registry from all Dutch centres performing esophagectomies for the period 2005–2014, during which most care was centralised in high volume centers, this defined as over 20 resections per center. Of the 533 patients included, 353 patients had induction therapy by the CROSS protocol, and 180 patients had surgery alone. Seventy-nine percent of patients had adenocarcinoma. Consistent with other series, under-staging was evident in 62% of cases. Propensity score matching (PSM) was used to compare the outcomes of 78 patients receiving neoadjuvant CRT to 78 who had surgery alone matched on age, gender, histology, surgical approach, referral for esophagectomy, year of diagnosis, and hospital volume. The pCR rate was 35%, with an improved R0 resection rate (98% versus 88%, $p < 0.001$) and a reduced proportion with lymph node metastases (82% vs. 55%, $p < 0.001$) in the neoCRT group. Overall survival at 5 years was 48% versus 36%, $p < 0.001$, and, in the PSM analysis, 46% versus 33%, $p = 0.017$ in favor of multimodal therapy. Although subject to many potential biases, the relatively

large numbers of patients with high quality data and standardised approach to treatment mean that this data is relatively strong, and consistent with a conclusion that multimodal therapy may confer some benefit in this cohort.

Characteristics of Patients Most Likely to Be Upstaged with cT2N0 Disease

In the absence of good RCT data, and the high probability of under-staging cT2N0, consideration can be made in decision making to the use of adverse tumor characteristics that reflect biological factors with prognostic significance for both survival and for under-staging of the disease. The National Cancer Database, which provides data on approximately 70% of esophageal cases in the US, reported that 45.7% of patients were under-staged at the time of diagnosis, and in these a higher tumour grade (OR 9.4; 95% CI 1.8–48.8, $P < 0.001$) and lymphovascular invasion (OR: 6.0; 95% CI 2.9–12.5, $p < 0.001$) were observed compared with patients who were accurately or over-staged at diagnosis [14]. In addition, a systematic review of seven studies of cT2N0 tumors ($n = 1650$) confirmed that depth of invasion, differentiation, tumor size and lymphovascular invasion were predictors of nodal metastases at the time of surgical resection [23]. This strongly suggests that proxy markers of poor biology such as these should lower the threshold for considering a neoadjuvant approach. It is hoped that current and future scientific research and clinical trials may determine whether common mutational driver events, or high mutational burden, or growth factors such as VEGF, Her2, or HGF may have an additional prognostic value in guiding treatment selection [24, 25].

Decision Analysis

In an attempt to integrate the best evidence into clinical decision making, Semenkovich et al. [26] performed a decision analysis study largely based on the data from the National Cancer Database (NCDB). This permitted testing of outcomes over a range of clinical scenarios, and included the limitations of EUS in this cohort and potential adverse postoperative morbidity. The probabilities for upstaging, same-staging and down-staging were set at 0.341, 0.243, and 0.416, respectively, and an assumption set that the ratio of upstaging with induction therapy compared to surgery upfront at 0.82. In the surgery upfront group a rate of 50% use of adjuvant therapy in those initially under-staged in the surgery upfront was chosen based on NCDB data [26]. Although the median survival for induction therapy and surgery only was similar in the baseline model, a threshold for a probability of upstaging with EUS was identified at 48.1%, whereby induction therapy would be more likely to result in benefit for patients compared to upfront surgery. The presence of any of three key variables (size ≥ 3 cm, high grade, or lymphovascular invasion) was associated with a greater than 48.1% risk of upstaging, with a purported advantage to induction chemoradiation based on the sensitivity analysis.

In another study using NCDB data, of 932 patients with cT2N0 where 52.2% had surgery alone, Samson et al. reported that 45.7% were upstaged, of whom 44.2% had adjuvant therapy, with a median overall survival of 27.5 ± 2.5 months compared with 43.9 ± 2.9 months for induction therapy [14]. Upstaged patients had higher lymphovascular invasion (OR 6; 95% CI: 1.8–48.4; $p < 0.001$), and tumor grade 3 (OR 9.4; 95% CI 1.8–48; $p = 0.007$). Although the caveat remains that all studies are subject to bias, this notwithstanding, the data is consistent with a thesis that tumor size, differentiation, and lymphovascular invasion are useful surrogates of understaging and adverse biology that can inform decision making in the absence of Level I evidence from RCTs.

Conclusions and Recommendations

Where systems exist, patients with cT2N0 adenocarcinomas should be prospectively entered into high quality databases with accurate recording of clinical variables so that their outcomes may be studied. Patients with longer tumours (≥3 cm), poor differentiation, or lymphovascular invasion are more likely to have lymph node involvement and therefore, should be considered for neoadjuvant induction therapy rather than surgery upfront. There are no high quality data to support the use of induction therapy in this cohort. Therefore, clinicians should be prepared to help patients make decisions consistent with their own values and preferences in a shared decision making approach. Proxies of adverse biology, or of predicted understaging, including tumor length, lymphovascular invasion, and poor differentiation, alone and particularly in combination, may support a decision to use induction therapy rather than upfront surgery.

Recommendations

- Patients with longer tumours (≥3 cm), poor differentiation, or lymphovascular invasion should be considered for neoadjuvant therapy followed by surgery (evidence quality low, weak recommendation).

A Personal View of the Data

Current NCCN guidelines [27] recommend upfront surgery for clinically staged T2N0 tumours which are <2 cm and well differentiated with no adverse pathologic features, and induction chemoradiation therapy for cT2N0 otherwise [14, 28]. However a stricter interpretation of the literature would denote tumor length ≥3 cm, poor differentiation, or lymphovascular invasion as being more likely to be understaged and hence a more compelling argument exists for neoadjuvant therapy. Conversely, if limited muscularis propria involvement is identified, and no adverse pathology exists, then EMR/ESD may merit consideration. Experience from the MD Anderson Cancer Center of attempted EMR in 30 of 75 patients staged with

cT2N0 resulted in successful removal of all tumor with negative margins in 17/30 patients, with 12 representing pT1a and five pT1b [29]. There were no perforations in this series. This was performed for older patients or smaller tumors, and low SUVmax, suggesting that EMR/ESD as advocated by the current AJCC/UICC guidelines will lead to improvements in T staging and a better selection of patients who may proceed to surgery without induction therapy, and possibly to an endoscopic therapy approach in pT1a patients. Where adverse biological features exist, as discussed above, we favour induction therapy at this time.

Clearly an RCT focused on cT2N0 in adenocarcinoma of the esophagus is desirable, comparing neoadjuvant best regimens such as CROSS or FLOT with surgery alone. However, a clinical trial addressing superiority or non-inferiority is likely to be a daunting undertaking with respect to power calculations, and it is possible that this will never be undertaken. The ESOPEC [7] and Neo-AEGIS [8] trials may provide some useful outcome data from subgroup analysis, particularly if data sets can be combined. For the moment, a pragmatic approach is to try to amalgamate high quality data from high volume systems with a uniform approach to staging and induction therapy techniques. Larger studies of well characterised patients will give us more certainty about whether, on balance, a large enough cohort of these patients benefit from induction with acceptable levels of harm.

There is clearly no strong evidence from RCTs, meta-analyses, or case series with or without propensity matching to support neoadjuvant therapy prior to surgery. The inaccuracy of staging, the inability to avoid bias, and lack of RCTs, are key factors. Another real difficulty in approach the individual patient is that not all patients are responders to induction therapy and therefore, the answer to the dilemma of what to recommend for patients with cT2N0 disease will be the ability to predict upfront whether a patient will respond to induction therapy regardless of their clinical stage. It is hoped that advances in technology and scientific understanding of the biology of esophageal adenocarcinoma will enable decision making in the future. For now, early EUS detected T2 lesions that are small and PET-negative should be considered for EMR/ESD, larger lesions with no clinical or pathologic adverse features should undergo surgery alone. Finally, outside of clinical trials, a reasonable interpretation of the literature is that larger lesions that are intensely FDG avid on PET scan, with adverse histological factors such as poor differentiation or lymphovascular invasion may be offered induction therapy due to high probability of understaging, particularly for node positively, and a more aggressive biology.

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References

1. van Hagen P, Hulshof MCCM, van Lanschot JJB, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BPL, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. New Engl J Med. 2012;366(22):2074–84.
2. Al-Batran S-E, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluoroura-

cil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019;393(10184):1948–57.
3. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681–92.
4. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol. 2008;26(7):1086–92.
5. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TPJ. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med. 1996;335(7):462–7. PubMed PMID: 8672151.
6. Mariette C, Dahan L, Mornex F, Maillard E, Thomas P-A, Meunier B, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol. 2014;32(23):2416–22.
7. Hoeppner J, Lordick F, Brunner T, Glatz T, Bronsert P, Röthling N, et al. ESOPEC: prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (NCT02509286). BMC Cancer. 2016;16(1):503.
8. Reynolds J, Preston S, O'neill B, Baeksgaard L, Griffin S, Mariette C, et al. ICORG 10-14: NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study (Neo-AEGIS). BMC Cancer. 2017;17(1):401.
9. van Vliet EP, Eijkemans MJ, Poley J-W, Steyerberg EW, Kuipers EJ, Siersema PD. Staging of esophageal carcinoma in a low-volume EUS center compared with reported results from high-volume centers. Gastrointest Endosc. 2006;63(7):938–47.
10. Markar SR, Gronnier C, Pasquer A, Duhamel A, Beal H, Thréaux J, et al. Role of neoadjuvant treatment in clinical T2N0M0 oesophageal cancer: results from a retrospective multi-center European study. Eur J Cancer. 2016;56:59–68.
11. Martin JT, Worni M, Zwischenberger JB, Gloor B, Pietrobon R, D'Amico TA, et al. The role of radiation therapy in resected T2 N0 esophageal cancer: a population-based analysis. Ann Thorac Surg. 2013;95(2):453–8.
12. Speicher PJ, Ganapathi AM, Englum BR, Hartwig MG, Onaitis MW, D'Amico TA, et al. Induction therapy does not improve survival for clinical stage T2N0 esophageal cancer. J Thorac Oncol. 2014;9(8):1195–201.
13. Crabtree TD, Kosinski AS, Puri V, Burfeind W, Bharat A, Patterson GA, et al. Evaluation of the reliability of clinical staging of T2 N0 esophageal cancer: a review of the Society of Thoracic Surgeons database. Ann Thorac Surg. 2013;96(2):382–90.
14. Samson P, Puri V, Robinson C, Lockhart C, Carpenter D, Broderick S, et al. Clinical T2N0 esophageal cancer: identifying pretreatment characteristics associated with pathologic upstaging and the potential role for induction therapy. Ann Thorac Surg. 2016;101(6):2102–11.
15. Atay SM, Correa A, Hofstetter WL, Swisher SG, Ajani J, Altorki NK, et al. Predictors of staging accuracy, pathologic nodal involvement, and overall survival for cT2N0 carcinoma of the esophagus. J Thorac Cardiovasc Surg. 2019;157(3):1264–72.e6.
16. Goense L, Visser E, Haj Mohammad N, Mook S, Verhoeven RHA, Meijer GJ, et al. Role of neoadjuvant chemoradiotherapy in clinical T2N0M0 esophageal cancer: a population-based cohort study. Eur J Surg Oncol. 2018;44(5):620–5.
17. Rice TW, Blackstone EH, Adelstein DJ, Zuccaro G Jr, Vargo JJ, Goldblum JR, et al. Role of clinically determined depth of tumor invasion in the treatment of esophageal carcinoma. J Thorac Cardiovasc Surg. 2003;125(5):1091–102.
18. Zhang JQ, Hooker CM, Brock MV, Shin J, Lee S, How R, et al. Neoadjuvant chemoradiation therapy is beneficial for clinical stage T2 N0 esophageal cancer patients due to inaccurate preoperative staging. Ann Thorac Surg. 2012;93(2):429–37.
19. Hardacker TJ, Ceppa D, Okereke I, Rieger KM, Jalal SI, LeBlanc JK, et al. Treatment of clinical T2N0M0 esophageal cancer. Ann Surg Oncol. 2014;21(12):3739–43.

20. Dolan J, Kaur T, Diggs B, Luna R, Sheppard B, Schipper P, et al. Significant understaging is seen in clinically staged T2N0 esophageal cancer patients undergoing esophagectomy. Dis Esophagus. 2016;29(4):320–5.
21. Mota F, Cecconello I, Takeda F, Tustumi F, Sallum R, Bernardo W. Neoadjuvant therapy or upfront surgery? A systematic review and meta-analysis of T2N0 esophageal cancer treatment options. Int J Surg. 2018;54:176–81.
22. Kidane B, Korst RJ, Weksler B, Farrell A, Darling GE, Martin LW, et al. Neoadjuvant therapy vs upfront surgery for clinical T2N0 esophageal cancer: a systematic review. Ann Thorac Surg. 2019;108(3):935–44.
23. Al-Kaabi A, van der Post RS, Huising J, Rosman C, Nagtegaal ID, Siersema PD. Predicting lymph node metastases with endoscopic resection in cT2N0M0 oesophageal cancer: a systematic review and meta-analysis. United European Gastroenterol J. 2020;8:35.
24. Visser E, Franken IA, Brosens LA, Ruurda JP, van Hillegersberg R. Prognostic gene expression profiling in esophageal cancer: a systematic review. Oncotarget. 2017;8(3):5566.
25. The Cancer Genome Atlas Research Network, Kim J, Bowlby R, Mungall AJ, Robertson AG, Odze RD, et al. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017;541:169.
26. Semenkovich TR, Panni RZ, Hudson JL, Thomas T, Elmore LC, Chang S-H, et al. Comparative effectiveness of upfront esophagectomy versus induction chemoradiation in clinical stage T2N0 esophageal cancer: a decision analysis. J Thorac Cardiovasc Surg. 2018;155(5):2221–30.e1.
27. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, et al. Esophageal and esophagogastric junction cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw. 2019;17(7):855–83.
28. Haisley KR, Hart KD, Fischer LE, Kunio NR, Bakis G, Tieu BH, et al. Increasing tumor length is associated with regional lymph node metastases and decreased survival in esophageal cancer. Am J Surg. 2016;211(5):860–6.
29. Nelson DB, Mitchell KG, Weston BR, Betancourt S, Maru D, Rice DC, et al. Should endoscopic mucosal resection be attempted for cT2N0 esophageal cancer? Dis Esophagus. 2019;32(10):1–6.

Can Frailty and Sarcopenia Be Mitigated in Esophagectomy Candidates?

27

Ana-Maria Misariu and Lorenzo Ferri

Introduction

Sarcopenia and Frailty as Predictors of Post-operative Outcomes

With a median age at diagnosis between 65 and 70 and a higher proportion of elderly patients being considered for curative multimodal therapy, esophageal cancer patients are considered high risk with associated deconditioning, increased comorbidities, polypharmacy, decreased functional capacity and cardiorespiratory fitness [1–5]. Given the aging population, pre-operative risk assessment and patient selection remain a challenge and functional age rather than chronological age should guide treatment decisions. Recently, the idea of assessing frailty and sarcopenia as surgical risk factors has been coming to the fore, as they are linked to a loss of physical and functional reserve [6–14]. Frailty confers vulnerability to physiological stressors and has been associated with increased surgical complications and hospital length of stay as well as post-discharge institutionalization [8, 15, 16]. Esophageal cancer patients are prone to develop sarcopenia, a syndrome characterised by progressive and generalised loss of skeletal muscle mass and function, as an individual and combined effect of esophageal tumour obstruction and dysphagia, as well as neoadjuvant or adjuvant treatment toxicity [5, 17–19]. Sarcopenia has been directly correlated with major post-operative complications as well as decreased overall and disease-free survival [20–24].

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Considering the association of frailty and sarcopenia with increase post-operative complications and length of stay, prolonged functional recovery, inability to complete neoadjuvant or adjuvant therapy and poor post-operative quality of life (QOL), strategies to mitigate their effect are mandated [25–28]. In the last decade, focus has shifted to the pre-operative period as it constitutes an opportune time to optimize an individual's functional capacity, nutritional status and psychological well-being to withstand the stress of major surgical intervention. This concept has been coined "prehabilitation" [29–31].

"Prehabilitation": A Fundamental Principle of ERAS

Traditionally, surgical recovery in Enhanced Recovery After Surgery (ERAS) has mostly been addressed through post-operative rehabilitation, with the pre-operative phases consisting of physiological and comorbidity optimization solely. Although the implementation of ERAS protocols have shown a positive effect on length of stay (LOS), resource use and short-term outcomes, complication rates following major abdominal surgery are still between 25% and 55% [20, 32–35]. While these outcomes have been of great interest to clinicians and researchers, in the patients' perspective a return to baseline function and daily activities is an essential aspect of recovery [36]. Surgeons often compare the stress of undergoing major surgery on one's body to that of running a marathon. However, running a marathon without physical, nutritional, and mental training seems absurd, and so does the concept of undergoing a complex surgery without similar training and optimization in functional capacity. Since strong evidence supports the relation between functional capacity and post-surgical outcomes, the implementation of multimodal prehabilitation programs consisting of nutritional intervention, psychological intervention (e.g., anxiety reduction), in addition to structured and goal-directed exercise programs have recently garnered interest [25, 37, 38]. This provides patients with the reserve to withstand the stress of major surgery in order to maximize functional recovery [30].

For instance, studies in colorectal surgery have shown that significant improvement in functional capacity can be achieved in as little as 3 weeks [39]. A study published by Minella et al. assessed the effect of trimodal prehabilitation (exercise, nutrition and anxiety reduction) 4 weeks before colorectal surgery by re-analyzing the data of one pilot study and two randomized control trials (one unpublished) from 2010 to 2015 at our center. The study found a significantly higher preoperative improvement in physical fitness in those patients who underwent multimodal prehabilitation [68 (60%) vs. 15 (21%), $p < 0.001$] as well as an increase in 6-min walk test (6 MWT) to above their baseline at 8 weeks post-operatively [40]. Results of similar RCTs and large cohort studies have been included in several systematic reviews which confirmed the ability of prehabilitation to improve physical performance and functional capacity [41–46].

Despite these interesting findings and promising results, few well-designed studies have evaluated the effect of multimodal prehabilitation in esophageal cancer

surgery and current recommendations by the ERAS guidelines have been limited to extrapolated results from previously mentioned RCTs in colorectal surgery or mixed "major abdominal" surgery [47]. This chapter aims to review whether frailty and sarcopenia in esophagectomy candidates can be mitigated using a multidisciplinary prehabilitation program.

Search Strategy

We conducted a literature search of English articles from 2000 to 2019 in MEDLINE and EMBASE (via OVID) and the Cochrane Central Register of Controlled Trials (CENTRAL) from 2000 to 2019. Table 27.1 shows the patient–intervention–comparison–outcome (PICO) scheme used to construct the search. The search strategy and search terms that were used for this research are detailed in Table 27.2. Additional studies were identified by a manual search of bibliographic references of relevant articles and existing reviews. Due to the limited number of studies assessing esophagectomy only, the search was extended to include patients undergoing gastric cancer surgery. Studies assessing mixed gastrointestinal surgeries or "major abdominal surgery" were excluded. Ten randomized control trials (RCTs) and four cohort studies were included in our analysis [48–61]. The data were classified using the GRADE system. A summary of the study characteristics and outcomes derived from our literature review using the search strategy previously described is provided in Table 27.3. A range of outcomes were reported, including functional capacity (as measured by 6 MWT, hand-grip strength or gait speed), overall complications, infective complications, pulmonary complications and LOS.

Results

Exercise

Exercise prehabilitation as a unimodal intervention was investigated in six studies. Preoperative exercise programs included either one or a combination of aerobic exercise, strength training and inspiratory muscle training (IMT) or breathing exercises. Among the five esophagectomy studies, two studies utilized a whole-body exercise program in combination with IMT and assessed pulmonary complications only, which were significantly decreased in patients undergoing the preoperative intervention in both studies [48, 51]. The remaining studies included IMT only and

Table 27.1 Patient–intervention–comparison–outcome (PICO) scheme

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Esophagogastric surgery patients	Prehabilitation prior to resection	Resection without prehabilitation	Functional capacity, postoperative outcomes, length of stay

Table 27.2 Search Strategy (application to MEDLINE Ovid and EMBASE)

1. Prehabilitation.mp.	19. ((stomach or gastric) adj3 (cancer∗ or neoplas∗ or carcinoma∗ or tum?or∗ or malignan∗)).ti,ab,kw,kf.
2. (pre-hab∗ or prehab∗).mp.	20. ((Gastro-Esophageal or "upper gastrointestinal∗" or "upper GI" or "upper abdominal" or gastroesophag∗) adj3 (cancer∗ or neoplas∗ or carcinoma∗ or tum?or∗ or malignan∗)).ti,ab,kw,kf.
3. rehabilitation/or early ambulation/	21. ("upper GI surg∗" or "upper gastrointestinal surg∗" or "upper abdominal surg∗").ti,ab,kw,kf.
4. rehabili∗.ti,ab,kw,kf.	22. or/16-21
5. preoperative period/	23. 5 or 6 or 7
6. Preoperative Care/	24. exp Nutrition Therapy/
7. ((preoperative or pre-operative) adj2 (care or procedure∗ or rehabilitation or period or education or evaluation or treatment)).ti,ab,kw,kf.	25. (nutrition∗ or diet∗).ti,ab,kw,kf.
8. exp Exercise/	26. ((exercis∗ or nutrition∗ or diet∗) adj2 optimization∗).ti,ab,kw,kf.
9. exercis∗.ti,ab,kw,kf.	27. 1 or 2 or 3 or 4 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 24 or 25 or 26
10. exp Exercise Therapy/	28. 23 and 27
11. preconditioning.ti,ab,kw,kf.	29. 22 and 28
12. physical therapy modalities/or exercise movement techniques/or breathing exercises/	30. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 24 or 25 or 26
13. physical therap∗.ti,ab,kw,kf.	31. 22 and 30
14. "Physical Education and Training"/	32. limit 31 to (english language and yr="2000 –Current")
15. "Physical Education and Training".ti,ab,kw,kf.	
16. esophageal neoplasms/or esophageal squamous cell carcinoma/	
17. ((Oesophag∗ or Esophag∗) adj3 (cancer∗ or neoplas∗ or carcinoma∗ or malignan∗ or tum?or∗)).ti,ab,kw,kf.	
18. Stomach Neoplasms/	

none of them found to have a significant difference in pulmonary complications or post-operative outcomes despite an improvement in pulmonary function [49, 50, 52]. A subgroup analysis of the PREPARE trial performed by Guinan et al. was the only study that assessed the impact of IMT on functional outcomes, which surprisingly were worse in the intervention group. The authors suggested that the observed effects were due to almost double the amount of moderate-intensity exercise

Table 27.3 Summary of included studies

Trial	Study type **(quality of evidence)**	N	Mean age	Prehab interventions	Duration	Outcomes measured	Functional capacity	Post-operative outcomes
Exercise								
Esophageal cancer								
Yamana et al. (2015) [48]	Non-blind RCT **(low)**	60	67.1	Pre-operative exercise program (Inspiratory training, resistance and aerobic training)	≥1 week	PPC		Reduced PPC (27.7% vs. 60%; p = 0.014)
Valkenet et al. (PREPARE) (2018) [49]	Single-blind RCT **(moderate)**	241	63.2	Preoperative IMT: IMT for ≥2 weeks preoperatively, performing 30 breaths, twice daily	≥2 weeks	Inspiratory strength and endurance, POC, PPC	Increase in preoperative inspiratory endurance and strength	– PPC: Rate of LRTI in intervention group was 39.2% vs. 35.5% in control ($p = 0.561$). – POC: No statistically significant difference

(continued)

Table 27.3 (continued)

Trial	Study type **(quality of evidence)**	N	Mean age	Prehab interventions	Duration	Outcomes measured	Functional capacity	Post-operative outcomes
Guinan et al. (2018) [50]	Re-analysis of PREPARE trial **(moderate)**	60	63.07 (i) 65.06 (c)	Preoperative IMT: IMT for ≥2 weeks preoperatively, performing 30 breaths, twice daily.	≥2 weeks	MIP, inspiratory muscle endurance, 6 MWT, physical activity, POC, PPC, LOS	– Significant improvement in preoperative MIP ($P = 0.03$) and inspiratory muscle endurance ($P = 0.04$). – Preoperative 6 MWT distance did not change. Postoperatively, control participants were more active on POD1, and from POD1–POD5 ($P = 0.04$). – mean (SD) 6 MWT: significantly lower in the IMT group (305.61 (116.3) m) compared to controls (380.2 (47.1) m, $P = 0.03$).	Postoperative recovery (hospital LOS, critical care LOS, and PPC) was comparable for both groups
Inoue et al. (2013) [51]	Retrospective cohort study **(low)**	100	66.5	IMT program + abdominal muscle training + 15 min aerobic exercise/day (supervised if inpatient)	>7 days	PPC		Significantly less PPC in prehab group

Dettling et al. (2013) [52]	Pilot non-randomised control trial **(low)**	83	65	IMT (7 sessions/week, 20 min, one supervised)	>2 weeks	MIP, PPC, LOS	Increase in MPI	No significant differences in post-pulmonary complications or LOS
Gastric cancer								
Cho et al. (2014) [53]	Matched-Pair Cohort **(low)**	72	63.1 (i) 66.1 (c)	Unsupervised aerobic exercise (3–7×/week) and resistance training (1–2×/week)	4 weeks	POC, PPP, LOS		– Significantly less serious POC in exercise group ($p = 0.008$) – Equivalent PPC ($p = 1.0$) – Reduced LOS (9 d vs. 10 d; $p = 0.038$)
Nutrition								
Esophageal cancer								
Kubota et al. (2014) [54]	Retrospective cohort study **(low)**	55	67	1000 mL/day of Impact (Ajinomoto Co, Tokyo, Japan)	5 days	POC, mortality, LOS		Effective strategy to reduce infectious complications, mortality, and hospitalization, and to improve short-term survival
Kitagawa et al. (2017) [55]	Non-blind RCT **(low)**	30	67.1 (i) 66.8 (c)	600 mL/day of MHN-02 (immunonutrition)	5 days	POC, PPP, LOS, SSI		No significant difference in POC
Mudge et al. (2018) [56]	Double-blind RCT **(high)**	276		Preoperative immunonutrition with Impact	7 days	Infective complications, POC, LOS		No benefit over standard nutrition in patients undergoing esophagectomy

(continued)

Table 27.3 (continued)

Trial	Study type **(quality of evidence)**	N	Mean age	Prehab interventions	Duration	Outcomes measured	Functional capacity	Post-operative outcomes
Gastric cancer								
Fukuda et al. (2015) [57]	Retrospective cohort study **(low)**	152	73	Provision of ≥25 kcal/kg ideal body weight per day through either oral intake, TPN or EN	≥10 days	SSI		The incidence of SSIs in malnourished patients was significantly lower in the well-supported group receiving adequate energy support for at least 10 days than in the poorly-supported group, which received inadequate or no energy support or adequate energy support for <10 days (17.0% vs. 45.4%; $p = 0.0006$)
Zhao et al. (2018) [58]	Non-blind RCT **(moderate)**	66	62	500 mL/day of EN suspension (Nutrison Fiber)	>7 days	LOS		– Decreased LOS (8 vs. 7; p = 0.004) and associated hospital costs (p = 0.016)
Multimodal								
Esophageal cancer								

Xu et al. (2015) [59]	Non-blind RCT **(low)**	59	59.6	Pre-operative exercise (supervised walking), nutritional advice	4–5 weeks	6 MWT, HGS, Nutritional status (Body weight), POC	– 6 MWT: Intervention 471–453 m, Control 437–319 m ($p = 0.012$) – HGS: intervention 32.4–31.3 kg vs. control 31.8–27.7 kg ($p = 0.002$) – Body weight: Intervention 58.2–57.4 kg vs. control 58.8–55.3 kg ($p < 0.001$)	No difference observed in outcomes.
Minella et al. (2018) [60]	Single-blind RCT **(moderate)**	51	67.3 (i) 68 (c)	Individualized, home-based aerobic and strength training exercises, nutritional assessment and whey protein supplementation	4 weeks (median 36 days)	6 MWT, POP, LOS	Improved functional capacity both before surgery (mean [SD] 6 MWD change, 36.9 [51.4] vs. −22.8 [52.5] m; $P < .001$) and after surgery (mean [SD] 6 MWD change, 15.4 [65.6] vs. −81.8 [87.0] m; $P < .001$)	Not powered to determine association between physical fitness and post-operative complications or length of stay.
Gastric cancer								
Yamamoto et al. (2017) [61]	Non-blind pilot RCT **(low)**	22	75	Pre-operative exercise (Resistance training, walking, HGS training) and nutritional supplementation	3 weeks (median 16 days)	Gait speed, body composition, POC	– Gait speed: 0.85 m/s control vs. 0.8 m/s in intervention ($p = 0.06$) – Body mass: 54.7 kg in control to 54.7 kg in intervention ($p = 0.98$)	Equivalent POC with nonsarcopenic patients (13.6% vs. 13.2%, $p = 0.96$)

N sample size, *i* intervention, *c* control, *RCT* randomized control trial, *HIT* high intensity training, *IMT* inspiratory muscle training, *EN* enteral nutrition, *TPN* total parenteral nutrition, *6MWT* 6-min walk test, *6MWD* 6 min walking distance, *HGS* hand grip strength, *POD* post-operative day, *POC* post-operative complications, *PPC* post-pulmonary complications, *SSI* surgical site infections, *MIP* maximum inspiratory pressure

recorded by the control group. While IMT has a positive effect on inspiratory function, it had minimal impact on overall functional status, and aerobic activity could be more effective [50]. The only gastrectomy study included was retrospective in nature and concluded that post-operative complications were reduced with the intervention, however measures of functional capacity were not reported [53].

Nutrition and Immunonutrition

Unimodal nutrition and immunonutrition was assessed in five trials with a duration of intervention ranging from 5 days to at least 10 days, and none assessed functional capacity as an outcome. Two RCTs analysing the role of pre-operative immunonutrition in esophagectomy concluded that immune-enhancing preoperative diet could not be recommended due to limited effects on post-operative outcomes [55, 56]. Only one retrospective study in esophagectomy found a reduction in overall complications [54]. In contrast, one retrospective study and one RCT assessing preoperative nutrition only in gastric cancer surgery found that infective complications and LOS were decreased [57, 58].

Multimodal Prehabilitation

Three RCTs looking at the effect of multimodal prehabilitation using combination of exercise, nutrition and mental well-being were identified. The two RCTs in esophagectomy patients revealed an improvement in functional capacity [59, 60]. A single-blind RCT performed at our centre, McGill University, which included 51 patients, showed an improvement in 6 MWD both before and after surgery, however no statistical difference in LOS or overall complications were demonstrated [60]. This is likely due to the fact that both RCTs were not powered to determine association between physical fitness and post-operative complications or length of stay. Patients undergoing gastrectomy in a small RCT of 22 patients by Yamamoto et al. found that prehabilitation in elderly sarcopenic patients led to a non-significant improvement in functional capacity as measured by gait speed, while body mass and complication rates were equivalent [61].

Conclusions and Recommendations

Prehabilitation studies in esophagectomy and gastrectomy are extremely heterogeneous in their prehabilitation regimen and reported outcomes, making results difficult to interpret. Currently, our center's single-blind RCT is the only available well-designed study providing moderate quality evidence on the ability of multimodal prehabilitation to improve functional capacity and mitigate the effects of sarcopenia and frailty in esophagectomy [60]. Additionally, extrapolated results from studies in upper gastrointestinal surgery and gastrectomy as well as major

abdominal oncologic surgery, including colorectal surgery, have shown that prehabilitation accelerates functional recovery and is mandated within ERAS as it represents its clinical and scientific development. Results of multiple ongoing trials, including one from our center, will allow for a better assessment of whether or not gains in physical fitness translate to significant improvements in clinical and oncological outcomes post-esophagectomy [62]. Future trials should utilize uniform end points to measure functional capacity, as well as ideal markers to gauge the global benefit of prehabilitation.

Recommendation

- We recommend that esophagectomy candidates undergo a multimodal prehabilitation program to improve functional capacity, hence mitigating the effect of sarcopenia and frailty (evidence quality low, recommendation grade strong).

A Personal View of the Data

Sarcopenia and frailty are prevailing adverse effects of esophagogastric cancer and its treatment, with negative consequences on post-operative recovery and quality of life as well as care adherence. However, these modifiable risk factors can be mitigated through prehabilitation, which, unlike the traditional approach of rehabilitation, prevents rather than cures functional consequences of cancer therapy. Despite the scarce number of trials on prehabilitation in esophagectomy, our recently published RCT demonstrated that a structured preoperative conditioning intervention is feasible, safe, and efficacious for preventing functional impairment before and after surgical treatment for upper gastrointestinal cancer. By extrapolating data from publications on prehabilitation in colorectal surgery and those from studies in major abdominal surgery, we recommend prehabilitation in our esophagectomy candidates. Emergent data from multiple ongoing trials will provide additional information to direct future recommendations.

References

1. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet. 2013;381:400–12.
2. Low DE, Alderson D, Cecconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy. Ann Surg. 2015;262:286–94.
3. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med. 2011;364:2128–37.
4. Andrici J, Eslick GD. Epidemiology and risk factors for esophageal cancer. In: Esophageal Cancer. New York, NY: Springer; 2015. p. 1–23.

5. Hodari A, Hammoud ZT, Borgi JF, Tsiouris A, Rubinfeld IS. Assessment of morbidity and mortality after esophagectomy using a modified frailty index. Ann Thorac Surg. 2013;96:1240–5.
6. Partridge JSL, Harari D, Dhesi JK. Frailty in the older surgical patient: a review. Age Ageing. 2012;41:142–7.
7. Wagner D, DeMarco MM, Amini N, Buttner S, Segev D, Gani F, Pawlik TM. Role of frailty and sarcopenia in predicting outcomes among patients undergoing gastrointestinal surgery. World J Gastrointest Surg. 2016;8:27–40.
8. Robinson TN, Wallace JI, Wu DS, Wiktor A, Pointer LF, Pfister SM, Sharp TJ, Buckley MJ, Moss M. Accumulated frailty characteristics predict postoperative discharge institutionalization in the geriatric patient. J Am Coll Surg. 2011;213:37–42.
9. Robinson TN, Eiseman B, Wallace JI, Church SD, Mcfann KK, Pfister SM, Sharp TJ, Moss M. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. Ann Surg. 2009;250:449–55.
10. Tsiouris A, Hammoud ZT, Velanovich V, Hodari A, Borgi J, Rubinfeld I. A modified frailty index to assess morbidity and mortality after lobectomy. J Surg Res. 2013;183:40–6.
11. Sündermann SH, Dademasch A, Seifert B, Biefer HRC, Emmert MY, Walther T, Jacobs S, Mohr F-W, Falk V, Starck CT. Frailty is a predictor of short- and mid-term mortality after elective cardiac surgery independently of age. Interact Cardiovasc Thorac Surg. 2014;18:580–5.
12. Dasgupta M, Rolfson DB, Stolee P, Borrie MJ, Speechley M. Frailty is associated with postoperative complications in older adults with medical problems. Arch Gerontol Geriatr. 2009;48:78–83.
13. Lee DH, Buth KJ, Martin B-J, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. Circulation. 2010;121:973–8.
14. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:146–56.
15. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 2010;210:901–8.
16. Won E. Issues in the management of esophagogastric cancer in geriatric patients. Surg Oncol Clin N Am. 2017;26:335–46.
17. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412–23.
18. West MA, Wischmeyer PE, Grocott MPW. Prehabilitation and nutritional support to improve perioperative outcomes. Curr Anesthesiol Rep. 2017;7:340–9.
19. Jack S, West M, Raw D, et al. The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery. Eur J Surg Oncol. 2014;40:1313–20.
20. Elliott JA, Doyle SL, Murphy CF, King S, Guinan EM, Beddy P, Ravi N, Reynolds JV. Sarcopenia: prevalence, and impact on operative and oncologic outcomes in the multimodal management of locally advanced esophageal cancer. Ann Surg. 2017;266:822–30.
21. Levolger S, Vugt JLAV, Bruin RWFD, Ijzermans JNM. Systematic review of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies. BJS. 2015;102:1448–58.
22. Makiura D, Ono R, Inoue J, Kashiwa M, Oshikiri T, Nakamura T, Kakeji Y, Sakai Y, Miura Y. Preoperative sarcopenia is a predictor of postoperative pulmonary complications in esophageal cancer following esophagectomy: a retrospective cohort study. J Geriatr Oncol. 2016;7:430–6.
23. Pamoukdjian F, Bouillet T, Lévy V, Soussan M, Zelek L, Paillaud E. Prevalence and predictive value of pre-therapeutic sarcopenia in cancer patients: a systematic review. Clin Nutr. 2018;37:1101–13.
24. Deng H-Y, Zha P, Peng L, Hou L, Huang K-L, Li X-Y. Preoperative sarcopenia is a predictor of poor prognosis of esophageal cancer after esophagectomy: a comprehensive systematic review and meta-analysis. Dis Esophagus. 2019;32:doy115. https://doi.org/10.1093/dote/doy115.

25. Wilson R, Davies S, Yates D, Redman J, Stone M. Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. Br J Anaesth. 2010;105:297–303.
26. Robinson TN, Wu DS, Pointer L, Dunn CL, Cleveland JC, Moss M. Simple frailty score predicts postoperative complications across surgical specialties. Am J Surg. 2013;206:544–50.
27. Moran J, Wilson F, Guinan E, Mccormick P, Hussey J, Moriarty J. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. Br J Anaesth. 2016;116:177–91.
28. Lawrence V, Hazuda H, Cornell J, Pederson T, Bradshaw P, Mulrow C, Page C. Functional independence after major abdominal abdominal surgery in the elderly. J Am Coll Surg. 2004;199:762–72.
29. Carli F, Zavorsky GS. Optimizing functional exercise capacity in the elderly surgical population. Curr Opin Clin Nutr Met Care. 2005;8:23–32.
30. Carli F, Gillis C, Scheede-Bergdahl C. Promoting a culture of prehabilitation for the surgical cancer patient. Acta Oncol. 2017;56:128–33.
31. Gillis C, Li C, Lee L, et al. Prehabilitation versus rehabilitation a randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology. 2014;121:937–47.
32. Christensen T, Bendix T, Kehlet H. Fatigue and cardiorespiratory function following abdominal surgery. BJS. 1982;69:417–9.
33. Li C, Ferri LE, Mulder DS, et al. An enhanced recovery pathway decreases duration of stay after esophagectomy. Surgery. 2012;152:606–16.
34. Lee L, Li C, Robert N, Latimer E, Carli F, Mulder DS, Fried GM, Ferri LE, Feldman LS. Economic impact of an enhanced recovery pathway for oesophagectomy. BJS. 2013;100:1326–34.
35. Preston SR, Markar SR, Baker CR, Soon Y, Singh S, Low DE. Impact of a multidisciplinary standardized clinical pathway on perioperative outcomes in patients with oesophageal cancer. BJS. 2012;100:105–12.
36. Kleinbeck SV, Hoffart N. Outpatient recovery after laparoscopic cholecystectomy. AORN J. 1994;60:394–402.
37. Smith TB, Stonell C, Purkayastha S, Paraskevas P. Cardiopulmonary exercise testing as a risk assessment method in non cardio-pulmonary surgery: a systematic review. Anaesthesia. 2009;64:883–93.
38. Snowden CP, Prentis J, Jacques B, Anderson H, Manas D, Jones D, Trenell M. Cardiorespiratory fitness predicts mortality and hospital length of stay after major elective surgery in older people. Ann Surg. 2013;257:999–1004.
39. Fearon KC, Jenkins JT, Carli F, Lassen K. Patient optimization for gastrointestinal cancer surgery. BJS. 2013;100:15–27.
40. Minnella EM, Bousquet-Dion G, Awasthi R, Scheede-Bergdahl C, Carli F. Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience. Acta Oncol. 2017;56:295–300.
41. Luther A, Gabriel J, Watson RP, Francis NK. The impact of total body prehabilitation on post-operative outcomes after major abdominal surgery: a systematic review. World J Surg. 2018;42:2781–91.
42. Vermillion SA, James A, Dorrell RD, Brubaker P, Mihalko SL, Hill AR, Clark CJ. Preoperative exercise therapy for gastrointestinal cancer patients: a systematic review. Syst Rev. 2018;7:103. https://doi.org/10.1186/s13643-018-0771-0.
43. Valkenet K, Port IGVD, Dronkers JJ, Vries WRD, Lindeman E, Backx FJ. The effects of preoperative exercise therapy on postoperative outcome: a systematic review. Clin Rehabil. 2011;25:99–111.
44. Odoherty A, West M, Jack S, Grocott M. Preoperative aerobic exercise training in elective intra-cavity surgery: a systematic review. Br J Anaesth. 2013;110:679–89.
45. Hijazi Y, Gondal U, Aziz O. A systematic review of prehabilitation programs in abdominal cancer surgery. Int J Surg. 2017;39:156–62. https://doi.org/10.1016/j.ijsu.2017.01.111.

46. Bolshinsky V, Li MH-G, Ismail H, Burbury K, Riedel B, Heriot A. Multimodal prehabilitation programs as a bundle of care in gastrointestinal cancer surgery. Dis Colon Rectum. 2018;61:124–38.
47. Low DE, Allum W, Manzoni GD, et al. Guidelines for perioperative care in esophagectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations. World J Surg. 2018;43:299–330.
48. Yamana I, Takeno S, Hashimoto T, Maki K, Shibata R, Shiwaku H, Shimaoka H, Shiota E, Yamashita Y. Randomized controlled study to evaluate the efficacy of a preoperative respiratory rehabilitation program to prevent postoperative pulmonary complications after esophagectomy. Dig Surg. 2015;32:331–7.
49. Valkenet K, Trappenburg JCA, Ruurda JP, et al. Multicentre randomized clinical trial of inspiratory muscle training versus usual care before surgery for oesophageal cancer. BJS. 2018;105:502–11.
50. Guinan EM, Forde C, O'Neill L, et al. Effect of preoperative inspiratory muscle training on physical functioning following esophagectomy. Dis Esophagus. 2019;32(2) https://doi.org/10.1093/dote/doy091.
51. Inoue J, Ono R, Makiura D, Kashiwa-Motoyama M, Miura Y, Usami M, Nakamura T, Imanishi T, Kuroda D. Prevention of postoperative pulmonary complications through intensive preoperative respiratory rehabilitation in patients with esophageal cancer. Dis Esophagus. 2013;26:68–74.
52. Dettling DS, Schaaf MVD, Blom RL, Nollet F, Busch OR, Henegouwen MIVB. Feasibility and effectiveness of pre-operative inspiratory muscle training in patients undergoing oesophagectomy: a pilot study. Physiother Res Int. 2013;18:16–26.
53. Cho H, Yoshikawa T, Oba MS, et al. Matched pair analysis to examine the effects of a planned preoperative exercise program in early gastric cancer patients with metabolic syndrome to reduce operative risk: the Adjuvant Exercise for General Elective Surgery (AEGES) Study Group. Ann Surg Oncol. 2014;21:2044–50.
54. Kubota K, Kuroda J, Yoshida M, Okada A, Deguchi T, Kitajima M. Preoperative oral supplementation support in patients with esophageal cancer. J Nutr Health Aging. 2014;18:437–40.
55. Kitagawa H, Namikawa T, Yatabe T, Munekage M, Yamasaki F, Kobayashi M, Hanazaki K. Effects of a preoperative immune-modulating diet in patients with esophageal cancer: a prospective parallel group randomized study. Langenbeck's Arch Surg. 2017;402:531–8.
56. Mudge LA, Watson DI, Smithers BM, Isenring EA, Smith L, Jamieson GG. Multicentre factorial randomized clinical trial of perioperative immunonutrition versus standard nutrition for patients undergoing surgical resection of oesophageal cancer. BJS. 2018;105:1262–72.
57. Fukuda Y, Yamamoto K, Hirao M, et al. Prevalence of malnutrition among gastric cancer patients undergoing gastrectomy and optimal preoperative nutritional support for preventing surgical site infections. Ann Surg Oncol. 2015;22:778–85.
58. Zhao Q, Li Y, Yu B, Yang P, Fan L, Tan B, Tian Y. Effects of preoperative enteral nutrition on postoperative recent nutritional status in patients with Siewert II and III adenocarcinoma of esophagogastric junction after neoadjuvant chemoradiotherapy. Nutr Cancer. 2018;70:895–903.
59. Xu Y-J, Cheng JC-H, Lee J-M, Huang P-M, Huang G-H, Chen CC-H. A walk-and-eat intervention improves outcomes for patients with esophageal cancer undergoing neoadjuvant chemoradiotherapy. Oncologist. 2015;20:1216–22.
60. Minnella EM, Awasthi R, Loiselle S-E, Agnihotram RV, Ferri LE, Carli F. Effect of exercise and nutrition prehabilitation on functional capacity in esophagogastric cancer surgery. JAMA Surg. 2018;153:1081.
61. Yamamoto K, Nagatsuma Y, Fukuda Y, et al. Effectiveness of a preoperative exercise and nutritional support program for elderly sarcopenic patients with gastric cancer. Gastric Cancer. 2016;20:913–8.
62. Zylstra J, Boshier P, Whyte G, Low D, Davies A. Peri-operative patient optimization for oesophageal cancer surgery – from prehabilitation to enhanced recovery. Best Pract Res Clin Gastroenterol. 2018;36-37:61–73.

Do Enhanced Recovery Programs for Esophagectomy Patients Improve Outcomes?

28

Sara H. Jamel and Sheraz R. Markar

Introduction

Enhanced recovery protocols are multi-modal with defined goals that are aimed at reducing the surgical stress response, improving postoperative recovery, and hastening return of functional status following major surgery. Enhanced recovery protocols were first introduced in 1997, focusing on risk factors associated with post-operative morbidity and length of stay [1]. This led to the introduction of a specific multimodality pathway in colonic surgery in 1999, and subsequent further widespread adoption. Several studies have shown improvements in clinical outcomes with the utilisation of enhanced recovery protocols in colonic surgery. It has been directly linked to decreases in length of stay [2, 3] and reductions in the incidence and severity of postoperative complications [4, 5]. This has led to a panacea in change to recovery in colonic surgery and the generation of a consensus statement for a standardised protocol for colonic surgery in 2005. This has provided the driving force for enhanced recovery to be adopted subsequently by several other subspecialties [6–15].

Despite advances in care, esophagectomy is still associated with high levels of mortality (30-day 2.4% and 90-day 4.5%) and morbidity rates varying between 40% and 80% [13]. There are potential barriers in utilisation of enhanced recovery protocols in esophagectomy due to the complexity of the procedure and the heterogeneity in surgical technical approaches used, as well as controversy regarding specific components of enhanced recovery such as early enteral nutrition. Enhanced

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recovery in the setting of esophageal cancer surgery was first introduced in 2004 [14], and since then several studies have investigated the effect of Enhanced Recovery After Surgery (ERAS) in this patient cohort. Recently, enhanced recovery recommendations specifically for esophagectomy have been published with the aim to standardise patients' perioperative care, allowing routine application and audit of compliance to improve patients' clinical outcomes [15].

Search Strategy

A systematic literature search was performed (January 1950 to August 2019) using MEDLINE, Embase, Web of Science, and the Cochrane Library databases. Search terms used were '(o)esophagectomy', 'enhanced recovery', 'fast track', 'clinical pathway', '(o)esophageal cancer', and '(o)esophageal disease', and the medical subject headings (MeSH) terms '(o)esophagectomy', '(o)esophageal neoplasm', 'critical pathways' were used in combination with Boolean operators AND or OR. The search strategy is highlighted in Table 28.1. Articles were excluded if they were not in English and if only single component of an enhanced recovery protocol was assessed rather that the full multi-component pathway.

Results

The initial search yielded 1230 articles, and 25 articles were selected for inclusion [15–39]: 18 cohort studies (both prospective and retrospective); one combined prospective and retrospective study; three non comparative studies; and three randomized controlled trials (Tables 28.2 and 28.3). There are variations in enhanced recovery protocols utilised in published studies, however, despite this there appears to be generalised consensus amongst studies regarding two domains: early mobilisation and removal of epidural catheters within 5 days post operatively.

General Outcomes

The key aim of enhanced recovery is to improve postoperative recovery, which is often measured by post-operative outcomes most commonly being length of hospital stay (defined at the time from surgery to discharge from hospital), in-hospital mortality, and postoperative complications, specifically anastomotic leak and

Table 28.1 PICO formatted terms for literature search

Patient population	Intervention	Comparator	Outcomes
Esophagectomy patients	Enhanced recovery protocol	No enhanced recovery protocol	LOS, anastomotic leak, morbidity, mortality, pulmonary complications

LOS length of hospital stay

Table 28.2 Overall morbidity and mortality in ERAS protocol studies

Studies	Year	Type of study	No. Group 1 (Non ERAS)	No. Group 2 (ERAS)	Mean age (Non ERAS)	Mean age (ERAS)	Overall morbidity Non ERAS (%)	Overall morbidity ERAS (%)	Mortality (%) Non ERAS	Mortality (%) ERAS
Cerfolio [15]	2004	Non comparative	–	90	–	63	–	16	–	4
Munitiz [23]	2010	Retrospective cohort	74	74	60.5	59	28	23	4	1
Tomaszek [24]	2010	Retrospective cohort	276	110	54	–	–	–	–	–
Jianjun [38]	2012	Non comparative	–	80	–	62	–	–	–	0
Cao [25]	2013	Retrospective cohort	55	57	55.6	55.5	16	27	3	1
Li [16]	2012	Prospective cohort	47	59	65	64	29	35	0	1
Preston [26]	2013	Retrospective cohort	24	86	68.5	65	18	39	–	–
Lee [27]	2013	Retrospective cohort	47	59	–	–	–	–	–	–
Tang [34]	2013	Retrospective and prospective cohort	27	36	68.5	64	7	6	1	2
Zhao [22]	2014	Randomised controlled trial	34	34	57.86	55.14	4	2	–	–
Blom [20]	2013	Prospective cohort	78	103	64	65	53	73	–	–
Markar [17]	2014	Prospective cohort	92	183	66	64	-	-	0	1
Findlay [18]	2015	Prospective cohort	55	77	66	64	47	38	3	1
Ford [19]	2014	Prospective cohort	121	80	–	–	–	–	–	–
Pan [28]	2014	Retrospective cohort—MIO	40	40	62.5	66	31	23	0	0
Shewale [29]	2015	Retrospective cohort	322	386	61	61	–	–	16	14
Gatenby [30]	2015	Retrospective cohort	16	9	–	–	–	–	–	–
Oakley [31]	2016	Retrospective cohort	81	66	78.8	78.8	–	–	–	–
Chen [35]	2016	Randomised controlled trial	132	128	55.72	56.43	16	11	2	2
Li [51]	2016	Prospective cohort study	55	55	67.73	67.00	–	–	–	–
Giacopuzzi [32]	2017	Retrospective cohort	17	22	66	61	–	–	–	–
Akiyama [21]	2017	Prospective cohort	21	33	64.9	64.7	–	–	0	–
Liu [33]	2017	Retrospective cohort	69	64	55.1	53.8	24	11	0	0
Underwood [37]	2017	Non comparative	-	81	-	66	–	9	–	0
Zhang [36]	2018	Randomised controlled trial	57	57	67.01	66.89	16	6	–	–
Total			1685	1924	63.2	62.7	24.1	23.3	2.6	1.9

Table 28.3 Specific complications and length of stay (LOS) in ERAS protocol studies

Studies	Year	Type of study	No. group 1 (Non ERAS)	No. group 2 (ERAS)	Pulmonary complications Non ERAS (%)	Pulmonary complications ERAS (%)	Anastomotic leak Non ERAS (%)	Anastomotic leak ERAS (%)	LOS (Days) Non ERAS	LOS (Days) ERAS
Cerfolio [15]	2004	Non comparative	–	90	–	12	–	0		7
Munitiz [23]	2010	Retrospective cohort	74	74	17	10	6	5	13	9
Tomaszek [24]	2010	Retrospective cohort	276	110	–	–	33	3	13	10
Jianjun [38]	2012	Non comparative	–	80	–	3		0		
Cao [25]	2013	Retrospective cohort	55	57	11	6	6	4	14.8	7.7
Li [16]	2012	Prospective cohort	47	59	16	13	5	8	10	8
Preston [26]	2013	Retrospective cohort	24	86	14	21	1	4	15	7.5
Lee [27]	2013	Retrospective cohort	47	59	–	–	–	–	10	8
Tang [34]	2013	Retrospective and prospective cohort	27	36	–	–	3	3	15	11
Zhao [22]	2014	Randomised controlled trial	34	34	–	–	1	0	12.52	7.15
Blom [20]	2013	Prospective cohort	78	103	18	15	18	15	1	4
Markar [17]	2014	Prospective cohort	92	183	–	–	3	12	10	8

Findlay [18]	2015	Prospective cohort	55	77	21	21	4	5	12	14
Ford [19]	2014	Prospective cohort	121	80	–	–	12	3	13	10
Pan [28]	2014	Retrospective cohort—MIO	40	40	5	7	3	3	12	7
Shewale [29]	2015	Retrospective cohort	322	386	88	76	45	49	12	8
Gatenby [30]	2015	Retrospective cohort	16	9	–	–	–	–	20.5	17
Oakley [31]	2016	Retrospective cohort	81	66	–	–	–	–	18	14
Chen [35]	2016	Randomised controlled trial	132	128	7	5	3	2	12.56	7.62
Li [51]	2016	Prospective cohort study	55	55	5.45	21.8	0	10.9	8.31	13.72
Giacopuzzi [32]	2017	Retrospective cohort	17	22	–	–	–	–	10	9
Akiyama [21]	2017	Prospective cohort	21	33	8	14	0	0	32.7	19.6
Liu [33]	2017	Retrospective cohort	69	64	10	4	4	2	14.6	9.5
Underwood [37]	2017	Non comparative	-	81	–	26	-	4		9
Zhang [36]	2018	Randomised controlled trial	57	57	–	–	–	–	13.51	9.47
Total			1685	1924	19.5	17	9.2	6.8	13.6	9.8

pulmonary complications. The studies have shown conclusive evidence of the positive effect of enhanced recovery on measured clinical outcomes. Early postoperative mobilization has advantages of improving cardiovascular and pulmonary functioning and reduces the risk of thromboembolic complications [1].

Complications

The most dreaded complication in esophagectomy is anastomotic leak. Interestingly, anastomotic leak was persistently lower in ERAS groups in comparison to non-ERAS groups [16, 18, 24, 26]. However, it is crucial to highlight that there was no standard definition of anastomotic complications in these different studies, and thus leaks may have also included subclinical manifestations. This may explain the difference in the absolute leak rate among studies and specifically the high rate of anastomotic leaks reported by Shewale et al. [29] in comparison to other reports.

Reduction in pulmonary complications and length of stay was evident in the ERAS groups, with a mean length of stay <12 days compared to a mean length of stay of up to 19 days in the conventional care groups. Enhanced recovery has also led to reduction in mortality rates in comparison to traditional care.

Effects of Individual Components of ERAS

In focusing on specific components, one can understand the differences in outcomes observed. Perioperative fluid management and fluid overload has been correlated with increased post-operative complications, particularly pulmonary complications [39, 40]. Interestingly, in esophagectomy cases, goal-directed fluid therapy has not been highlighted in most enhanced recovery protocol studies. Goal-directed fluid therapy to avoid hypervolemia is advocated, as fluid overload has been shown to be associated with higher rates of anastomotic leak and pneumonia [41]. In addition, goal-directed fluid therapy has been shown to improve postoperative gastrointestinal recovery and ambulation as well as postoperative nutritional status and protein synthesis [42, 43].

Immediate postoperative extubation demonstrated its beneficial effect in other types of surgery with measurable improvements in length of ICU stay [44, 45]. However, no difference was found for the enhanced recovery post-esophagectomy studies not implementing this in their protocol.

Routine NG tube placement and removal within 5 days, with or without confirmatory contrast study to ensure conduit emptying, is the current practice in the majority of published studies. Only a few studies provided evidence against the routine use of NG tube by showing that NG tubes can increase the risk of postoperative respiratory tract infection and also are potentially associated with higher rates of anastomotic leak [46, 47].

A fundamental aspect of enhanced recovery is early enteral feeding, which remains the most controversial and discussed component in oesophagectomy patients due the concern that early feeding can lead to anastomotic leak and

aspiration. Early enteral feeding in gastrointestinal surgery has been shown to lead to a significant reduction in major infectious complications, respiratory complications, and gastrointestinal complications specifically anastomotic leak [48]. In esophageal surgery, early jejunostomy feeding on the day of surgery along with oral intake on day 4 did not seem to have an effect on the anastomotic leak rate [49]. Similarly, enteral feeding via feeding tube was shown to reduce anastomotic leak, wound and other infections, pneumonia, and mortality, and had an associated reduction of length of stay [49].

A major challenging component of postoperative care is pain control, as sufficient pain control decreases cardiopulmonary complications, length of hospital stay, and mortality. There is still controversy regarding optimal postoperative analgesic protocols for esophagectomy, and heterogeneous surgical techniques from open to hybrid to minimally invasive approaches may have different analgesic requirements. Epidural analgesia is currently the gold standard for analgesia post esophagectomy, which is associated with improved postoperative pain relief, earlier recovery of gastrointestinal function, earlier extubation, and earlier mobilization. However, anastomotic leak was not statistically different with the use of epidural [50]. In later studies, Li et al. [51] in a cohort of 587 patients have shown that the use of epidural in esophagectomy has led to significantly reduced rate of pneumonia from 32% to 19.7% and anastomotic leak from 23.0% to 14.0%. Michelet et al. [52] have also shown that that epidural analgesia is associated with a decreased incidence of anastomotic leak. In addition, paravertebral blocks have been used for the chest and abdominal incisions in esophagectomy, as the paravertebral space is continuous between the thorax and abdomen. The benefits of paravertebral blocks in the setting of thoracotomy have been reported [53, 54]. Paravertebral block in the setting of esophagectomy was first reported in 1988 with a limited number of reports published subsequently [55]. A randomised prospective study of bilateral paravertebral blocks demonstrated better preservation of pulmonary function and reduced length of hospital stay in comparison to intravenous patient controlled analgesia (PCA) [56]. Furthermore, combining epidural analgesia with paravertebral block has been shown to be safe and effective, with a reduced frequency of hypotensive episodes and a shorter time to ambulation [57].

Early postoperative enteral nutrition from feeding jejunostomy reduces the production of inflammatory cytokines by preserving the gut mucosal barrier and preventing bacterial translocation [58]. Indeed, early enteral nutrition reduced the duration of systematic inflammatory response syndrome after esophagectomy in our previous study [59, 60].

Minimally invasive surgery has been a major advancement in the field with minimally invasive esophagectomy (MIE) being first introduced in 1992 [61]. MIE has been shown to be a feasible technique with good oncological outcomes [62–64]. However, to date the majority of resections are carried out through an open technique [65]. No studies have yet been conducted comparing MIE as an element of enhanced recovery program to conventional care with an open surgical approach, and the impact of a minimally invasive approach as part of an enhanced recovery protocol on recovery could not be assessed as only one study used MIE in the context of enhanced recovery [16].

Overall quality of life improvement is a crucial aspect to consider when implementing changes to care pathways. However, only one study of patients aged >60 years assessed this, showing that quality of life was improved in patients on an enhanced recovery protocol in comparison to controls, along with a similar pattern for psychological impact [59].

Conclusions and Recommendations

In summary, enhanced recovery protocols in esophagectomy show wide variations in practice due to the complexity of the procedure. Enhanced recovery has been shown to reduce hospital stay and morbidity following esophagectomy. It has been advocated that early mobilisation, early enteral feeding, early removal of chest tubes, limiting the use of nasogastric decompression, and optimizing the use of epidural anaesthesia or analgesia facilitates early discharge of patients (Table 28.4). Recommendations for standardised pathway post esophagectomy have been recently published by ERAS study group, which will allow the outcomes to be assessed in a unified manner as well as allowing the auditing of enhanced recovery pathways. From a patient perspective, enhanced recovery has preoperative, intraoperative and post-operative aspects, and patient engagement in all aspects is crucial for the success of its implementation. From a clinician perspective, a standardized protocol should be followed, and patients should be following the protocol. Adherence to this recommendation according to the guidelines could be used as a quality criterion or a performance indicator. With regards to policy, the recommendation should be adopted as a performance indicator in patient care pathways.

Recommendation

- Use of a multidisciplinary, multicomponent enhanced recovery pathway is recommended for esophagectomy patients (evidence quality moderate, strong recommendation).

Table 28.4 Goals for enhanced recovery protocols in the setting of esophagectomy

Target of enhanced recovery protocol	Quality of the evidence (GRADE)	Findings
Ambulation	Low	Early post-operative mobilisation reduces pulmonary complications and length of hospital stay
Feeding	Moderate	Early enteral feeding is safe
Length of stay	Moderate	Length of hospital is reduced with utilisation of enhanced recovery protocol
Overall morbidity	Moderate	A standardised protocol results in reduced morbidity and specifically anastomotic leaks
Anastomotic leak	Moderate	A standardized protocol results in reduced anastomotic leaks

A Personal View of the Data

Esophagectomy remains a procedure with a significant incidence of postoperative complications and adverse effects on patients' long-term quality of life. Patients undergoing this complex procedure will benefit from ERAS models of care, as several studies indicate that ERAS for esophagectomy provides a structured multidisciplinary approach to improving postoperative outcomes. The pattern of change in surgical practice internationally is towards robotics and minimally invasive techniques, however these techniques are solely centered on improving intraoperative events to enhance recovery. Therefore, ERAS protocols will still remain critical in order to standardize the postoperative pathway of these patients to ensure optimal outcomes are achieved.

References

1. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth. 1997;78:606–17.
2. Martin TD, Lorenz T, Ferraro J, et al. Newly implemented enhanced recovery pathway positively impacts hospital length of stay. Surg Endosc. 2016;30:4019–28.
3. Gustafsson UO, Scott MJ, Schwenk W, et al. 2013 Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. World J Surg. 2013;37:259–84.
4. Spanjersberg WR, Reurings J, Keus F, et al. Fast track surgery versus conventional recovery strategies for colorectal surgery. Cochrane Database Syst Rev. 2011;2:CD007635.
5. Pecorelli N, Hershorn O, Baldini G, et al. Impact of adherence to care pathway interventions on recovery following bowel resection within an established enhanced recovery program. Surg Endosc. 2017;31:1760–71.
6. Lassen K, Soop M, Nygren J, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg. 2009;144:961–9.
7. Mortensen K, Nilsson M, Slim K, et al. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Br J Surg. 2014;101:1209–29.
8. Thorell A, MacCormick AD, Awad S, et al. Guidelines for perioperative care in bariatric surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. World J Surg. 2016;40:2065–83.
9. Melloul E, Hubner M, Scott M, et al. Guidelines for perioperative care for liver surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. World J Surg. 2016;40:2425–40.
10. Nelson G, Altman AD, Nick A, et al. Guidelines for pre- and intra-operative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations, part I. Gynecol Oncol. 2016;140:313–22.
11. Nelson G, Altman AD, Nick A, et al. Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations, part II. Gynecol Oncol. 2016;140:323–32.
12. Wu PC, Posner MC. The role of surgery in the management of oesophageal cancer. Lancet Oncol. 2003;4:481–8.
13. Low DE, Alderson D, Cecconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg. 2015;262:286–94.
14. Low DE, Allum W, De Manzoni G, et al. Guidelines for perioperative care in esophagectomy: Enhanced Recovery After Surgery (ERAS®) Society Recommendations. World J Surg. 2019;43:299.

15. Cerfolio RJ, Bryant AS, Bass CS, et al. Fast racking after Ivor Lewis esophagectomy. Chest. 2004;126(4):1187–94.
16. Li C, Ferri LE, Mulder DS, et al. An enhanced recovery pathway decreases duration of stay after esophagectomy. Surgery. 2012;152:606–14.
17. Markar SR, Schmidt H, Kunz S, et al. Evolution of standardized clinical pathways: refining multidisciplinary care and process to improve outcomes of the surgical treatment of esophageal cancer. J Gastrointest Surg. 2014;18:1238–46.
18. Findlay JM, Tustian E, Millo J, et al. The effect of formalizing enhanced recovery after esophagectomy with a protocol. Dis Esophagus. 2015;28(6):567–73.
19. Ford SJ, Adams D, Dudnikov S, et al. The implementation and effectiveness of an enhanced recovery programme after oesophago-gastrectomy: a prospective cohort study. Int J Surg. 2014;12:320–4.
20. Blom RL, van Heijl M, Bemelman WA, et al. Initial experiences of an enhanced recovery protocol in esophageal surgery. World J Surg. 2013;37:2372–8.
21. Akiyama Y, Iwaya T, Endo F, et al. Effectiveness of intervention with a perioperative multidisciplinary support team for radical esophagectomy. Support Care Cancer. 2017;25:3733–9.
22. Zhao G, Cao S, Cui J. Fast-track surgery improves postoperative clinical recovery and reduces postoperative insulin resistance after esophagectomy for esophageal cancer. Support Care Cancer. 2014;22:351–8.
23. Munitz V, Martinez-de-Haro LF, Ortiz A, et al. Effectiveness of a written clinical pathway for enhanced recovery after transthoracic (Ivor Lewis) oesophagectomy. Br J Surg. 2010;97(5):714–8.
24. Tomaszek SC, Cassivi SD, Allen MS, et al. An alternative postoperative pathway reduces length of hospitalisation following oesophagectomy. Eur J Cardiothorac Surg. 2010;37:807–13.
25. Cao S, Zhao G, Gui J, et al. Fast-track rehabilitation program and conventional care after esophagectomy: a retrospective controlled cohort study. Support Care Cancer. 2013;2:707–14.
26. Preston SR, Markar SR, Baker CR, et al. Impact of a multidisciplinary standardized clinical pathway on perioperative outcomes in patients with oesophageal cancer. Br J Surg. 2013;100(1):105–12.
27. Lee L, Li C, Robert N, et al. Economic impact of an enhanced recovery pathway for oesophagectomy. Br J Surg. 2013;100(10):1326–34.
28. Pan H, Hu X, Yu Z, et al. Use of a fast-track surgery protocol on patients undergoing minimally invasive oesophagectomy: preliminary results. Interact Cardiovasc Thorac Surg. 2014;19:441–7.
29. Shewale JB, Correa AM, Baker CM, et al. Impact of a fast-track esophagectomy protocol on esophageal cancer patient outcomes and hospital charges. Ann Surg. 2015;261(6):1114–23.
30. Gatenby PA, Shaw C, Hine C, et al. Retrospective cohort study of an enhanced recovery programme in oesophageal and gastric cancer surgery. Ann R Coll Surg Engl. 2015;97:502–7.
31. Oakley B, Lamb C, Vohra R, et al. Achieving long term survival in oesophagectomy patients aged over 75. Ann Med Surg (Lond). 2016;13(9):15–21.
32. Giacopuzzi S, Weindelmayer J, Treppiedi E, et al. Enhanced recovery after surgery protocol in patients undergoing esophagectomy for cancer: a single center experience. Dis Esophagus. 2017;30(4):1–6.
33. Liu YW, Yan FW, Tsai DL, et al. Expedite recovery from esophagectomy and reconstruction for esophageal squamous cell carcinoma after perioperative management protocol reinvention. J Thorac Dis. 2017;9:2029–37.
34. Tang J, Humes DJ, Gemmil E, et al. Reduction in length of stay for patients undergoing oesophageal and gastric resections with implementation of enhanced recovery packages. Ann R Coll Surg Engl. 2013;95:323–8.
35. Chen L, Sun L, Lang Y, et al. Fast-track surgery improves postoperative clinical recovery and cellular and humoral immunity after esophagectomy for esophageal cancer. BMC Cancer. 2016;16:449.

36. Zhang Z, Zong L, Xu B, et al. Observation of clinical efficacy of application of enhanced recovery after surgery in perioperative period on esophageal carcinoma patients. J BUON. 2018;23:150–6.
37. Underwood TJ, Noble F, Madhusudan N, et al. The development, application and analysis of an enhanced recovery programme for major oesophagogastric resection. J Gastrointest Surg. 2017;21:614–21.
38. Jianjun O, Yin L, Wenqun X, et al. Fast track program for esophagectomy patients. Thorac Cancer. 2012;3:55–9.
39. Lobo DN, Bostock KA, Neal KR, et al. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomized controlled trial. Lancet. 2002;359:1812–8.
40. Glatz T, Kulemann B, Marjanovic G, et al. Postoperative fluid overload is a risk factor for adverse surgical outcome in patients undergoing esophagectomy for esophageal cancer: a retrospective study in 335 patients. BMC Surg. 2017;17:6.
41. Chappell D, Jacob M. Influence of non-ventilatory options on postoperative outcome. Best Pract Res Clin Anaesthesiol. 2010;24:267–81.
42. Hjort Jakobsen D, Sonne E, Basse L, et al. Convalescence after colonic resection with fast-track versus conventional care. Scand J Surg. 2004;93:24–8.
43. Taniguchi H, Sasaki T, Fujita H, et al. Effects of goal-directed fluid therapy on enhanced postoperative recovery: an interventional comparative observational study with a historical control group on oesophagectomy combined with ERAS program. Clin Nutr ESPEN. 2018;23:184–93.
44. Mandell MS, Lezotte D, Kam I, et al. Reduced use of intensive care after liver transplantation: influence of early extubation. Liver Transpl. 2002;8:676–81.
45. Chamchad D, Horrow JC, Nachamchik L, et al. The impact of immediate extubation in the operating room after cardiac surgery on intensive care and hospital lengths of stay. J Cardiothorac Vasc Anesth. 2010;24:780–4.
46. Daryaei P, Vaghef Davari F, Mir M, Harirchi I, Salmasian H. Omission of nasogastric tube application in postoperative care of esophagectomy. World J Surg. 2009;33:773–7.
47. Nguyen NT, Slone J, Woolridge J, et al. Minimally invasive oesophagostomy without the use of postoperative nasogastric tube decompression. Am Surg. 2009;75:929–31.
48. Martos-Benítez DF, Gutiérrez-Noyola I, Soto-García A, et al. Program of gastrointestinal rehabilitation and early postoperative enteral nutrition: a prospective study. Surgery. 2018;70:105–11.
49. Lewis SJ, Egger M, Sylvester PA, et al. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. BMJ. 2001;323(7316):773–6.
50. Tsui SL, Law S, Fok M, et al. Postoperative analgesia reduces mortality and morbidity after esophagectomy. Am J Surg. 1997;173:472–8.
51. Li W, Li Y, Huang Q, et al. Short and long-term outcomes of epidural or intravenous analgesia after esophagectomy: a propensity-matched cohort study. PLoS One. 2016;11(4):e0154380.
52. Michelet P, D'Journo XB, Roch A, et al. Perioperative risk factors for anastomotic leak- age after esophagectomy: influence of thoracic epidural analgesia. Chest. 2005;128:3461–6.
53. Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy — a systematic review and meta-analysis of randomized trials. Br J Anaesth. 2006;96:418–26.
54. Ding X, Jin S, Niu X, Ren H, Fu S, Li Q. A comparison of the analgesia efficacy and side effects of paravertebral compared with epidural blockade for thoracotomy: an updated meta-analysis. PLoS One. 2014;9:e96233.
55. Sabanathan S, Smith PJ, Pradhan GN, Hashimi H, Eng JB, Mearns AJ. Continuous intercostal nerve block for pain relief after thoracotomy. Ann Thorac Surg. 1988;46:425–6.
56. Zhang W, Fang C, Li J, et al. Single-dose, bilateral paravertebral block plus intravenous sufentanil analgesia in patients with esophageal cancer undergoing combined thoracoscopic-laparoscopic esophagectomy: a safe and effective alternative. J Cardiothorac Vasc Anesth. 2014;28:966–72.

57. Niwa Y, Koike M, Torii K, et al. Combination of continuous paravertebral block and epidural anesthesia in postoperative pain control after esophagectomy. Esophagus. 2016;13:42–7.
58. Deitch EA. Bacterial translocation: the influence of dietary variables. Gut. 1994;35:S23–7.
59. Kobayashi K, Koyama Y, Kosugi S, Ishikawa T, Sakamoto K, Ichikawa H, Wakai T. Is early enteral nutrition better for postoperative course in esophageal cancer patients? Nutrients. 2013;5:3461–9.
60. Muneoka Y, Ichikawa H, Kosugi S, et al. Hyperbilirubinemia predicts the infectious complications after esophagectomy for esophageal cancer. Ann Med Surg (Lond). 2019;39:16–21.
61. Cuschieri A, Shimi S, Banting S. Endoscopic oesophagectomy through a right thoracoscopic approach. J R Coll Surg Edinb. 1992;37:7–11.
62. Biere SS, van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet. 2012;379:1887–92.
63. Mariette C, Meunier B, Pezet D, et al. Hybrid minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicenter, open-label, randomized phase III controlled trial, the MIRO trial. J Clin Oncol. 2015;33(Suppl 3):5.
64. Avery KN, Metcalfe C, Berrisford R, et al. The feasibility of a randomized controlled trial of esophagectomy for esophageal cancer — the ROMIO (Randomized Oesophagectomy: Minimally Invasive or Open) study: protocol for a randomized controlled trial. Trials. 2014;15:200.
65. Allum WH, Bonavina L, Cassivi SD, et al. Surgical treatment for esophageal cancers. Ann N Y Acad Sci. 2014;1325:242–68.

Does Jejunostomy Tube Feeding Improve Outcomes After Esophagectomy?

29

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Introduction

Esophagectomy with gastric conduit reconstruction is the standard treatment for locally advanced esophageal cancer, achieving a 5-year survival rate of 40–50% when it is preceded by neoadjuvant chemo- or chemoradiotherapy [1, 2]. Aiming to protect the esophagogastric anastomosis and avoid aspiration of food after esophagectomy, patients are traditionally kept on a nil by mouth regimen for the first few days [3]. Enteral feeding support is mostly preferred over parenteral nutrition during this phase, as it better preserves the gut barrier and is associated with fewer postoperative complications following gastro-intestinal surgery [4, 5]. While enteral feeding support can also be provided through nasoenteric (i.e. nasoduodenal or nasojejunal) tubes, many surgeons prefer jejunostomy tubes in patients undergoing esophagectomy. However, jejunostomy tubes are not without risks, as was demonstrated by a previous review that reported jejunostomy-associated complications in 13–38% of patients undergoing esophagectomy [6]. While most of these complications were relatively minor (e.g. dislocation, local site infection), these numbers warrant a critical appraisal of the need for routine jejunostomy tube feeding following esophagectomy.

Over the recent years, the principles of enhanced recovery after surgery (ERAS) have been increasingly applied to a variety of surgical procedures, such as gastrectomy, pancreaticoduodenectomy, and colorectal resection [7–15]. Early postoperative resumption of oral intake is an important aspect of ERAS protocols, aiming to decrease (feeding-related) complications and accelerate recovery. However, the safety and feasibility of early oral intake remain topics of debate in the setting of

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esophagectomy. Although several studies reported that early resumption of oral intake is safe for patients who underwent esophagectomy, others suggested that this feeding strategy is associated with a higher anastomotic leakage rate [16, 17]. Furthermore, early oral intake may be challenging in patients who suffer from complications following esophagectomy.

Due to the inconsistency in literature regarding the outcomes of different feeding strategies following esophagectomy, no consensus has been reached regarding the role of jejunostomy tube feeding in relation to other alternatives for this patient population [18]. This chapter addresses the merits and risks of jejunostomy tube feeding in relation to other feeding strategies for esophageal cancer patients undergoing esophagectomy.

Search Strategy

Based on the clinical question at hand (Table 29.1), a literature search through the PubMed and Embase libraries was carried out to identify studies that compared jejunostomy tube feeding to other feeding strategies in patients undergoing esophagectomy for esophageal cancer. No date limits were set. The following search terms were used: (jejunostomy OR "jejunal tube" OR "jejunal feeding" OR "tube feeding" OR "enteral tube" OR "enteral feeding") AND (esophagectomy OR "oesophagectomy" OR "esophageal resection" OR "oesophageal resection"). The current primary endpoints included feeding related complications, length of hospital stay, nutritional outcomes, mortality, quality of life, and survival. Studies that compared jejunostomy tube feeding with total parenteral nutrition, nasoenteric tube feeding, early oral feeding, or 'no jejunostomy tube feeding' were included in case at least one of the aforementioned primary endpoints was reported. Studies that did not exclusively evaluate patients undergoing esophagectomy were only considered in case subgroup analyses were reported. Furthermore, studies that compared jejunostomy tube feeding to no feeding at all were excluded. Lastly, studies were excluded in case no English full-text was available or when they involved case reports, small case series (<10 patients), reviews, poster abstracts, study protocols, or animal studies.

Table 29.1 PICO formatted terms for literature search

Patients	Intervention	Comparators	Outcomes of interest
Patients undergoing esophagectomy for esophageal cancer	Jejunostomy tube feeding	1. Nasoenteric tube feeding 2. Total parenteral nutrition 3. No jejunostomy tube feeding 4. Early oral feeding	Feeding related complications, length of hospital stay, nutritional outcomes, mortality, quality of life, survival

The search yielded 1319 hits (i.e. 335 PubMed and 984 Embase). After removing duplicates, applying exclusion criteria, and screening titles and abstracts, the full-texts of 35 studies were assessed and 15 studies were included. In those studies, jejunostomy tube feeding was compared with total parenteral nutrition (four studies), nasoenteric tube feeding (three studies), or early oral feeding (two studies). The remaining studies compared patients who received jejunostomy tube feeding with patients who did not, although the compared alternative feeding strategy was not always clearly defined (six studies). The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was used to grade the quality of evidence (i.e. very low, low, moderate, high, or very high quality) and to classify the strength of the ensuing recommendations (i.e. weak or strong recommendation) [19–21].

Results and Recommendations

Jejunostomy Versus Nasoenteric Tube Feeding

In three studies (i.e. two randomized controlled trials [22, 23] and one retrospective cohort study [24]), jejunostomy tube feeding was compared with nasoenteric tube feeding in patients undergoing esophagectomy. Table 29.2 summarizes the key findings of these studies, which indicate that there is moderate evidence that jejunostomy tubes are associated with less tube removals by the patient, and fewer tube dislocations due to other causes, but more episodes of bowel obstruction when compared with nasoenteric feeding tubes. In addition, there is moderate evidence that jejunostomy and nasoenteric tubes can achieve comparable outcomes regarding length of hospital stay, realization of nutritional aims, duration of enteral feeding, and mortality. However, patient reported outcome measures were only investigated in one randomized controlled trial, which found superior quality of life scores at 1 week after esophagectomy in patients who received jejunostomy tube feeding. As such, there is moderate quality evidence that jejunostomy tube feeding provides short-term quality of life benefits over nasoenteric tube feeding in this context. The use of jejunostomy tube feeding is therefore weakly recommended over the use of nasoenteric tube feeding after esophagectomy.

Jejunostomy Tube Versus Total Parenteral Nutrition

Postoperative feeding by means of a jejunostomy tube was compared with total parenteral nutrition in four studies (i.e. two randomized controlled trials [25, 26] and two retrospective cohort studies [27, 28]). The key findings of these studies are shown in Table 29.3. In light of the limited number of comparative studies on this topic, there is moderate evidence that jejunostomy tube feeding provides benefits over total parenteral nutrition in terms of postoperative weight loss, fluid balance, and immunological recovery. Moreover, there is low quality evidence that

Table 29.2 Overview of evidence and recommendations regarding the use of jejunostomy tube feeding versus nasoenteric tube feeding in patients undergoing esophagectomy according to the GRADE system

Summary of key findings	Study type	Evidence grade	Recommendation	Strength of recommendation
Compared with nasoenteric tube feeding, jejunostomy tube feeding is associated with:				
• Better quality of life scores at 1 week postoperative follow-up (60.2 vs. 39.5, P < 0.001)	RCT [22]	Moderate	Jejunostomy tube feeding is recommended over naso-enteric tube feeding for nutritional support after esophagectomy	Weak
• Less tube removal by the patient (15% vs. 0%, P = 0.001) and dislocations due to other causes (19% vs. 10%, P = 0.023)	RCT [22]	Moderate		
• More bowel obstructions (7% vs. 0%, P = 0.035)	RCT [22]	Moderate		
• Similar achievement of nutritional aims, duration of feeding support, tolerance to enteral feeding, and mortality	RCT [23]	Moderate		
• Similar rate of overall tube-related complications and length of hospital stay	RCT [23], RS [24]	Moderate		

RCT randomized controlled trial, *RS* retrospective study

jejunostomy tube feeding is associated with earlier return of bowel function and shorter length of hospital stay, while achieving similar nutritional outcomes when compared with total parenteral nutrition. The use of a jejunostomy tube is therefore weakly recommended over total parenteral nutrition.

Jejunostomy Tube Feeding Versus 'No Jejunostomy Tube Feeding'

Jejunostomy tube feeding was compared with no jejunostomy tube feeding in patients undergoing esophagectomy by six studies (i.e. one randomized controlled trial [29], two population based cohort studies [30, 31], and three retrospective cohort studies [32–34]). In the randomized controlled trial, preoperatively malnourished patients were allocated to either minimally invasive esophagectomy with jejunostomy tube feeding until 3 months after surgery or open esophagectomy with nasoenteric tube feeding until hospital discharge [29]. When the nutritional

Table 29.3 Overview of evidence and recommendations regarding the use of jejunostomy tube feeding versus total parenteral tube feeding in patients undergoing esophagectomy according to the GRADE system

Summary of key findings	Study type	Evidence grade	Recommendation	Strength of recommendation
Compared with total parenteral tube feeding, jejunostomy tube feeding is associated with:				
• Less weight loss at 2 weeks postoperative follow-up (−2.9% vs. −5.1%, P = 0.020)	RCT [25]	Moderate	Jejunostomy tube feeding is recommended over total parenteral nutrition for nutritional support after esophagectomy	Weak
• Less fluid loss from urine and drains (2534 mL vs. 2891 mL, P = 0.011)	RCT [25]	Moderate		
• Faster recovery of the total lymphocyte count (~1350 lymphocytes/mL vs. ~950 lymphocytes/mL on postoperative day 9, P < 0.05)	RCT [26]	Moderate		
• Earlier return of bowel movement (postoperative day 4 versus postoperative day 8, P < 0.001) and shorter total length of hospital stay (26 days vs. 43 days, P < 0.001)	RS [27]	Low		
• Similar nutritional outcomes in terms of serum total protein and albumin levels	RS [28]	Low		

RCT randomized controlled trial, *RS* retrospective study

outcomes were compared between both groups at 3 months postoperative follow-up, the authors found better outcomes regarding body mass index, serum albumin, and overall quality of life in patients who had been fed through their jejunostomy tube following a minimally invasive esophagectomy procedure. Moreover, this group had fewer complaints of fatigue, nausea and vomiting, pain, and loss of appetite at 3 months after surgery when compared to the group of patients who underwent open esophagectomy followed by nasoenteric feeding until hospital discharge. Although the authors suggested that enteral feeding at home can increase the quality of life and decrease the risk of malnutrition in malnourished patients undergoing esophagectomy, the reported analyses were likely heavily influenced by the surgical approach (i.e. minimally invasive versus open) [29].

Two population-based studies compared the outcomes of patients who received jejunostomy tube feeding versus patients who did not after esophagectomy, although the alternative feeding strategy was not described for patients who were not fed through a jejunostomy [30, 31]. Jejunostomy tube feeding was found to be associated with similar results in terms of postoperative re-interventions [30], length of

hospital stay [30, 31], discharge destination [31], mortality [30], and overall survival [30]. Furthermore, no differences in weight loss [31] or quality of life [30] were found at 3 months after esophagectomy. These results were partially reproduced by some retrospective cohort studies, which also found similar weight loss [32, 33] and quality of life outcomes [32] between patients who received jejunostomy tube feeding and patients who did not. However, one retrospective study reported an increased length of hospital stay (30 days vs. 18 days, $P < 0.001$) and more intestinal torsions (12% vs. 0%, $P < 0.001$) in patients who received jejunostomy tube feeding [34].

Based on this literature, there is both very low quality evidence that jejunostomy tube feeding until 3 months after esophagectomy improves nutritional outcomes and quality of life and very low quality evidence that that jejunostomy tube feeding does not provide benefits regarding short-term clinical outcomes and intermediate-term weight loss and quality of life in patients undergoing esophagectomy. No clear recommendations can be made based on these studies.

Jejunostomy Tube Feeding 'Versus' Early Oral Feeding

To date, only two studies (one randomized controlled trial and one retrospective cohort study) from the same authors compared jejunostomy tube feeding with early oral intake after esophagectomy, which represent a relatively new strategy [35, 36]. In one of these studies, patients were included from three centers and randomly allocated to receive either jejunostomy tube feeding or early oral nutrition, although patients in both study arms had a jejunostomy in place to ensure sufficient nutritional intake in case oral intake was insufficient during the postoperative phase. Although no significant difference between those groups was found regarding the primary outcome measure (the day of functional recovery), an important finding of that study was that both groups had comparable results regarding clinical outcomes, particularly anastomotic leakage and aspiration pneumonia, indicating that early resumption of oral intake was safe in this trial setting [35]. The other study retrospectively included patients from four centers and primarily compared the long term outcomes of patients who received jejunostomy or nasoenteric tube feeding with those of patients who were allowed early oral feeding, although the latter group also had a 'stand-by' jejunostomy tube that was only used in case oral intake was insufficient or contra-indicated because of complications [36]. In that study, patients who received jejunostomy or nasoenteric tube feeding lost significantly less weight between surgery and 1 month postoperative follow-up when compared to patients who were on an early oral feeding regimen (−2.0 kg vs. −4.0 kg, $p = 0.004$). However, the opposite result was found between 1 and 3 months postoperative follow-up (−2.3 kg vs. −1.0 kg, $p = 0.039$) and no significant difference was observed between 6 and 12 months after esophagectomy. Furthermore, no significant difference was found in the incidence of nutritional re-interventions. Hence, the authors concluded that the feeding protocols were comparable regarding overall postoperative weight loss and number of nutritional re-interventions [36] (Table 29.4).

Table 29.4 Overview of evidence and recommendations regarding the use of jejunostomy tube feeding versus 'no jejunostomy tube feeding' or early oral feeding

Summary of key findings	Study type	Evidence grade	Recommendation	Strength of recommendation
Compared with 'no jejunostomy tube feeding', jejunostomy tube feeding is associated with				
• Similar outcomes regarding re-intervention rates, length of hospital stay, discharge destination, mortality, survival, and quality of life	RS [30–33]	Very low	No recommendation can be made	–
• More intestinal torsions (12% vs. 0%, P < 0.001)	RS [34]	Very low		
Compared to an early oral feeding regimen combined with a stand-by jejunostomy, jejunostomy tube feeding is associated with:				
• Similar functional recovery	RCT [35]	Moderate	Placement of a standby jejunostomy tube during esophagectomy is recommended in patients who will be on an early oral feeding regimen after esophagectomy	Weak
• Similar anastomotic leakage and aspiration pneumonia rates	RCT [35] and RS [36]	Moderate		
• Similar weight loss and nutritional re-intervention rates	RS [36]	Moderate		

RCT randomized controlled trial, *RS* retrospective study

Conclusions and Recommendations

These results from currently available literature suggest that jejunostomy tube feeding is associated with comparable results regarding functional recovery, postoperative complications (particularly anastomotic leakage and aspiration pneumonia), nutritional re-interventions, and weight loss when compared to with early oral intake. However, importantly, all patients who received early oral feeding also had a jejunostomy tube in those studies. Therefore, there is moderate quality evidence that early oral intake, combined with a standby jejunostomy tube, provides similar outcomes when compared to jejunostomy or nasoenteric tube feeding in patients undergoing esophagectomy. Placement of a standby jejunostomy tube during esophagectomy is therefore weakly recommended in patients who will be on an early oral feeding regimen.

Recommendations

- Jejunostomy tube feeding is preferred over nasoenteric tube feeding (evidence quality moderate, weak recommendation) and total parenteral nutrition (evidence quality moderate, weak recommendation) for the immediate postoperative period after esophagectomy.
- In case an early oral feeding regimen is planned, placement of a standby jejunostomy tube during esophagectomy is advised to allow immediate enteral supplementation in case oral intake is insufficient or contraindicated because of complications (evidence quality moderate, weak recommendation)

A Personal View of the Data

Considering the findings in this review, the use of jejunostomy tubes seems valuable in the standard care of patients undergoing esophagectomy, either to allow routine enteral feeding or to serve as a back-up in case an early oral feeding regimen cannot be fulfilled due to conditions that prohibit or restrict oral intake, such as anastomotic leakage, increased aspiration risk, or delayed gastric conduit emptying [37]. Furthermore, home tube feeding has been suggested to contribute to fast recovery after esophagectomy, which can be facilitated by intraoperative jejunostomy placement. It should be noted, however, that our previous study did not find any differences in length of hospital stay, number of re-admissions, and weight loss until 6 months after esophagectomy between patients who received jejunostomy tube feeding until discharge and patients who had their jejunostomy tube feeding continued after discharge until oral intake was considered sufficient [38]. In light of potential complications, the necessity of routinely creating long term enteral access by means of a jejunostomy may be questioned. Furthermore, total parenteral nutrition might also suffice as a back-up feeding strategy in the context of an early oral feeding regimen, as was suggested by the results of a recent randomized controlled trial that compared early oral feeding combined with total parenteral nutrition versus nasoenteric tube feeding in patients undergoing minimally invasive three-stage esophagectomy [39]. Even so, jejunostomy tubes allow for long periods of nutritional support and are relatively easy to manage, which may be valid arguments to prefer a jejunostomy tube over nasoenteric tubes or total parenteral nutrition.

In our center, robot-assisted minimally invasive esophagectomy (RAMIE) with intraoperative jejunostomy tube placement is the current standard of care [40, 41]. In case a two-stage approach is possible, the jejunostomy is created by a (robot-assisted) laparoscopic technique at the end of the abdominal phase. Although we only encountered mild and manageable complications so far (i.e. local infection and tube luxation), surgeons should always remain cautious of potential more serious

complications, most importantly intestinal torsion and intra-abdominal abscess. Future studies should aim to identify technical or patient-related factors that are associated with jejunostomy-associated complications, which may aid to further decrease the morbidity associated with this feeding strategy.

References

1. Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090–8.
2. van der Sluis PC, Ruurda JP, Verhage RJ, van der Horst S, Haverkamp L, Siersema PD, et al. Oncologic long-term results of robot-assisted minimally invasive thoraco-laparoscopic esophagectomy with two-field lymphadenectomy for esophageal cancer. Ann Surg Oncol. 2015;22(Suppl 3):S1350–6.
3. Kingma BF, Steenhagen E, Ruurda JP, van Hillegersberg R. Nutritional aspects of enhanced recovery after esophagectomy with gastric conduit reconstruction. J Surg Oncol. 2017;116:623.
4. Peng J, Cai J, Niu ZX, Chen LQ. Early enteral nutrition compared with parenteral nutrition for esophageal cancer patients after esophagectomy: a meta-analysis. Dis Esophagus. 2016;29(4):333–41.
5. Mazaki T, Ebisawa K. Enteral versus parenteral nutrition after gastrointestinal surgery: a systematic review and meta-analysis of randomized controlled trials in the English literature. J Gastrointest Surg. 2008;12(4):739–55.
6. Weijs TJ, Berkelmans GH, Nieuwenhuijzen GA, Ruurda JP, van Hillegersberg R, Soeters PB, et al. Routes for early enteral nutrition after esophagectomy. A systematic review. Clin Nutr. 2015;34(1):1–6.
7. Mortensen K, Nilsson M, Slim K, Schafer M, Mariette C, Braga M, et al. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Br J Surg. 2014;101(10):1209–29.
8. Temple-Oberle C, Shea-Budgell MA, Tan M, Semple JL, Schrag C, Barreto M, et al. Consensus review of optimal perioperative care in breast reconstruction: Enhanced Recovery after Surgery (ERAS) Society Recommendations. Plast Reconstr Surg. 2017;139(5):1056e–71e.
9. Melloul E, Hubner M, Scott M, Snowden C, Prentis J, Dejong CH, et al. Guidelines for perioperative care for liver surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World J Surg. 2016;40(10):2425–40.
10. Nelson G, Altman AD, Nick A, Meyer LA, Ramirez PT, Achtari C, et al. Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations--Part II. Gynecol Oncol. 2016;140(2):323–32.
11. Thorell A, MacCormick AD, Awad S, Reynolds N, Roulin D, Demartines N, et al. Guidelines for perioperative care in bariatric surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World J Surg. 2016;40(9):2065–83.
12. Cerantola Y, Valerio M, Persson B, Jichlinski P, Ljungqvist O, Hubner M, et al. Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS((R))) society recommendations. Clin Nutr. 2013;32(6):879–87.
13. Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN, et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS((R))) Society recommendations. World J Surg. 2013;37(2):285–305.
14. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Clin Nutr. 2012;31(6):783–800.

15. Lassen K, Coolsen MM, Slim K, Carli F, de Aguilar-Nascimento JE, Schafer M, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Clin Nutr. 2012;31(6):817–30.
16. Berkelmans GH, van Workum F, Weijs TJ, Nieuwenhuijzen GA, Ruurda JP, Kouwenhoven EA, et al. The feeding route after esophagectomy: a review of literature. J Thorac Dis. 2017;9(Suppl 8):S785–91.
17. Zheng R, Devin CL, Pucci MJ, Berger AC, Rosato EL, Palazzo F. Optimal timing and route of nutritional support after esophagectomy: a review of the literature. World J Gastroenterol. 2019;25(31):4427–36.
18. Low DE, Allum W, De Manzoni G, Ferri L, Immanuel A, Kuppusamy M, et al. Guidelines for perioperative care in esophagectomy: Enhanced Recovery After Surgery (ERAS((R))) Society Recommendations. World J Surg. 2019;43(2):299–330.
19. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94.
20. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6.
21. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ, et al. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008;336(7651):995–8.
22. Tao Z, Zhang Y, Zhu S, Ni Z, You Q, Sun X, et al. A prospective randomized trial comparing jejunostomy and nasogastric feeding in minimally invasive McKeown esophagectomy. J Gastrointest Surg. 2019; https://doi.org/10.1007/s11605-019-04390-y.
23. Han-Geurts IJ, Hop WC, Verhoef C, Tran KT, Tilanus HW. Randomized clinical trial comparing feeding jejunostomy with nasoduodenal tube placement in patients undergoing oesophagectomy. Br J Surg. 2007;94(1):31–5.
24. Elshaer M, Gravante G, White J, Livingstone J, Riaz A, Al-Bahrani A. Routes of early enteral nutrition following oesophagectomy. Ann R Coll Surg Engl. 2016;98(7):461–7.
25. Takesue T, Takeuchi H, Ogura M, Fukuda K, Nakamura R, Takahashi T, et al. A prospective randomized trial of enteral nutrition after thoracoscopic esophagectomy for esophageal cancer. Ann Surg Oncol. 2015;22(Suppl 3):S802–9.
26. Aiko S, Yoshizumi Y, Sugiura Y, Matsuyama T, Naito Y, Matsuzaki J, et al. Beneficial effects of immediate enteral nutrition after esophageal cancer surgery. Surg Today. 2001;31(11):971–8.
27. Gabor S, Renner H, Matzi V, Ratzenhofer B, Lindenmann J, Sankin O, et al. Early enteral feeding compared with parenteral nutrition after oesophageal or oesophagogastric resection and reconstruction. Br J Nutr. 2005;93(4):509–13.
28. Alvarez-Sarrado E, Mingol Navarro F, J Rosellon R, Ballester Pla N, Vaque Urbaneja FJ, Muniesa Gallardo C, et al. Feeding jejunostomy after esophagectomy cannot be routinely recommended. Analysis of nutritional benefits and catheter-related complications. Am J Surg. 2019;217(1):114–20.
29. Wu Z, Wu M, Wang Q, Zhan T, Wang L, Pan S, et al. Home enteral nutrition after minimally invasive esophagectomy can improve quality of life and reduce the risk of malnutrition. Asia Pac J Clin Nutr. 2018;27(1):129–36.
30. Klevebro F, Johar A, Lagergren J, Lagergren P. Outcomes of nutritional jejunostomy in the curative treatment of esophageal cancer. Dis Esophagus. 2019;32(7) https://doi.org/10.1093/dote/doy113.
31. Martin L, Lagergren J, Jia C, Lindblad M, Rouvelas I, Viklund P. The influence of needle catheter jejunostomy on weight development after oesophageal cancer surgery in a population-based study. Eur J Surg Oncol. 2007;33(6):713–7.
32. Scarpa M, Cavallin F, Noaro G, Pinto E, Alfieri R, Cagol M, et al. Impact of jejunostomy during esophagectomy for cancer on health related quality of life. Chin J Cancer Res. 2014;26(6):678–84.

33. Kroese TE, Tapias L, Olive JK, Trager LE, Morse CR. Routine intraoperative jejunostomy placement and minimally invasive oesophagectomy: an unnecessary step? Eur J Cardiothorac Surg. 2019;56(4):746–53.
34. Koterazawa Y, Oshikiri T, Hasegawa H, Yamamoto M, Kanaji S, Yamashita K, et al. Routine placement of feeding jejunostomy tube during esophagectomy increases postoperative complications and does not improve postoperative malnutrition. Dis Esophagus. 2020;33(1) https://doi.org/10.1093/dote/doz021.
35. Berkelmans GHK, Fransen LFC, Dolmans-Zwartjes ACP, Kouwenhoven EA, van Det MJ, Nilsson M, et al. Direct oral feeding following minimally invasive esophagectomy (NUTRIENT II trial): an international, multicenter, open-label randomized controlled trial. Ann Surg. 2020;271(1):41–7.
36. Berkelmans GHK, Fransen L, Weijs TJ, Lubbers M, Nieuwenhuijzen GAP, Ruurda JP, et al. The long-term effects of early oral feeding following minimal invasive esophagectomy. Dis Esophagus. 2018;31(1):1–8.
37. Berkelmans GHK, Kingma BF, Fransen LFC, Nieuwenhuijzen GAP, Ruurda JP, van Hillegersberg R, et al. Feeding protocol deviation after esophagectomy: a retrospective multicenter study. Clin Nutr. 2020;39:1258. pii: S0261-5614(19)30229-8. https://doi.org/10.1016/j.clnu.2019.05.018.
38. Weijs TJ, van Eden HWJ, Ruurda JP, Luyer MDP, Steenhagen E, Nieuwenhuijzen GAP, et al. Routine jejunostomy tube feeding following esophagectomy. J Thorac Dis. 2017;9(Suppl 8):S851–60.
39. Sun HB, Li Y, Liu XB, Zhang RX, Wang ZF, Lerut T, et al. Early oral feeding following Mckeown minimally invasive esophagectomy: an open-label, randomized, controlled, noninferiority trial. Ann Surg. 2018;267(3):435–42.
40. van Hillegersberg R, Boone J, Draaisma WA, Broeders IA, Giezeman MJ, Borel Rinkes IH. First experience with robot-assisted thoracoscopic esophagolymphadenectomy for esophageal cancer. Surg Endosc. 2006;20(9):1435–9.
41. van der Sluis PC, van der Horst S, May AM, Schippers C, Brosens LAA, Joore HCA, et al. Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer: a randomized controlled trial. Ann Surg. 2019;269(4):621–30.

30 Surgery Versus Definitive Chemoradiotherapy for Regionally Advanced Esophageal Squamous Cell Cancer

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Introduction

The ideal treatment for regionally advanced squamous cell carcinoma (SCC) of the thoracic esophagus remains unclear. Traditionally, surgery has been the standard treatment for these tumors. However, although advanced algorithms for patient selection and the use of more minimally invasive techniques have produced significantly better perioperative outcomes and survival after esophagectomies in the early twenty-first century, the outcomes of patients with regionally advanced squamous cell carcinoma who undergo surgery alone remain poor [1–4], with high morbidity and mortality and low 5-year survival rates [5–7].

Recent efforts have shown that the incorporation of chemoradiotherapy (CRT) prior to surgery for SCC improves patient survival [8–10]. Indeed, some advocate that surgery should be reserved for selected patients with an incomplete response to induction CRT [11]. In contrast, where complete tumor response is present after treatment with chemotherapy and radiation alone, surgery may not add a benefit to survival of these patients. Recent developments in molecular medicine and personalized therapies have pushed to the forefront the issue of whether definitive chemoradiation is superior to surgery. This chapter explores available evidence in an effort to determine whether and when definitive CRT is superior to CRT plus surgery in patients with advanced SCC of the esophagus.

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Search Strategy

A literature search was performed for available English language publications to identify data relevant to the issue at hand. The following databases were included in the search: PubMed and Cochrane Evidenced Based Medicine. The research focused on articles from 2005 to 2019 in order to provide the latest evidence. The types of publications sought included randomized controlled trials, meta-analyses, observational studies, retrospective studies, and reviews. The search terms included: esophageal squamous cell carcinoma, regionally advanced esophageal cancer, surgery, chemoradiation/chemoradiotherapy and esophagectomy. Studies were excluded if esophageal resection alone was one of the study groups. Five studies were identified, including four randomized controlled trails and one systematic review that compared CRT plus surgery to definitive CRT. All publications were reviewed and classified using the GRADE System.

Results

Optimal therapy for SCC of the esophagus is a complex issue that largely is dependent on the location of the tumor. For cervical esophageal cancers, the standard of care is definitive concurrent chemotherapy and radiation therapy [12, 13]. However, for SCC of the thoracic esophagus, optimal treatment is not well defined, and the role of CRT is developing. The question remains as to whether patients who show complete response to CRT may be better served by forgoing surgery (Table 30.1).

Definitive CRT Versus CRT Plus Surgery

Two large trials have compared definitive CRT with CRT plus surgical resection in SCC. Stahl and his colleagues performed a prospective randomized multicenter trial that included 172 patients with locally advanced SCC (T3-4, N0-1) [14]. Half of the patients received induction chemotherapy followed by CRT plus an esophagectomy while the other half of the patients received induction chemotherapy followed by CRT with an increased radiation dose only and no surgery (65 Gy vs. 40 Gy in the surgical arm). The esophagectomy group had a higher treatment-related mortality rate as compared to the CRT group (12.8% vs. 3.5%; $p = 0.03$). Two patients died preoperatively due to neutropenic infection; seven out of 62 patients died postoperatively in hospital related to anastomotic leak, pneumonia, injury of the left

Table 30.1 PICO formatted terms for literature search

Patient population	Intervention	Comparator	Outcomes
Patients with regionally advanced esophageal squamous cell cancer	Induction chemoradiation followed by esophageal resection	Definitive chemoradiation	Overall survival

main bronchus, and heart failure; and three patients died from late toxicities. However, researchers found no difference in overall survival (OS) between the two cohorts (35.4% vs. 39.9%). The progression-free survival rate was significantly better for the group that underwent esophageal resection after CRT (64.3% vs. 40.7%; p = 0.003) [14]. At the 10-year follow-up, no overall survival difference between CRT plus surgery versus definitive CRT was observed [17]. This suggests that, while the addition of an esophagectomy increases the local control and reduces the rates of local recurrence in comparison to definitive CRT, resection does not have a significant impact on survival in patients with regionally advanced SCC.

The second trial comparing definitive CRT with CRT plus surgical resection in SCC, FFCD 9102, included 451 patients, of whom 259 with regionally advanced SCC were randomized [15]. No difference in 2-year survival was found between the two groups. However, patients who underwent esophagectomy after CRT had higher mortality rates (9.3% vs. 0.8%) due to surgical complications, disease progression, and other causes. A Cochrane review of these two trials confirmed that that there was adequate data and quality of evidence, supporting the conclusion that surgery after CRT did not improve survival [18].

In a long-term follow up study of a subset of patients of the FFCD 9102 clinical trial, researchers examined those patients who did not have a clinical response to initial CRT (192 patients in the study were not randomized and of those, 111 were clinical non-responders). When comparing those clinical non-responders who were operated on versus those clinical non-responders who did not receive surgery after definitive CRT, the median OS in patients who underwent surgery after induction CRT was longer than in those patients who had definitive CRT (17 months vs. 5.5 months). Interestingly, patients who had a clinical response after CRT who did not undergo resection had an equivalent OS to patients who did not respond to induction CRT and underwent a surgical resection (Table 30.2) [16].

Conclusions and Recommendations

Regionally advanced SCC of the thoracic esophagus requires a multimodality therapeutic approach. Multiple randomized controlled trials and meta-analyses have demonstrated the benefits of induction therapy with CRT with or without surgical resection. After induction CRT, patients should be divided into clinical responders and non-responders. While resection appears to provide a higher rate of local control of the disease, it does not affect OS. The role of surgical resection in regionally advanced SCC of the thoracic esophagus is not completely defined. The decision regarding whether to recommend surgery after induction therapy with CRT should be evaluated on an individual level based on the particular specifics of each patient. In patients with a complete response after induction therapy, close surveillance is a safe alternative to immediate surgery. For local invasion of paraesophageal organs, such as the diaphragm, pericardium or pleura, the literature is very limited and larger prospective, multicenter trials are needed to clarify the role of each therapeutic modality.

Table 30.2 Quality of evidence

Author [Reference]	Year	Type of study	Patients with SCC	Stage	Treatment	Effect	Quality of evidence
Stahl [14]	2005	RCT	172	T3-4 N0-1	Induction CRT + Esophagectomy vs. Definitive CRT	OS at 2 years: Equivalent DFS: Improved in esophagectomy arm	Moderate
Bedenne [15]	2007	RCT	239	T3 N0-1	Induction CRT + Esophagectomy vs. Definitive CRT	OS at 2 years: equivalent	High
Stahl [17]	2008	RCT	169	T3-4 N0-1	Induction CRT + Esophagectomy vs. Definitive CRT	OS at 10 years: equivalent	Moderate
Vincent [16]	2015	RCT (studied nonrandomized patients of FFCD9102 trial)	117	T3 N0-1	Induction CRT + Esophagectomy vs. Definitive CRT in non-responders to induction CRT	OS: Higher in esophagectomy arm	Moderate
Vellayappan [18]	2017	CSR	431	T3 or N+	Induction CRT + Surgery vs. CRT	OS: equivalent Freedom from local-regional relapse improved with esophagectomy	High Moderate

C chemotherapy, *CRT* chemoradiotherapy, *CROSS* chemoradiotherapy for oesophageal cancer followed by surgery study, *CSR* Cochrane systematic review, *DFS* disease free survival, *OS* overall survival, *RCT* randomized controlled trial, *SCC* squamous cell carcinoma

Recommendation

- The data are inconclusive with respect to whether CRT alone or followed by esophageal resection should be recommended to patients with regionally advanced SCC of the esophagus (quality of evidence moderate, no recommendation).

A Personal View of the Data

Without further evidence and larger, randomized trials comparing definitive CRT versus CRT plus surgery in regionally advanced SCC of the thoracic esophagus, it is difficult to determine whether surgery should be completely abandoned in all patients. Instead, evaluating individual responses to CRT provides the best course of action at this time. In my practice, patients with regionally advanced SCC of the thoracic esophagus are evaluated by a multidisciplinary team, and we generally recommend induction therapy with CRT followed by esophagectomy if the patient can tolerate surgery. More trials comparing a personalized molecular approach with a minimally invasive esophageal resection would be of great significance since this often provides the best outcomes in other types of cancer.

References

1. Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg. 2002;236(2):177–83. https://doi.org/10.1097/00000658-200208000-00005. PubMed PMID: 12170022, PMCID: PMC1422563.
2. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, Stalmeier PF, ten Kate FJ, van Dekken H, Obertop H, Tilanus HW, van Lanschot JJ. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;347(21):1662–9. https://doi.org/10.1056/NEJMoa022343. PubMed PMID: 12444180.
3. Bosset JF, Gignoux M, Triboulet JP, Tiret E, Mantion G, Elias D, Lozach P, Ollier JC, Pavy JJ, Mercier M, Sahmoud T. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med. 1997;337(3):161–7. https://doi.org/10.1056/NEJM199707173370304. PubMed PMID: 9219702.
4. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. Ann Surg. 1999;230(3):392–403. https://doi.org/10.1097/00000658-199909000-00012. PubMed PMID: 10493486, PMCID: PMC1420884.
5. Batra R, Malhotra GK, Singh S, Are C. Managing squamous cell esophageal cancer. Surg Clin North Am. 2019;99(3):529–41. https://doi.org/10.1016/j.suc.2019.02.006. PubMed PMID: 31047040.
6. Dimick JB, Goodney PP, Orringer MB, Birkmeyer JD. Specialty training and mortality after esophageal cancer resection. Ann Thorac Surg. 2005;80(1):282–6. https://doi.org/10.1016/j.athoracsur.2005.01.044. PubMed PMID: 15975382.
7. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med. 2003;349(22):2117–27. https://doi.org/10.1056/NEJMsa035205. PubMed PMID: 14645640.

8. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J. Australasian Gastro-Intestinal Trials G. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol. 2007;8(3):226–34. https://doi.org/10.1016/S1470-2045(07)70039-6. PubMed PMID: 17329193.
9. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, Gebski V. Australasian Gastro-Intestinal Trials G. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681–92. https://doi.org/10.1016/S1470-2045(11)70142-5. PubMed PMID: 21684205.
10. Yang H, Liu H, Chen Y, Zhu C, Fang W, Yu Z, Mao W, Xiang J, Han Y, Chen Z, Yang H, Wang J, Pang Q, Zheng X, Yang H, Li T, Lordick F, D'Journo XB, Cerfolio RJ, Korst RJ, Novoa NM, Swanson SJ, Brunelli A, Ismail M, Fernando HC, Zhang X, Li Q, Wang G, Chen B, Mao T, Kong M, Guo X, Lin T, Liu M, Fu J, Group AMETSC. Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus (NEOCRTEC5010): a phase III multicenter, randomized, open-label clinical trial. J Clin Oncol. 2018;36(27):2796–803. https://doi.org/10.1200/JCO.2018.79.1483. PubMed PMID: 30089078, PMCID: PMC6145832.
11. Valmasoni M, Pierobon ES, Zanchettin G, Briscolini D, Moletta L, Ruol A, Salvador R, Merigliano S. Cervical esophageal cancer treatment strategies: a cohort study appraising the debated role of surgery. Ann Surg Oncol. 2018;25(9):2747–55. https://doi.org/10.1245/s10434-018-6648-6. PubMed PMID: 29987601.
12. Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Besh S, Chao J, Das P, Denlinger C, Fanta P, Fuchs CS, Gerdes H, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Jasperson K, Keswani RN, Kleinberg LR, Korn WM, Leong S, Lockhart AC, Mulcahy MF, Orringer MB, Posey JA, Poultsides GA, Sasson AR, Scott WJ, Strong VE, Varghese TK Jr, Washington MK, Willett CG, Wright CD, Zelman D, McMillian N, Sundar H, National Comprehensive Cancer Network. Esophageal and esophagogastric junction cancers, version 1.2015. J Natl Compr Cancer Netw. 2015;13(2):194–227. https://doi.org/10.6004/jnccn.2015.0028. PubMed PMID: 25691612.
13. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v50–v7. https://doi.org/10.1093/annonc/mdw329. PubMed PMID: 27664261.
14. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, Klump B, Budach W, Teichmann R, Schmitt M, Schmitt G, Franke C, Wilke H. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol. 2005;23(10):2310–7. https://doi.org/10.1200/JCO.2005.00.034. PubMed PMID: 15800321.
15. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, Pezet D, Roullet B, Seitz JF, Herr JP, Paillot B, Arveux P, Bonnetain F, Binquet C. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol. 2007;25(10):1160–8. https://doi.org/10.1200/JCO.2005.04.7118. PubMed PMID: 17401004.
16. Vincent J, Mariette C, Pezet D, Huet E, Bonnetain F, Bouche O, Conroy T, Roullet B, Seitz JF, Herr JP, Di Fiore F, Jouve JL, Bedenne L. Federation Francophone de Cancerologie D. Early surgery for failure after chemoradiation in operable thoracic oesophageal cancer. Analysis of the non-randomised patients in FFCD 9102 phase III trial: chemoradiation followed by surgery versus chemoradiation alone. Eur J Cancer. 2015;51(13):1683–93. https://doi.org/10.1016/j.ejca.2015.05.027. PubMed PMID: 26163097.
17. Stahl M, Wilke H, Lehmann N, Stuschke M. Long-term results of a phase III study investigating chemoradiation with and without surgery in locally advanced squamous cell carcinoma (LA-SCC) of the esophagus. J Clin Oncol. 2008;26:4530.
18. Vellayappan BA, Soon YY, Ku GY, Leong CN, Lu JJ, Tey JC. Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer. Cochrane Database Syst Rev. 2017;(8):CD010511.

31

Robotic Minimally Invasive Esophagectomy (RAMIE) vs. Open Esophagectomy (OE) for Resectable Esophageal Cancer

John J. Brady, Tadeusz Witek, and Inderpal S. Sarkaria

Introduction

The use of robotics in thoracic surgery continues to increase, including its application to esophagectomy [1, 2]. Early case series have established feasibility for robotic assisted minimally invasive esophagectomy (RAMIE), but comparisons of this technique to traditional open esophagectomy (OE) are limited [3]. This review will focus on comparison of the two techniques with regards to post-operative complications, oncologic outcomes, and post-operative quality of life. Other areas of controversy, including costs of robotic utilization, and robotic versus non-robotic minimally invasive esophagectomy are outside the scope of this review.

In general, there is a paucity of data addressing this question. The results of the recently published ROBOT trial, a single center randomized controlled trial of RAMIE versus OE, represents the only randomized controlled trial in this domain [4]. This study makes up a significant portion of the higher quality data in this chapter.

It is important to note that differences in surgical techniques and approaches to these operations are ubiquitous throughout the literature. Furthermore, the definition of "robotic assisted" varies to a great degree and introduces significant inherent bias to the comparisons. From the prospective data available, there is currently only one comparison of open esophagectomy to a completely robotic approach by Sarkaria et al., with other studies performing portions of the procedure with robotic assistance in a hybrid manner [3, 5, 6].

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Search Strategy

A literature search of English language publications was used to identify published data on robotic esophagectomy compared to open for articles published 1990 through 2019 (Table 31.1). Databases searched included PubMed, Medline, EBSCOhost, and ScienceDirect. Keywords utilized were "robotic esophagectomy," "robotic esophageal," "robotic" AND "esophagectomy," and "RAMIE". Case series articles and review articles were excluded. Articles were also excluded if they did not directly compare RAMIE to open esophagectomy. Articles included in discussion were one randomized control trial, three prospective cohort studies, and four retrospective cohort studies (Table 31.2).

Table 31.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparators)	O (Outcomes)
Patients with resectable esophageal cancer	Robotic assisted minimally invasive esophagectomy (RAMIE)	Open esophagectomy (OE)	Post-operative complications, oncologic outcomes, post-operative quality of life

Table 31.2 Included studies

Author	Year	Surgical approach	RAMIE #	OE #	Study type	Grade of evidence
van der Sluis	2019	Three field: laparoscopic, robotic thoracoscopic	56	56	Randomized controlled trial	High
Sarkaria	2019	Ivor Lewis: robotic laparoscopic, robotic thoracoscopic	63	106	Prospective cohort	Moderate
Meredith	2019	Ivor Lewis: details not described	144	475	Prospective cohort	Low
Sugawara	2019	Transhiatal: robotic laparoscopic	18	19	Prospective cohort	Low
Espinoza-Mercato	2019	Not described	433	3542	Retrospective cohort	Low
Weksler	2017	Not described	581	6257	Retrospective cohort	Low
Joeng	2016	Three field: laparotomy, robotic thoracoscopic	88	159	Retrospective cohort	Low
Mori	2016	Transhiatal: robotic laparoscopic	22	139	Retrospective cohort	Low

Results

Post-operative Complications

The ROBOT trial represents the only prospective, randomized, controlled trial, and compared post-operative complications (Clavien-Dindo classification grade 2 or higher) between RAMIE and OE approaches [4]. A total of 112 patients were randomized, and after exclusions, 54 underwent RAMIE, and 55 underwent OE. Overall surgery-related complications were 59% vs. 80% for RAMIE and OE, respectively ($p = 0.02$). Both pulmonary complications (32% vs. 58%; $p = 0.005$) and cardiac complications (22% vs. 47%; $p = 0.006$) were statistically less frequent in the RAMIE arm. Other complications, including anastomotic leak, conduit necrosis, chylothorax, and recurrent laryngeal nerve injury, were similar between the two groups. ICU length of stay, overall length of stay, in hospital mortality, 30 day mortality, 60 day mortality, and 90 day mortality were not statistically different.

Sarkaria et al. prospectively enrolled and compared 63 RAMIE and 106 OE operations. Patient cohorts were well-matched in this non-randomized study [6]. Pulmonary (14.1% vs. 34%) and infectious (17.2% vs. 35.8%) complications were significantly less in the RAMIE group ($p = 0.014$, $p = 0.029$). The anastomotic leakage rate (grade 2–4) was less in RAMIE (3.1% vs. 9.4%), but not statistically significantly different. There was no difference in ICU length of stay, readmission rate, total readmission length of stay, major complications, and 30 day or 90 day mortality.

Meredith et al. noted a lower overall post-operative complication rate for RAMIE vs. OE (23.6 vs. 30.5%, $p = 0.003$) [7]. Pulmonary complications (9.7% vs. 17.1%), anastomotic leak, (2.8% vs. 4.8%) chyle leak (0.7% vs. 1.1%), and wound infection (0.7% vs. 5.3%) were also less in RAMIE but direct statistical comparison to OE was not reported. Median length of stay was 10 days for both approaches. Postoperative mortality was similar between RAMIE and OE at 1.4% and 1.5%, respectively.

Mori et al. compared 22 non-transthoracic robotic esophagectomies performed with a video-assisted neck approach and combined laparoscopic and robotic transhiatal approach to 139 transthoracic OE cases [8]. The robotic platform was used for specifically for transhiatal mediastinal dissection after completion of the laparoscopic abdominal and video-assisted neck dissections. There were no conversions and no intraoperative complications. Mean operative time was longer with the RAMIE approach (524 min vs. 428 min, $p < .0001$), and hospital length of stay was reduced from 24 days to 18 days ($p = 0.0013$). There was a trend to lower pneumonia rates with the robotic approach (0% vs. 14%, $p = 0.07$). There were no differences in other peri-operative outcomes, and mortality was low in both robotic and non-robotic groups (0% vs. 1.4%).

Two National Cancer Database (NCDB) reviews have been reported [1, 9]. In their NCDB cohort, Weksler et al. looked at short term outcomes and performed a propensity score matched comparison of RAMIE to OE. Thirty-day readmission

rates were similar between the groups, and although not statistically significant, 30-day mortality appeared higher in the RAMIE group (5.6% vs. 2.7%, p = 0.061). Ninety-day mortality was similar (7.8% vs. 7.9%). In a follow up NCDB analysis, which included the dataset in the previous study by Weksler et al., Espinoza-Mercato and colleagues utilized data up to 2015, an additional 2 years from the previous NCDB analysis. In matched cohorts, 30 day readmission, 30 day mortality, and 90 day mortality were all similar between RAMIE and OE. The early increased mortality seen in the Weksler et al. study was surmised to be due to the significant learning curve associated with the procedure, with mortality decreased to similar levels given the additional two years of experience with RAMIE in the updated study [1, 3, 10].

Jeong et al. looked specifically at post-operative delirium and its risk factors in RAMIE vs. OE in propensity score matched cohorts [11]. RAMIE had lower post-operative delirium (30% vs. 42%, p = 0.035), and the robotic approach had a decreased risk of delirium (OR = 0.55, p = 0.027) compared to the open approach.

Overall, the aforementioned studies suggest a benefit of RAMIE over OE in terms of pulmonary and infectious complications, with other post-operative complications being similar between the two approaches. The grade of evidence is moderate, given the findings of one high quality randomized controlled trial and one moderate quality prospective matched cohort trial.

Oncologic Outcomes

There is limited data on long term cancer survival as the RAMIE technique still remains in its relative infancy. Oncologic outcomes are thus primarily extrapolated from previously described outcome measures for esophagectomy, regardless of the approach.

The ROBOT trial data has not yet matured in terms of survival outcomes given the trial's primary focus on early perioperative outcomes and quality of life [4]. Certain facets of technical oncologic operative outcomes were discussed and evaluated. The majority of patients underwent neoadjuvant chemoradiotherapy (79% RAMIE vs. 80% OE) or chemotherapy alone (11% RAMIE vs. 7% OE) and the remaining patients were without any neoadjuvant therapy. R0 resections were comparable between RAMIE and OE (93% vs. 96% p = 0.35). It is important to note that this was an intention to treat design and two patients (4%) in the RAMIE arm were found to be unresectable and the cases aborted, but still were included in the analysis. Median lymph nodes retrieved were comparable for RAMIE and OE (27 vs. 25 nodes). At a median follow up of 40 months, overall survival and disease free survival were not statistically significant between the RAMIE and OE arms. Long term outcome data from this randomized trial is currently unavailable.

Prospective and retrospective trials suggest a benefit to the RAMIE approach, particularly with improved lymph node evaluation in the RAMIE group. Sarkaria et al. obtained a significantly higher median number of lymph nodes removed (25 vs. 22, p = 0.045) with the RAMIE approach compared to open [6]. Meredith et al. noted a higher mean number of nodes harvested in RAMIE (20 ± 9 vs. 10 ± 6), but

direct statistical comparison was not reported [7]. Weksler et al. identified more lymph nodes harvested by RAMIE, but the difference was not statistically significant (16 vs. 13; p = 0.087) [9]. The follow up NCDB study by Espinoza-Mercado et al. noted more lymph nodes harvested with RAMIE vs. OE (17 vs. 13, p < 0.001) [1]. Given the potential beneficial impact of the number of surgically removed nodes on overall cancer survival, improved lymphadenectomy with RAMIE may be advantageous from an oncologic standpoint [12].

Quality of Life

Improved quality of life after esophagectomy can be a predictor of long term survival outcomes [13, 14]. Functional recovery, immediate and chronic pain, and physical, social, and emotional well-being are all are facets of complete perioperative recovery, and represent targets for potential improvement after esophagectomy.

In the ROBOT trial, several quality of life end points were evaluated [4]. Functional recovery was defined as absence of chest tubes, tolerating solid oral intake, off intravenous hydration, independent mobilization, and pain control with oral analgesics. Functional recovery at 14 days was more frequent in the RAMIE arm compared to the OE arm (70% vs. 51%, p = 0.04). Median time to functional recovery was less in patients undergoing RAMIE versus OE (10 days vs. 13 days), but the difference was not statistically significant (p = 0.14). Mean overall postoperative pain scores were less in RAMIE vs. OE (p < 0.001) and in 11 of 14 days postoperative days, daily mean pain scores were statistically significantly less in the RAMIE arm. As measured by Quality of Life Questionnaire Core 30 (QLQ-C30), discharge and 6 week health-related quality of life and physical functioning were both statistically improved after RAMIE compared to OE.

Sarkaria et al. evaluated quality of life outcomes for RAMIE or OE utilizing the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) questionnaire [6]. This includes a total score and subset scores for physical, social, emotional, functional, and esophageal-specific well-being. Overall, there was no difference in the total FACT-E scores between RAMIE or OE (p = 0.84), or in any specific subset. Both approaches to surgery yielded lower physical well-being scores at 1 month (p < 0.001), with improvement at 4 months (p = <0.001), but without returning to baseline (p = 0.011); findings for emotional well-being scores were similar. Postoperative pain was evaluated with patient reported scores through the Brief Pain Inventory instrument. Compared to OE, RAMIE had lower pain scores (p = 0.005) and pain interference scores (p = 0.002) in the early post-operative period.

Sugawara and coworker also analyzed quality of life outcomes up to 24 months post operatively [15]. RAMIE patients had higher physical and emotional function scores at 3, 6, and 18 months and 6, 18, and 24 months, respectively, compared to the open cohort. Generalized pain scores were lower in the RAMIE group at 3, 6, 12, and 24 months post-operatively, and esophageal specific pain scores were less at 3 and 18 months as well. Fatigue and insomnia at 24 months were less frequently

reported in the RAMIE group. Comparisons between postoperative complications or outcomes were not reported. Importantly, this study was associated with significant bias due to the comparison of a robotic transhiatal approach with an open Ivor Lewis approach.

Conclusions and Recommendations

Overall, the data suggests specific improved peri-operative and quality of life outcomes with RAMIE compared to OE, and similar outcomes in most other domains. However, the overall strength of evidence is moderate at best, with only one randomized prospective trial, and one comparative cohort trial directly comparing the two procedures. The randomized prospective ROBOT trial provides a high level evidence in favor of RAMIE with its association with decreased overall, pulmonary, and cardiac complications, without increasing the rate of complications in other aspects of care, or overall mortality [4]. Quality of life was improved with RAMIE in this study as well. The prospective cohort comparison trial from Memorial Sloan Kettering Cancer Center also favored RAMIE in terms of pulmonary and infectious complications, as well as short term post-operative pain outcomes with a moderate level of evidence given the well-matched cohorts [6]. While there is a suggestion of selected improvement in peri-operative outcomes, including blood loss and a greater number of lymph nodes harvested, the overall level of evidence is weak. To our knowledge, there is currently no evidence examining survival outcomes between these cohorts. The remainder of the trials provide low or very low levels of evidence generally supporting the better quality trials.

Recommendations

- RAMIE is recommended over OE for improved post-operative outcomes, specifically pulmonary and other infections (evidence quality moderate, strong recommendation)
- RAMIE is recommended over OE for improved short-term quality of life, specifically pain and earlier recovery from surgery (evidence quality moderate, strong recommendation)
- RAMIE is recommended over OE for equivalent or possibly improved oncologic outcomes (evidence quality low, weak recommendation)

A Personal View of the Data

Overall, we believe the level of data is strong enough to reasonably suggest RAMIE is an acceptable alternative to OE for resectable esophageal cancer, and may provide some advantages over OE. However, while beyond the scope of this chapter, the far

greater depth and quality of data identifying similar advantages of non-robotic minimally invasive esophagectomy (MIE) over OE may be applied to RAMIE, given the perspective that the procedure can be considered a subtype of MIE simply performed with a different tool. In our own practice, RAMIE has become a routine and acceptable alternative to standard MIE, with both procedures performed routinely based on surgeon experience and preference. Similarly, patients who are candidates for minimally invasive esophagectomy (MIE) would, in turn, be candidates for RAMIE. We believe either approach is certainly preferred over open approaches given the rapid accumulation of evidence from several institutions, not just our own, strongly suggesting clear peri-operative clinical benefits. However, when interpreting these data, the reader is cautioned to carefully consider the experience of the operator with the given techniques, and consideration of one technique over the other must be tempered by the surgeon's position on the learning curve for these complex procedures. As the experience increases, complications seen early in the learning curve can be expected to decrease, and overall outcomes improve with increasing and more widespread penetration of RAMIE into thoracic practice.

References

1. Espinoza-Mercado F, Imai TA, Borgella JD, et al. Does the approach matter? Comparing survival in robotic, minimally invasive, and open esophagectomies. Ann Thorac Surg. 2019;107:378–85.
2. Latif MJ, Park BJ. Robotics in general thoracic surgery procedures. J Visc Surg. 2017;3:44.
3. Sarkaria IS, Rizk NP, Grosser R, et al. Attaining proficiency in robotic-assisted minimally invasive esophagectomy while maximizing safety during procedure development. Innovations. 2016;11:268–73.
4. van der Sluis PC, Ruurda JP, van der Horst S, et al. Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer, a randomized controlled trial (ROBOT trial). Trials. 2012;13:230.
5. Sarkaria IS, Rizk NP, Finley DJ, et al. Combined thoracoscopic and laparoscopic robotic-assisted minimally invasive esophagectomy using a four-arm platform: experience, technique and cautions during early procedure development. Eur J Cardiothorac Surg. 2013;43:e107–15.
6. Sarkaria IS, Rizk NP, Goldman DA, et al. Early quality of life outcomes after robotic-assisted minimally invasive and open esophagectomy. Ann Thorac Surg. 2019;108(3):920–8.
7. Meredith KL, Maramara T, Blinn P, Lee D, Huston J, Shridhar R. Comparative perioperative outcomes by esophagectomy surgical technique. J Gastrointest Surg. 2020;24:1261–8. https://doi.org/10.1007/s11605-019-04269-y.
8. Mori K, Yamagata Y, Aikou S, et al. Short-term outcomes of robotic radical esophagectomy for esophageal cancer by a nontransthoracic approach compared with conventional transthoracic surgery. Dis Esophagus. 2016;29:429–34.
9. Weksler B, Sullivan JL. Survival after esophagectomy: a propensity-matched study of different surgical approaches. Ann Thorac Surg. 2017;104:1138–46.
10. Park SY, Kim DJ, Kang DR, Haam SJ. Learning curve for robotic esophagectomy and dissection of bilateral recurrent laryngeal nerve nodes for esophageal cancer. Dis Esophagus. 2017;30:1–9.
11. Jeong DM, Kim JA, Ahn HJ, Yang M, Heo BY, Lee SH. Decreased incidence of postoperative delirium in robot-assisted thoracoscopic esophagectomy compared with open transthoracic esophagectomy. Surg Laparosc Endosc Percutan Tech. 2016;26:516–22.

12. Rizk NP, Ishwaran H, Rice TW, et al. Optimum lymphadenectomy for esophageal cancer. Ann Surg. 2010;251:46–50.
13. van Heijl M, Sprangers MA, de Boer AG, et al. Preoperative and early postoperative quality of life predict survival in potentially curable patients with esophageal cancer. Ann Surg Oncol. 2010;17:23–30.
14. Safieddine N, Xu W, Quadri SM, et al. Health-related quality of life in esophageal cancer: effect of neoadjuvant chemoradiotherapy followed by surgical intervention. J Thorac Cardiovasc Surg. 2009;137:36–42.
15. Sugawara K, Yoshimura S, Yagi K, et al. Long-term health-related quality of life following robot-assisted radical transmediastinal esophagectomy. Surg Endosc. 2019;34(4):1602–11. https://doi.org/10.1007/s00464-019-06923-7.

Two-Field vs. Three-Field Lymphadenectomy for Esophageal Adenocarcinoma

32

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Introduction

The concept of three-field lymph node dissection for carcinoma of the esophagus was introduced and has been practiced by Japanese surgeons since the early 1980s. The "third field" is typically defined as the cervical nodal basin accessed from the neck, but is also used in Western series to describe recurrent laryngeal nerve lymph nodes reached from the chest. Dissection of this higher field was prompted by studies showing that the cervical lymph nodes were the site of tumor recurrence in 30–40% of patients with squamous cell carcinoma in whom a curative esophageal resection had been performed [1]. In 1990, results of a nationwide study on three-field dissection performed at 35 institutions throughout Japan [2] demonstrated that one third of patients had unsuspected metastasis to the cervical lymph nodes. The frequency of nodal metastases increased with increasing depth of tumor penetration through the esophageal wall.

Despite these results, most European and North American centers have not routinely pursued three-field dissection for esophageal cancer. In Western centers, adenocarcinoma is the most common histologic subtype, typically arising in the lower esophagus or at the gastroesophageal junction. It remains unclear how often such tumors drain to the recurrent laryngeal or cervical nodal basins. Furthermore, it is generally assumed that patients with adenocarcinoma of the esophagus with

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extensive lymph node involvement have the equivalent of systemic disease. This may be particularly true for those patients with lower esophageal or gastroesophageal junction adenocarcinoma with metastases to the upper thoracic and cervical field. Cure after resection in this situation has often been considered more dependent upon the biologic behavior of the tumor and upon systemic therapy, rather than upon the surgical strategy pursued for local and regional control. As such, Western centers more commonly utilize neoadjuvant chemotherapy and radiation therapy or even definitive chemoradiation for such tumors. When esophagectomy is undertaken, the role of three-field dissection in this setting is lacking data and therefore less clear. Concern also exists that a three-field lymph node dissection may be associated with increased hospital morbidity, particularly injury to one or both recurrent nerves, potentially leading to increased pulmonary complications and a negative impact on long term survival.

Search Strategy

To identify relevant studies, a literature search was conducted of the PubMed database from inception to present. The search terms included a combination of [1] "esophageal cancer" or "oesophageal cancer" AND [2] "three-field", "3-field", "cervical lymphadenectomy", "recurrent laryngeal nodes" (Table 32.1). Titles and abstracts of studies were scanned and full texts of relevant studies reviewed. Two randomized control trials, two meta-analyses, one propensity score-matched comparison, and several retrospective case series were included in the analysis. The data was classified using the GRADE system.

Results

Randomized Trials

No randomized trials exist on patients exclusively with esophageal adenocarcinoma. Trials in squamous cell carcinoma patients may be relevant to those with adenocarcinoma, particularly for patients with tumors above the lower esophagus. Two such randomized control trials (RCTs) were performed in Japan. The first trial

Table 32.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with locally advanced esophageal adenocarcinoma	Three-field dissection	Two field dissection	Rates of node positivity
			Perioperative morbidity
			Local and regional control
			Survival

including 150 patients of whom 95% had squamous cell carcinoma, and randomized patients to three-field dissection versus abdominal and mediastinal lymph node dissection only **[**3**].** Patients undergoing three-field dissection had more total lymph nodes resected (69.0 vs. 36.4, $p < 0.01$). The overall rate of positive lymph nodes in the study was 64.7% and was similar between the two groups. In patients undergoing neck dissection, 26% had metastases in lymph nodes in the third field. Patients undergoing three-field dissection demonstrated improved 5-year survival compared to patients undergoing two-field dissection only (48.7% versus 33.7%, $p < 0.01$).

A second small RCT included 62 patients with squamous cell carcinoma randomized to conventional abdominal and thoracic lymph node dissection versus extended dissection including the cervical and superior mediastinal nodal basins [4]. The overall rate of nodal positivity was 38% and 43% in the two arms. Although positive cervical nodes were found in only one patient in the extended group, it is notable that the rate of positive intrathoracic recurrent laryngeal nodes exceeded 20% in both groups. The difference in 5-year survival favored patients undergoing extended lymphadenectomy, although not statistically significant in this small trial (66.2% vs. 48.0%, $p = 0.192$).

Meta-Analyses

Meta-analyses have been performed to investigate the effect of three-field lymph node dissection on survival and on complications in esophageal cancer patients. The first included 13 studies for qualitative analysis, including both of the previously described RCTs **[**5**].** The meta-analysis included 2379 patients, predominantly including patients with squamous cell carcinoma. The hazard ratio for 5-year overall survival favored patients undergoing three-field lymphadenectomy versus those undergoing two-field lymphadenectomy (HR 0.64, CI 0.56–0.73, $p < 0.001$). The authors found no difference in perioperative mortality (risk ratio 0.64, CI 0.38–1.10) after three-field lymphadenectomy, but significant increases in anastomotic leak (RR 1.46, CI 1.19–1.79, $p < 0.001$). On sub-group analysis (four studies), the authors found that three-field dissection improved survival for patients with pathologically positive nodes (HR 0.39, CI 0.31–0.46, $p < 0.001$) and particularly for those with positive intrathoracic recurrent nerve nodes (HR 0.32, CI 0.23–0.41, $p < 0.001$). A benefit of three-field dissection was noted for patients with positive nodes for all tumor locations, including those of the lower esophagus.

The second meta-analysis included patient data from 20 publications **[**6**].** Three-year OS was evaluated in 2598 patients undergoing three-field node dissection and in 3961 patients undergoing two-field node dissection, and was worse in patients undergoing two-field dissection (RR 1.44, CI 1.19–1.75, $p < 0.00001$). Similar results were reported for 5-year OS, with worse survival for two-field dissection (RR 1.37, CI 1.18–1.59, $p = 0.0002$). Three-field dissection was associated with higher rates of recurrent nerve palsy (RR 1.48, CI 1.13–1.92) and of anastomotic leak (RR 1.32, CI 0.97–1.81), but not of pulmonary complications (RR 0.93, CI 0.75–1.16). The authors found superiority of three-field dissection for patients with positive recurrent laryngeal nodes and for those with upper or middle third esophageal cancer.

Propensity Matched Comparison

Shao et al. described their modern experience with two-field versus three-field lymph node dissection in patients without neoadjuvant therapy [7]. The author's propensity matched 282 patients from each of the two- and three-field groups. Patients undergoing three-field node dissection had more total lymph nodes removed (38.5 vs. 25.5, $p = 0.017$) and more nodes involved with metastatic disease (3.5 vs. 1.6, $p < 0.001$). There was no difference in 3-year or 5-year OS. More complications occurred in patients undergoing three-field lymph node dissection (34.8% vs. 25.5%, $p = 0.017$), particularly more anastomotic leaks (14.9% vs. 4.3%, $p < 0.001$). This same center has completed enrollment of a randomized clinical trial (NCT01807936) comparing two- versus three-field lymph node dissection for patients with middle or lower squamous cell esophageal carcinoma. Results have not yet been reported.

Key Case Series

Esophagectomy with three-field lymph node dissection has only rarely been practiced in Western centers and in patients with adenocarcinoma. In one report, esophagectomy with three-field lymph node dissection was performed in 192 patients between 1991 and 1999, of whom 174 patients had a primary R0 resection, including 36 patients with carcinoma of the gastroesophageal junction [8]. Patients without nodal metastasis had a 5-year survival of 80% compared with a 5-year survival of 25% for node-positive patients. Patients with middle-third squamous cell carcinoma and positive cervical nodes had a 5-year survival of 27%. In contrast, patients with distal-third adenocarcinoma and positive cervical nodes had a 4-year survival of 36%, but a 5-year survival of just 12%. In patients presenting with adenocarcinoma of the gastroesophageal junction and positive cervical nodes, there were no 5-year survivors, indicating that adding the third field does not contribute to long-term survival in those patients.

A second series evaluated 185 patients treated with esophagectomy and three-field lymph node dissection, including 96 (52%) patients who had received neoadjuvant chemotherapy [9]. Only 17% of patients ultimately found to have positive nodes in the third field had clinical nodal disease in that basin on preoperative studies, highlighting the need for careful intraoperative evaluation rather than simple reliance upon clinical staging. Overall, 20% of adenocarcinoma patients had metastases to the recurrent laryngeal or cervical nodes. For adenocarcinoma patients, the likelihood of positive nodes in the third field could be predicted by tumor depth and tumor location. Only 7% of patients with GEJ tumors had positive recurrent laryngeal or cervical lymph nodes, compared to 23% for lower esophageal tumors and 38% for middle esophageal tumors. The median overall survival was 3.0 years with an overall survival of 39.9% at 5 years. Patients with metastasis to the recurrent laryngeal or cervical nodes had an overall 5 year survival of 24.9%, compared to 44.8% for patients without positive recurrent laryngeal or cervical nodes.

Current Treatment Paradigms

Treatment algorithms have changed significantly since the publication of most of the studies above describing three-field dissection during esophagectomy. Neoadjuvant therapy is now the standard of care for locally advanced esophageal cancer in Western countries. The effect of neoadjuvant therapy on the rate of recurrent laryngeal and cervical lymph node metastases has not been well studied. It appears that although the inclusion of radiation therapy as part of the induction regimen does not improve long term survival, it likely decreases the number of pathologically positive nodes found at surgery [10, 11]. However, it should be acknowledged that the radiation field may not always include the upper paratracheal and cervical nodal basins, particularly for tumors of the lower esophagus. Regardless, at least 31–35% of patients will have persistent nodal metastases despite preoperative radiation to involved nodal basins. This may be particularly true of patients with adenocarcinoma which is generally less responsive to chemoradiation.

It would therefore seem that neoadjuvant chemoradiation or chemotherapy does not circumvent the need for pathologic assessment of the third field in patients with locally advanced esophageal cancer. Indeed, extended lymphadenectomy, as defined by the Worldwide Oesophageal Cancer Collaboration guidelines, predicts improved survival even after neoadjuvant therapy (HR 0.50, CI 0.29–0.85, $p = 0.011$) [12]. Even in patients with persistent nodal metastases (the majority with adenocarcinoma), patients who have an optimal lymphadenectomy demonstrate a trend towards improved 3-year overall survival (55% vs. 36%, $p = 0.087$), suggesting that there may be a therapeutic effect to lymphadenectomy even after neoadjuvant therapy.

Many treatment centers have adopted minimally invasive techniques to perform transthoracic esophagectomy, even after neoadjuvant therapy. Several centers have demonstrated the feasibility of a minimally invasive approach to dissection of the high recurrent laryngeal nodes in the chest [13–15]. Although predominantly performed for squamous cell carcinoma, one of these studies, by Hong et al. included 114 consecutive patients with Siewert type I adenocarcinoma [14]. Encouragingly, the rate of vocal cord paralysis (0% vs. 15%, $p = 0.003$) and pulmonary morbidity (9% vs. 29%, $p = 0.008$) were both lower in the minimally invasive group.

With the inclusion of both neoadjuvant treatment regimens and minimally invasive techniques, an argument could be made for a selective strategy of third field dissection [9, 16, 17]. For patients with middle and lower third adenocarcinomas, the decision whether to perform a three-field dissection should be heavily influenced by the clinical presentation of the patient. Only 11% of patients with clinical stage I or II esophageal adenocarcinoma will have positive recurrent laryngeal or cervical nodes, compared to 29% of patients clinically staged as III or IV (based on nodal distribution in the sixth edition) [9]. Intraoperatively, the probability of recurrent and laryngeal nodal metastases is determined in part by the presence or absence of nodal metastases at other stations. If one can reliably stage adenocarcinoma patients as pN0 in the rest of the chest, then dissection of the third field can be omitted. However, in patients with positive nodes in other intrathoracic or upper abdominal nodal stations, the incidence of recurrent laryngeal nodal metastases is 29% [9].

This high prevalence of nodal involvement suggests that three-field dissection should be considered in this patient population, at least the thoracic dissection of the upper mediastinal and recurrent laryngeal nodes.

Conclusions and Recommendations

A considerable number of patients with esophageal cancer will be inaccurately staged and susceptible to locoregional recurrence after esophagectomy with only lower two-field lymph node dissection. The importance of accurately determining the number of involved lymph nodes is in the American Joint Committee on Cancer staging system, in which nodal classification is defined by the total number of positive lymph nodes. Between 15% and 30% of patients will have their tumor-node-metastasis (TNM) classification upstaged as a result of an extended procedure including dissection of the third field. Although most surgeons readily concede the impact of the extended lymphadenectomy on tumor staging, its impact on survival is controversial due to a lack of large, well performed RCTs.

For patients with adenocarcinoma, data derived from Western series of three-field dissection indicate that 20–30% of patients may have occult nodal disease in upper thoracic or cervical lymph node stations. Therefore, patients who undergo only a two-field lymph node dissection will potentially be understaged and may not be rendered disease-free. Although the impact of three-field lymph node dissection on survival remains unproven, it is difficult to construct a rational argument for an isolated two-field dissection that relegates 20–30% of the patients to an incomplete resection. The impact of such incomplete resections on survival is not clearly established, but there is general agreement that R1 or R2 resections are associated with a dismal prognosis and little chance of survival beyond 2 years. Therefore, for patients with locally advanced adenocarcinoma, the rate of recurrent laryngeal nodal metastasis is sufficiently high to warrant consideration of dissection of at least the upper thoracic third field in select cases.

Recommendation

- In patients with esophageal adenocarcinoma with clinically positive intrathoracic nodes, we recommend dissection of the third field to optimize pathological staging and local and regional control (evidence quality low, weak recommendation).

A Personal View of the Data

Our personal opinion is that too little data exists regarding the role of three-field lymph node dissection for patients with esophageal adenocarcinoma to make definitive recommendations regarding clinical practice. In our own practice, for patients

in whom a three-hole esophagectomy and cervical anastomosis are planned, we typically dissect the upper thoracic third field, whether through an open thoracotomy or with a minimally invasive approach. Dissection of the third field is particularly likely to yield positive nodes when lower thoracic nodes are already demonstrated to be positive. In these patients, particularly for those who received neoadjuvant chemotherapy alone, we believe that an en bloc esophagectomy with three-field dissection is a critical component of local and regional control. We generally do not dissect the third field in patients with GEJ tumors, particularly those who received neoadjuvant chemoradiation in whom a thoracic anastomosis is planned.

References

1. Isono K, Onoda S, Okuyama K, Sato H. Recurrence of intrathoracic esophageal cancer. Jpn J Clin Oncol. 1985;15:49–60. [PMID: 3981814].
2. Isono K, Ochiai T, Okuyama K, Onoda S. The treatment of lymph node metastasis from esophageal cancer by extensive lymphadenectomy. Jpn J Surg. 1990;20:151–7. https://doi.org/10.1007/BF02470762. [PMID:2342235]
3. Kato H, Watanabe H, Tachimori Y, Iizuka T. Evaluation of neck lymph node dissection for thoracic esophageal carcinoma. Ann Thorac Surg. 1991;51:931–5. https://doi.org/10.1016/0003-4975(91)91008-J. [PMID: 2039322].
4. Nishihira T, Hirayama K, Mori S. A prospective randomized trial of extended cervical and superior mediastinal lymphadenectomy for carcinoma of the thoracic esophagus. Am J Surg. 1998;175:47–51. https://doi.org/10.1016/S0002-9610(97)00227-4. [PMID: 9445239].
5. Ye T, Sun Y, Zhang Y, et al. Three-field or two-field resection for thoracic esophageal cancer: a meta-analysis. Ann Thorac Surg. 2013;96:1933–41.
6. Ma GW, Situ DR, Ma QL, et al. Three-field vs two-field lymph node dissection for esophageal cancer: a meta-analysis. World J Gastroenterol. 2014;20:18022–30.
7. Shao L, Ye T, Ma L, Lin D, Hu H, Sun Y, Shzng Y, Xiang J, Chen H. Three-field versus two-field lymph node dissection for thoracic esophageal squamous cell carcinoma: a propensity matched comparison. J Thorac Dis. 2018;10(5):2924–32.
8. Lerut T, Nafteux P, Moons J, et al. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. Ann Surg. 2004;240:962–74.
9. Stiles BM, Mirza F, Port JL, Lee PC, Paul S, Christos P, Altorki NK. Predictors of cervical and recurrent laryngeal nodal metastases from esophageal cancer. Ann Thorac Surg. 2010;90(6):1805–11.
10. Spicer JD, Stiles BM, Sudarshan M, Correa AM, Ferri LE, Altorki NK, Hofstetter WL. Preoperative chemoradiation versus chemotherapy in patients undergoing modified en bloc esophagectomy for locally advanced esophageal adenocarcinoma: is radiotherapy beneficial? Ann Thorac Surg. 2016;101(4):1262–9.
11. Klevebro F, Alexandersson von Döbeln G, Wang N, Johnsen G, Jacobsen AB, Friesland S, Hatlevoll I, Glenjen NI, Lind P, Tsai JA, Lundell L, Nilsson M. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol. 2016;27(4):660–7.
12. Stiles BM, Nasar A, Mirza FA, Lee PC, Paul S, Port JL, Altorki NK. Worldwide Oesophageal Cancer Collaboration guidelines for lymphadenectomy predict survival following neoadjuvant therapy. Eur J Cardiothorac Surg. 2012;42(4):659–64.

13. Noshiro H, Iwasaki H, Kobayashi K, Uchiyama A, Miyasaka Y, Masatsugu T, Koike K, Miyazaki K. Lymphadenectomy along the left recurrent laryngeal nerve by a minimally invasive esophagectomy in the prone position for thoracic esophageal cancer. Surg Endosc. 2010;24(12):2965–73.
14. Hong L, Zhang Y, Zhang H, Yang J, Zhao Q. The short-term outcome of three-field minimally invasive esophagectomy for Siewert type I esophagogastric junctional adenocarcinoma. Ann Thorac Surg. 2013;96(5):1826–31.
15. Udagawa H, Ueno M, Haruta S, Tanaka T, Mizuno A, Ohkura Y. Re-evaluation of the role of thoracoscopic esophagectomy as a Japanese-style radical surgery. Esophagus. 2017;14(2):165–70.
16. Li H, Yang S, Zhang Y, Xiang J, Chen H. Thoracic recurrent laryngeal lymph node metastases predict cervical node metastases and benefit from three-field dissection in selected patients with thoracic esophageal squamous cell carcinoma. J Surg Oncol. 2012;105(6):548–52. https://doi.org/10.1002/jso.22148. Epub 2011 Nov 21.
17. Taniyama Y, Nakamura T, Mitamura A, Teshima J, Katsura K, Abe S, Nakano T, Kamei T, Miyata G, Ouchi N. A strategy for supraclavicular lymph node dissection using recurrent laryngeal nerve lymph node status in thoracic esophageal squamous cell carcinoma. Ann Thorac Surg. 2013;95(6):1930–7. https://doi.org/10.1016/j.athoracsur.2013.03.069. Epub 2013 May 1.

What Is the Appropriate Extent of Lymph Node Dissection in Esophageal Cancer

33

Traves D. Crabtree and James W. Feimster

Introduction

For esophageal cancer, a lymphadenectomy should be standard of care during esophagectomy and is essential for staging purposes. Some debate persists about the optimal lymphadenectomy and the impact on overall survival. This chapter will review the extent of lymphadenectomy that should be performed during esophagectomy, different lymph node prognostic indicators of survival, and recommendations for standardization of nodal dissection in patients with esophageal cancer.

Regional nodal involvement remains one of the most important prognostic indicators in resectable esophageal cancer and is reflected in the most recent American Joint Committee on Cancer (AJCC) TNM staging system [1–3]. In the National Comprehensive Cancer Network (NCCN) most current recommendation for lymph node dissection during esophagectomy, at least 15 nodes should be sampled for patients without induction chemoradiation. For patients undergoing induction therapy, the NCCN reports that the optimal number of nodes is unknown, however a similar lymphadenectomy is recommended [4].

Current NCCN guidelines are based on a number of non-randomized studies. A retrospective analysis utilizing the Surveillance Epidemiology and End Results (SEER) database with 4882 patients demonstrated that patients undergoing esophagectomy for esophageal cancer who had ≥12 lymph nodes sampled had significantly reduced mortality when compared to those who had <12 nodes sampled (OR, 1.69; 95% CI: 1.44–1.98) [4, 5]. Additionally, the Worldwide Esophageal Cancer

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Collaboration (WECC) database examined 4627 patients demonstrating that a greater extent of lymphadenectomy was associated with increased survival for node-positive disease [4, 6].

While the NCCN guidelines and other studies have emphasized the importance of a thorough lymphadenectomy, esophageal surgeons in the US have consistently failed to meet the criteria for adequate nodal dissection. Samson and colleagues using the National Cancer Data Base (NCDB) found that from 1998 to 2012, among 4686 esophagectomies performed, only 29.8% of patients had ≥15 nodes sampled [7]. Failure to meet this threshold was more common in low volume centers (less than 3.7 esophagectomies per year) versus high volume centers (greater than 20 esophagectomies per year). Among low volume centers 74.4% did not complete an R0 resection with ≥15 lymph nodes resected, compared to 56.8% of high volume centers [7]. In the ACS Oncology Group Z0060 trial, 4% of patients undergoing esophagectomy had absolutely no lymph nodes sampled, and 11% had three or fewer lymph nodes sampled [8].

Only a minority of surgeons are currently meeting the recommended number of lymph nodes sampled for esophageal cancer resections. Correction of this disparity should lead to better standardization of surgical practice and institutional quality measures with the end goal of improved overall patient care and survival.

Search Strategy

A literature search was performed to include articles from 2004 to 2019. Using PubMed, terms that were searched included: "esophageal cancer", "lymphadenectomy", "lymph nodes", "esophagectomy", "lymph node excision", "esophageal neoplasms", "extent of lymph node excision", "three-field lymphadenectomy", "surgery for esophageal cancer", "transhiatal", "transthoracic", "induction therapy", "neoadjuvant treatment", and "lymphadenectomy complications". Publications that were included were in English and regarded esophageal cancer in humans, or were cited sources in important articles related to the topic of esophageal cancer and lymph nodes. Table 33.1 lists the PICO formatted search terms. Data were classified using the GRADE system.

Table 33.1 PICO formatted terms for literature search

Patients	Intervention	Comparator	Outcomes
Patients with esophageal cancer, histologic types adenocarcinoma and squamous cell carcinoma	Esophagectomy with lymphadenectomy or lymph node excision	More lymph nodes excised versus less lymph node excised	Mortality
		Two-field versus three-field lymphadenectomies	Survival
		Transhiatal versus transthoracic	Prognostic indicators
		Upfront esophagectomy versus esophagectomy after induction therapy	Complications

Results

Extent of Lymphadenectomy

Without Neoadjuvant Therapy

Many studies have attempted to define the optimal number of lymph nodes harvested during esophagectomy (Table 33.2) [5, 6, 9–13]. Samson et al., using the NCDB from 2006 to 2012, found that the largest decrease in mortality hazard in upfront esophagectomy was in patients with ≥25 lymph nodes sampled (HR 0.77, 95% CI 0.67–0.89, $P < 0.001$) [9]. In a separate international study, a database from nine specialty centers similarly examined the number of lymph nodes removed during esophagectomy. They concluded that the number of lymph nodes sampled was an independent predictor of survival, and to maximize survival benefit a total of 23 lymph nodes need to be sampled [11]. Sentinel lymph node biopsy for esophageal cancer has been examined with limited success, as sentinel node mapping is technically challenging with significant variability in this population [14].

Table 33.2 Number of lymph nodes resected to maximize survival

Author	Source	No. of patients	Neoadjuvant therapy patients included	Primary outcome	No. of lymph nodes	Grade
Groth [5]	SEER	4882	Yes	All-cause and cancer-specific mortality	>30	Moderate
Rizk [6]	Single institution	336	No	5-year survival	≥18	Low
Samson [9]	NCDB	18,777	Yes	Overall survival	20–25	Moderate
Greenstein [10]	SEER	977	No	Disease-specific survival	≥18	Moderate
Peyre [11]	International database	2303	No	5-year survival	23	Moderate
Lagergren [12]	Single institution	606	Yes	All-cause and disease-specific 5-year mortality	N/A	Low
van Der Schaaf [13]	National database	1044	Yes	All-cause 5-year mortality	N/A	Low

NCDB National Cancer Database, *SEER* Surveillance, Epidemiology, and End Results database
All studies examined patients with esophageal squamous cell carcinoma and esophageal adenocarcinoma

To the contrary of harvesting more lymph nodes, Lagergren and colleagues suggested that the extent of lymphadenectomy performed may not influence 5-year survival [12]. This single institution study examined 606 patients undergoing esophagectomy for esophageal cancer and demonstrated that patients who had 21–52 lymph nodes sampled had no statistically significant benefit in all-cause 5-year mortality when compared to patients with 0–10 lymph nodes sampled (HR, 0.86; 95% CI, 0.63–1.17) [12]. These results have also been shown in a population-based study from Sweden that determined that patients with 7–114 nodes resected did not have any benefit in overall 5-year mortality when compared to patients with <7 nodes resected (adjusted HR, 1.00; 95% CI, 0.99–1.01) [13]. The authors suggested that a more aggressive approach to lymphadenectomy may increase perioperative complications and may not be necessary. Interestingly, these data also demonstrated that a higher ratio of positive nodes to total nodes dissected was a strong predictor of mortality, which would be difficult to determine without some minimal threshold of node dissection.

With Neoadjuvant Therapy

In patients with locally advanced disease, neoadjuvant therapy has become standard [15]. The NCCN guidelines do not specifically address the number of lymph nodes to be sampled in patients with induction therapy, however it is recommend that a lymphadenectomy be performed in a similar fashion to up-front esophagectomies [4]. A multicenter randomized controlled trial examining neoadjuvant chemoradiation compared to surgery alone showed a 27% decrease in the mean number of nodes sampled ($P = 0.001$) [16]. In this same study the overall survival for patients with neoadjuvant therapy did not differ between those who had ≥15 or <15 nodes sampled [16]. Samson and colleagues also showed using the NCDB that induction therapy was associated with a decreased likelihood of having 15 nodes sampled (OR 0.70, 0.65–0.76, $P < 0.001$) [9]. However, in this study overall survival was improved if induction therapy patients had >10 nodes sampled (HR 0.81, 95% CI 0.74–0.90, $P < 0.001$) [9].

Lymph Node Ratio

As an alternative measure from the absolute number of lymph nodes dissected, a different prognostic tool has been suggested which examines the ratio of positive nodes to total nodes sampled, known as the lymph node ratio (LNR) [17–19] (Table 33.3). The LNR reflects the degree of lymph node metastases and may decrease issues of stage migration. In a 2014 study by Tan and colleagues of 700 esophageal squamous cell carcinoma patients, the LNR was determined to be an independent prognostic factor regardless of the total number of lymph nodes sampled [17]. An additional study by Ruffato et al. corroborated these data in patients with esophageal adenocarcinoma patients, demonstrating that LNR correlated with better cancer-specific survival ($P = 0.01$) [18]. Others have suggested that a ratio of ≤0.20 had greater prognostic capabilities than the conventional staging system [19].

Table 33.3 Lymph node ratio

Author	Study type	Cancer type	Surgery	Lymph node ratio results	Grade
Tan [17]	Retrospective cohort	ESCC	Tri-incisional esophagectomy	LNR independent prognostic factor; used LNR percentiles of 0%, 1–25%, and >25% (RR 1.849, 95% CI 1.258–2.718, $P = 0.002$)	Low
Ruffato [18]	Retrospective cohort	EA	Transthoracic esophagectomy	LNR positively correlated with cancer-specific survival ($P = 0.01$); patients with LNR ≤ 0.04 significantly better survival than patients with LNR > 0.04 ($P = 0.0001$)	Low
Mariette [19]	Retrospective cohort	EA and ESCC	Transthoracic and transabdominal esophagectomy	LNR > 0.2 statistically significant factor predictive of survival ($P = 0.014$, OR 1.6, 95% CI 1.1–2.3). In adequately staged patients (LNs examined ≥15) LNR > 0.2 not predictive of survival ($P = 0.114$, OR 1.9, 95% CI 0.9–4.4)	Low

ESCC esophageal squamous cell carcinoma, *EA* esophageal adenocarcinoma, *LNs* lymph nodes, *LNR* lymph node ratio, *RR* relative risk, *CI* confidence interval, *OR* odds ratio

As an example, a patient with 1 metastatic node out of 2 sampled versus a patient with 1 metastatic node out of 20 sampled would both be classified as N1 under the conventional staging system. However, the LNR would be 0.5 and 0.05, respectively. It is likely that the patient with two nodes sampled was inadequately staged [9].

Surgical Approach During Lymphadenectomy

When comparing transthoracic or transhiatal approaches there has been no statistically significant difference in survival or tumor recurrence [8, 20, 21]. However, it has been suggested that the transthoracic approach may result in better lymphadenectomy with more accurate pathologic staging and possibly better prognostication, as nodal stations are better visualized compared to the transhiatal approach [8, 20].

The likelihood of cervical lymph node involvement in esophageal squamous cell carcinoma (ESCC) has been well established and can be as high as 46% in patients with upper esophageal cancers [22]. These upper esophageal tumors likely benefit from a three-field lymphadenectomy that would encompasses abdominal, mediastinal, and cervical lymph nodes, which include paraesophageal nodes, supraclavicular nodes, and lymph nodes lateral to the carotids [23].

With regards to distal esophageal carcinoma, some institutions favor a three-field lymphadenectomy approach, although it is uncertain if this is appropriate for all patients. Studies examining patients with adenocarcinoma of the lower esophagus have shown that lymph node involvement above the carina ranges widely from 5% to 36% [24–26]. Many studies have tried to determine if a more extensive lymphadenectomy is associated with more complications or increased 30-day mortality with varying results (Table 33.4) [9, 26–30]. Complications specific to an aggressive lymphadenectomy, three-field or otherwise, include recurrent laryngeal nerve injury

Table 33.4 Examination of complications with extended lymphadenectomy

Author	Cancer type	Comparison of lymphadenectomies	Results	Grade
Samson [9]	EA and ESCC	0–14 LN vs. ≥15 LN	30-day and 90-day mortality decreased in ≥15 LN group (4.4% vs. 3.7%, $P = 0.04$. 9.6% vs. 7.7%, $P < 0.001$, respectively). No increase in 30-day readmission (8.1% vs. 7.9%, $P = 0.68$)	Moderate
Altorki [26]	EA and ESCC	3-field	In 80 patients, 5% 30-day mortality, 26% pulmonary complications, 15% cardiac complications, 11% anastomotic complications, 9% recurrent nerve injury	Low
Schandl [27]	EA and ESCC	0–8 LN vs. 9–14 LN vs. 15–24 LN vs. 25–81 LN	Larger number of lymph nodes removed did not decrease health-related quality of life at 6 months or 5 years after surgery	Low
D'Journo [28]	EA	Standard 2-field vs. Extended 2-field	No increase in mortality during hospital stay (11% vs. 9%, $P = 0.69$). Increase risk in extended 2-field for respiratory complications (25% vs. 49%, $P = 0.02$), atrial arrhythmia (0% vs. 10%, $P = 0.04$), and need for blood transfusion (1.6 vs. 3.6, $P = 0.04$)	Low
Lagergren [29]	EA and ESCC	0–7 LN vs. 8–15 LN vs. 16–114 LN	No increased risk of reoperation/30-day mortality with greater lymph node harvest (RR = 0.98, 95% CI 0.96–1.00)	Low
Maruyama [30]	EA and ESCC	2-field vs. 3-field	Examining more than 60 nodes and/or 3-field dissection have increased risk of tracheobronchial lesions (OR 5.39, 95% CI 1.60–21.6, $P = 0.009$. OR 8.11, 95% CI 2.07–54.1, $P = 0.008$, respectively)	Low

EA esophageal adenocarcinoma, *ESCC* esophageal squamous cell carcinoma, *LN* lymph node, *RR* relative risk, *OR* odds ratio

(as high as 20%), tracheal erosion, tracheal ulcer, fistula, thoracic duct leak, need for tracheostomy, reintubation, need for transfusion, anastomotic leak, and infection (wound, abscess, etc.) [30, 31]. In experienced hands the complications associated with three-field lymphadenectomy may be mitigated with the potential benefit of increased lymph node harvest [26].

Standardization of Lymph Node Analysis

In the United States there is a wide variety of surgical techniques and reporting of pathology specimens. A secondary analysis of the American College of Surgeons Oncology Group Z0060 trial showed that 38% of specimens were submitted to pathology with no distinct lymph node station indicated, and that among patients with at least 15 nodes sampled the pathologist was credited for lymph node identification in 38% of specimens [8]. Overall lack of standardization of this process results in wide variability in the quality and accuracy of staging for esophageal carcinoma. It is ultimately the responsibility of the surgeon to institute consistent methods of nodal assessment either by accounting for lymph nodes independent of the pathologist or working closely with the pathologist to ensure accurate and reliable pathologic staging.

Conclusions and Recommendations

A lymphadenectomy is standard practice for patients undergoing esophagectomy for esophageal carcinoma. The approach to a lymphadenectomy is complex and dependent on many variables. A standardized approach to surgical practice and institutional quality measures may lead to superior results from a lymphadenectomy, potentially resulting in better patient outcomes.

Based on the most recent data a lymphadenectomy should at least include 15 lymph nodes sampled in patients with up-front esophagectomy and esophagectomy after induction therapy via surgeons preferred technique (transhiatal vs. transthoracic). The operation should include at least a two-field node dissection depending on the tumor histology and location, and the institution should have a standardized technique for submitting lymph nodes to pathology and for nodal assessment of the submitted specimen for the most accurate TNM staging.

Recommendations

- The lymphadenectomy during esophagectomy should at least include 15 lymph nodes (evidence quality low, weak recommendation).
- An esophagectomy should include at least a two-field node dissection depending on the tumor histology and location (evidence quality low, weak recommendation).
- Each institution should have a standardized technique for submitting lymph nodes to pathology and nodal assessment of the submitted specimen for the most accurate TNM staging (evidence quality low, weak recommendation).

A Personal View of the Data

The trend with many malignancies such as breast cancer utilizing sentinel node biopsy is to prevent potential complications associated with a more aggressive nodal dissection while maintaining the ability to assess nodes for prognostic purposes and for decisions regarding adjuvant treatment. The complexity and multidirectional lymphatic drainage of the esophagus poses challenges to simplified focused nodal assessment for esophageal cancer. On the one hand it could be argued that a more aggressive nodal dissection improves identification of occult nodal metastases for prognostic discussion and for selection of adjuvant therapy, while others may argue that resection of multiple negative lymph nodes, while reassuring, is not necessary and identification of positive nodes is simply a reflection of disseminated disease and therefore the outcome is predetermined. This seems to be somewhat of a nihilistic view but the ultimate answer is likely much more complex. A reasoned approach would suggest that the adequacy of nodal dissection is a threshold that maximizes the cancer specific survival benefit of identification of nodal disease without incurring dissection related morbidity or mortality that might diminish the cancer-related benefits of nodal dissection. Such an approach would thus be impacted by tumor factors, surgical technique, surgical volume, and surgeon experience. The threshold may evolve over time but the current NCCN guidelines create a reasonable foundation or standard that at the very least creates a surrogate measure for quality.

References

1. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A III, editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2009. p. 253–70.
2. Rice TW, Rusch VW, Apperson-Hansen C, Allen MS, Chen LQ, Hunter JG, Kesler KA, Law S, Lerut TE, Reed CE, Salo JA, Scott WJ, Swisher SG, Watson TJ, Blackstone EK. Worldwide Esophageal Cancer Collaboration. Dis Esophagus. 2009;22:1–8.
3. Rice TW, Kelsen DP, Blackstone EH. Esophagus and esophagogastric junction. In: Amin MB, Edge SB, Greene FL, et al., editors. AJCC cancer staging manual. 8th ed. New York: Springer; 2017. p. 185–202.
4. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, Denlinger CS, Enzinger PC, Fanta P, Farjah F, Gerdes H, Gibson M, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Johung KL, Keswani RN, Kleinberg LR, Leong S, Ly QP, Matkowskyj KA, McNamara M, Mulcahy MF, Paluri RK, Park H, Perry KA, Pimiento J, Poultsides GA, Roses R, Strong VE, Wiesner G, Willett CG, Wright CD, McMillian NR, Pluchino LA. Esophageal and esophagogastric junction cancers, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Comprehensive Cancer Netw. 2019;17(7):855–83.
5. Groth SS, Virnig BA, Whitson BA, DeFor T, Li Z, Tuttle T, Maddaus M. Determination of the minimum number of lymph nodes to examine to maximize survival in patients with esophageal carcinoma: data from the Surveillance Epidemiology and End Results database. J Thorac Cardiovasc Surg. 2010;139:612–20.
6. Rizk NP, Ishwaran H, Rice TW, Chen L, Schipper P, Kesler K, Law S, Lerut T, Reed C, Salo J, Scott W, Hofstetter W, Watson T, Allen M, Rusch V, Blackstone E. Optimum lymphadenectomy for esophageal cancer. Ann Surg. 2010;251:46–50.

7. Samson P, Puri V, Broderick S, Alexander Patterson G, Meyers B, Crabtree T. Adhering to quality measures in esophagectomy is associated with improved survival in all stages of esophageal cancer. Ann Thorac Surg. 2017;103(4):1101–8.
8. Veeramachaneni NK, Zoole JB, Decker PA, Putnam JB, Meyers BF. Lymph node analysis in esophageal resection: American College of Surgeons Oncology Group Z0060 Trial. Ann Thorac Surg. 2008;86:418–21.
9. Samson P, Puri V, Broderick S, Alexander Patterson G, Meyers B, Crabtree T. Extent of lymphadenectomy is associated with improved overall survival after esophagectomy with or without induction therapy. Ann Thorac Surg. 2017;103(2):406–15.
10. Greenstein A, Litle V, Swanson S, Divino C, Packer S, Wisnivesky J. Effect of the number of lymph nodes sampled on postoperative survival of lymph node-negative esophageal cancer. Cancer. 2008;112:1239–46.
11. Peyre C, Hagen J, DeMeester S, Altorki N, Ancona E, Griffin SM, Holscher A, Lerut T, Law S, Rice T, Ruol A, van Lanschot JJB, Wong J, DeMeester T. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg. 2008;248:549–56.
12. Lagergren J, Mattsson F, Zylstra J, Chang F, Gossage J, Mason R, Lagergren P, Davies A. Extent of lymphadenectomy and prognosis after esophageal cancer surgery. JAMA Surg. 2016;151(1):32–9.
13. van Der Schaaf M, Johar A, Wijnhoven B, Lagergren P, Lagergren J. Extent of lymph node removal during esophageal cancer surgery and survival. J Natl Cancer Inst. 2015;107(5):djv043.
14. Takeuchi H, Kawakubo H, Takeda F, Omori T, Kitagawa Y. Sentinel node navigation surgery in early-stage esophageal cancer. Ann Thorac Cardiovasc Surg. 2012;18(4):306–13.
15. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366:2074–84.
16. Robb WB, Dahan L, Mornex F, Maillard E, Thomas PA, Meunier B, Boige V, Pezet D, Le Brun-Ly V, Bosset JF, Mabrut JY, Triboulet JP, Bedenne L, Seitz JF, Mariette C. Impact of neoadjuvant chemoradiation on lymph node status in esophageal cancer: post hoc analysis of a randomized controlled trial. Ann Surg. 2015;261:902–8.
17. Tan Z, Ma G, Yang H, Zhang L, Rong T, Lin P. Can lymph node ratio replace pN categories in the tumor-node-metastasis classification system for esophageal cancer? J Thorac Oncol. 2014;9:1214–21.
18. Ruffato A, Lugaresi M, Mattioli N, Simone M, Peloni A, Daddi N, Montanari A, Anderlucci L, Mattioli S. Total lymphadenectomy and nodes-based prognostic factors in surgical intervention for esophageal adenocarcinoma. Ann Thorac Surg. 2016;101:1915–20.
19. Mariette C, Piessen G, Briez N, Triboulet JP. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. Ann Surg. 2008;247:365–71.
20. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, Stalmeier PF, ten Kate FJ, van Dekken H, Obertop H, Tilanus HW, van Lanschot JJ. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;347:1662–9.
21. Davies AR, Sandhu H, Pillai A, Sinha P, Mattsson F, Forshaw MJ, Gossage JA, Lagergren J, Allum WH, Mason RC. Surgical resection strategy and the influence of radicality on outcomes in oesophageal cancer. BJS. 2014;101:511–7.
22. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg. 1994;220:364–72.

23. Nafteux P, Depypere L, Van Veer H, Coosemans W, Lerut T. Principles of esophageal cancer surgery, including surgical approaches and optimal node dissection (2- vs. 3-field). Ann Cardiothorac Surg. 2017;6(2):152–8.
24. Feith M, Stein HJ, Siewert JR. Adenocarcinoma of the esophagogastric junction: surgical therapy based on 1602 consecutive resected patients. Surg Oncol Clin N Am. 2006;15:751–64.
25. Lagarde SM, Ha C, Hulscher JB, Tilanus HW, Ten Kate FJ, Obertop H, van Lanschot JJ. Prospective analysis of patients with adenocarcinoma of the gastric cardia and lymph node metastasis in the proximal field of the chest. BJS. 2005;92:1404–8.
26. Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg. 2002;236(2):177–83.
27. Schandl A, Johar A, Lagergren J, Lagergren P. Lymphadenectomy and health-related quality of life after oesophageal cancer surgery: a nationwide, population-based cohort study. BMJ Open. 2016;6:e012624.
28. D'Journo XB, Doddoli C, Michelet P, Loundou A, Trousse D, Giudicelli R, Fuentes PA, Thomas PA. Transthoracic esophagectomy for adenocarcinoma of the oesophagus: standard versus extended two-field mediastinal lymphadenectomy? Eur J Cardiothorac Surg. 2005;27(4):697–704.
29. Lagergren J, Mattsson F, Davies A, Lindblad M, Lagergren P. Lymphadenectomy and risk of reoperation or mortality shortly after surgery for oesophageal cancer. Sci Rep. 2016;6:36092.
30. Maruyama K, Motoyama S, Sato Y. Tracheobronchial lesions following esophagectomy: erosions, ulcers, and fistulae, and the predictive value of lymph node-related factors. World J Surg. 2009;33:778–84.
31. Isono K, Sato H, Nakayama K. Results of a nation-wide study on the three-field lymph node dissection of esophageal cancer. Oncology. 1991;48:411–20.

Salvage Esophagectomy for Persistent or Recurrent Disease After Chemoradiation

34

Nicolas Zhou, Erin M. Corsini, and Wayne L. Hofstetter

Introduction

Preoperative chemoradiation (CXRT) has revolutionized the treatment paradigm for locally advanced esophageal cancer. Early studies demonstrated improvement in survival with a multi-modality approach compared to surgery or radiation alone [1, 2]. Several studies have also shown that chemoradiation followed by surgery improves survival [3, 4], and trimodality (chemoradiation followed by surgery) patients have better local disease control compared to chemoradiation alone [4–6]. However, the role of surgery in locally-advanced esophageal cancer remains controversial. Roughly half of squamous cell carcinoma (SCC) and 25% of adenocarcinoma (AC) patients achieve a pathologic complete response after neoadjuvant chemotherapy, which has led surgeons to question the role of esophagectomy in the setting of clinical complete response [7]. RTOG0246 demonstrated the efficacy of a selective surgical resection strategy [8], selecting only patients with persistent or recurrent disease as candidates for surgical resection. Thereafter, an understanding of the optimal populations who stand to benefit from a potentially morbid salvage resection has been a topic of great debate within the surgical community. With the pre-SANO trial, diagnostic tools for assessment of clinical complete response were established and are being utilized in the ongoing Phase III SANO trial [9] comparing up-front surgery to a watch-and-wait strategy. The results from this trial will help to provide some clarity on the topic of observation versus planned surgical resection after CXRT. Notwithstanding, this chapter is not designed to discuss the relative merits of definitive chemoradiation versus CXRT + surgery. Patients arrive at consultation for salvage resection for multiple reasons; planned observation after

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CXRT, poor performance after preoperative therapy, or patient/physician choice to avoid surgery, to name a few. Our task is to discuss the merits and pitfalls of salvage resection once at that decision point.

Though salvage esophagectomy is defined in most studies as surgery performed for persistent or recurrent disease after treatment with definitive chemoradiotherapy, a firm grasp on this population, particularly in the setting of retrospective investigations, is elusive. This is largely due to the fact that it becomes difficult to separate true salvage from delayed planned resection. Similarly, distinguishing early recurrence from true persistence has posed challenges. Nonetheless, we have attempted to outline the current literature regarding the outcomes of patients undergoing salvage esophagectomy in this chapter.

Search Strategy

A Pubmed search was undertaken using the MeSH terms "esophagus," "salvage therapy," "esophagectomy," "adenocarcinoma," and "esophageal squamous cell carcinoma" (Table 34.1). Additional queries were performed with the keywords "esophagus, "surgery," and "resection." Original articles, systematic reviews, and meta-analyses published from 2012 through 2019 were included for evaluation. In total, this approach revealed 111 abstracts for review. Due to the preponderance of retrospective investigations with a relative lack of randomized data comparing salvage surgery to alternative treatment modalities, a priority was placed on systematic reviews and larger retrospective reports. Only studies published in the English language were included.

Results

Multiple investigations have shed light upon the role of salvage esophagectomy for recurrent or persistent cancer. In this section, we review the results of such reports, first outlining the data describing outcomes of both adenocarcinoma and squamous cell carcinoma (Table 34.2). We then present results separately for each histology based on studies that investigated individual cohorts.

Table 34.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with persistent or recurrent cancer after completion of definitive chemoradiotherapy	Salvage esophagectomy	Non-operative management, including chemotherapy, radiation therapy, combination therapy, and observation	Survival, morbidity

Table 34.2 Series on salvage esophagectomy following definitive chemoradiation

Author, year	Total patients	Salvage surgery	SCC/ AC	Study design	Salvage definition	Quality of evidence
Markar et al., 2015 [10]	848	308	515/319	Comparative study (salvage vs. planned resection, matched)	Recurrence/ persistent	Low
Cohen et al., 2018 [11]	308	308	193/115	Case series	Recurrence/ persistent	Very low
Faiz et al., 2019 [12]	954	954	660/224	Meta-analysis	Recurrence and/or persistent	Very low
Marks et al., 2012 [13]	586	65	–/65	Comparative study (salvage vs. planned resection, matched)	Recurrence/ persistent	Very low
Taniyama et al., 2018 [17]	100	100	100/–	Comparative (recurrent vs. persistent disease, unmatched)	Recurrent/ persistent	Very low
Sohda et al., 2017 [15]	40	40	40/–	Case series	Recurrent/ persistent	Very low
Wang et al., 2014 [16]	104	104	104/–	Comparative (recurrent vs. persistent disease, unmatched)	Recurrent/ persistent	Very low
Watanabe et al., 2015 [14]	63	63	63/–	Case series	Recurrent/ persistent	Very low
Mitchell et al., 2019 [18]	41	35	35/–	Comparative study (salvage vs. planned resection, unmatched)	Recurrent/ persistent	Very low
Buckstein et al., 2019 [19]	37		37/–	Review		Very low
Kumagai et al., 2016 [20]	219	136	219/–	Meta-analysis: (salvage vs. second-line CRT, unmatched)		Very low

SCC squamous cell carcinoma, *AC* adenocarcinoma, *CRT* chemoradiotherapy

Studies That Combined Esophageal Adenocarcinoma and Squamous Cell Carcinoma

Survival

Two retrospective studies containing both SCC and AC histology were derived from a single database for 30 French-speaking European hospitals. In the first study, Markar et al. reported on 848 patients who underwent either neoadjuvant chemoradiotherapy followed by surgery, or definitive chemoradiotherapy and subsequently had salvage surgery [10]. Cohen et al. also evaluated the same 308 salvage patients to specifically determine factors associated with morbidity and mortality [11]. Among these populations, approximately 60% had SCC, and all patients received bimodality concurrent chemoradiation. Most salvage patients had persistent disease compared to recurrent (76% vs. 24%). Trimodality-treated patients were more likely to have tumors of the lower esophagus, for which Ivor-Lewis esophagectomy was typically performed. Patients with persistent disease were more likely to be malnourished with higher pathological stage compared to those with recurrent disease. Results showed that no significant differences were found for in-hospital mortality between salvage and planned trimodality patients (8.4% vs. 9.3%) [10]. However, among the salvage group, patients had significantly increased rates of in-hospital mortality in several subsets of patients: (a) for those undergoing surgery at a low-volume center, (b) patients who received a total radiation dose ≥55 Gy, and (c) patients who had squamous histology [10, 11]. The authors postulated that high doses of radiotherapy may be correlated with observed increased rates of anastomotic leak and resultant in-hospital mortality.

Cohen et al. later confirmed this hypothesis, demonstrating an increased rate of death secondary to anastomotic leak in those with radiation ≥55 Gy (54.5% vs. 14.3%, $p = 0.017$). However, at 3 years, salvage and planned trimodality patients continued to show no differences in overall survival (43.3% vs. 40.1%) or progression-free survival (39.2% vs. 32.8%) [10]. Cohen et al. further identified independent risk factors associated with increased mortality among salvage patients, namely radiation dose ≥55 Gy, postoperative complications, pathologic stage III disease or higher, and R1 or R2 resection [11]. Persistent disease patients did not differ in terms of short-term survival compared to those with recurrent disease; however, survival differences were more apparent when evaluating long-term survival (Table 34.3), as well as locoregional (20.6% vs. 13.9%) and distant recurrence rates (26.5% vs. 18.7%), though not statistically significant [10].

A meta-analysis by Faiz et al. included 28 studies comprising 1076 patients from 2007 to 2017 [12]. Nearly all salvage patients in this study received ≥50 Gy radiotherapy. Most patients had definitive bimodality treatment, while a lesser proportion (110/1076, 10%) received planned trimodality therapy. The indication for salvage esophagectomy was unknown in 73.6% patients, and of the remainder, most patients had persistent disease compared to recurrent (17.5% vs. 8.9%). The pooled 3-year survival rate for salvage patients in this meta-analysis was 39% [12]. R0 resection was associated with better 3- and 5-year survival, but no survival differences were found between persistent and recurrent disease (Table 34.4).

Table 34.3 Perioperative mortality and long-term survival

Author, year	In-hospital mortality	90-day mortality	1-year OS	3-year OS	5-year OS
Markar et al., 2015 [10]	Salvage: 8.4% Persistent: 9.8% Recurrent: 4.1% Planned: 9.3%			Salvage: 43.3% Persistent: 39.1% Recurrent: 56.2% Planned: 40.1%	
Cohen et al., 2018 [11]	8.4%			43.3%	34%
Faiz et al., 2019 [12]		8%		39%	19.4%
Marks et al., 2012 [13]		Salvage: 4.6% Planned: 7.7%		Salvage: 48% Planned: 55%	Salvage: 32% Planned: 45%
Taniyama et al., 2018 [17]	Residual: 5.8% Recurrent: 2.1%		Residual: 57.1% Recurrent: 89.6%		Residual: 13.1% Recurrent: 46.9%
Sohda et al., 2017 [15]	5%				
Wang et al., 2014 [16]			Residual: 66.3% Recurrent: 87.8%	Residual: 29.7% Recurrent: 56%	Residual: 20.1% Recurrent: 42.5%
Watanabe et al., 2015 [14]	7.9%			30%	15%
Mitchell et al., 2019 [18]		Salvage 17.1% Planned 9.8%	Salvage: 68.6% Planned: 80.5%	Salvage: 45.7% Planned: 72.6%	Salvage: 24.2% Planned: 66.7%
Buckstein et al. 2019 [19]				33–70%	
Kumagai et al., 2016 [20]	0–22% (not reported in 3 of 4 studies for second-line CRT)			Salvage: 17–58% Second-line CRT: 0–12%	

OS overall survival, *CRT* Chemoradiotherapy

Morbidity

Postoperative morbidity is common after esophagectomy, especially after preoperative chemoradiation. Among the described cohorts, 63.6% of salvage patients and 58.9% of planned trimodality patients had any complication, including 13.1% with anastomotic leak (salvage: 17.2% vs. planned: 10.7%) [10]. In salvage populations,

Table 34.4 Postoperative complications

Author, year	Pulmonary complication	Cardiovascular complication	Anastomotic leak	Postoperative morbidity
Markar et al., 2015 [10]	Salvage: 42.9% Persistent: 42.9% Recurrence: 43.2% Planned: 40.9%	Salvage: 13.6% Persistent: 14.5% Recurrent: 10.8% Planned: 13.5%	Salvage: 17.2% Persistent: 16.2 Recurrent: 20.3% Planned: 10.7%	Salvage: 63.6% Persistent: 52.6% Recurrent: 58.1% Planned: 58.9%
Cohen et al., 2018[a] [11]	25.3%	10.9%	12.7%	34.7%
Faiz et al., 2019 [12]	29.3%	6.7%	17.2%	
Marks et al., 2012 [13]	Salvage: 23.1% Planned: 18.5%		Salvage: 18.5% Planned: 16.9%	Salvage: 35.4% Planned: 30.8%
Taniyama et al., 2018 [17]	Residual[b]: 30.8% Recurrent[b]: 14.6%	Residual[c]: 23.1% Recurrent[c]: 14.6%	Residual[d]: 28% Recurrent[d]: 23.9%	Residual: 78.8% Recurrent: 72.9%
Sohda et al., 2017 [15]	25%	2.50%	20%	50%
Watanabe et al., 2015 [14]				65.1%
Mitchell et al., 2019 [18]	Salvage: 40% Planned: 17.1%	Salvage: 48.6% Planned: 19.5%	Salvage: 11.4% Planned: 12.2%	Salvage: 71.4% Planned: 36.6%
Buckstein et al. 2019 [19]				42%

[a]All complications are Clavien-Dindo III or greater
[b]Post-operative pneumonia only
[c]Arrhythmia only
[d]Full thickness gastrointestinal defect involving anastomotic staple line or conduit confirmed by endoscopy or by contrast radiography in all cases

those with recurrent disease appeared to be at the greatest risk of leak (20.3%). Rates of surgical site infection also differed between salvage and planned resection populations (salvage: 18.5% vs. planned: 12.2%), and these differences persisted after propensity score matching. No differences were found for other complications such pulmonary infections (42.9% vs. 40.9%) and cardiovascular complications (13.6% vs. 13.5%) [10].

Cohen et al. evaluated only complications classified as Clavien-Dindo grade III and above, noting that 34.7% of salvage patients had a clinically significant complication, including 12.7% with anastomotic leak, 25.3% with pulmonary

complications, and 8.4% with cardiovascular complications [11]. The authors identified cervical anastomosis ($p < 0.001$) to be an independent risk factor associated with anastomotic leak in multivariable Cox regression analysis. Due to the anastomotic leak-related perioperative mortality mentioned above, the authors argued that attempts to avoid an intrathoracic leak by way of a cervical anastomosis is not justified. Though they did not find statistically significant rates of leak among patients receiving greater than or less than 55 Gy of radiation, they cautioned that the radiation dose must be taken into consideration when making surgical decision.

Studies with only Esophageal Adenocarcinoma

Patients

We identified one single-institution, retrospective study which exclusively addressed AC patients. In the cohort assembled by Marks et al., more than 95% of all tumors were in the lower third of esophagus [13]. Radiation doses were similar between salvage and planned resection patients. The median delay from therapy to surgery was 216 days for salvage patients compared to 50 days for planned resection. Salvage patients tended to be older, ever-smokers and diabetics, with higher American Society of Anesthesiologist class score. Clinical and pathologic stages also differed between groups. The authors reported results regarding short and long-term outcomes. Salvage patients were less likely to have R0 resection, had fewer lymph nodes retrieved, and had higher intensive care unit (ICU) admission rates.

Survival

Despite some minor differences in short-term outcomes, salvage and planned resection did not differ in terms of 30-day (3.1% vs. 4.6%) or 90-day mortality (4.6% vs. 7.7%) [13]. Survival rates at 3 and 5 years for salvage versus planned resection were (48% vs. 55%) and (32% vs. 45%), respectively, and were not significantly different. Age, smoking status, tumor stage, and number of positive nodes were all independent predictors of mortality among the entire cohort of patients undergoing salvage and planned resections. However, surgical strategy (planned vs. salvage) and time to surgery were not significant predictors of death, highlighting the lack of difference between the two groups in terms of survival outcomes. In a subgroup analysis of salvage patients only, tumor location in the lower third of the esophagus or gastroesophageal junction, radiation dose >45 Gy, number of nodes resected, and number of positive nodes were independent predictors of worse overall survival, although only 3/65 patients had tumor in the upper two-thirds.

Morbidity

Approximately one-third of all patients suffered a postoperative complication (salvage: 35.4% vs. planned 30.8%). Salvage patients had significantly more postoperative blood transfusions (26.2% vs. 14.8%, $p = 0.019$) and ICU readmissions (21.5% vs. 8.6%, $p = 0.001$) compared to those undergoing resection in a planned fashion. There were no significant differences between groups with regard to anastomotic

leak, pulmonary events, conduit loss, chylothorax, or recurrent laryngeal nerve injuries. Multivariate analysis showed that type of resection was the only factor in predicting major events, with those undergoing a minimally invasive or three-field esophagectomy to be at increased risk of perioperative morbidity (reference, open Ivor Lewis, odds ratio 2.3 and 3.64, respectively).

Esophageal Squamous Cell Carcinoma

Patients

The median number of patients evaluated in the studies we reviewed was 76 (range 37–219). Though all investigations evaluated patients who had undergone chemoradiation, two studies were included in which a small percentage of patients received neoadjuvant radiation alone [14, 15]. Most studies included patients who received doublet 5-fluorouracil and cisplatin, and other platinum-based agents were infrequently used. Two investigations included a subset of patients who received only single-agent chemotherapy. Regarding radiation dose, the majority of studies included patients whose cumulative radiation dose was between 50 and 70 Gy.

In order to elucidate the optimal patient population most likely to benefit from salvage esophagectomy, a variety of inclusion criteria and methodological approaches were outlined. Two studies compared the outcomes of patients with persistent versus recurrent disease [16, 17]. Using trimodality therapy as a reference, one investigation compared salvage resection to standard planned approach, including patients with either persistent or recurrent disease [18]. One remaining study evaluated salvage compared to second line chemoradiation therapy, and the remaining three investigations reported the outcome of patients undergoing salvage alone without a comparator [14, 15, 19, 20].

Survival

Several investigations outlined the factors which may contribute to differential prognoses among patients undergoing salvage resection. Sohda et al. contributed a retrospective report of the outcomes of 40 patients undergoing salvage esophagectomy for recurrent or persistent disease [15]. Though their investigation contributes to the relatively small field of literature on this topic, interpretation of the data therein is limited by the fact that only 27 (68%) patients received neoadjuvant chemoradiation, while the remainder had only radiation therapy. Though the study may be underpowered to detect meaningful results, and may potentially have an overfit multivariable model, only persistent tumor was associated with survival outcomes in their investigation.

Similarly, Watanabe et al. reviewed the outcomes of 63 patients undergoing salvage resection for SCC following definitive CXRT [14]. Similar to Sohda et al., the report presented by Watanabe included a minority of patients (12, 19%) who only received neoadjuvant radiation therapy alone. The mortality rate was 8%, and 3-year survival was 30%. These survival data were corroborated by Buckstein et al., who reported 3-year survival ranging from 33 to 70% among the studies evaluated [19].

Of importance, no in-hospital mortality occurred for patients with cT1-2 or cN0 disease, or among patients who achieved pathologic complete response following neoadjuvant CXRT. Persistent disease and higher ypT category were associated with an increased hazard of death upon multivariate analysis. Additionally, the authors noted that although univariable analysis revealed that tumor depth and response to neoadjuvant therapy were predictive of R0 resection, no factors could be identified which were independently associated with this outcome on multivariate analysis.

To further define the patient populations undergoing salvage resection, two authors aimed to evaluate the disparate cohorts of patients: those with persistent versus recurrent disease. Among patients undergoing esophagectomy for SCC in the investigation by Taniyama et al., those undergoing salvage resection for persistent disease demonstrated worse 5-year survival when compared to those with recurrent cancers (13% vs. 47%), though this appears to have been derived from unadjusted Kaplan-Meier analyses only, without supportive multivariate models [17]. While long-term survival is typically quite poor for esophageal cancer overall, additional factors in the setting of a salvage resection were demonstrated to be of additional prognostic importance.

Sharing their institutional experience, a study by Wang et al. likewise evaluated the survival outcomes of patients undergoing salvage esophagectomy for persistent or recurrent disease [16]. Similar to the report by Taniyama, Wang et al. demonstrated superior survival among patients with recurrent disease, in comparison to those with persistent tumor following definitive CXRT. Three-year survival rates were 56% (recurrent) and 30% (persistent). However, it should be noted that 9 of 113 patients suffered perioperative death and were excluded from analysis. Multivariate analysis showed that completeness of resection and recurrent disease was associated with prolonged survival times, although the selected final model may suffer from collinearity (due to duplicate inclusions of individual T, N, and M categories as well as composite TNM stage), which weakens these findings.

Aiming to answer a question of whether salvage surgery in SCC has similar short and long-term outcomes to salvage resection, Mitchell et al. retrospectively evaluated the perioperative morbidity and survival of 76 patients undergoing planned or salvage esophagectomy for SCC from 2004 to 2016 in their single center experience [18]. The study included 35 patients who underwent a salvage operation, while the remaining 41 underwent planned resection following CXRT as a component of trimodality therapy. The authors demonstrated prolonged survival times for patients undergoing planned compared to salvage resection, with 3-year survival rates of 73% and 46%, respectively. However, the authors caution against direct comparisons between the two groups, as selection biases are prevalent between these cohorts. These data suggest that among patients with squamous tumors, surgery, when feasible, should not be delayed.

Given the high risks of a salvage operation in SCC patients, Kumagai et al. sought to review the available literature, comparing salvage to second line CXRT [20]. Their report compiled results from 4 retrospective comparative studies, and included 219 patients with persistent or recurrent disease following CXRT, 136

(62%) of whom underwent salvage resection compared to second-line therapy. In this review, the authors reported survival rates at 3 years to be 17–58% in the salvage group, compared to 0–12% in the second-line chemoradiotherapy population. Rates of perioperative mortality across studies ranged from 0% to 22% for patients undergoing resection, though only 1 study included reported on CXRT-related mortality rates. Using a pooled meta-analysis, patients undergoing salvage resection were noted to have a reduced hazard of death in comparison to a reference category of CXRT (HR 0.42). However, it should be noted that a high degree of heterogeneity across investigations was noted, which limits precise interpretation and extrapolation of these data.

Morbidity

Among the included investigations, the risk profile of salvage surgery portrays a highly morbid and potentially life-threatening operation. Taniyama et al. importantly demonstrated similar perioperative outcomes among patients with persistent and recurrent disease, with comparable rates of nerve palsy, anastomotic leak, pneumonia, arrhythmia, and chyle leak between groups [17]. In their review of two retrospective investigations, Buckstein et al. reported concerning rates of perioperative events [19]. Similar to the aforementioned studies, a high rate of complications was noted (42%) in one trial evaluated, with a relatively high incidence of tracheal-related complications following radiation.

Importantly, poor perioperative outcomes were demonstrated in an investigation by Mitchell et al., in which salvage patients experienced increased number and severity of complications as compared to those undergoing planned resection [18]. Such results highlight that timeliness of resection in patients with SCC may be important, as salvage resection may not yield similar risks to planned resection [13]. Nonetheless, significant selection bias in all the retrospective studies needs to be considered when interpreting these data.

The modest report by Sohda et al. included a concerning perioperative profile [15]. Though the authors' patient cohort includes heterogeneous treatment algorithms, as some patients received only neoadjuvant radiation therapy, 20 (50%) patients suffered complications, including 8 (20%) with anastomotic leak. Pulmonary complication rates were quite high among their patients, with 7 (18%) patients suffering a fatal pneumonia following surgery (survival range after surgery: 2.7–41 months). Troubling rates of perioperative morbidity were corroborated by Watanabe et al., with 41 (65%) patients suffering complications postoperatively, though specific details regarding such events are lacking [14].

Conclusions and Recommendations

Salvage esophagectomy continues to be a consideration for patients with persistent or recurrent disease. Although the available studies provide a low quality of evidence overall, they describe different outcomes following salvage surgery for the two distinct histological groups. For AC patients, salvage surgery did not differ in

terms of perioperative morbidity or long-term survival when compared to planned trimodality therapy [13]. These data suggest that salvage esophagectomy may provide equivalent oncologic outcomes at no greater morbidity risk in carefully selected populations with AC.

The same outcomes have not been identified in SCC patients. Although salvage surgery seems to offer survival benefit compared to second-line CXRT [20], salvage esophagectomy in this population is associated with an increased risk for postoperative complications, which may be severe in many instances, as well as higher perioperative mortality when compared to planned resection [18]. Among patients requiring salvage resection, surgery for residual disease portended a poorer outcome in comparison to recurrent disease [16, 17]. In a salvage resection cohort including both histologies, SCC and radiation dose ≥55 Gy were independent risk factors for in-hospital mortality. The same study showed that higher radiation doses were also associated with anastomotic leaks and subsequent complication-related deaths [11]. These results, although retrospective in nature, describe SCC as a disease which warrants timely surgery, rather than to save for salvage, whenever feasible in appropriate surgical candidates. Among all evaluated studies, patients with recurrent disease had higher overall survival rates compared to persistent disease [10, 16, 17]. In selecting patients for salvage esophagectomy, histology, high radiation dose, and indication should be considered and evaluated by the surgeon and discussed with the patient.

Recommendations

- Esophageal adenocarcinoma patients with locally recurrent or persistent cancer after definitive chemoradiation may be considered for salvage esophagectomy (evidence quality low; weak recommendation).
- Esophageal squamous cell carcinoma patients with persistent cancer after definitive chemoradiation should be considered for planned esophagectomy without delay when feasible (evidence quality low; weak recommendation).
- For esophageal squamous cell carcinoma patients with recurrent disease after a prolonged disease-free interval following definitive chemoradiation, salvage esophagectomy may be considered in a highly selected group of patients who are good surgical candidates (evidence quality low; weak recommendation).

A Personal View of the Data

Although this chapter focuses on the outcomes of salvage surgery, it is not an endorsement of definitive chemoradiation. Nor can we conclude from the data reviewed that planned resection is superior to salvage. The data reviewed is solely retrospective in nature, even when systematic review or meta-analyses were

employed. There are only two randomized trials that are in the literature, both mainly focusing on SCC. When viewed from the lens of complete clinical response as an entry point to observation rather than surgery, outcomes seem to show equipoise to planned surgical resection. Yet, significant drawbacks of both of these trials have been leveled in criticism. They are underpowered, and perioperative mortality seems excessive in comparison to AC patient populations and large volume centers. We are looking forward to the results of the SANO study, which may add further data to validating (or not) the concept of selective surgery for patients obtaining an excellent response to chemoradiation.

As for the retrospective reviews, we can only surmise a few take-home points. Salvage surgery is a reasonable option for patients who have recurred after definitive CXRT, but these are data on a very selected subgroup of patients. Concluding that selective surgery after chemoradiation is a viable treatment strategy is not an appropriate interpretation of any of these retrospective studies. However, we note that only that those few who were able to undergo salvage did reasonably well (for AC histology). Further, there are subgroups who do not perform as well with salvage surgery (SCC), and this may be a result of the inherent risks in the patient cohort, but further data are required.

At our own institution, our practice preference is trimodality therapy, with completion of surgical resection in a planned fashion, in those who can tolerate the procedure safely with an acceptable risk profile, even in spite of complete clinical response. Among those treated with definitive bimodality therapy who demonstrate disease recurrence, salvage surgery, again in patients able to undergo such a procedure, is considered.

References

1. Medical Research Council Oesophageal Cancer Working Party. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet. 2002;359:1727–33.
2. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA. 1999;281:1623–7.
3. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol. 2008;26:1086–92.
4. Shapiro J, van Lanschot JJB, Hulshof M, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16:1090–8.
5. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol. 2005;23:2310–7.
6. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol. 2001;19:305–13.
7. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366:2074–84.

8. Swisher SG, Moughan J, Komaki RU, et al. Final results of NRG Oncology RTOG 0246: an organ-preserving selective resection strategy in esophageal cancer patients treated with definitive chemoradiation. J Thorac Oncol. 2017;12:368–74.
9. Noordman BJ, Spaander MCW, Valkema R, et al. Detection of residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO): a prospective multicentre, diagnostic cohort study. Lancet Oncol. 2018;19:965–74.
10. Markar S, Gronnier C, Duhamel A, et al. Salvage surgery after chemoradiotherapy in the management of esophageal cancer: is it a viable therapeutic option? J Clin Oncol. 2015;33:3866–73.
11. Cohen C, Tessier W, Gronnier C, et al. Salvage surgery for esophageal cancer: how to improve outcomes? Ann Surg Oncol. 2018;25:1277–86.
12. Faiz Z, Dijksterhuis WPM, Burgerhof JGM, et al. A meta-analysis on salvage surgery as a potentially curative procedure in patients with isolated local recurrent or persistent esophageal cancer after chemoradiotherapy. Eur J Surg Oncol. 2019;45:931–40.
13. Marks JL, Hofstetter W, Correa AM, et al. Salvage esophagectomy after failed definitive chemoradiation for esophageal adenocarcinoma. Ann Thorac Surg. 2012;94:1126–33.
14. Watanabe M, Mine S, Nishida K, et al. Salvage esophagectomy after definitive chemoradiotherapy for patients with esophageal squamous cell carcinoma: who really benefits from this high-risk surgery? Ann Surg Oncol. 2015;22:4438–44.
15. Sohda M, Kumakura Y, Saito H, et al. Clinical significance of salvage esophagectomy for patients with esophageal cancer and factors of influencing long-term survival. Anticancer Res. 2017;37:5045–51.
16. Wang S, Tachimori Y, Hokamura N, Igaki H, Nakazato H, Kishino T. Prognostic analysis of salvage esophagectomy after definitive chemoradiotherapy for esophageal squamous cell carcinoma: the importance of lymphadenectomy. J Thorac Cardiovasc Surg. 2014;147:1805–11.
17. Taniyama Y, Sakurai T, Heishi T, et al. Different strategy of salvage esophagectomy between residual and recurrent esophageal cancer after definitive chemoradiotherapy. J Thorac Dis. 2018;10:1554–62.
18. Mitchell KG, Nelson DB, Corsini EM, et al. Morbidity following salvage esophagectomy for squamous cell carcinoma: the MD Anderson experience. Dis Esophagus. 2019;33(3):doz067. https://doi.org/10.1093/dote/doz067.
19. Buckstein M, Liu J. Cervical esophageal cancers: challenges and opportunities. Curr Oncol Rep. 2019;21:46.
20. Kumagai K, Mariosa D, Tsai JA, et al. Systematic review and meta-analysis on the significance of salvage esophagectomy for persistent or recurrent esophageal squamous cell carcinoma after definitive chemoradiotherapy. Dis Esophagus. 2016;29:734–9.

Early Oral Feeding After Esophagectomy

35

Hai-Bo Sun, Megan Schultz, and Andrew C. Chang

Introduction

Despite improvements in the surgical techniques for esophagectomy, postoperative care remains similar between MIE and open surgical approaches, particularly regarding the resumption of oral intake. Several studies have investigated implementation of Enhanced Recovery After Surgery (ERAS) protocols in patients undergoing esophagectomy [1–3], particularly since esophagectomy has been identified as a complex operation with well-documented high rates of perioperative morbidity and mortality. Such protocols have included earlier resumption of oral intake. There are three possible routes for enteral nutrition (EN) following esophagectomy: via early oral intake, surgical jejunostomy, or nasoenteric tube placement. At present, there is no consensus about the best feeding route and the proper timing of postoperative oral feeding after esophagectomy. We performed a systematic literature review of studies evaluating early oral feeding (EOF) after esophagectomy.

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Table 35.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Esophagectomy patients	Early postoperative feeding	Delayed postoperative feeding	Complications
			Nutritional status
			Time to recovery of bowel function
			Time to hospital discharge

Search Strategy

A literature search of English language publications from 2000 to 2019 was used to identity published data on early oral feeding after esophagectomy. Our search strategy was to use the terms ((("2000"[Date – Publication]:"2019"[Date – Publication])) AND (("controlled clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]))) AND (early oral feeding OR early feeding OR ERAS) AND (esophagectomy OR esophageal surgery) on PUBMED. This strategy is outlined in the Table 35.1.

Results

Enteral Feeding After Esophagectomy: Why?

Traditionally, patients were not fed enterally after gastrointestinal surgery until there was clinical evidence that the ileus had resolved, usually in the form of flatus. However, it is now accepted that enteral nutritional support is safer and more efficacious whenever possible, with supporting data including several studies of early enteral nutrition (via jejunostomy) following major upper GI resection [4]. It is important to use the gastrointestinal tract to achieve a trophic effect and activity in the small intestine mucosa, a goal which could probably be achieved by only a small amount of enteral nutrition. As little as 300 mL/day is required to prevent the changes of intestinal permeability caused by total starvation [5]. Establishing enteral nutrition in the early postoperative period reduces the incidence of life-threatening complications and decreases postoperative hospital length of stay following esophagectomy [6].

Table 35.2 shows studies evaluating early enteral tube feeding after esophagectomy. Aiko et al. [7] compared total parenteral nutrition (TPN) alone with TPN and enteral nutrition per jejunostomy combined after esophageal cancer surgery. Results show that serum bilirubin and C-reactive protein levels were higher and serum lymphocyte count was lower in the combined group than in the TPN alone group. There were no other statistically significant differences in postoperative complications or nutritional status at 7 days between the two groups, suggesting per the authors that, biochemically at least, enteral feeding carries some benefit [7]. Gabor et al. [8]

Table 35.2 Overview of relevant publications for early enteral tube feeding (EEF) compared total parenteral nutrition (TPN) after esophagectomy

Author	Year	Objectives	Primary outcomes	Conclusion	Study type (quality of evidence)
Swails et al. [32]	1985	EEF (n = 13) vs. TPN (n = 12)	Complications: NS Length of hospital stay: NS Mortality: None reported	No statistical significant advantages of EN over no feeding	Randomized controlled (high)
Baigrie et al. [33]	1996	EEF (n = 50) vs. TPN (n = 47)	Complications: NS	EN is safe	Randomized controlled (high)
Aiko et al. [7]	2001	EEF + PN (n = 13) vs. TPN (n = 11)	Mortality: NS, Nutritional Status: NS ICU and hospital stay: shorter in EEF group	Patient might benefit the most from EEF	Randomized controlled (high)
Page et al. [34]	2002	EEF (n = 20) vs. TPN (n = 20)	Complications: NS Length of hospital stay: NS Mortality: NS	NJ feeding is safe and effective but shows no detectable objective benefits	Randomized controlled (high)
Gabor et al. [8]	2005	EEF + PN (n = 44) vs. TPN (n = 44)	Complications: NS First bowel movement: early (4 days vs. 7.95 days) 30 days mortality: NS Length of ICU stay: reduced (10 days vs. 19 days) Length of hospital stay: reduced (26 days vs. 43 days)	Compared to TPN, EEF may shorten both the stay on the ICU and in the hospital.	Retrospective cohort (low)
Shiraishi et al. [35]	2005	EEF vs. TPN	Mortality: NS Nutritional status: NS	Early enteral nutrition might be recommended as standard nutritional care	Randomized controlled (high)
Fujita et al. [6]	2012	PN (n = 88) vs. EN (n = 76)	Complications: NS Life-threatening complications: lower (30.6% in PN group vs. 15.7% in EN group, P = 0.02)	Early enteral nutrition reduces the incidence of life-threatening surgical complications	Randomized controlled (high)

(continued)

Table 35.2 (continued)

Author	Year	Objectives	Primary outcomes	Conclusion	Study type (quality of evidence)
Mashhadi [36]	2015	EEF (n = 20) vs. TPN (n = 20)	Inflammation: reduced Bowel movement: quicker Costs: reduced Nutritional outcomes: similar	Compared to TPN, EEF may reduce inflammation, fasten bowel function recovery and reduce costs.	Randomized controlled (high)
Han et al. [37]	2018	EEF (n = 403) vs. TPN (n = 262)	Complications: NS Hospital charges: reduced Length of postoperative stay: reduced	Compared to TPN, EEF may shorten postoperative stay and reduce hospital charges	Retrospective cohort (low)

EN enteral nutrition, late oral feeding, *NS* statistically not significant, *PN* parenteral nutrition, *NJ* nasojejunal feeding

similarly compared a combined regimen (jejunostomy feeding and TPN) with TPN alone in a case-control study. Intensive care and overall hospital stay were shorter in the combined group. However, this study was striking for an extremely high reported anastomotic leak rate (48% for combined routes and 52% TPN alone). A study from Kobayashi et al. [9] showed early EN started within 3 days was safe and effective for postoperative esophageal cancer patients; its advantages included reducing the use of albumin infusion and TPN, promoting early recovery of intestinal motility, and promoting early recovery from systemic inflammation.

At present, although increasingly more surgeons accept the concept that "when the gut works, use it," there is no consensus about the duration of enteral feeding via tube. Several centers have reported on the value of home enteral feeding in selected patients after esophagectomy [10, 11]. The results from a randomized controlled trial of 6 weeks of home enteral nutrition versus standard care after esophagectomy or gastrectomy for cancer showed that home enteral feeding by jejunostomy was feasible, safe, and acceptable to patients and their caretakers [12]. The investigators also concluded that determining whether home enteral feeding could be a cost-effective therapy for usual practice would require confirmation in an appropriately powered, multi-center study [12]. A presumed benefit of jejunostomy tube feeding is reduction of weight loss and a more rapid functional recovery. However, significant weight loss is observed in most patients at 6 months postoperatively, despite routine application of jejunostomy tube feeding following esophagectomy [13]. This may be explained in part by the catabolic impact of esophagectomy, leading to significant loss of peripheral tissue mass [14], and partly explained by the difficulty to meet nutritional requirements orally after esophagectomy. The practice of routine home enteral feeding after esophagectomy has not been established.

Early Oral Feeding After Esophagectomy: Why Not?

Although tube-feeding after esophagectomy is widely accepted, tube-feeding also may carry adverse effects after esophagectomy. Dependence on tube feeding may lead to impaired swallowing ability, potentially due to decreased use of swallowing musculature [15]. Weijs et al. [16] showed that surgical placement of a jejunostomy feeding tube during esophagectomy is associated with a mortality rate of 0–0.5% and a reoperation rate of 0–2.9%. Minor complications occur frequently, such as entry site infection in 0.4–16%, entry site leakage in 1.4–25%, and gastrointestinal tract symptoms in 10–39%. The main drawback of using nasojejunal tubes as feeding route is frequent dislocation, occurring in 20–35% of all patients during their postoperative hospitalization.

In addition, the physical, psychological and emotional consequences of living with a feeding jejunostomy tube and the associated feedings are unknown, from both the patient and caretaker perspectives. The majority of patients with tube feedings report gustatory deprivation experiences related to tasting, chewing and swallowing food, drinking liquids, exposure to prohibited foods and unsatisfied appetite for certain food, the experiences of thirst, and dry mouth [17]. In addition, patients report suffering due to the deprivation of social contacts usually associated with eating together with relatives and friends [18].

Oral feeding is thought to be the best route physiologically for nutritional support after esophagectomy. Saliva is normally produced when eating and keeps the mouth clean. However, saliva production is often reduced during tube feeding nutritional support and the oral mucosa can develop sores. Feeding tubes may alter oropharyngeal colonization in tube-fed patients because of reduced salivary flow. Increased incidence of oropharyngeal colonization with respiratory pathogens is also caused by impairment of salivary clearance [19]. Concerns about immediate oral feeding after esophagectomy include the risk for anastomotic leakage, pulmonary complications arising from aspiration, and potential effects of delayed gastric emptying.

Early Oral Feeding After Esophagectomy: Where We Are?

At present, there is no consensus about when to start oral intake and what type of diet to try first in patients with esophagectomy. In 2008, the results of a randomized control trial (RCT) showed that allowing patients to eat regular food at will from the first day after major upper GI surgery did not increase morbidity compared with traditional nil by mouth and enteral feeding [20]. However, only eight patients with esophagectomy were enrolled in this randomized study, including two undergoing transhiatal esophagectomy and six undergoing a transthoracic approach; subgroup analysis was not performed.

At present there are only five studies that evaluate the feasibility and safety of early oral feeding (EOF) after esophagectomy (Table 35.3). A prospective multicenter non-randomized clinical trial from the Netherlands showed that immediate

postoperative oral nutrition did not increase the pneumonia rate (28% in EOF group, 40% in the LOF group, P = 0.202) or anastomotic leak (14% in EOF group, 24% in the LOF group, P = 0.202) [21]. The 90-day mortality rate was the same in the two groups (2%). Hospital stay and intensive care unit stay were significantly shorter among patients who received immediate oral intake [21]. The authors concluded

Table 35.3 Overview of relevant publications for the early oral feeding (EOF) compared to late oral feeding (LOF) after esophagectomy

Author	Year	N	Outcomes	Conclusion	Study type (quality of evidence)
Mahmoodzadeh et al. [22]	2015	EOF (n = 54) vs. LOF (n = 55)	Complications: NS Time to start soft diet: early (4 days vs. 6 days) Time to gas passage: shorter (3 days vs. 4 days) Postoperative hospital stay: shorter (6 days vs. 8 days)	EOF is safe and is associated with favorable outcomes	Randomized controlled (high)
Sun et al. [23]	2015	EOF (n = 68) vs. LOF (n = 65)	Complications: EOF, 20.6% vs. LOF, 29.2% (P = 0.249) Time to first flatus: shorter (2.1 days vs. 3.2 days) Time to first bowel movement: shorter (4.4 days vs. 6.5 days) Length of postoperative stay: shorter (9.2 days vs. 10.7 days)	EOF is feasible and safe.	Prospective cohort (low)
Weijs [21]	2016	EOF (n = 50) vs. LOF (n = 50)	Complications: pneumonia rate (28% in EOF vs. 40% in LOF, p = 0.202); anastomotic leakage rate (14% in EOF vs. 24% in LOF, p = 0.202). 90-day mortality: 2% in both group Hospital stay and ICU stay: shorter in EOF group QOL evaluation: better	EOF is feasible and does not increase complications	Prospective cohort (low)

(continued)

Table 35.3 (continued)

Author	Year	N	Outcomes	Conclusion	Study type (quality of evidence)
Sun et al. [24]	2018	EOF (n = 140) vs. LOF (n = 140)	Complications: noninferior Time to first flatus: shorter (2 days vs. 3 days) Time to first bowel movement: shorter (3 days vs. 4 days) QOL evaluation: better	EOF is noninferior to the standard of care with regard to postoperative complications with a quicker recovery of bowel function and improved QOL	Single-center randomized controlled (high)
Berkelmans et al. [27]	2019	EOF (n = 65) vs. LOF (n = 67)	Time to functional recovery: (7 days vs. 8 days, P = 0.436) Anastomotic leakage rate:(18.5% in EOF vs. 16.4% in LOF, P = 0.757) Pneumonia:(24.6% in EOF vs. 34.3% in LOF, P = 0.221)	EOF does not affect functional recovery and did not increase incidence or severity of postoperative complications	Multicenter randomized controlled (high)

that immediate start of oral nutrition following esophagectomy seems to be feasible and does not increase complications compared to a retrospective cohort and literature review. However, in this study the median caloric intake achieved at POD 5 in the EOF group was 58% of required. In addition, 38% of the EOF patients required supplemental nonoral nutrition [21]. Furthermore, this study only included patients undergoing Ivor Lewis esophagectomy.

A RCT by Mahmoodzadeh et al. [22] showed that EOF after resection of esophageal and gastric tumors was safe and was associated with favorable early in-hospital outcomes, earlier return to physiological gastrointestinal function, and shorter hospital length of stay. However, this study not only included the patients with esophagectomy but also included patients with gastrectomy. The risk for bias was high, since patients with complications were excluded.

In 2015, one retrospective study showed that postoperative gastric emptying is faster than preoperative gastric emptying with EOF and that EOF in patients with thoracolaparoscopic esophagectomy is feasible and safe [23].

In 2018, the results of an RCT comparing EOF with traditional nil-by-mouth for 1 week after MIE showed that EOF after McKeown MIE is noninferior to the standard of care with regard to postoperative cardiac, respiratory, and gastrointestinal (CRG) complications (30.0% in the EOF group vs. 32.9% in the LOF group; 95% confidence interval of the difference: −13.8% to 8.0%). In addition, patients in the EOF group had a quicker recovery of bowel function and improved short-term

quality of life [24]. This may be beneficial for patients' recovery after esophagectomy. Based on the RCT, the authors further investigated the impact of EOF protocol on inflammatory cytokines (interleukin-6, IL-6; interleukin-8, IL-8; tumor necrosis factor alpha, TNF-α and monocyte chemotactic protein-1, MCP-1) after esophagectomy. The results showed that, compared with conventional rehabilitation programs, the EOF protocol may decrease stress response after McKeown MIE [25]. However this RCT was a single-center study, and only patients with hand-sewn cervical anastomosis were included [26].

Recently, the only multicenter RCT investigating the feasibility of EOF after esophagectomy was published [27]. Patients in this study were randomized to immediately start oral feeding (intervention) after a MIE with intrathoracic anastomosis or to receive nil-by-mouth and tube feeding for 5 days postoperatively (control group). The results showed that functional recovery was 7 days for patients receiving direct oral feeding compared with 8 days in the control group (P = 0.436). Anastomotic leakage rate did not differ between the intervention group (18.5%) and control group (16.4%, P = 0.757). Pneumonia rates were comparable between the intervention group (24.6%) and control group (34.3%, P = 0.221). The investigators concluded that early oral feeding after esophagectomy does not affect functional recovery nor the incidence or severity of postoperative complications [27].

Early Oral Feeding After Esophagectomy: Ongoing Problems

Although some RCTs were published recently, the evidence supporting EOF protocol for all patients with esophagectomy is still weak. Some investigators suggest that, in clinical practice, a decision-making algorithm might be developed to identify patients who may benefit from EOF after undergoing esophagectomy [28]. Based on this review, we believe that more studies should be initiated to explore the benefits of EOF compared with traditional tube feeding after esophagectomy.

Before we apply EOF protocols as a routine clinical practice for patients with esophagectomy, two problems should be addressed. First, oral feeding immediately after esophagectomy may increase the risk of aspiration. The incidence of recurrent laryngeal nerve (RLN) injury can be greater for patients who have had a cervical anastomosis, especially for patients who underwent three field lymphadenectomy, and RLN injury is associated with increased aspiration risk [29, 30]. Second, after esophagectomy, oral feeding may not be sufficient to meet the patient's caloric goals. Prior studies investigating EOF after esophagectomy showed that most patients cannot meet the required caloric goals when discharged home [24, 27].

Conclusions and Recommendations

Although current evidence surrounding the potential benefits of early oral feeding after esophagectomy is limited, the relevant published studies suggest that EOF is safe and feasible. Some studies also suggest that recovery of bowel function may be

faster, hospital stay may be shorter, and quality of life may be improved with early oral feeding. The data about complication rates are mixed. In the setting of these limited published data, we can only provide a weak recommendation to implement an early oral feeding protocol in appropriate esophagectomy patients in whom aspiration risk is deemed to be low.

In conclusion, evidence supporting an optimal route for nutritional support in post-esophagectomy patients is moderate. The evidence supporting early oral feeding after esophagectomy is weak. Further research investigating the safety and effectiveness of early postoperative oral feeding will require multidisciplinary input to provide optimal care for patients undergoing esophagectomy.

Recommendation

- Early oral feeding may be implemented in patients undergoing esophagectomy who are deemed to have a low aspiration risk (evidence quality moderate, weak recommendation).

A Personal View of the Data

One of the primary goals in esophageal resection is not only to treat the primary disease, malignant or benign, but also to restore comfortable swallowing. Historically, anastomotic complications have been associated with considerable morbidity, such as stricture or need for reintervention, and mortality. With advances in perioperative care the risk of death from complications of esophagectomy, including anastomotic leak, has decreased considerably [31] but pulmonary complications remain the most common of complications following this operation. Although the risks of anastomotic leakage do not appear to be increased with early oral feeding, efforts to address this complication often include the delayed resumption of oral feeding, and this practice remains standard for many groups. While the evidence to resume early oral feeding is weak, the studies to date encompass both Asian and Western populations and diets. These studies have demonstrated that this practice may be safe but it remains vitally important to consider individual patient characteristics, to include an assessment of aspiration risk, and to continue to minimize pulmonary complications for this potentially morbid operation.

References

1. Findlay JM, Gillies RS, Millo J, Sgromo B, Marshall RE, Maynard ND. Enhanced recovery for esophagectomy: a systematic review and evidence-based guidelines. Ann Surg. 2014;259(3):413–31.
2. Giacopuzzi S, Weindelmayer J, Treppiedi E, Bencivenga M, Ceola M, Priolo S, et al. Enhanced recovery after surgery protocol in patients undergoing esophagectomy for cancer: a single center experience. Dis Esophagus. 2017;30(4):1–6.

3. Low DE, Allum W, De Manzoni G, Ferri L, Immanuel A, Kuppusamy M, et al. Guidelines for perioperative care in esophagectomy: Enhanced Recovery After Surgery Society Recommendations. World J Surg. 2019;43(2):299–330.
4. Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. BMJ. 2001;323(7316):773–6.
5. Elia M, Goren A, Behrens R, Barber RW, Neale G. Effect of total starvation and very low calorie diets on intestinal permeability in man. Clin Sci (Lond). 1987;73(2):205–10.
6. Fujita T, Daiko H, Nishimura M. Early enteral nutrition reduces the rate of life-threatening complications after thoracic esophagectomy in patients with esophageal cancer. Eur Surg Res. 2012;48(2):79–84.
7. Aiko S, Yoshizumi Y, Sugiura Y, Matsuyama T, Naito Y, Matsuzaki J, et al. Beneficial effects of immediate enteral nutrition after esophageal cancer surgery. Surg Today. 2001;31(11):971–8.
8. Gabor S, Renner H, Matzi V, Ratzenhofer B, Lindenmann J, Sankin O, et al. Early enteral feeding compared with parenteral nutrition after oesophageal or oesophagogastric resection and reconstruction. Br J Nutr. 2005;93(4):509–13.
9. Kobayashi K, Koyama Y, Kosugi S, Ishikawa T, Sakamoto K, Ichikawa H, et al. Is early enteral nutrition better for postoperative course in esophageal cancer patients? Nutrients. 2013;5(9):3461–9.
10. Martin L, Lagergren P. Long-term weight change after oesophageal cancer surgery. Br J Surg. 2009;96(11):1308–14.
11. Tomaszek SC, Cassivi SD, Allen MS, Shen KR, Nichols FC 3rd, Deschamps C, et al. An alternative postoperative pathway reduces length of hospitalisation following oesophagectomy. Eur J Cardiothorac Surg. 2010;37(4):807–13.
12. Bowrey DJ, Baker M, Halliday V, Thomas AL, Pulikottil-Jacob R, Smith K, et al. A randomised controlled trial of six weeks of home enteral nutrition versus standard care after oesophagectomy or total gastrectomy for cancer: report on a pilot and feasibility study. Trials. 2015;16:531.
13. Couper G. Jejunostomy after oesophagectomy: a review of evidence and current practice. Proc Nutr Soc. 2011;70(3):316–20.
14. Sakurai Y. Response to nutritional support and therapeutic approaches of amino acid and protein metabolism in surgical patients. J Gastroenterol Hepatol. 2013;28(Suppl 4):123–30.
15. Langmore S, Krisciunas GP, Miloro KV, Evans SR, Cheng DM. Does PEG use cause dysphagia in head and neck cancer patients? Dysphagia. 2012;27(2):251–9.
16. Weijs TJ, Berkelmans GH, Nieuwenhuijzen GA, Ruurda JP, van Hillegersberg R, Soeters PB, et al. Routes for early enteral nutrition after esophagectomy. A systematic review. Clin Nutr. 2015;34(1):1–6.
17. Padilla GV, Grant MM. Psychosocial aspects of artificial feeding. Cancer. 1985;55(1 Suppl):301–4.
18. Gibbs-Ward AJ, Keller HH. Mealtimes as active processes in long-term care facilities. Can J Diet Pract Res. 2005;66(1):5–11.
19. Palmer LB, Albulak K, Fields S, Filkin AM, Simon S, Smaldone GC. Oral clearance and pathogenic oropharyngeal colonization in the elderly. Am J Respir Crit Care Med. 2001;164(3):464–8.
20. Lassen K, Kjaeve J, Fetveit T, Trano G, Sigurdsson HK, Horn A, et al. Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. Ann Surg. 2008;247(5):721–9.
21. Weijs TJ, Berkelmans GH, Nieuwenhuijzen GA, Dolmans AC, Kouwenhoven EA, Rosman C, et al. Immediate postoperative oral nutrition following esophagectomy: a multicenter clinical trial. Ann Thorac Surg. 2016;102(4):1141–8.
22. Mahmoodzadeh H, Shoar S, Sirati F, Khorgami Z. Early initiation of oral feeding following upper gastrointestinal tumor surgery: a randomized controlled trial. Surg Today. 2015;45(2):203–8.

23. Sun HB, Liu XB, Zhang RX, Wang ZF, Qin JJ, Yan M, et al. Early oral feeding following thoracolaparoscopic oesophagectomy for oesophageal cancer. Eur J Cardiothorac Surg. 2015;47(2):227–33.
24. Sun HB, Li Y, Liu XB, Zhang RX, Wang ZF, Lerut T, et al. Early oral feeding following McKeown minimally invasive esophagectomy: an open-label, randomized, controlled, noninferiority trial. Ann Surg. 2018;267(3):435–42.
25. Sun HB, Li Y, Liu XB, Wang ZF, Zhang RX, Lerut T, et al. The impact of an early oral feeding protocol on inflammatory cytokine changes after esophagectomy. Ann Thorac Surg. 2019;107:912–20.
26. Sun HB, Li Y, Liu XB, Zhang RX, Wang ZF, Zheng Y, et al. Embedded three-layer esophagogastric anastomosis reduces morbidity and improves short-term outcomes after esophagectomy for cancer. Ann Thorac Surg. 2016;101(3):1131–8.
27. Berkelmans GHK, Fransen LFC, Dolmans-Zwartjes ACP, Kouwenhoven EA, van Det MJ, Nilsson M, et al. Direct oral feeding following minimally invasive esophagectomy (NUTRIENT II Trial): an international, multicenter, open-label randomized controlled trial. Ann Surg. 2020;271(1):41–7.
28. Liu XB, Xing WQ, Sun HB. Early oral feeding following esophagectomy. J Thorac Dis. 2019;11(Suppl 5):S824–S30.
29. Baba M, Aikou T, Yoshinaka H, Natsugoe S, Fukumoto T, Shimazu H, et al. Long-term results of subtotal esophagectomy with three-field lymphadenectomy for carcinoma of the thoracic esophagus. Ann Surg. 1994;219(3):310–6.
30. Fujita H, Kakegawa T, Yamana H, Shima I, Toh Y, Tomita Y, et al. Mortality and morbidity rates, postoperative course, quality of life, and prognosis after extended radical lymphadenectomy for esophageal cancer. Comparison of three-field lymphadenectomy with two-field lymphadenectomy. Ann Surg. 1995;222(5):654–62.
31. Whooley BP, Law S, Murthy SC, Alexandrou A, Wong J. Analysis of reduced death and complication rates after esophageal resection. Ann Surg. 2001;233(3):338–44.
32. Swails WS, Babineau TJ, Ellis FH, Kenler AS, Forsef RA. The role of enteral jejunostomy feeding after esophagogastrectomy: a prospective, randomized study. Dis Esophagus. 1995;8:193–9.
33. Baigrie RJ, Devitt PG, Watkin DS. Enteral versus parenteral nutrition after oesophagogastric surgery: a prospective randomized comparison. Aust N Z J Surg. 1996;66(10):668–70.
34. Page RD, Oo AY, Russell GN, Pennefather SH. Intravenous hydration versus naso-jejunal enteral feeding after esophagectomy: a randomised study. Eur J Cardiothorac Surg. 2002;22(5):666–72.
35. Shiraishi T, Kawahara K, Yamamoto S, Maekawa T, Shirakusa T. Postoperative nutritional management after esophagectomy: is TPN the standard of nutritional care? Int Surg. 2005;90(1):30–5.
36. Rajabi Mashhadi MT, Bagheri R, Ghayour-Mobarhan M, Zilaee M, Rezaei R, Maddah G, et al. Early post operative enteral versus parenteral feeding after esophageal cancer surgery. Iran J Otorhinolaryngol. 2015;27(82):331–6.
37. Han H, Pan M, Tao Y, Liu R, Huang Z, Piccolo K, et al. Early enteral nutrition is associated with faster post-esophagectomy recovery in Chinese esophageal cancer patients: a retrospective cohort study. Nutr Cancer. 2018;70(2):221–8.

Stent vs. Primary Repair for Esophageal Perforation

36

Brian P. Fleischer and Mark K. Ferguson

Introduction

Esophageal perforation is a relatively uncommon phenomenon, but one that is associated with very high morbidity and mortality (10–40%), especially when systemic sequelae of the injury have already manifested as a result of delayed diagnosis [1]. Several studies have concluded that delayed diagnosis, defined as greater than 24 h from the time of injury, is associated with worse outcomes [2]. Surgical intervention has traditionally included resection or primary repair of esophageal perforations, depending on surgeon experience and patient presentation. Approximately 30% of patients continue to leak after primary repair, with 40% of patients requiring additional procedures [3]. In recent years, stenting has been introduced to mitigate this problem and the technique has transitioned to first line therapy in the hands of some physicians [3, 4]. With the understanding that optimal treatment of esophageal perforation is dependent upon a multitude of factors, we compared primary repair and esophageal stenting with respect to success, complications, length of stay, and rate of operative re-intervention.

Search Strategy

We searched the PubMed database using the following key terms: "esophageal perforation", "esophageal repair", and "esophageal stent". We reviewed manuscripts published 2004–2019, with an emphasis on those published since 2014. We excluded those articles that discussed leak after esophageal anastomosis. Table 36.1 defines the PICO terms employed for the formulation of our central question.

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Table 36.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with iatrogenic or spontaneous esophageal perforation	Stenting	Primary repair	Success
			Complications
			Length of stay
			Re-intervention
			Quality of life

Results

Perforations can occur anywhere along the length of the esophagus, with approximately 24% in the cervical esophagus, 66% in the thoracic esophagus, and 10% in the abdominal esophagus. The most common presenting symptoms regardless of etiology are dysphagia and/or pain (67–95.8%), followed by fever (44%), dyspnea (26–40.8%), and emphysema/crepitus (25–48.3%) [5–7]. Regardless of etiology or location of injury, time to diagnosis and treatment remains paramount with an emphasis on the first 24 h [2, 4, 8–10]. For the purpose of our discussion, we will focus on the comparison between the most commonly employed operative technique of debridement and primary tissue repair and endoluminal stenting.

Abbas et al. developed a Perforation Severity Score (PSS) with the aim of utilizing clinical variables as indicators of injury severity and patient outcome. When correlating clinical variables such as age, tachycardia, leukocytosis, fever, presence of pleural effusion/uncontained leak, respiratory distress, and hypotension, they were able to demonstrate an association between increased score and worse rates of morbidity and mortality as well as increased length of stay [11]. The PSS has subsequently been studied with mixed results, as there currently exists a relative paucity of work examining its validity. Wigley et al. studied the validity of the score using a cohort of 87 cases from the United Kingdom and noted that, while the PSS wasn't found to be significantly predictive of post-perforation complications in their overall population of patients, subgroup analysis did note it to be significantly predictive for those patients with Boerhaave's disease [12]. Conversely, a multi-national study further examined the PSS in a cohort of 288 patients and found that regardless of etiology, the scoring system was associated with the severity and potential consequences of esophageal injury [13].

Freeman et al. published a propensity matched cohort analysis of patients with esophageal perforation who underwent either endoluminal stenting or primary operative repair and noted many significant differences between the two populations. Those patients who underwent stenting had significantly shorter ICU stay (2 days vs. 4 days, $p = 0.001$), total length of stay (6 days vs. 11 days, $p = 0.0007$), and overall morbidity (17% vs. 43%, $p = 0.02$), while demonstrating a trend towards decreased rates of dysphagia (7% vs. 27%) and readmission (7% vs. 17%) in the stent group. Additionally, there were significant differences in total inpatient costs ($59,000 vs. $87,000, $p < 0.0001$), total outpatient costs ($32,000 vs. $55,000, $p < 0.0001$), and total overall costs ($91,000 vs. $142,000, $p < 0.0001$), all favoring stenting [14].

A meta-analysis performed by Biancari et al. included 75 published studies related to the care of patients with esophageal perforation and noted a pooled mortality of 9.5% for those patients who underwent primary repair, while those who underwent endoscopic stent placement had a pooled mortality of 7.3%. The authors caution that, while the endoscopic stent group demonstrated improved mortality rates, this could be due to patient selection bias and varying surgeon experience. Further, in concert with findings from several other studies, they noted that treatment initiated within 24 h of injury resulted in a significantly lower mortality rate (7.4% vs. 20.3%, risk ratio 2.28) [15].

Analysis of relevant current studies elucidates some interesting trends as seen in Tables 36.2 [3, 6, 9, 14, 16–21] and 36.3 [2, 6, 14, 21–24]. Endoluminal stenting appears to have a higher pooled success rate (88.44%) than primary repair (76.83%) and is associated with a lower incidence of operative reintervention (9.3% vs. 16.9%). These results are roughly in line with other reviews, which note a success rate of 92–100% for stenting [4]. Length of stay was variably reported, but also had a smaller pooled mean than primary repair (14 days vs. 17.9 days) while mortality was slightly higher in the stent group (7.1% vs. 6.0%). The most commonly encountered and discussed complication of endoluminal stenting– stent migration– was noted to occur 18.6% of the time, roughly on par with other reviews which note rates of 6–35%, and often required repositioning of the current stent or placement of a second stent [3, 4, 9, 16, 17]. Fully covered stents are typically associated with higher migration rates; partially covered stents promote tissue in-growth but are more difficult to remove. Development of strictures or dysphagia was inadequately reported, but tended to be lower in those patients undergoing stenting (0–7% vs. 20–27%).

Conclusions and Recommendations

Although various groups have proposed treatment algorithms, there currently exists a paucity of reliable, reproducible data that informs a superior intervention strategy. Most studies examining stenting and primary repair focus on intra-thoracic perforations; cervical stents are not well tolerated and abdominal perforations have an unacceptably high rate of stent migration. Unsurprisingly, prolonged time to treatment was often found to negatively impact mortality rates irrespective of treatment modality employed [2, 4, 8–10, 18, 20, 22]. Current evidence supports the use of esophageal stents for the treatment of esophageal perforation in patients who are hemodynamically stable, but high-quality RCTs are lacking, leaving treatment decisions to be informed by retrospective data, case series, and expert opinion.

Recommendation

- Esophageal stenting is recommended for first line treatment of esophageal perforation in hemodynamically stable patients (evidence quality low, weak recommendation).

Table 36.2 Summary of recent studies on endoluminal stenting for esophageal perforation

Author	Year	Patients	Stent type	Mean LOS (days)	Success (%)	Migration	Dysphagia/ stricture	Operative reintervention (%)	In-hospital mortality	Quality of evidence
Kiev [3]	2007	14	SEPS	12	100	21%	NR	7	14%	Low
Lindenmann [6]	2013	37	SEMS	8	100	NR	NR	0	NR	Low
Suzuki [16]	2016	10	SEMS	NR	100	40%	0%	0	0%	Low
Freeman [17]	2007	17	SEPS	8	94	18%	NR	6	NR	Low
Freeman [9]	2009	19	SEPS	9	89	24%	0%	11	0%	Low
Johnsson [18]	2005	22	SEMS	10.5	95	14%	0%	9	14%	Moderate
Navaneethan [19]	2014	20	SEMS	15	77	15%	NR	1	10%	Low
Persson [20]	2014	40	SEMS	33	83	NR	NR	17	7.5%	Moderate
Freeman [14]	2015	30	SEMS/SEPS	6	83	13%	7%	3	3%	Moderate
Law [21]	2017	13	SEPS	NR	62	NR	NR	38	NR	Very low

NR not reported, *SEPS* self expandable plastic stent, *SEMS* self expandable metallic stent, *LOS* length of stay

Table 36.3 Summary of recent studies on primary repair for esophageal perforation

Author	Year	Patients	Mean LOS (days)	Success (%)	Stricture/ dysphagia	Operative reintervention (%)	Overall morbidity	In-hospital mortality	Quality of evidence
Shaker [2]	2010	21	31	66.67	20%	4.8	28.5%	17.4%	Low
Lindenmann [6]	2013	13	9.2	69.2	NR	30.8	NR	15.40%	Low
Freeman [14]	2015	30	11	80	27%	13	NR	7%	Moderate
Law [21]	2017	16	NR	75	NR	13	NR	NR	Very low
Masoom [22]	2018	15	NR	73	NR	27	NR	0%	Low
Sudarshan [23]	2016	20	20	60	NR	35	33%	10%	Low
Vinh [24]	2019	63	NR	87	NR	13	NR	0%	Very low

NR not reported, *LOS* length of stay

A Personal View of the Data

While there are several case series and cohort studies that compare and discuss the merits of stenting vs. primary repair for esophageal perforations, there is still great need for a well-designed, prospective randomized controlled trial. There is current evidence to support the use of endoluminal stenting over primary tissue repair for non-septic, hemodynamically stable patients with thoracic esophageal perforations. In our experience, for those patients with cervical and abdominal disruptions we pursue wide local drainage and primary tissue repair while our goal for those with thoracic perforations is to manage the injury primarily with stenting. Additionally, we have found that thoracic esophageal perforations that are necessarily initially managed in an operative fashion often benefit from a combined approach with stenting as an adjunct to the surgical repair.

References

1. Nirula R. Esophageal perforation. Surg Clin N Am. 2014;94:35–41.
2. Shaker H, Elsayed H, Whittle I, et al. The influence of the 'golden 24-h rule' on the prognosis of oesophageal perforation in the modern era. Eur J Cardiothorac Surg. 2010;38:216–22.
3. Kiev J, Amendola M, Bouhaidar D, et al. A management algorithm for esophageal perforation. Am J Surg. 2007;194:103–6.
4. Chirica M, Champault A, Dray X, et al. Esophageal perforations. J Visc Surg. 2010;147:117–28.
5. Hasimoto CN, Cataneo DC, Eldib R, et al. Efficacy of surgical versus conservative treatment in esophageal perforation. A systematic review of case series studies. Acta Cir Bras. 2013;28:266–71.
6. Lindenmann J, Matzi V, Neuboech N, et al. Management of esophageal perforation in 120 consecutive patients: clinical impact of a structured treatment algorithm. J Gastrointest Surg. 2013;17:1036–43.
7. Aloreidi K, Patel B, Ridgway T, et al. Non-surgical management of Boerhaave's syndrome: a case series study and review of the literature. Endosc Int Open. 2018;6:E92–7.
8. Herrera A, Freeman RK. The evolution and current utility of esophageal stent placement for the treatment of acute esophageal perforation. Thorac Surg Clin. 2016;26:305–14.
9. Freeman RK, Van Woerkom JM, Vyverberg A, et al. Esophageal stent placement for the treatment of spontaneous esophageal perforations. Ann Thorac Surg. 2009;88:194–9.
10. Koivukangas V, Biancari F, Merilainen S, et al. Esophageal stenting for spontaneous esophageal perforation. J Trauma Acute Care Surg. 2012;73:1011–3.
11. Abbas G, Schuchert MJ, Pettiford BL, et al. Contemporaneous management of esophageal perforation. Surgery. 2009;146:749–56.
12. Wigley C, Athanasiou A, Bhatti A, et al. Does the Pittsburgh severity score predict outcome in esophageal perforation? Dis Esophagus. 2018;32:1–8.
13. Schweigert M, Sousa HS, Solymosi N, et al. Spotlight on esophageal perforation: a multinational study using the Pittsburgh esophageal perforation severity scoring system. J Thorac Cardiovasc Surg. 2016;5:1002–11.
14. Freeman RK, Herrera A, Ascioti AJ, et al. A propensity-matched comparison of cost and outcomes after esophageal stent placement or primary surgical repair for iatrogenic esophageal perforation. J Thorac Cardiovasc Surg. 2015;149:1550–5.
15. Biancari F, D'Andrea V, Paone R, et al. Current treatment and outcome of esophageal perforations in adults: systematic review and meta-analysis of 75 studies. World J Surg. 2013;37:1051–9.

16. Suzuki T, Siddiqui A, Taylor LJ, et al. Clinical outcomes, efficacy, and adverse events in patients undergoing esophageal stent placement for benign indications: a large multicenter study. J Clin Gastroenterol. 2016;50:373–8.
17. Freeman RK, Van Woerkom JM, Ascioti AJ. Esophageal stent placement for the treatment of iatrogenic intrathoracic esophageal perforation. Ann Thorac Surg. 2007;83:2003–8.
18. Johnsson E, Lundell L, Liedman B. Sealing of esophageal perforation or ruptures with expandable metallic stents: a prospective controlled study on treatment efficacy and limitations. Dis Esophagus. 2005;18:262–6.
19. Navaneethan U, Lourdusamy V, Duvuru S, et al. Timing of esophageal stent placement and outcomes in patients with esophageal perforation: a single-center experience. Surg Endosc. 2015;29:700–7.
20. Persson S, Elbe P, Rouvelas I, et al. Predictors for failure of stent treatment for benign esophageal perforations - a single center 10-year experience. World J Gastroenterol. 2014;20:10613–9.
21. Law TT, Chan JYL, Chan DKK, et al. Outcomes after oesophageal perforation: a retrospective cohort study of patients with different aetiologie. Hong Kong Med J. 2017;23:231–8.
22. Masoom SHF, Dalouee MN, Fattahi AS, et al. Surgical management of early and late esophageal perforation. Asian Cardiovasc Thorac Ann. 2018;26:685–9.
23. Sudarshan M, Elharram M, Spicer J, et al. Management of esophageal perforation in the endoscopic era: is operative repair still relevant? Surgery. 2016;160:1104–10.
24. Vinh VH, Quang NVD, Khoi NV. Surgical management of esophageal perforation: role of primary closure. Asian Cardiovasc Thorac Ann. 2019;27:192–8.

Endoluminal Vacuum Therapy vs. Stenting for Esophageal Anastomotic Leaks

37

Kody Wyant and Richard K. Freeman

Introduction

Despite advancements in surgical techniques and instrumentation, intrathoracic anastomotic leak after esophagectomy is unfortunately not an uncommon occurrence. A recent review of The Society of Thoracic Surgeons general thoracic surgery database reported a leak rate of 12.9% [1]. This is most likely an underestimate based on a systematic review of the literature with rates reported as high as 25% [2]. Anastomotic leak is also a significant source of morbidity for these patients, with associated rates as high as 30–60% compared to less than 10% in those without a leak [3, 4].

The treatment of an intrathoracic anastomotic leak remains controversial as the indications for surgical, non-operative and endoscopic therapy lack standardization even at individual facilities [3]. Historically, for those with a significant anastomotic leak after esophagectomy, re-operative surgical intervention was the standard of care. These procedures could be extremely difficult as evidenced by the relatively high rates of associated morbidity. If primary repair was not possible or failed, diversion was the only remaining alternative.

With technological improvements in the late 1990s, esophageal stents have gained favor, becoming the mainstay in the non-surgical management of post-esophagectomy anastomotic leaks in many institutions. Stents have produced high rates of success with minimal associated rates of complications when removed

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promptly [5]. An added benefit is the relatively low rate of post repair stenosis when compared to either operative repair or non-operative healing by secondary intention.

More recently, endoluminal vacuum therapy (E-Vac) has been described in the literature as a novel treatment for upper gastrointestinal leaks and perforations [6]. Initially reported in several European series, the technique of E-Vac has produced significant rates of healing of anastomotic leaks following esophagogastrostomy with minimal complications. However, this technique is labor intensive, requiring multiple endoscopies for dressing changes. [7, 8].

Non-surgical endoscopic therapy using each of these techniques has each been demonstrated in multiple reviews to be safe and effective in the treatment of such patients [9–11]. Despite this, there have only been a few studies designed to determine a definitive standardized practice in the role these therapies play. The objective of this review is to not only compare the efficacy, safety, and costs of these techniques, but attempt to make recommendations as to when surgery, esophageal stenting, or E-Vac should be utilized in the care of these complex patients.

Search Strategy

A PubMed search was conducted using the keywords esophageal leak; anastomotic leak; esophagectomy; treatment; management; endoscopic/endoluminal vacuum therapy; endoscopy; vacuum; stent; self-expanding esophageal stent (Table 37.1). Searches were conducted for the period 2009–2019. Prospective and retrospective studies were included in this review. Individual papers were also searched for appropriate cross reference material to include. All studies included in this analysis were selected at the discretion of the authors based on the following criteria; the search was limited to studies published within the past 10 years and articles written in English were selected for review. Studies that did not report data specific for the treatment of anastomotic leak after esophagectomy were excluded. Costs of care were derived from Medicare allowable charges. This allows a standardization of a cost representation to be made across multiple sites of care for comparison. A blended model of daily cost was used for all patients since environments of care encompassed intensive care, progressive care, and standard care units as well as migration between all three. Cost of care represents facility charges. Professional fees, where applicable, were excluded.

Table 37.1 PICO formatted terms for literature search

Patients of interest	Intervention	Comparator	Outcomes of interest
Anastomotic leak after esophagectomy	Endoluminal vacuum assisted therapy (E-Vac)	Esophageal stents	Overall success, treatment duration, LOS, costs

Results

Evidence Quality

In total, 34 studies which met the inclusion criteria were identified and their data is included in our analysis. This data encompasses, to the best of our knowledge, all reported cases of anastomotic leak after esophagectomy treated with either esophageal stent or E-Vac therapy in the past 10 years. No randomized clinical trials were identified.

The data discussed in this analysis is derived from multiple sources of varying quality as typically seen in retrospective studies with small numbers. While our analysis is based on the crude data available to us in reviewing these studies, we are unable to account for the inherent inconsistencies, bias, and confounders present across each individual study. Therefore, the overall quality of evidence and strength of our recommendations based on this data is interpreted as low as guided by the GRADE framework put forth by the GRADE Working Group [12].

Findings

This meta-analysis of 34 studies found the total number of patients in the E-Vac and stent groups to be 218 and 477, respectively. The overall clinical success of the E-Vac treatment group was 91%, while the overall clinical success for the esophageal stent treatment group was 75.5% (Tables 37.2, 37.3, and 37.4). This difference was statistically significant ($p < 0.0001$). Operative mortality in the E-Vac group was 10.8% versus the stent group at 15.8%, without a statistically significant difference ($p = 0.64$). Due to limitations in the study design and inconsistencies in reporting, overall complication rates for the two groups were not able to be calculated.

Table 37.2 Outcomes of stent and E-Vac therapy for anastomotic leak after esophagectomy

	Stent	E-Vac	P value
Patients	477	218	
Number of interventions (mean)	1.6 ± 0.6	6.1 ± 2	<0.0001
Treatment duration (mean days)	36.8 ± 15.3	20.1 ± 6.2	<0.0001
Total length of stay (mean days)	44 ± 19.5	50 ± 16.8	0.0002
Overall mortality	15.8%	10.8%	.64
Successful resolution	75.5%	91%	<0.0001
Costs			
Interventions (mean)	$6322 ± 2216	$25188 ± 7433	<0.0001
Treatment duration (mean)	$78874 ± 32722	$43083 ± 13173	<0.0001
Total length of stay (mean)	$93630 ± 41791	$107345 ± 35899	<0.0001
Total length of stay + interventions	$97944 ± 41829	$163882 ± 50568	<0.0001

Table 37.3 Outcomes of E-Vac for treatment of anastomotic leaks

Author	Pts	Clinical success (%)	Treatment duration (mean days)	Number of interventions (mean)	Total LOS (mean days)	Mortality (%)	Complication rate (%)	Study type	Quality of evidence
Mennigen et al. [13]	22	86.3	26.5	6.5	58	13.6	n/a	Comparison	Low
Schniewind et al. [14]	17	88.2	n/a	n/a	57	11.8	n/a	Comparison	Low
Hwang et al. [15]	7	100	19.5	4.3	37	0	0%	Comparison	Low
Berlth et al. [16]	35	85.7	12	3	39	11.4	14.2%	Comparison	Low
Min et al. [17]	20	95	14.5	5	49	5	35%	RR	Low
Lenzen et al. [18]	3	100	29	7	46	0	0%	RR	Low
Wedemeyer et al. [19]	8	87.5	23	7	n/a	0	0%	RR	Low
Weidenhagen et al. [20]	6	100	20	10	95	16.7	0%	RR	Low
Ahrens et al. [21]	5	100	28	9	36	20	40%	RR	Low
Pournaras et al. [22]	7	100	n/a	7	35	0	28.6%	RR	Low
Laukoetter et al. [23]	39	92.3	20	6	60	12.8	17.9%	P	Moderate
Bludau et al. [24]	8	87.5	10.75	3.6	n/a	12.5	n/a	RR	Low
Bludau et el. [25]	36	77.8	12.6	3.9	n/a	25	n/a	RR	Low
Kuehn et al. [26]	3	66.7	18	6	39	33	n/a	RR	Low
Mencio et al. [27]	2	100	27.5	6.5	n/a	0	0%	RR	Low

RR retrospective review, *P* prospective

Table 37.4 Outcomes of esophageal stents for treatment of anastomotic leaks

Author	Pts	Clinical success (%)	Treatment duration (mean days)	Number of interventions (mean)	Total LOS (mean days)	Mortality (%)	Migration (%)	Complication rate (%)[a]	Stent type	Study type	Quality of evidence
Menninen et al. [13]	23	60.9	36	1	53	34.8%	n/a	n/a	SEMS	RR	Low
Schniewind et al [14]	12	58.3	n/a	n/a	62	41.7%	n/a	25%	n/a	RR	Low
Hwang et al. [15]	11	63.6	27	1.6	87	0%	27.2%	n/a	SEMS	RR	Low
Berlth et al. [16]	76	72.4	28	1	37	13.2%	18.4%	3.9%	SEMS	RR	Low
Eizaguirre et al. [28]	13	92.3	42	n/a	44	7.7%	0%	n/a	SEMS	RR	Low
Freeman et al. [29]	17	94.1	17	1.2	18	0%	17.6%	0%	SEPS/ SEMS	RR	Low
Zisis et al. [30]	9	77.8	56.8	n/a	n/a	0%	n/a	n/a	SEMS	RR	Low
Gonzalez et al. [31]	35	68.6	44	2.6	n/a	17.1%	25.7%	n/a	n/a	RR	Low
Persson et al. [2]	33	60.6	34	1.75	54	33%	n/a	n/a	n/a	RR	Low
Leenders et al. [32]	15	80	80	1.7	27.7	33%	40%	0%	SEMS	RR	Low
Schweigert et al. [33]	12	83.3	48.4	n/a	n/a	16.7%	n/a	8.3%	SEMS	RR	Low

(continued)

Table 37.4 (continued)

Author	Pts	Clinical success (%)	Treatment duration (mean days)	Number of interventions (mean)	Total LOS (mean days)	Mortality (%)	Migration (%)	Complication rate (%)[a]	Stent type	Study type	Quality of evidence
D'Cunha et al. [34]	22	59.1	40.5	1.7	n/a	18.2%	18.2%	13.6%	SEMS/ SEPS	RR	Low
Plum et al. [35]	70	70	27	1.24	37	12.8%	18.6%	10%	SEMS	RR	Low
Nguyen et al. [36]	9	100	42	1	15.9	0%	n/a	0%	SEMS	RR	Low
Khatian et al. [37]	38	78.9	23	n/a	n/a	n/a	10.5%	n/a	SEMS	RR	Low
Suzuki et al. [38]	5	80	23.8	3	n/a	0%	0%	0%	n/a	RR	Low
Gubler et al. [39]	18	72.2	15	1.32	n/a	33%	55.6%	n/a	SEMS	RR	Low
El Hajj et al. [40]	29	72.4	48	1.83	n/a	n/a	n/a	n/a	SEMS/ SEPS	RR	Low
Dai et al. [41]	30	90	30	1.9	45	6.7%	46.7%	n/a	SEPS	RR	Low

SEMS self-expanding metal stent, *SEPS* self-expanding plastic stent, *RR* retrospective review

[a]Rate does not include associated stent migrations, which is reported separately

Treatment duration in mean days is defined as the amount of time each treatment strategy was employed until clinical success or failure was determined. For the E-Vac group, this time was significantly shorter than the stent group of patients at 20.1 ± 6.2 days vs. 36.8 ± 15.3 days, respectively ($p < 0.0001$). However, in contrast to treatment duration, the total length of stay (LOS) for the stent group was 44 ± 19.5 days which was significantly less than the E-Vac group at 50 ± 16.8 days ($p = .0002$). In addition, the stent group underwent significantly fewer endoscopic interventions than the E-Vac group at 1.6 ± 0.6 vs. 6.1 ± 2 ($p < 0.0001$).

Also extrapolated from this data are associated costs related to both groups. The stent group had significantly less associated total costs ($97944 ± 41829) than the E-Vac group ($163882 ± 50568) ($p < 0.0001$). These differences are primarily related to the differences in the number of procedures (predominantly endoscopies) required by the E-Vac cohort. This difference in cost is actually reduced by the longer length of stay in the stent cohort, a finding which is not intuitive and may be the result of other confounding factors not identifiable in this review.

The principle complication of esophageal stenting remains stent migration. In this review, stent migration was reported in 12 studies and a subgroup analysis of these reports found a migration rate of 23% (Table 37.4). This rate remains consistent with previous reports in the literature [9, 10] and the authors' experience. While stent migration is reported as a complication, it does not correlate with an increased number of interventions or treatment failure. Additional but less frequent complications included stricture, hemorrhage, aspiration pneumonia, reflux, and pain.

E-Vac therapy may be associated with fewer clinically important complications. Among these, sponge dislocation, hemorrhage, and pain appear to occur less frequently in patients treated with E-vac therapy. Future studies should carefully report complication rates and their management as this appears to be lacking in the current literature.

Conclusions and Recommendations

Initial operative exploration should be reserved for patients with anastomotic or conduit disruption, conduit necrosis, or in centers without the ability to perform esophageal stenting or E-Vac therapy. If operative exploration is performed, primary repair with muscle buttressing is preferred. Diversion should be avoided if at all possible.

Based on the current literature, superiority in the management of esophageal anastomotic leaks cannot be confirmed for either E-Vac or stents. Stent placement has a high rate of success with the major detractor of its use being the potential for migration. It is reasonable to consider stent placement as first line therapy for intrathoracic anastomotic leaks after esophagogastrostomy in patients who did not require prolonged mechanical ventilation and/or tracheostomy, who would potentially be able to tolerate oral intake if not for their leak, and who could otherwise be managed in the outpatient setting at some point during their treatment.

In centers with experience in the use of E-Vac therapy, early outcomes suggest this treatment strategy for anastomotic leaks has a high rate of success with few complications. Its definitive role in managing these patients is awaits future clinical studies and development of a standardized treatment algorithm. At present, E-Vac therapy is an appropriate initial therapy in the management of patients who require prolonged mechanical ventilation and/or tracheostomy. It could also be considered for intrathoracic esophagogastrostomy anastomotic leaks that have failed stent placement or are too proximal for stent placement, and for recalcitrant smaller leaks after re-operative repair prior to considering esophageal diversion.

Recommendation

- Esophageal stent placement or E-Vac are recommended as first line therapy for the management of an intrathoracic anastomotic leak after esophagectomy in patients who do not require surgical intervention as initial therapy (quality of evidence low; strength of recommendation weak).

A Personal View of the Data

Treatment of anastomotic leaks after esophagectomy remains a challenging problem for thoracic surgeons and a source of significant morbidity and mortality for patients. Over the past two decades, surgical re-exploration with primary repair or diversion has diminished in frequency as initial therapy for these patients except in specific circumstances. Improvement in stent technology and the development of E-Vac has allowed for less invasive first line therapies for intrathoracic anastomotic leak following esophagogastrostomy.

The difficulty in choosing either of these treatment strategies is a lack of standardization in the literature. Ideally, randomized controlled trials comparing these two modes of therapy in similar patients would allow treatment algorithms to be developed based on identified best practices for each technique. Unfortunately, this is unlikely to occur in the foreseeable future because of the relatively low number of patients who are candidates for such an investigation and the current classification of these techniques as “off label”.

At present, the best that can be done is to recognize the knowledge gaps that exist, identify the advantages and disadvantages of each treatment modality, and make reasonable recommendations for consideration by the thoracic surgery community to consider and evaluate. The success rate of E-Vac deserves to be recognized and included in the treatment algorithm of intrathoracic anastomotic leak following esophagogastrostomy. Stent placement similarly has found utility in the management of these patients over the last decade with continued refinement of indications, contraindications and stent dwell times by our group and others. Operative exploration and repair or diversion remains the ultimate intervention for patients who require it.

The choice between E-Vac and stent use will likely be individualized at this point as previously discussed. One factor in the decision will likely be the clinician's level of experience with each technique. Other factors to consider should be the preferred use of stents in patients who could otherwise tolerate oral nutrition, be treated in the outpatient setting, or who have a persistent leak after an initial operative repair. E-Vac therapy should be considered when stenting is not feasible because of the location of the leak, recurrent stent migrations, patients expected to remain mechanically ventilated for an extended period of time, and patients in whom stent therapy has not resulted in healing.

My personal approach to patients with an intrathoracic anastomotic leak depends on the size of the leak, the overall condition of the patient, and any associated findings. In general, my initial response to a very small leak would be to continue pleural drainage, enteral nutrition, and npo status with a repeat esophagram in 7 days. This treatment would occur in the outpatient setting, if possible. For large anastomotic leaks in a patient otherwise progressing, I would place an esophageal stent for 10–14 days. If an esophagram demonstrated resolution of the leak after stent placement, I would allow a soft mechanical diet until the stent was removed. For patients who have other findings requiring re-exploration, such as a leak from the gastric conduit, I would perform a primary repair of the anastomosis. Any leak after such a primary repair could be treated with temporary stent placement.

My personal experience with E-Vac therapy has been in patients who continue to require mechanical ventilation and have no indications for reoperative surgery but have a medium sized anastomotic leak. Patients in this stage of recovery are able to undergo repeated endoscopies for E-vac adjustment as needed in the ICU. They are also not inconvenienced with the vacuum line traversing the naso/oropharynx.

References

1. Raymond D, Seder C, Wright C, et al. Predictors of major morbidity or mortality after resection for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database Risk Adjustment Model. Ann Thorac Surg. 2016;102:207–14.
2. Persson S, Rouvelas I, Kumagai K, Song H, Lindblad M, Lundell L, Nilsson M, Tsai J. Treatment of esophageal anastomotic leakage with self-expanding metal stents: analysis of risk factors for treatment failure. Endosc Int Open. 2016;4:E420–6.
3. Schaheen L, Blackmon S, Nason K. Optimal approach to the management of intrathoracic esophageal leak following esophagectomy: a systematic review. Am J Surg. 2014;208:536–43.
4. Junemann-Ramirez M, Awan M, Khan Z, Rahamim J. Anastomotic leakage post-esophagogastrectomy for esophageal carcinoma: retrospective analysis of predictive factors, management and influence on longterm survival in a high volume centre. Eur J Cardiothorac Surg. 2005;27:3–7.
5. Freeman R, Ascioti A, Dake M, Mahidhara R. An assessment of the optimal time for removal of esophageal stents used in the treatment of an esophageal anastomotic leak or perforation. Ann Thorac Surg. 2015;100:422–8.
6. Leeds S, Burdick J, Fleshman J. Endoluminal vacuum therapy for esophageal and upper intestinal anastomotic leaks. JAMA Surg. 2016;151:573–4.
7. Loske G, Schorsch T, Müller C. Endoscopic vacuum sponge therapy for esophageal defects. Surg Endosc. 2010;24:2531–5.

8. Wedemeyer J, Schneider A, Manns M, Jackobs S. Endoscopic vacuum-assisted closure of upper intestinal anastomotic leaks. Gastrointest Endosc. 2008;67:708–11.
9. Halsema E. Clinical outcomes of self-expandable stent placement for benign esophageal diseases: a pooled analysis of the literature. World J Gastrointest Endosc. 2015;7:135–53.
10. Dasari B, Neely D, Kennedy A, Spence G, Rice P, Mackle E, Epanomeritakis E. The role of esophageal stents in the management of esophageal anastomotic leaks and benign esophageal perforations. Ann Surg. 2014;259:852–60.
11. Newton N, Sharrock A, Rickard R, Mughal M. Systematic review of the use of endoluminal topical negative pressure in oesophageal leaks and perforations. Dis Esophagus. 2016;30(3):1–5. https://doi.org/10.1111/dote.1253.
12. Chandar A, Falck-Ytter Y, Ferguson M. In: Ferguson MK, editor. Difficult decisions in thoracic surgery: an evidence based approach. 3rd ed. New York: Springer; 2014. p. 17–33.
13. Mennigen R, Harting C, Lindner K, Vowinkel T, Rijcken E, Palmes D, Senninger N, Laukoetter M. Comparison of endoscopic vacuum therapy versus stent for anastomotic leak after esophagectomy. J Gastrointest Surg. 2015;19:1229–35.
14. Schniewind B, Schafmayer C, Voehrs G, et al. Endoscopic endoluminal vacuum therapy is superior to other regimens in managing anastomotic leakage after esophagectomy: a comparative retrospective study. Surg Endosc. 2013;27:3883–90.
15. Hwang J, Jeong Y, Park Y, Yoon H, Shin C, Kim N, Lee D. Comparison of endoscopic vacuum therapy and endoscopic stent implantation with self-expandable metal stent in treating postsurgical gastroesophageal leakage. Medicine. 2016;95:e3416.
16. Berlth F, Bludau M, Plum P, Herbold T, Christ H, Alakus H, Kleinert R, Bruns C, Hölscher A, Chon S. Self-expanding metal stents versus endoscopic vacuum therapy in anastomotic leak treatment after oncologic gastroesophageal surgery. J Gastrointest Surg. 2018;23:67–75.
17. Min Y, Kim T, Lee H, et al. Endoscopic vacuum therapy for postoperative esophageal leak. BMC Surg. 2019;19:1–37. https://doi.org/10.1186/s12893-019-0497-5.
18. Lenzen H. Successful treatment of cervical esophageal leakage by endoscopic-vacuum assisted closure therapy. World J Gastrointest Endosc. 2013;5:340–5.
19. Wedemeyer J, Brangewitz M, Kubicka S, Jackobs S, Winkler M, Neipp M, Klempnauer J, Manns M, Schneider A. Management of major postsurgical gastroesophageal intrathoracic leaks with an endoscopic vacuum-assisted closure system. Gastrointest Endosc. 2010;71:382–6.
20. Weidenhagen R, Hartl W, Gruetzner K, Eichhorn M, Spelsberg F, Jauch K. Anastomotic leakage after esophageal resection: new treatment options by endoluminal vacuum therapy. Ann Thorac Surg. 2010;90:1674–81.
21. Ahrens M, Schulte T, Egberts J, Schafmayer C, Hampe J, Fritscher-Ravens A, Broering D, Schniewind B. Drainage of esophageal leakage using endoscopic vacuum therapy: a prospective pilot study. Endoscopy. 2010;42:693–8.
22. Pournaras D, Hardwick R, Safranek P, Sujendran V, Bennett J, Macaulay G, Hindmarsh A. Endoluminal vacuum therapy (E-Vac): a treatment option in oesophagogastric surgery. World J Surg. 2018;42:2507–11.
23. Laukoetter M, Mennigen R, Neumann P, Dhayat S, Horst G, Palmes D, Senninger N, Vowinkel T. Successful closure of defects in the upper gastrointestinal tract by endoscopic vacuum therapy (EVT): a prospective cohort study. Surg Endosc. 2016;31:2687–96.
24. Bludau M, Hölscher A, Herbold T, Leers J, Gutschow C, Fuchs H, Schröder W. Management of upper intestinal leaks using an endoscopic vacuum-assisted closure system (E-VAC). Surg Endosc. 2013;28:896–901.
25. Bludau M, Fuchs H, Herbold T, et al. Results of endoscopic vacuum-assisted closure device for treatment of upper GI leaks. Surg Endosc. 2017;32:1906–14.
26. Kuehn F, Schiffmann L, Rau B, Klar E. Surgical endoscopic vacuum therapy for anastomotic leakage and perforation of the upper gastrointestinal tract. J Gastrointest Surg. 2012;16:2145–50.
27. Mencio M, Ontiveros E, Burdick J, Leeds S. Use of a novel technique to manage gastrointestinal leaks with endoluminal negative pressure: a single institution experience. Surg Endosc. 2018;32:3349–56.

28. Eizaguirre E, Larburu S, Asensio J, Rodriguez A, Elorza J, Loyola F, Urdapilleta G, Navascués J. Treatment of anastomotic leaks with metallic stent after esophagectomies. Dis Esophagus. 2015;29:86–92.
29. Freeman R, Vyverberg A, Ascioti A. Esophageal stent placement for the treatment of acute intrathoracic anastomotic leak after esophagectomy. Ann Thorac Surg. 2011;92:204–8.
30. Zisis C, Guillin A, Heyries L, Lienne P, D'Journo X, Doddoli C, Giudicelli R, Thomas P. Stent placement in the management of oesophageal leaks. Eur J Cardiothorac Surg. 2008;33:451–6.
31. Gonzalez J, Servajean C, Aider B, Gasmi M, D'Journo X, Leone M, Grimaud J, Barthet M. Efficacy of the endoscopic management of postoperative fistulas of leakages after esophageal surgery for cancer: a retrospective series. Surg Endosc. 2016;30:4895–903.
32. Leenders B, Stronkhorst A, Smulders F, Nieuwenhuijzen G, Gilissen L. Removable and repositionable covered metal self-expandable stents for leaks after upper gastrointestinal surgery: experiences in a tertiary referral hospital. Surg Endosc. 2013;27:2751–9.
33. Schweigert M, Dubecz A, Stadlhuber R, Muschweck H, Stein H. Treatment of intrathoracic esophageal anastomotic leaks by means of endoscopic stent implantation. Interact Cadiovasc Thorac Surg. 2011;12:147–51.
34. D'Cunha J, Rueth N, Groth S, Maddaus M, Andrade R. Esophageal stents for anastomotic leaks and perforations. J Thorac Cardiovasc Surg. 2011;142:39–46.e1.
35. Plum P, Herbold T, Berlth F, Christ H, Alakus H, Bludau M, Chang D, Bruns C, Hölscher A, Chon S. Outcome of self-expanding metal stents in the treatment of anastomotic leaks after Ivor Lewis esophagectomy. World J Surg. 2018;43:862–9.
36. Nguyen N, Rudersdorf P, Smith B, Reavis K, Nguyen X, Stamos M. Management of gastrointestinal leaks after minimally invasive esophagectomy: conventional treatments vs. endoscopic stenting. J Gastrointest Surg. 2011;15:1952–60.
37. Liang D, Hwang E, Meisenbach L, Kim M, Chan E, Khaitan P. Clinical outcomes following self-expanding metal stent placement for esophageal salvage. J Thorac Cardiovasc Surg. 2017;154:1145–50.
38. Suzuki T, Siddiqui A, Taylor L, Cox K, Hasan R, Laique S, Mathew A, Wrobel P, Adler D. Clinical outcomes, efficacy, and adverse events in patients undergoing esophageal stent placement for benign indications. J Clin Gastroenterol. 2016;50(5):373–8.
39. Gubler C, Bauerfeind P. Self-expandable stents for benign esophageal leakages and perforations: long-term single-center experience. Scand J Gastroenterol. 2013;49:23–9.
40. El Hajj I, Imperiale T, Rex D, Ballard D, Kesler K, Birdas T, Fatima H, Kessler W, DeWitt J. Treatment of esophageal leaks, fistulae, and perforations with temporary stents: evaluation of efficacy, adverse events, and factors associated with successful outcomes. Gastrointest Endosc. 2014;79:589–98.
41. Dai Y, Chopra S, Kneif S, Hünerbein M. Management of esophageal anastomotic leaks, perforations, and fistulae with self-expanding plastic stents. J Thorac Cadiovasc Surg. 2011;141:1213–7.

Thoracoscopic Versus Endoscopic Therapy for Small Sub-epithelial Esophageal Tumors

38

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Introduction

Sub-epithelial tumors (SETs) are lesions that form beneath the mucosal layer of the GI tract resulting in a mucosa-covered protrusion. SETs are rare in the esophagus, accounting for less than 1% of esophageal tumors [1]. Esophageal SETs can involve or arise from the muscularis mucosa, submucosa, or muscularis propria (MP), and although the lesions have a broad differential diagnosis, leiomyomas account for 70–80%, followed less frequently by gastrointestinal stromal tumors (GISTs), hemangiomas, granular cell tumors, and schwannomas [2–4]. These lesions are typically incidentally found during endoscopy or on radiologic studies, as they are usually small (<2 cm) and asymptomatic. Although typically benign, some SETs can be symptomatic with bleeding or obstruction, and some have the potential to become malignant with metastatic dissemination [5].

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have become well-established procedures that can remove small deep mucosal or superficial submucosal lesions without disrupting the integrity of the MP. In patients in whom small esophageal SETs involve only the deep mucosa or submucosa, EMR and ESD are safe and highly effective, and currently are the standard of

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care [6]. However, when pre-malignant or malignant lesions either arise from or involve the MP, these standard techniques are unable to be used due to the risk of perforation or incomplete resection. In these cases, surgical removal of SETs can achieve clinical cure, and is therefore broadly accepted as the first option in patients who exhibit larger tumor sizes (>3–4 cm) and/or symptoms that might require a pathological diagnosis to rule out the possibility of malignancy.

The management of small, asymptomatic esophageal SETs involving the MP remains an area of debate. Some experts advocate resection of all tumors regardless of size while others have recommended surveillance due in part to the low rate of malignant conversion, morbidity with invasive organ resection surgery, and locations in which laparoscopic resection is difficult (e.g. middle and upper third of the esophagus). However, with recent advances in surgical and endoscopic technologies, the management of smaller SETs is evolving.

Thoracoscopic approaches have undergone significant improvements since first being reported in 1992 [7] and have transitioned the field from open thoracotomy to video-assisted thoracoscopic surgery (VATS) including robot assisted VATS [8–11]. At the same time, evolution in endoscopic tools for resection and the increasing availability of endoscopic devices that can provide a durable, full-thickness closure have led to novel endoscopic methods including endoscopic full thickness resection (EFTR) and sub-mucosal tunneling endoscopic resection (STER). This chapter reviews the different minimally invasive surgical and endoscopic resection techniques for small esophageal SETs involving the MP.

Search Strategy

A systematic literature search was performed in English databases including PubMed, Embase, Web of Science, and the Cochrane Library. Relevant published articles were identified from 1986 to 2020. The medical terms “full-thickness endoscopic resection esophagus,” “submucosal tunneling endoscopic resection esophagus,” “STER esophagus,” “submucosal tunnel esophagus,” “gastrointestinal tumor esophagus resection,” “leiomyoma,” “Robotic enucleation esophagus,” “VATS esophagus enucleation”, “video-assisted thoracoscopic surgery esophagus enucleation,” and “minimally invasive esophagus enucleation” were used in the search. References of relevant articles were also scanned for potential missed studies. A total of 280 articles were identified and 36 were selected for inclusion. Studies were chosen based upon relevance to the procedures and population of the topic (Table 38.1).

Table 38.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes of interest)
Patients with small subepithelial esophageal tumors	Endoscopic enucleation	Minimally invasive surgical enucleation	Recurrence, complications, need for reintervention, costs

Minimally Invasive Approaches for Esophageal SETs

Minimally Invasive Surgical Enucleation

Depending on the location, SETs in the esophagus can provide a therapeutic surgical dilemma. The surgeon often must decide between esophageal resection or surgical tumor enucleation. Open thoracotomy has been largely replaced by minimally invasive methods for enucleation. For smaller esophageal SETs, VATS or laparoscopic enucleation has proven to be safe, decreasing the morbidity associated with open thoracotomy or laparotomy, and reducing the hospital length of stay for patients [12, 13].

The short and long-term post-operative outcomes after VATS for benign esophageal SETs remains limited to several small case series in the literature [14–17]. These studies confirm that VATS enucleation is a technically feasible and safe option that reduces surgical trauma relative to open thoracotomy without sacrificing functional results [16]. In regards to long-term outcomes, it is important to determine the clinical success by recurrence rates, symptomatic improvement, and complications. High risk GISTs have been reported to recur after esophagectomy [18], although a recently published literature review notes no reported recurrence after VATS enucleation with low to intermediate risk esophageal GISTs [19]. Only one study of VATS enucleation of benign SETs has demonstrated tumor recurrence in a series of studies with follow-up ranging between 3 months and 10 years [12, 15, 16, 20–22]. In the one study with recurrence, SETs had a 100% en bloc resection rate with thoracoscopic enucleation, and recurrence in 1.9% of the patients (1/52) with an average of 42 months of surveillance [22]. Although patients are typically asymptomatic with small esophageal SETs, in case series of symptomatic patients, VATS enucleation provides durable symptom resolution in 89–95% of patients at 5 years [15, 16, 20]. A surgical concern with VATS enucleation is post-operative dysphagia secondary to the formation of a pseudodiverticulum from inadequate myotomy closure, however long-term follow up of modern VATS enucleation techniques has not demonstrated an increased rate of pseudodiverticulum formation [4].

Robotic Assisted Thoracoscopic Surgery for Resection/ Enucleation

The use of robotic surgical platforms has increasingly been reported as a method for minimally invasive resection. However, the current published literature for robotic enucleation of the esophagus remains limited to anecdotal case reports of robotic assisted esophageal enucleation of SETs [8]. In two case reports, robotic enucleation was performed in patients with 2 cm esophageal leiomyomas without evidence of mucosal injury or complications [23, 24]. Additional studies will be needed to determine if robotic-assisted thoracoscopic approaches are superior to established VATS or novel endoscopic approaches as there are currently no comparative studies.

Endoscopic Approaches for Esophageal SETs

With the advent of reliable endoscopic closure devices, endoscopic full thickness resection (EFTR) has emerged as a novel, less invasive therapeutic option for complete removal of small SETs [6]. The rationale for endoscopic resection includes: (1) SETs rarely exhibit malignant potential when small, (2) tumors are frequently diagnosed in locations not amenable surgical enucleation, (3) organ resection (i.e. esophagectomy) is too extensive with higher risk of morbidity and (4) endoscopic removal of SETs using EFTR techniques has been demonstrated to be safe and performed relatively quickly [25].

EFTR techniques include methods that are "exposed" and "non-exposed" [6]. In exposed EFTR procedures, there is temporary exposure of the thoracic cavity to the esophageal lumen. The exposed EFTR techniques can further be sub-divided into tunneled (i.e. STER) and non-tunneled methods. In non-exposed EFTR, the area of the gastrointestinal tract that contacts the lesion is invaginated toward the lumen to allow secure serosa-to-serosa apposition and lesion isolation prior to resection.

Non-exposed EFTR of Esophageal SETs

In 2011, endoscopic submucosal resection with a ligation device (ESMR-L) was demonstrated by Lee et al. to be an effective method for resection of esophageal SETs with a 100% en bloc resection rate, and rapid mean procedure time of 5 min and 26 s [26]. However, the ligation device was limited to tumors less than 1 cm (range 3–13 mm) and the SETs resected in this case series were localized to the muscularis mucosa or submucosa.

Non-tunneled, Exposed EFTR of Esophageal SETs

ESD is has not been extensively studied in the treatment of esophageal SETs in the muscularis propria [27]. Modified ESD approaches have been developed for SETs involving the MP such as endoscopic enucleation and endoscopic excavation. Endoscopic muscularis dissection was first reported by Liu et al. in which a modified ESD was performed in 31 patients (14 = esophageal tumor, 17 = gastric tumor) [28]. Modified ESD has been shown in case series to be effective even in patients with tumors in the muscularis propria with an en bloc resection rate of ~95%, however there appears to be a significant risk of perforation with this technique, ranging between 8.9% and 12.9% [28, 29]. Despite the promising success rate of ESD and reported ability to treat tumors in the muscularis propria, the relatively high perforation rate, difficulty closing circumferential, non-linear defects, and requirement for full thickness closure has limited its use in esophageal SETs.

STER of Esophageal SETs

Submucosal tunnel endoscopic resection (STER) was developed in order to improve clinical outcomes of endoscopic SET resection with decreased risk of peritonitis and mediastinitis. As a result, STER is almost always the preferred endoscopic technique in esophageal SET resection. Inoue et al. first reported the technique for per-oral endoscopic submucosal tumor resection of esophageal or gastric cardia SETs ≤4 cm in size [30]. In the STER technique a lifting solution is injected into the submucosal layer, creating a submucosal tunnel approximately 1–2 to 5 cm above the tumor [25]. The endoscope is advanced through a mucosal flap into a tunnel and the tumor is dissected from the muscular layer. The tunnel entry site is closed with hemostatic clips or endoscopic suturing at the completion of the resection.

In 2017, a systematic review and meta-analysis included 28 studies of STER for upper-GI SETs, mostly leiomyomas and GISTs [31]. Twenty retrospective and 8 prospective series comprising 1041 patients and 1085 lesions were included, of which 807 of the lesions were located in the esophagus or esophagogastric junction. The pooled complete resection and en-bloc resection rates were 97.5% (95% CI, 96.0–98.5%), and 94.6% (95% CI, 91.5–96.7%), respectively. The pooled prevalence of perforation was 5.6% (95% CI, 3.7–8.2%), and subcutaneous emphysema and/or pneumomediastinum was reported in 14.8% (95% CI, 10.5–20.5%).

In the largest reported experience to date, STER for upper esophageal and cardia SETs involving the MP was performed in 290 consecutive patients [32]. In this series, the median tumor size was 21 mm (range 10–70 mm), and the median sizes of leiomyomas and GISTs were 25.0 mm (range 10–70 mm) and 16.0 mm (range 10–45 mm), respectively. Thirteen SETs were located in the upper esophagus (4.5%), 96 in the middle esophagus (33.1%), 90 in the lower esophagus (31.0%), 68 in the esophagogastric junction (23.5%), and 23 in stomach (7.9%). Lesions were identified as 226 leiomyomas (77.9%), 53 GISTs (18.3%), 5 schwannomas (1.7%), 3 calcifying fibrous tumors (1.0%), and 3 glomus tumors (1.0%). STER achieved an *en bloc* resection rate of 89.3% (259/290) for the upper GI SETs with a median procedure time of 43 min (range 15–200 min). There was an overall complication rate of 23.4% (68/290). Complications included subcutaneous emphysema (21.0%), pneumothorax (7.6%), pneumoperitoneum (5.2%), thoracic effusions (16.9%), mucosal injury (1.0%), and major bleeding (1.7%).

In another large series of only esophageal SETs, STER was performed in 119 lesions from 115 patients [33]. The SETs were primarily located in the mid and lower third of the esophagus and averaged 19.4 ± 10.0 mm. The mean operation duration was 46.7 ± 25.6 min, and the mean duration of hospitalization was 5.9 ± 2.8 days. The total en bloc resection rate and the complete resection rate were 97.5% and 100%, respectively. There were 9 (7.8%) cases of perforation, 2 (1.7%) cases of pneumothorax, and 9 (7.8%) cases of subcutaneous emphysema.

Limitations with Endoscopic EFTR Techniques

EFTR techniques for esophageal SETs still have limitations which require further larger prospective studies and comparison with surgery to evaluate their safety and efficacy. The challenges and limitations for EFTR include technical as well as training issues [6]. From a technical standpoint, leakage of carbon dioxide insufflation in exposed EFTR can make visualization difficult or, if not addressed, can lead to tension pneumomediastinum or peritoneum. Similarly, leakage of gastrointestinal lumen contents can result in mediastinitis or peritonitis. In STER there is a limitation to the size of the SET that can be removed through the tunnel (typically <4 cm). Additionally, it is challenging to maintain tumor capsule integrity when performing dissection within the narrow confines of a submucosal tunnel. Finally, in all current techniques of EFTR, lymph node resection is unable to be performed and thus is inadequate for tumors with suspected lymph node involvement.

Comparison of SET Resection Using Thoracoscopic Surgery vs. Endoscopy

Only a few studies have directly compared thoracoscopic vs. endoscopic techniques in the management of SETs [22, 34–37]. The majority of studies are retrospective in nature comparing STER and thoracoscopic enucleation and are summarized in Table 38.2. The comparison between STER and VATS enucleation demonstrates comparable treatment efficacy for en-bloc resection and complication rates, however STER demonstrates advantages over VATS enucleation with decreased operative time, lower decrease in hemoglobin levels, and decreased cost.

In a 2018, Chai et al. reported the first prospective, randomized trial of 66 patients with small esophageal SETs comparing VATS enucleation to STER [36]. Complete resection was achieved in 100% of the patients who underwent VATS compared to the STER rate of 83.3% (p = NS). No residual tumor or recurrence was observed in any of the patients during follow up for both STER and VATS enucleation groups.

In regards to operation times, cost, and number of operators needed, VATS enucleation produced inferior outcomes with a median operation time of 106.5 min, a median cost of 6137.32 USD, and a median of 5 operators required, compared to STER outcomes with medians of 44.5 min, 4499.46 USD, and 2 operators required [1]. The significant difference in this data shows that in terms of cost, time, and personnel effectiveness, STER may be superior to VATS. However, no significant difference in time of hospital stay was found between STER and VATS with both having a median of 7 days hospital time.

Safety outcomes from the study by Chai et al. further report significant differences in postoperative pain scores and hemoglobin loss [36]. Patients who underwent VATS showed a median pain score of 4 compared to a median score of 2 for STER patients. Similarly, postoperative hemoglobin level decrease and wound effusion was more prevalent in VATS patients, although no patients either group required a blood transfusion.

Table 38.2 Comparative studies of thoracoscopic enucleation vs. endoscopic resection for esophageal sub-epithelial tumors

Study	Study design	N, total	N, procedure	Tumor location u/m/l/gj	Tumor size, mm	Operation time, min	En bloc resection rate, %	LOS, day	Compli-cations, %	Pathology	Cost, USD	Follow up, months	Recurrence	Evidence quality
Tan [34] 2016	Retro	31	18 STER	2/10/6/NR	40.56	**75.00 (±27.2)**	88.9	**6.00 (±1.2)**	16.7%	Leio (n = 18)	**3379.4 (±702.8)**	**18.9**	None	Low
			13 VATS	2/6/5/NR	40.69	**123.46 (±50.2)**	100	**8.85 (±2.6)**	15.4%	Leio (n = 13)	**4614.7 (±862.3)**	**38.8**	None	
Chen [35] 2017	Retro, "large SETs"	166	91 STER	4/28/24/35	55 (50–120)	**78 (23–250)**	84.6	**4 (1–29)**	7.7%	Leio (n = 88) Schwann (n = 2), GIST (n = 1)	NR	32 (12–65)	None	Low
			75 VATS	3/25/19/28	60 (50–120)	**120 (35–215)**	86.7	**5 (2–58)**	5.3%	Leio (n = 72), Schwann (n = 1), GIST (n = 2)	NR	NR	NR	
Li [22] 2017	Retro, <40 mm	126	74 STER	**4/31/39/NR**	18.9 (±7.2)	**55.68 (±34.6)**	98.6	**5.34 (±1.7)**	9.5%	**Leio (n = 67), GIST (n = 7)**	4637.4 (±1216.24)	**19.5**	2.7% (2/74)	Low
			52 VATS	**4/34/14/NR**	21.3 (±10.8)	**123.4 (±60.8)**	100	**10.36 (±16.2)**	7.7%	**Leio (n = 38), GIST (n = 14)**	5583.9 (±4046.97)	**42**	1.9% (1/52)	
Chai [36] 2018	Prosp, random	66	30 STER	1/16/13/NR	16.4 (10.0–45.0)	**44.5 (15–130)**	83.3	7 (5–16)	16.7%	Leio (n = 29), GIST (n = 0), Fibrous tumor (n = 1)	**4499.46 (2928–6915)**	9.5 (1–32)	None	Moderate

(continued)

Table 38.2 (continued)

Study	Study design	N, total	N, procedure	Tumor location u/m/l/gj	Tumor size, mm	Operation time, min	En bloc resection rate, %	LOS, day	Compli-cations, %	Pathology	Cost, USD	Follow up, months	Recurrence	Evidence quality
			28 VATS	0/19/9/NR	19.1 (12.0–50.0)	**106.5 (55–263)**	100	7 (3–16)	35.7%	Leio (n = 25), GIST (n = 3), Fibrous tumor (n = 0)	**6137.32 (2930–148,514)**	11 (1–26)	None	
Zhang [37] 2019	Retro	137	27 STER	**1/15/11/NR**	**16.7 (±7.1, 8–40)**	**84.05 (±45.5, 32–174)**	**81.5**	**9.05 (±2.95)**	3.7%	Leio (n = 25), GIST (n = 1), Schwann (n = 1)	**3726.59 (±724, 2198–5259)**	NR	None	Low
			42 ESD	**4/26/12/NR**	**7.4 (±4.6, 2–20)**	**57.59 (±47.9, 24–226)**	**95.2**	**10.7 (±3.4)**	7.1%	Leio (n = 39), GIST (n = 2), Schwann (n = 1)	**4993.30 (±910, 3663–6765)**	NR	None	
			68 VATS	**0/54/14/NR**	**21.3 (12.6, 2–20)**	**140.16 (±66.2, 28–390)**	**100**	**14.8 (±7.1)**	8.8%	Leio (n = 63), GIST (n = 1), Schwann (n = 4)	**8725.89 (±3428, 4175–26,733)**	NR	None	

Bold, indicates significant difference, p < 0.05; tumor location: *u* upper, *m* middle, *l* lower, *gj* gastroesophageal junction, *ESD* endoscopic submucosal dissection, *GIST* Gastrointestinal stromal tumor, *Leio* Leiomyoma, *LOS* length of stay, *NR* not reported, *prosp* prospective, *random* randomized, *retro* retrospective, *Schwann* schwannoma, *SETs* sub-epithelial tumors, *STER* submucosal tunneling endoscopic resection, *VATS* video-assisted thoracoscopic surgery

Conclusions and Recommendations

Endoscopic procedures have seen increased use and popularity as a treatment option for small esophageal SETs due to increased safety, shorter procedure duration, and lower cost with fewer operational personnel compared to thoracoscopic surgery. STER in particular has advantages over other EFTR techniques in the esophagus as the tubular shape is more amenable to tunneling and the linear mucosal incision is technically easier to close. However, thoracoscopic approaches offer significant advantages compared to endoscopy including the ability to remove larger SETs and perform a simultaneous lymph node dissection. Although minimally invasive thoracoscopic and endoscopic techniques appear to be safe and feasible, there remains a lack of larger multi-center, randomized studies detailing the risks and benefits of either endoscopic procedures or thoracoscopic procedures.

There is also limited data for long-term clinical success and recurrence rates of esophageal SETs after VATS or EFTR. While studies assessing follow up and recurrence rates after VATS and EFTR/STER with respect to final pathologic assessment of malignant potential would be ideal, the low risk and slow growth of most lesions, lack of compliance with long-term follow-up, and likelihood of 'early recurrence' being incompletely resected of macroscopic tissue as opposed to microscopic residual disease, will make proving long term success in these procedures challenging.

In summary, after diagnosis and determination that an esophageal SET lesion requires resection, endoscopic and thoracoscopic approaches both offer safe and effective methods for resection. Esophageal SET lesions >4 cm are challenging for any endoscopic approach and a thoracoscopic method is recommended. However, for low risk esophageal SET lesions <2 cm, endoscopic techniques, and particularly STER, appears to be emerging as the optimal method of resection.

Recommendation

- We recommend endoscopic enucleation using STER for small subepithelial esophageal tumors (<2 cm) and minimally invasive surgical enucleation for larger tumors (evidence quality moderate, weak recommendation).

A Personal View of the Data

Patients with esophageal SETs are frequently referred to our advanced endoscopy practice for diagnostic endoscopic ultrasound and consideration of therapeutic endoscopic resection. Similar to the published literature, the vast majority of these patients are asymptomatic and the lesions are identified incidentally on upper endoscopy. In my practice, for an esophageal SET referral, evaluation begins with endoscopic ultrasound with fine-needle biopsy to diagnose the lesion, assess the

size/characteristics/layer of origin of the lesion, as well as identify pathologic lymphadenopathy. Appropriate diagnosis and lesion assessment (e.g. wall layer of origin) are vital to treatment planning, determining the risks/benefits of resection, and the appropriate resection technique.

The most frequently encountered esophageal SETs, leiomyomas, are believed to have a lower malignant potential, and thus my approach for small (<2 cm) asymptomatic leiomyomas or undifferentiated lesions <1 cm in size is annual surveillance. For ≤2 cm SETs that are symptomatic, carry high risk endoscopic features (e.g. calcifications), or have increased malignant risk, such as GISTs [38], I recommend STER with en-bloc resection. For larger lesions or any pathologic lymphadenopathy, I recommend minimally invasive surgical enucleation. The current data supports the feasibility, procedural outcomes, and safety of STER for ≤2 cm SETs however, there remains a lack of evidence for long-term post-resection surveillance and non-universal technical expertise that limits widespread adoption.

References

1. Postlethwait RW, Musser AW. Changes in the esophagus in 1,000 autopsy specimens. J Thorac Cardiovasc Surg. 1974;68(6):953–6.
2. Standards of Practice C, Faulx AL, Kothari S, Acosta RD, Agrawal D, Bruining DH, et al. The role of endoscopy in subepithelial lesions of the GI tract. Gastrointest Endosc. 2017;85(6):1117–32.
3. Mutrie CJ, Donahue DM, Wain JC, Wright CD, Gaissert HA, Grillo HC, et al. Esophageal leiomyoma: a 40-year experience. Ann Thorac Surg. 2005;79(4):1122–5.
4. Thomas DKA. Thoracoscopic management of benign submucosal tumors. In: Grams J, Perry K, Tavakkoli A, editors. The SAGES manual of foregut surgery. Cham: Springer; 2019.
5. Humphris JL, Jones DB. Subepithelial mass lesions in the upper gastrointestinal tract. J Gastroenterol Hepatol. 2008;23(4):556–66.
6. Committee AT, Aslanian HR, Sethi A, Bhutani MS, Goodman AJ, Krishnan K, et al. ASGE guideline for endoscopic full-thickness resection and submucosal tunnel endoscopic resection. VideoGIE. 2019;4(8):343–50.
7. Everitt NJ, Glinatsis M, McMahon MJ. Thoracoscopic enucleation of leiomyoma of the oesophagus. Br J Surg. 1992;79(7):643.
8. Khalaileh A, Savetsky I, Adileh M, Elazary R, Abu-Gazala M, Abu Gazala S, et al. Robotic-assisted enucleation of a large lower esophageal leiomyoma and review of literature. Int J Med Robot. 2013;9(3):253–7.
9. Elli E, Espat NJ, Berger R, Jacobsen G, Knoblock L, Horgan S. Robotic-assisted thoracoscopic resection of esophageal leiomyoma. Surg Endosc. 2004;18(4):713–6.
10. DeUgarte DA, Teitelbaum D, Hirschl RB, Geiger JD. Robotic extirpation of complex massive esophageal leiomyoma. J Laparoendosc Adv Surg Tech A. 2008;18(2):286–9.
11. Compean SD, Gaur P, Kim MP. Robot assisted thoracoscopic resection of giant esophageal leiomyoma. Int J Surg Case Rep. 2014;5(12):1132–4.
12. von Rahden BH, Stein HJ, Feussner H, Siewert JR. Enucleation of submucosal tumors of the esophagus: minimally invasive versus open approach. Surg Endosc. 2004;18(6):924–30.
13. Luh SP, Hou SM, Fang CC, Chen CY. Video-thoracoscopic enucleation of esophageal leiomyoma. World J Surg Oncol. 2012;10:52.
14. Bonavina L, Segalin A, Rosati R, Pavanello M, Peracchia A. Surgical therapy of esophageal leiomyoma. J Am Coll Surg. 1995;181(3):257–62.

15. Samphire J, Nafteux P, Luketich J. Minimally invasive techniques for resection of benign esophageal tumors. Semin Thorac Cardiovasc Surg. 2003;15(1):35–43.
16. Lee LS, Singhal S, Brinster CJ, Marshall B, Kochman ML, Kaiser LR, et al. Current management of esophageal leiomyoma. J Am Coll Surg. 2004;198(1):136–46.
17. Kent M, d'Amato T, Nordman C, Schuchert M, Landreneau R, Alvelo-Rivera M, et al. Minimally invasive resection of benign esophageal tumors. J Thorac Cardiovasc Surg. 2007;134(1):176–81.
18. Robb WB, Bruyere E, Amielh D, Vinatier E, Mabrut JY, Perniceni T, et al. Esophageal gastrointestinal stromal tumor: is tumoral enucleation a viable therapeutic option? Ann Surg. 2015;261(1):117–24.
19. Cohen C, Pop D, Icard P, Berthet JP, Venissac N, Mouroux J. Is there a place for thoracoscopic enucleation of esophageal gastrointestinal stromal tumors? Thorac Cardiovasc Surg. 2019;67(7):585–8.
20. Jiang G, Zhao H, Yang F, Li J, Li Y, Liu Y, et al. Thoracoscopic enucleation of esophageal leiomyoma: a retrospective study on 40 cases. Dis Esophagus. 2009;22(3):279–83.
21. Obuchi T, Sasaki A, Nitta H, Koeda K, Ikeda K, Wakabayashi G. Minimally invasive surgical enucleation for esophageal leiomyoma: report of seven cases. Dis Esophagus. 2010;23(1):E1–4.
22. Li QY, Meng Y, Xu YY, Zhang Q, Cai JQ, Zheng HX, et al. Comparison of endoscopic submucosal tunneling dissection and thoracoscopic enucleation for the treatment of esophageal submucosal tumors. Gastrointest Endosc. 2017;86(3):485–91.
23. Augustin F, Schmid T, Bodner J. The robotic approach for mediastinal lesions. Int J Med Robot. 2006;2(3):262–70.
24. Chiu PK, Chiu PW, Teoh AY, Wong SK, Ng EK. Robotic-assisted thoracoscopic enucleation of esophageal leiomyoma. J Robot Surg. 2011;5(3):227–9.
25. Zhang X, Modayil R, Criscitelli T, Stavropoulos SN. Endoscopic resection for subepithelial lesions-pure endoscopic full-thickness resection and submucosal tunneling endoscopic resection. Transl Gastroenterol Hepatol. 2019;4:39.
26. Lee DG, Kim GH, Park DY, Jeong JH, Moon JY, Lee BE, et al. Endoscopic submucosal resection of esophageal subepithelial lesions using band ligation. Endoscopy. 2011;43(9):822–5.
27. Kim SY, Kim KO. Endoscopic treatment of subepithelial tumors. Clin Endosc. 2018;51(1):19–27.
28. Liu BR, Song JT, Qu B, Wen JF, Yin JB, Liu W. Endoscopic muscularis dissection for upper gastrointestinal subepithelial tumors originating from the muscularis propria. Surg Endosc. 2012;26(11):3141–8.
29. Ye LP, Zhu LH, Zhou XB, Mao XL, Zhang Y. Endoscopic excavation for the treatment of small esophageal subepithelial tumors originating from the muscularis propria. Hepato-Gastroenterology. 2015;62(137):65–8.
30. Inoue H, Ikeda H, Hosoya T, Onimaru M, Yoshida A, Eleftheriadis N, et al. Submucosal endoscopic tumor resection for subepithelial tumors in the esophagus and cardia. Endoscopy. 2012;44(3):225–30.
31. Lv XH, Wang CH, Xie Y. Efficacy and safety of submucosal tunneling endoscopic resection for upper gastrointestinal submucosal tumors: a systematic review and meta-analysis. Surg Endosc. 2017;31(1):49–63.
32. Chen T, Zhang C, Yao LQ, Zhou PH, Zhong YS, Zhang YQ, et al. Management of the complications of submucosal tunneling endoscopic resection for upper gastrointestinal submucosal tumors. Endoscopy. 2016;48(2):149–55.
33. Tu S, Huang S, Li G, Tang X, Qing H, Gao Q, et al. Submucosal tunnel endoscopic resection for esophageal submucosal tumors: a multicenter study. Gastroenterol Res Pract. 2018;2018:2149564.
34. Tan Y, Lv L, Duan T, Zhou J, Peng D, Tang Y, et al. Comparison between submucosal tunneling endoscopic resection and video-assisted thoracoscopic surgery for large esophageal leiomyoma originating from the muscularis propria layer. Surg Endosc. 2016;30(7):3121–7.

35. Chen T, Lin ZW, Zhang YQ, Chen WF, Zhong YS, Wang Q, et al. Submucosal tunneling endoscopic resection vs thoracoscopic enucleation for large submucosal tumors in the esophagus and the esophagogastric junction. J Am Coll Surg. 2017;225(6):806–16.
36. Chai N, Du C, Gao Y, Niu X, Zhai Y, Linghu E, et al. Comparison between submucosal tunneling endoscopic resection and video-assisted thoracoscopic enucleation for esophageal submucosal tumors originating from the muscularis propria layer: a randomized controlled trial. Surg Endosc. 2018;32(7):3364–72.
37. Zhang M, Wu S, Xu H. Comparison between submucosal tunneling endoscopic resection (STER) and other resection modules for esophageal muscularis propria tumors: a retrospective study. Med Sci Monit. 2019;25:4560–8.
38. Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Cancer Netw. 2010;8(Suppl 2):S1–41.

Laparoscopic vs. Endoscopic Therapy for Achalasia

39

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Introduction

Achalasia is a motility disorder of the esophagus characterized by an absence of relaxation of the lower esophageal sphincter (LES) and disorganized or absent peristalsis of the esophageal body, leading to symptoms such as dysphagia, regurgitation, respiratory distress, heartburn, weight loss, and chest pain [1]. Therapy is palliative in nature with the goal to reduce the resting and swallow-induced pressure of the LES, which leads to improvement in dysphagia and other symptoms. Although there are a number of medical and procedural options available, myotomy has been shown to be the most efficacious in providing long-term relief of symptoms.

Laparoscopic Heller myotomy (LHM) is a time-tested treatment for esophageal achalasia that has been shown to be safe in large case series. The mortality approaches zero, it is highly efficacious in long-term symptom relief, and it results in a high degree of patient satisfaction [2–11]. Due to the high incidence of reflux after myotomy, partial fundoplication is recommended after Heller myotomy to reduce pathologic reflux [12].

Peroral endoscopic myotomy (POEM), in which the myotomy is performed endoscopically, was developed by Inoue and colleagues in 2008 and was first published in 2010 [13]. POEM is an attractive option in the treatment of achalasia because it affords all of the benefits of natural orifice transluminal endoscopic surgery (lack of incisions, less pain, minimal blood loss) while also offering a single stage option to palliate symptoms. Other benefits include easy extension of the

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myotomy, which is particularly useful in patients with type III achalasia and diffuse esophageal spasm (DES), less risk of injury to the vagus nerve, and, theoretically, a lowered risk of reflux as attachments of the esophagus such as the phrenoesophageal membrane are not disrupted as they are with Heller myotomy [14]. Evidence from large-scale registries and case series have demonstrated that peroral endoscopic myotomy is safe, at least in the short-term, and leads to decreased symptoms and improved quality of life [15–21].

Since its introduction, this technique has gained widespread adoption at specialized centers worldwide because of its minimally invasive approach. Although it has been rapidly adopted, there is still a paucity of long-term follow-up data, and there have been no randomized clinical trials comparing POEM and Heller myotomy. Moreover, concerns have been raised regarding the rates of post-operative reflux after POEM due to the lack of any concurrent anti-reflux procedure. The purpose of this chapter is to review the published literature regarding safety, efficacy, perioperative outcomes, and risks of laparoscopic Heller myotomy compared with POEM.

Search Strategy

A Pub-med search was performed of the literature published in the English language between 01/01/2010 and 07/01/2019 using the following search terms, either alone or in combination in order to obtain the maximal number of articles: “peroral endoscopic myotomy”, “POEM”, “Heller myotomy”, “laparoscopic myotomy”, “laparoscopic myotomy and fundoplication”, “achalasia” (Table 39.1). The reference lists of the identified papers as well as topic reviews were checked for additional articles for inclusion.

Results

There are a number of papers that directly compare LHM to POEM. The results of those studies, with particular attention to clinical response, adverse events, length of stay and rates of postoperative reflux, are summarized in Table 39.2 [22–31]. Additionally, there have been three meta-analyses comparing LHM and POEM, the results of which are summarized in Table 39.3 [32–34].

Table 39.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with achalasia	Laparoscopic Heller myotomy	Peroral endoscopic myotomy (POEM)	Clinical response
			Length of stay
			Adverse events gastroesophageal reflux

Table 39.2 Recent publications comparing surgical and endoscopic treatments

Author	Study period	P (Patients)	Clinical response	Length of stay (days)	Adverse events	Postoperative reflux	Quality of evidence
Hungness [24]	2004–2012	POEM 18 LHM 55	POEM 1 (0–9) LHM not reported (Eckardt scores at median 6 (range, 1–18) month follow up)	POEM 1 (1–13) LHM 1 (1–19) p = 0.63 Median (range)	POEM 23% LHM 15% (Combined major and minor; p = 0.45, 0.71)	POEM 39% LHM not reported (GerdQ score > 7 and/or esophagitis on EGD)	Very low
Ujiki [22]	2009–2013	POEM 18 LHM 21	POEM 0.7 ± 0.5 LHM 1.0 ± 0.4 (p = ns) (Eckardt score at follow-up)	POEM 3.4 ± 1.3 LHM 3.4 ± 3.4 (p = ns)	POEM 17% LHM 5% (p = ns)	POEM 27.8% LHM 19% (p = ns)	Low
Teitelbaum [23]	2004–2012	POEM 12 LHM 17	POEM 1 ± 1 (0–3) LHM 1 ± 2 (0–5) p = 0.77 (Postoperative Eckardt score)	Not reported	Not reported	POEM 17% LHM 31% (p = ns) (GerdQ ≥ 7 at follow-up)	Very low
Bhayani [25]	2007–2012	POEM 37 LHM 64	POEM 1.2 LHM 1.7 p = 0.1 (Long term Eckardt score at follow up)	POEM 1.1 ± 0.6 LHM 2.2 ± 1.9 p < 0.0001	POEM 14% LHM 19% p = ns (Full thickness injury and return to OR for bleeding)	POEM 9% LHM 10% p = 0.4 (DeMeester score ≥ 14.7)	Low
Kumbhari [29]	2010–2013	POEM 49 LHM 26	POEM 98.0% Heller 80.8% p = 0.01 (Patients with Eckardt stage≤1 at last follow-up)	POEM 3.3 ± 1.9 LHM 3.2 ± 2.3 p = 0.68	POEM 6% LHM 27% p = 0.01	POEM 38.8% LHM 46.1% p = 0.7 (Defined as ongoing PPI requirement)	Low

(continued)

Table 39.2 (continued)

Author	Study period	P (Patients)	Clinical response	Length of stay (days)	Adverse events	Postoperative reflux	Quality of evidence
Schneider [30]	2004–2016	POEM 25 LHM 25	POEM 1.04 Heller 1 p = 0.911 (Eckardt score at follow up)	Not reported	POEM 28% LHM 16% p = 0.157 (Inadvertent mucosotomies)	POEM 50% LHM 30% p = 0.369 DeMeester score > 14.7	Moderate
Chan [26]	2000–2014	POEM 33 LHM 23	POEM 0 (0–2) LHM 0 (0–2) Median (range) p = 0.073 (Dysphagia score at 6 months)	POEM 3.15 ± 1.1 LHM 3.4 ± 1.4 p = 0.728	POEM 15% LHM 13% p = 0.512	POEM 15.2% LHM 26% p = 0.311 (GERD symptoms)	Low
Peng [31]	2009–2012	POEM 13 LHM 18	POEM 2.6 ± 1.5 LHM 2.8 ± 1.3 p = 0.69 (3 year follow up)	POEM 4.0 (3.5–4.5) LHM 5.0 (4.0–6.0) p = 0.17	POEM 7.7% LHM 5.6% p = 1.00	POEM 8.3% LHM 6.7% p = 1.00 (GerdQ ≥ 9)	Very low
Leeds [27]	2014–2017	POEM 12 LHM 11	POEM 1.2 ± 1.6 LHM 3.0 ± 0.7 p = 0.08	POEM 1.6 ± 1.2 LHM 2.0 ± 1.9 p = 0.53	POEM 25% LHM 27% p = NA	Not reported	Very low
Wirsching [28]	2014–2017	POEM 23 LHM 28	POEM = 0 (0–2) LHM = 0 (0–2) p = 1.0; median (range) (Eckardt score at late follow up (30–180 days))	POEM = 1 (1–2) LHM = 1 (1–4) p = 1.0	POEM 8.7% LHM 14.3% p = 0.827	Not reported	Low

POEM peroral endoscopic myotomy, *LHM* laparoscopic Heller myotomy, *GerdQ* gastroesophageal reflux quality of life score, *OR* operating room, *PPI* proton pump inhibitor

Table 39.3 Meta-analyses comparing meta-analyses surgical and endoscopic treatments

Author	Year	Patients	Clinical response	Length of Stay	Adverse Events	Postoperative reflux
Zhang [32]	2016	POEM 125 LHM 192	Patients in POEM group had lower Eckardt score after surgery (MD = −0.30, 95% CI −0.42 to −0.18; p < 0.001)	No difference between POEM and LHM groups (MD = −0.42, 95% CI: −1.26 to 0.43; p = 0.33)	No difference between POEM and LHM groups (OR 1.53, 95% CI 0.65–3.59; p = 0.22)	Not reported
Marano [33]	2016	POEM 196 LHM 290	No difference between POEM and LHM groups Eckardt scores (MD = −0.659, 95% CI −1.70 to 0.38, p = 0.217)	Lower hospital time of POEM compared to LHM (MD = −0.629, 95% CI: −1.256 to −0.002, p = 0.049)	No difference in rate of overall complications (OR = 1.11, 95% CI: 0.5–2.44, p = 0.796)	Reduced rates of symptomatic GERD in LHM vs. POEM (OR = 1.81, 95% CI: 1.11–2.95, p = 0.017)
Schlottmann [34]	2018	POEM 1958 LHM 5824	Predicted probabilities for improvement in dysphagia at 12 months 93.5% for POEM and 91.0% for LHM (p = 0.01), and at 24 months 92.7% for POEM and 90.0% for LHM (p = 0.01)	On average, length of hospital stay was 1.03 days longer after POEM (p = 0.04)	Not enough data to perform statistical analysis	POEM patients more likely to develop GERD symptoms (OR 1.69, 95% CI 1.33–2.14, p < 0.0001), GERD evidenced by erosive esophagitis (OR 9.31, 95% CI 4.71–18.85, p < 0.0001), and GERD evidenced by pH monitoring (OR 4.30, 95% CI 2.96–6.27, p < 0.0001)

POEM peroral endoscopic myotomy, *LHM* laparoscopic Heller myotomy, *MD* mean difference, *CI* confidence interval, *GERD* gastroesophageal reflux disease

Clinical Response

A primary metric by which POEM has been judged is the adequacy of clinical response when compared to Heller myotomy. Follow up for patients who underwent Heller myotomy is typically longer because POEM is a relatively newer procedure. In most studies, the Eckardt symptom score, which measures the frequency of the primary symptoms of achalasia (dysphagia, regurgitation, chest pain and weight loss; each on a scale of 0–3; total score range 0–12), is used. Authors use various cut-offs to define therapeutic response, usually a follow-up Eckardt score ≤ 3.

Early studies comparing POEM and Heller myotomy consist of retrospective reviews with small sample sizes and with short-term follow up that evaluated therapeutic success based on Eckardt scores. Most studies reported significant decreases in Eckardt scores pre- to postoperatively with no significant difference between LHM and POEM groups [22–28]. Kumbhari specifically studied patients with type III achalasia and found that a satisfactory clinical response at the time of last clinical follow-up was significantly more frequent in the POEM cohort (98.0% vs. 80.8%; $p = 0.01$) [29]. Schneider performed a matched cohort analysis based on preoperative Eckardt scores and three quality of life metrics, and found that treatment success was not significantly different between groups ($p = 0.444$) [30]. More recently, a study published by Peng found that, with follow-up as long as 3 years, there was no difference between LHM and POEM groups [31].

The results of two early systematic analyses published in 2016 were mixed, with Zhang finding that POEM patients had slightly lower Eckardt scores at follow up, and Marano reporting no significant difference [32, 33]. The latest and largest systematic review and meta-analysis was published in 2018 by Schlottmann, in which they report on over 7500 patients, 5834 who underwent LHM (53 studies) and 1958 who underwent POEM (11 studies). They report on percentage of dysphagia improvement and found that, averaged across all studies, dysphagia improvement was reported in 93.2% of patients who underwent POEM and 87.7% after LHM; predicted probabilities for improvement in dysphagia at both 12 months and 24 months favored POEM (both $p = 0.01$) [34].

Adverse Events

Most published studies comparing the rate of complications between LHM and POEM groups have found no difference in the rate of adverse events [22, 24–26, 28, 30, 31]. In one particular study that did show a difference, Kumbhari reported a statistically significantly higher rate of adverse events in the LHM cohort (27.0% vs. 6%; $p = 0.01$), with a higher percentage graded as moderate events in the LHM cohort. However, there were no serious adverse events in either group [29]. Leeds et al. reported too few complications to be compared statistically but found non-serious adverse events occurred in three patients in each group [27].

In the meta-analyses published by Zhang and Marano, both found that there was no statistically significant difference in the rate of complications between the POEM

and LHM groups (odds ratio (OR) 1.53, 95% confidence interval (CI) 0.65–3.59; P = 0.22 and OR 1.11, 95% CI: 0.5–2.44, p = 0.796, respectively; both favoring LHM, however). Schlottmann only considered complications of Clavien grade III, IV and V and, due to the extremely low rate of morbidity and mortality, they were not able to perform any statistical analyses.

Length of Stay

Seven studies [22, 24, 26–29, 31] found that length of stay between the LHM and POEM groups was not statistically significantly different. In their meta-analysis, Zhang found that in four studies that reported length of stay there was no difference between POEM and LHM groups (mean difference (MD) = −0.42, 95% CI: −1.26 to 0.43; P = 0.33). In studies that did show a difference, Bhayani found that LHM patients had a longer average length of hospitalization (2.2 vs. 1.1 days, $p < 0.0001$) [25]. In their meta-analysis, Marano found a lower length of stay in POEM patients compared with LHM patients (MD = −0.629, 95% CI: −1.256 to −0.002, $P = 0.049$). Conversely, Schlottmann surprisingly found that patients who underwent POEM stayed in the hospital an average of a day longer than patients who received LHM ($p = 0.04$), although they admit that the early stage of development of POEM in the studies included in their meta-analysis may have contributed to this finding.

Postoperative Reflux

A primary concern with POEM is the rate of postoperative reflux. There is wide variation in how reflux is reported in studies comparing LHM and POEM. Overall, all studies are plagued with the issue of loss of follow-up, and objective measures of reflux are limited to a minority of patients in most studies.

Multiple studies reported on GERD postoperatively based on questionnaire and survey data at follow-up and found no significant differences between the POEM and LHM groups [22–24, 26, 31]. Kumbhari used proton pump inhibitor (PPI) use postoperatively as a surrogate for symptomatic GERD and found no significant differences between the POEM and LHM groups [29]. More recent studies have used pH testing to determine rates of reflux. Bhayani and Schneider both found that a similar percentage of patients in groups had an abnormal DeMeester score on postoperative 48-h pH testing [25, 30].

Two meta-analyses considered the issue of postoperative reflux. Marano found that there was a trend toward a significant reduction in symptomatic gastroesophageal reflux rate in favor of LHM compared to POEM (OR 1.81, 95% CI: 1.11–2.95, P = 0.017) [33]. Schlottmann examined the incidence of postoperatively reflux using a variety of measures. They found that GERD symptoms, and to a greater extent presence of reflux esophagitis and abnormal 24-h pH monitoring, were all significantly more common in POEM patients postoperatively. Overall, their data suggested that, although GERD symptoms were present in a more similar number

of patients in each group, there was much greater difference in rates of reflux when based on objective modalities such as EGD and pH monitoring [34].

Conclusions and Recommendations

Both Heller myotomy with fundoplication and POEM are highly efficacious in palliating symptoms, with POEM being slightly more successful in a recently published large meta-analysis, and have similar rates of perioperative complications. In recent years, rates of reflux have been the primary concern in comparing the two approaches. Overall, based on the results of recently published systematic reviews and meta-analyses, we make a weak recommendation to choose POEM over laparoscopic Heller myotomy with fundoplication due to a slightly better clinical response with no difference in adverse events.

Recommendation

- We recommend POEM rather than laparoscopic esophageal myotomy for patients with achalasia (evidence quality low; weak recommendation).

A Personal View of the Data

The relative benefits of POEM include satisfactory palliation of symptoms, minimal rate of compilations, potential for same day discharge [35], lack of incisions, and equal or better efficacy when compared to Heller myotomy. The only downside is the inability to perform a fundoplication, and GERD rates are higher with POEM [36, 37]. In our practice, we routinely discharge patients the same day after POEM and the next day after Heller myotomy, and maintain all patients with achalasia who undergo myotomy on PPI therapy for a minimum of 1 year and then have them return for esophagogastroduodenoscopy and Bravo pH testing off therapy to evaluate for reflux-associated changes (stricture, esophagitis, Barrett's esophagus). At this point, accepted therapies for reflux after POEM include lifelong PPI therapy or laparoscopic fundoplication. With emerging endoscopic therapies being developed, our hope is that in the future a fully endoscopic method will become feasible and safe to permit myotomy and fundoplication after POEM [38].

References

1. Boeckxstaens GE, Zaninotto G, Richter JE. Achalasia. Lancet. 2014;383:83–93.
2. Wright AS, Williams CW, Pellegrini CA, Oelschlager BK. Long-term outcomes confirm the superior efficacy of extended Heller myotomy with Toupet fundoplication for achalasia. Surg Endosc. 2007;21:713–8.

3. Yamamura MS. Laparoscopic Heller myotomy and anterior fundoplication for achalasia results in a high degree of patient satisfaction. Arch Surg. 2000;135:902–6.
4. Bonatti H, Hinder RA, Klocker J, Neuhauser B, Klaus A, Achem SR, de Vault K. Long-term results of laparoscopic Heller myotomy with partial fundoplication for the treatment of achalasia. Am J Surg. 2005;190:883–7.
5. Zaninotto G, Costantini M, Rizzetto C, et al. Four hundred laparoscopic myotomies for esophageal achalasia: a single centre experience. Ann Surg. 2008;248:986–93.
6. Sasaki A, Obuchi T, Nakajima J, Kimura Y, Koeda K, Wakabayashi G. Laparoscopic Heller myotomy with Dor fundoplication for achalasia: long-term outcomes and effect on chest pain: achalasia and chest pain. Dis Esophagus. 2009;23:284–9.
7. Jeansonne LO, White BC, Pilger KE, Shane MD, Zagorski S, Davis SS, Hunter JG, Lin E, Smith CD. Ten-year follow-up of laparoscopic Heller myotomy for achalasia shows durability. Surg Endosc. 2007;21:1498–502.
8. Cowgill SM, Villadolid D, Boyle R, Al-Saadi S, Ross S, Rosemurgy AS. Laparoscopic Heller myotomy for achalasia: results after 10 years. Surg Endosc. 2009;23:2644–9.
9. Youssef Y, Richards WO, Sharp K, Holzman M, Sekhar N, Kaiser J, Torquati A. Relief of dysphagia after laparoscopic Heller myotomy improves long-term quality of life. J Gastrointest Surg. 2007;11:309–13.
10. Rosemurgy AS, Morton CA, Rosas M, Albrink M, Ross SB. A single institution's experience with more than 500 laparoscopic Heller myotomies for achalasia. J Am Coll Surg. 2010;210:637–45.
11. Campos GM, Vittinghoff E, Rabl C, Takata M, Gadenstätter M, Lin F, Ciovica R. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. Ann Surg. 2009;249:45–57.
12. Richards WO, Torquati A, Holzman MD, Khaitan L, Byrne D, Lutfi R, Sharp KW. Heller myotomy versus Heller myotomy with Dor fundoplication for achalasia: a prospective randomized double-blind clinical trial. Ann Surg. 2004;240:405–15.
13. Inoue H, Minami H, Kobayashi Y, Sato Y, Kaga M, Suzuki M, Satodate H, Odaka N, Itoh H, Kudo S. Peroral endoscopic myotomy (POEM) for esophageal achalasia. Endoscopy. 2010;42:265–71.
14. Stavropoulos SN, Friedel D, Modayil R, Iqbal S, Grendell JH. Endoscopic approaches to treatment of achalasia. Ther Adv Gastroenterol. 2013;6:115–35.
15. Von Renteln D, Fuchs K, Fockens P, et al. Peroral endoscopic myotomy for the treatment of achalasia: an international prospective multicenter study. Gastroenterology. 2013;145:309–311.e3.
16. Chen X, Li Q, Ji G, Ge X, Zhang X, Zhao X, Miao L. Two-year follow-up for 45 patients with achalasia who underwent peroral endoscopic myotomy. Eur J Cardiothorac Surg. 2015;47:890–6.
17. Worrell SG, Alicuben ET, Boys J, DeMeester SR. Peroral endoscopic myotomy for achalasia in a thoracic surgical practice. Ann Thorac Surg. 2016;101:218–25.
18. Ramchandani M, Reddy DN, Darisetty S, Kotla R, Chavan R, Kalpala R, Galasso D, Lakhtakia S, Rao GV. Peroral endoscopic myotomy for achalasia cardia: treatment analysis and follow up of over 200 consecutive patients at a single center: POEM for achalasia cardia. Dig Endosc. 2016;28:19–26.
19. Inoue H, Sato H, Ikeda H, Onimaru M, Sato C, Minami H, Yokomichi H, Kobayashi Y, Grimes KL, Kudo S. Per-oral endoscopic myotomy: a series of 500 patients. J Am Coll Surg. 2015;221:256–64.
20. Perbtani YB, Mramba LK, Yang D, Suarez J, Draganov PV. Life after per-oral endoscopic myotomy: long-term outcomes of quality of life and their association with Eckardt scores. Gastrointest Endosc. 2018;87:1415–1420.e1.
21. Li H, Peng W, Huang S, Ren Y, Peng Y, Li Q, Wu J, Fu X, Tang X. The 2 years' long-term efficacy and safety of peroral endoscopic myotomy for the treatment of achalasia: a systematic review. J Cardiothorac Surg. 2019;14:1.

22. Ujiki MB, Yetasook AK, Zapf M, Linn JG, Carbray JM, Denham W. Peroral endoscopic myotomy: a short-term comparison with the standard laparoscopic approach. Surgery. 2013;154:893–900.
23. Teitelbaum EN, Rajeswaran S, Zhang R, Sieberg RT, Miller FH, Soper NJ, Hungness ES. Peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy produce a similar short-term anatomic and functional effect. Surgery. 2013;154:885–92.
24. Hungness ES, Teitelbaum EN, Santos BF, Arafat FO, Pandolfino JE, Kahrilas PJ, Soper NJ. Comparison of perioperative outcomes between peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy. J Gastrointest Surg. 2013;17:228–35.
25. Bhayani NH, Kurian AA, Dunst CM, Sharata AM, Rieder E, Swanstrom LL. A comparative study on comprehensive, objective outcomes of laparoscopic Heller myotomy with per-oral endoscopic myotomy (POEM) for achalasia. Ann Surg. 2014;259:1098–103.
26. Chan SM, Wu JCY, Teoh AYB, Yip HC, Ng EKW, Lau JYW, Chiu PWY. Comparison of early outcomes and quality of life after laparoscopic Heller's cardiomyotomy to peroral endoscopic myotomy for treatment of achalasia: POEM for achalasia. Dig Endosc. 2016;28:27–32.
27. Leeds SG, Burdick JS, Ogola GO, Ontiveros E. Comparison of outcomes of laparoscopic Heller myotomy versus per-oral endoscopic myotomy for management of achalasia. Bayl Univ Med Cent Proc. 2017;30:419–23.
28. Wirsching A, Boshier PR, Klevebro F, Kaplan SJ, Seesing MFJ, El-Moslimany R, Ross A, Low DE. Comparison of costs and short-term clinical outcomes of per-oral endoscopic myotomy and laparoscopic Heller myotomy. Am J Surg. 2019;218(4):706–11.
29. Kumbhari V, Tieu A, Onimaru M, et al. Peroral endoscopic myotomy (POEM) vs laparoscopic Heller myotomy (LHM) for the treatment of Type III achalasia in 75 patients: a multicenter comparative study. Endosc Int Open. 2015;3:E195–201.
30. Schneider AM, Louie BE, Warren HF, Farivar AS, Schembre DB, Aye RW. A matched comparison of per oral endoscopic myotomy to laparoscopic Heller myotomy in the treatment of achalasia. J Gastrointest Surg. 2016;20:1789–96.
31. Peng L, Tian S, Du C, Yuan Z, Guo M. Outcome of Peroral endoscopic myotomy (POEM) for treating achalasia compared with laparoscopic Heller myotomy (LHM). Surg Laparosc Endosc Percutan Tech. 2017;27:60–4.
32. Zhang Y, Wang H, Chen X, Liu L, Wang H, Liu B, Guo J, Jia H. Per-oral endoscopic myotomy versus laparoscopic Heller myotomy for achalasia: a meta-analysis of nonrandomized comparative studies. Medicine (Baltimore). 2016;95:e2736.
33. Marano L, Pallabazzer G, Solito B, et al. Surgery or peroral esophageal myotomy for achalasia: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95:e3001.
34. Schlottmann F, Luckett DJ, Fine J, Shaheen NJ, Patti MG. Laparoscopic Heller myotomy versus peroral endoscopic myotomy (POEM) for achalasia: a systematic review and meta-analysis. Ann Surg. 2018;267:451–60.
35. Benias PC, Korrapati P, Raphael KL, et al. Safety and feasibility of performing peroral endoscopic myotomy as an outpatient procedure with same-day discharge. Gastrointest Endosc. 2019;90(4):570–8.
36. Repici A, Fuccio L, Maselli R, et al. GERD after per-oral endoscopic myotomy as compared with Heller's myotomy with fundoplication: a systematic review with meta-analysis. Gastrointest Endosc. 2018;87:934–943.e18.
37. Sanaka MR, Thota PN, Parikh MP, Hayat U, Gupta NM, Gabbard S, Lopez R, Murthy S, Raja S. Peroral endoscopic myotomy leads to higher rates of abnormal esophageal acid exposure than laparoscopic Heller myotomy in achalasia. Surg Endosc. 2019;33:2284–92.
38. Inoue H, Ueno A, Shimamura Y, et al. Peroral endoscopic myotomy and fundoplication: a novel NOTES procedure. Endoscopy. 2019;51:161–4.

Laparoscopy or Endoscopic Therapy for Recurrent Symptoms from Achalasia

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Introduction

Esophageal achalasia is an uncommon disease with an estimated incidence of between 0.7 and 2.3 new patients per every 100,000 inhabitants a year, however, the prevalence of achalasia is estimated to be ten times higher than its incidence. It has been estimated that some 10–23 persons per 100,000 inhabitants have the disease [1]. There are no clear geographical, race, or gender associations [2, 3]. No etiologic therapy for achalasia is available—treatment is symptomatic and aimed at eliminating or reducing the functional obstruction of the cardia, thus allowing the free passage of a solid or liquid bolus into the stomach. In the short term most of the current therapies are effective. However, achalasia remains a chronic disease with potential recurrence after successful primary treatment, and patients often require multiple interventions throughout their lives. A large population study, based on administrative health data in Ontario, Canada, has shown that in a 5-year period 20% of patients treated with laparoscopic Heller myotomy (LHM) required a pneumatic

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dilation of the cardia, 9% had a redo LHM, and 2% had an esophageal resection [4]. A similar recent population-based cohort study from the United Kingdom showed that nearly 14% of patients treated with LHM required further interventions over a 10 year follow-up period [5].

These figures are indicative of the challenges of managing achalasia patients who have already received a primary "single shot" treatment (myotomy). The recent introduction of peroral endoscopic myotomy (POEM) [6] as a therapeutic option for achalasia has made it even more complex for patients and their caregivers to decide on an optimal treatment strategy when achalasia symptoms recur.

The aim of this chapter is to offer a review of the different options for treating symptomatic recurrence of achalasia based as much as possible on evidence, considering the available literature is limited mostly to retrospective cohort studies with a low to very low GRADE quality. For the purpose of this chapter we have decided to limit our review only to the treatment of recurrences after the two most invasive, single-shot therapies: LHM and POEM.

Search Strategy

A comprehensive search in English was carried out using the Medline and EMBASE databases to identify literature commenting on the management of symptom recurrence in achalasia. Search terms used included 'achalasia', 'refractory achalasia', 'achalasia treatment failure', 'laparoscopic Heller myotomy', 'per-oral endoscopic myotomy', 'achalasia treatment reintervention', and 'achalasia recurrence' (Table 40.1). The literature review included all articles published between January 2000 and June 2019 and was limited to human subjects. Articles that did not report data on follow-up or that reported incomplete data or considered the outcome of different types of retreatment together were excluded.

In total, 36 cohort studies, 3 systematic reviews, 2 review articles and 1 guideline were included in the review. The GRADE system was used to analyze the literature. The Newcastle-Ottawa scale was used to assess cohort studies. The Newcastle-Ottawa Scale (NOS) is a risk of bias assessment tool for observational studies that is recommended by the Cochrane Collaboration Group [7]. NOS evaluates three main parameters: Selection (of the exposed and non-exposed cohort), comparability, and outcome. A study can be given a maximum of one star for each numbered item within the selection and outcome categories and a maximum of two stars for comparability. The studies are considered good quality if they have 3 or 4 stars in a

Table 40.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with achalasia	Laparoscopic Heller myotomy Peroral endoscopic myotomy Pneumatic dilation	Previous laparoscopic Heller myotomy Previous POEM	Improvement of symptoms/ quality of life/therapeutic success Complications of interventions Recurrence of symptoms

selection domain, 1 or 2 stars in a comparability domain, and 2 or 3 stars in an outcome/exposure domain; the studies are ranked fair quality if they have 2 stars in a selection domain, 1 or 2 stars in a comparability domain and 2 or 3 stars in an outcome/exposure domain; they are ranked poor quality if they have 0 or 1 star in a selection domain OR 0-1 stars in a comparability domain OR 0 or 1 stars in an outcome/exposure domain

Results

Definition of Failure and Patient Evaluation

Currently there is no unequivocal definition for "failure" after primary treatment of achalasia. A comprehensive definition of recurrence suggested by the International Society for Diseases of the Esophagus (ISDE) Achalasia Guidelines is: "the development of symptoms compatible with achalasia after an initial improvement resulting from an endoscopic or surgical treatment" [1].

The six randomized controlled trials (RCTs) comparing pneumatic dilation to LHM have used different criteria to measure the outcome, spanning from a vague "successful symptomatic relief" to the Eckardt score [8], the Watson dysphagia score [9], the Hellemans and Vantrappen criteria [10], the DeMeester score [11], the achalasia severity questionnaire, and the generic Short Form 36 Generic Quality of Life Questionnaire [12]. This lack of definition and heterogeneity in symptomatic assessment makes it difficult to compare patients from different studies. The Eckardt score, which grades four items (dysphagia, regurgitation, chest-pain and weight loss) from 0 to 4, is probably the most used due to its simplicity. Most of the non-RCT cohort studies report the outcome of treatment using it, with a post-operative score >3 considered a failure. Some authors have used a less strict definition for failure by setting the threshold at 4 [13]. The Eckardt score, however, has not been validated as a measure to assess the recurrence of achalasia.

Persistence or recurrence of symptoms after myotomy performed either endoscopically (POEM) or laparoscopically (LHM) may have different etiologies: an insufficient myotomy (leaving uncut muscle fibers, especially on the gastric side or upward in the esophageal body in case of type III spastic achalasia), as well as scarring across the myotomy, a fundoplication that is too tight or incorrect, gastroesophageal reflux disease (GERD), peptic stricture, or esophageal cancer.

Very few articles consider persistence of symptoms (i.e. patients whose symptoms never sufficiently improve or symptoms that recur within 6 months from the primary treatment) separately from recurrence (i.e. patient who had recurrence of symptom after a long-lasting improvement) [14–17], and this makes it difficult to differentiate between these two clearly different clinical situations. Recurrent symptoms may be more etiologically complex and difficult to interpret than symptoms in treatment naive achalasia patients. Acid reflux may play a relevant role in treated patients, as reflux may be perceived differently by patients after myotomy [18, 19] and recurrent achalasia may be difficult to differentiate from a peptic stricture.

A correct diagnosis of recurrent achalasia is paramount for achieving successful further treatment. A careful history of dominant patient symptoms and previous treatment(s) should be taken and, if possible, any video footage of the previous intervention should be reviewed. Objective testing by means of high-resolution esophageal manometry, barium swallow, 24-h pH monitoring and impedance, and upper gastro-intestinal endoscopy should be performed and compared with those test results from prior to the first intervention [20–23].

In cases of long-standing disease and late recurrence in patients with a decompensated and tortuous esophagus, endoscopy should be performed after cleaning the esophageal lumen of food debris to visualize the mucosa correctly, and multiple biopsies should be taken of any identifiable lesions (i.e. Barrett segments or nodules) or randomly along the lumen to exclude underlying malignancy [24]. Special staining for p53 expression in the esophageal biopsies may help in detecting dysplastic areas [25] and therefore indicate the need for a more radical treatment (esophagectomy). In such patients, a CT scan of the abdomen and of chest and full staging work-up is also indicated.

Symptom persistence or recurrence is not necessarily related to failure of achalasia treatment. This is particularly relevant for chest-pain (that may be extremely troublesome for the patient), but it is not always related to a difficult transit through the cardia or to acidic reflux.

Management of Recurrent Symptoms After Laparoscopic Heller Myotomy

Three options may be offered to patients after failure of LHM, namely graded pneumatic dilations, re-do laparoscopic Heller myotomy, or POEM.

Pneumatic Dilation

Table 40.2 reports the outcomes of PD after LHM in six retrospective studies [14, 26–31]. Of interest is the absence in all the studies of any recorded perforation due to the pneumatic dilations, suggesting that PD may be less risky in patients after myotomy than in naïve achalasia patients. The success rate ranges between 50% and 79% at a follow-up interval of 12 months to 12 years, however most patients required more than 1 dilation (range 1.5–2).

Re-do Laparoscopic Heller Myotomy

Table 40.3 reports the outcomes of re-do LHM [17, 22, 32–34]. The success rate is slightly better than for PD, ranging from 64% to 92%, although the median follow-up reported in this group of patients is shorter than for PD (range 11 months to 63 months). The rates of conversion, esophageal mucosal tear, and postoperative complications are much higher than in primary LHM, indicating that re-do LHM is a technically more complex operation. In 18 patients the operation was limited to take down of the previous fundoplication, confirming that a misplaced fundoplication or a fundoplication that was too tight was the cause of relapsing of dysphagia.

Table 40.2 Results of pneumatic dilation after failed Heller myotomy

Author year NOS scale	Number of patients	Time since operation	Pneumatic dilator size (mm)	Number of dilations	Follow-up interval	Remission of symptoms
Zaninotto [14] 2002	9 (LHM)	Between 1 month and 1 year	30/35/40 according to symptomatic response	2 (median)	14.5 months	77%
Guardino [26] 2004 ★★	10 (HM)	60 months median	35/40	2	Not reported	50%
Kumbhari [27] 2013 ★, ★★	27 (HM) range 1–45 years	7 months (median)	30/35/40 2–4 weeks interval, according to symptomatic response	Not reported.	12 months 30 months (median)	89% 66%*
Legros [28] 2014 ★, ★★	18 (HM)	18 months (median; range 0–42)	30/35/40 8 months interval according to symptomatic response	1.5 (median; range 1–2.25)	33 months (median)	77.8%**
Amani [29] 2015 ★★, ★★★	30 (6 LHM, 24 thoracotomy Heller)	6.7 ± 7.1 years	30 (30 pts) 35 (17 pts) 40 (4 pts)	1.7 (mean)	11.8 ± 6.3 years	70%
Saleh [30] 2016 ★, ★★	21 (LHM)	29 months (range 3–108)	30 (8 pts) 30/35 (4 pts) 30/35/40 (9 pts)	1.8 (mean)	6.5 years (1 PD) 11 years (2 PDs)	57%***
Stewart [31] 2018 ★★, ★★★	14 (LHM)	28 months (range 17.3–43.2)	30 (14 pts) 30/35 (7 pts) 30/35/40 (2 pts)	1.6 (mean)	21.7 months	79%

HM Heller myotomy, *LHM* laparoscopic Heller myotomy, *Pts* patients
*Success rate at 30 months
**44% of patients needed further PDs during the follow-up interval
***All 9 patients who were treated with dilations up to 40 mm failed. No differences of the success rate in the three types of achalasia: type 1 54%; type 2 67%; type III 50%

POEM

Table 40.4 reports the outcomes of POEM after LHM failure [21, 35–39]. POEM has a shorter history as a revisional procedure for LHM failures, with the first reports originating in 2013. The findings seem very encouraging, with good results rate ranging between 90% and 100%, however this very optimistic report is based on only an handful of patients with a very short follow-up of 5 months. Most of the procedures were completed endoscopically. The rate of mucosal tears was not

Table 40.3 Results of Re-do Laparoscopic Heller Myotomy after failed Myotomy

Author/year NOS scale	Number of patients	Time from first myotomy (range)	Complications, conversions, mucosal tears	Follow-up median (range)	Good outcome (%)
Rakita [32] 2007 ★★	12	3 years (4 days-25 years)	Conversion: 0 Mucosal tears: 2 (25%)	24.1 months (not reported)	75%
Gockel [22] 2007 ★, ★★	12 (open HM)	15 months (4–156)	Mucosal tears: 2 (16%)	38 months (2–206)	92%
Loviscek [23] 2013 ★, ★★	43 (3 take down of fundoplication only, 40 LHM)	10.7 years (not reported)	Conversion: 0 Mucosal tears: 2 (5%)	63 months (12–157)	75%*
Wood [33] 2015 ★★	38 LHM	Not reported	Conversion: 3 30-day mortality 8%***	11 months (not reported)	83%
Veenstra [34] 2016 ★★	58 LHM (15 patients only take down of the fundo)	32 months (1–480)	Conversion: 2 Mucosal tears: 11 (19%) Complication grade C-D > 3: 5 (8%)	34 months (6–203)	64%**
Fumagalli [17] 2016 ★, ★★	9 HM	10.4 months (0.7-33.2)	Conversion 1 Mucosal tears: 3 (30%) Complication: 1 gastroparesis	17.5 months (not reported)	77.7%

LHM laparoscopic Heller myotomy, *HM* Heller myotomy
*19 patients no long term follow-up
**16 patients no long-term follow-up
***Causes of death unrelated to re-do LHM

different from that achieved treating naïve achalasia patients, and all were repaired during the procedure. Only two serious adverse events (mediastinitis) were observed. No differences were found in outcomes among the different achalasia subtypes.

Management of Recurrent Symptoms After POEM

There are a few studies reporting the modality of treatment of failures after POEM. In the first study by Tyberg et al. [38] 46 patients were included. Clinical success was achieved in 41 (85%) with a 17% incidence of adverse events (mainly bleeding during the re-do POEM). The other study is from a high volume center with 15 POEM failures in over 1454 POEM patients [15]. The success rate of re-do POEM was 100% at 6 month follow-up, though 20% had complications during POEM (mucosal tears, immediately repaired) and 40% of patients experienced post-operative adverse effects such as pneumomediastinum [3], pleural effusion [4],

Table 40.4 Results of POEM after failed Heller Myotomy

Author/year O-N scale	Number of patients	Time from first myotomy (range)	Complications/ adverse events	Follow-up median (range)	Good outcome (%)
Onimaru [35] 2013 ★★	10 (2 thoracotomy.)	10 years (0.7–45)	None	3 months	90%*
Vigneswaran [21] 2014 ★★	5 (LHM)	Not reported	None	5 months	100%
Kristensen [36] 2017 ★★	14	Not reported	Not reported	14 pts 3 months 7 pts 24 months	ES** 4 (1–11) ES** 5 (3–10)
Ngamruengphong [37] 2017 ★★★	90	Not reported	8% (in 2 pts POEM was not completed)	8.5 months	81%
Tyberg [38] 2018 ★★★	51 (48 LHM 3 OHM 45 HM + Dor) Type I 13 pts Type II 29 pts Type III 6 pts 3 pts other dysmotility disorder	113.5 months (2–672)	6 mucosal tears 2 mediastinitis	24.4 months (12–52)	94%
Zhang [39] 2018 ★★★	46 Type I 30 pts Type II 5 pts Type III 6 pts Unknown 5	6 years (0.5–45)	13 mucosal tears	28 months (3–46)	94%

LHM laparoscopic Heller myotomy, *Pts* patients

*One patient had an Eckardt score >3 after rescue POEM, though improved compared to 9 pre-operatively

**ES: Eckardt Score No data on single patients failure are given

focal atelectasis [3], pneumonia [1] and minor subcutaneous emphysema [1]. All but one was without clinical consequences.

Conclusions and Recommendations

Patients with recurrent symptoms after endoscopic or surgical myotomy should receive an extensive evaluation with barium swallow, upper endoscopy, high resolution manometry, and 24-h pH monitoring [1, 16, 40]. Recurrent or persistent symptoms after myotomy may have multiple etiologies that span from an erroneous initial diagnosis of achalasia, technical errors in performing the myotomy or in creating the fundoplication, reflux disease and induced peptic stricture, scar healing of the myotomy, megaesophagus with a siphon shaped cardia passage, and cancer. Correct identification of the etiology provides the foundation for the decision of

whether a re-intervention is indicated and which type of intervention should be implemented to maximize the probability of achieving good results.

Given the relative rarity of esophageal achalasia, and since only a minority of patients require re-treatment, it is not surprising that there are no RCTs dealing with the management of recurrences. Management of patients with recurrent symptoms after endoscopic or surgical myotomy should start with the least invasive procedure, i.e. pneumatic dilation. The evidence is based on cohort studies with low numbers of patients, most of them retrospective, and therefore this leads to a very low quality of evidence and weak recommendations. A criterion for the choice of the re-treatment is to start with a series of pneumatic dilations because this is less invasive than the other options. No major complications or perforations using PD after myotomy are reported. This represents a substantial difference from dilation in naïve achalasia patients, in whom the perforation rate is reported as 2–3.5% [41]. Between 1 and 2 PDs are necessary to achieve a clinical success in 50–77% of patients after LHM. There is limited data on the use of PD after POEM and it is possible that the success in this case is lower than after LHM. Patients should be informed that the probability of being cured with PD after failed myotomy is not high, but the risks are minimal.

If graded PD fails as first line re-do therapy, patients with recurrent symptoms after surgical myotomy should be offered POEM or re-do LHM. Re-do LHM has the advantage of addressing some of the specific causes of failure such as a twisted fundoplication or one that is too tight. In studies by Loviscek [23] and Veenstra [34] the re-intervention consisted only of taking down the fundoplication in 7% and 26%, respectively. It is unclear what the results of using POEM in these pathologies would be, but it is unlikely to be effective. Of note, the literature consistently confirms that re-do LHM is a difficult operation. The number of mucosal tears is between 5% and 30% with 4 studies reporting mucosal tears in 25% [31], 16% [22], 8% [33] and 30% [17] of the patients, respectively. Considering that in naïve achalasia patients the number of perforation is 2.5% [42] and 0.8% [43] in two large single institutions studies and 6.9% [44] in a systematic review, we can assume that a 5 times higher rate of mucosal tears is a good proxy for the difficulty of the operation. Major complications are not uncommon either: one study reported a morbidity grade of C-D in 8% of patients and another study the 30-day mortality was 8%, although the causes of death were not related to the re-interventions.

POEM is a very attractive option in patients with failure after LHM for several reasons. First, POEM uses a different approach and avoids the adhesions around the cardia and between the lower face of the left liver lobe and the exposed mucosa of the anterior surface of the esophagus, especially if the myotomy is not protected by an anterior fundoplication. POEM may be performed through a complete posterior submucosal tunnel or with a tunnel that enters at 2 o'clock, as for POEM in naïve patients, but rotates posteriorly to avoid the scar of the previous myotomy [35]. Second, POEM may be easily extended upward in the thoracic esophagus, and directly addresses the spastic muscle of type III achalasia [39]. Third, if an antireflux partial fundoplication is already present, this may prevent the occurrence of iatrogenic post-POEM gastroesophageal reflux. The results of POEM after LHM

are very good, with a range of success between 100% [21] and 81% [37], although the studies reporting better results have a short follow-up and a small number of patients. However, POEM after LHM seems to have a higher risk than POEM in naïve patients, with at least one study reporting some severe complications [38].

We have no specific recommendations for management of recurrent symptoms after POEM because the data are insufficient regarding such patients. In the few available relevant studies, all retrospective in nature and with few treated patients, redo POEM seems to be the best option.

Any therapeutic option for recurrent achalasia after myotomy offers a lower probability of success than primary treatment and—apart from pneumatic dilation—is more complex and has a greater burden of complications. A good strategy is to start with the least invasive option and progress to more invasive options. POEM is a very promising treatment, but expectations regarding POEM as "THE re-do treatment" need to be substantiated by larger studies and longer follow-up. In any case, it should be remembered that any conservative treatment should be used before esophagectomy, which should be considered the final option.

Recommendations

- Management of patients with recurrent symptoms after endoscopic or surgical myotomy should start with the least invasive procedure, i.e. pneumatic dilation (weak recommendation, quality of evidence very low).
- If graded pneumatic dilation fails as first line re-do therapy, patients with recurrent symptoms after surgical myotomy should be offered POEM or re-do LHM (weak recommendation, quality of evidence very low).
- We make no specific recommendation regarding management of recurrent symptoms after POEM.

A Personal View of the Data

The first—and probably most important—question that we should ask ourselves when an achalasia patient complains of recurrent symptoms is whether he/she has a real recurrence requiring a re-do treatment. Symptoms are not always reliable in such patients: they may change during time and are not easily interpreted. The picture of a real-life achalasia patient post-operatively, with regard to their symptoms, is not always white (no recurrence) or black (failure); instead, there is a palette of grays in between that makes it difficult to make a decision. Barium swallow, better if timed (TBS), is the first test we perform. It allows an assessment of transit and permits comparison images with those obtained pre-operatively and/or with those taken earlier in the follow-up. If the TBS confirms the recurrence, the patient should undergo a full evaluation, including 24-h pH-monitoring, especially if the patient

complains of chest pain. If the patient was referred by another centre/hospital or only had a water-perfused stationary manometry pre-operatively, it is considered mandatory to perform high resolution manometry. This will help establish if the patient has a prior unrecognized type III achalasia. In this case, PD most likely will result in unsuccessful treatment and should be avoided, whereas POEM is indicated. In all other cases (except for the few patients in whom esophageal resection is indicated) PD is our first choice. In our opinion, when PDs fail, a relevant factor in deciding between a re-do LHM or POEM is the presence and the type of fundoplication added to the myotomy. If no fundoplication was added or the patient received a posterior fundoplication (Toupet), the adhesion between the exposed esophageal mucosa and the lower part of the left liver lobe may make the dissection of the distal esophagus very difficult and increase the risk of perforations. In these cases, POEM is probably less risky and equally effective. For all patients with an anterior fundoplication (Dor) protecting the myotomy, our personal preference is a re-do LHM performed on the right border of the esophagus.

References

1. Zaninotto G, Bennett C, Boeckxsatens G, et al. The 2018 ISDE achalasia guidelines. Dis Esophagus. 2018;31:1–29.
2. Gennaro N, Portale G, Gallo C, et al. Esophageal achalasia in the Veneto region: epidemiology and treatment. Epidemiology and treatment of achalasia. J Gastrointest Surg. 2011;15(3):423–8.
3. Duffield JA, Hamer PW, Heddle R, Holloway RH, Myers JC, Thompson SK. Incidence of achalasia in South Australia based on esophageal manometry findings. Clin Gastroenterol Hepatol. 2017;15(3):360–5.
4. Lopushinsky SR, Urbach DR. Pneumatic dilatation and surgical myotomy for achalasia. JAMA. 2006;296(18):2227–33.
5. Markar SR, Mackenzie H, Askari A, Faiz O, Hoare J, Zaninotto G, Hanna GB. Population-based cohort study of surgical myotomy and pneumatic dilatation as primary interventions for oesophageal achalasia. Br J Surg. 2018;105:1028–35.
6. Inoue H, Minami H, Kobayashi Y, et al. Peroral endoscopic myotomy (POEM) for esophageal achalasia. Endoscopy. 2010;42(4):265–71.
7. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 11 Feb 2020.
8. Boeckxstaens GE, Annese V, des Varannes SB, et al. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. N Engl J Med. 2011;364(19):1807–16.
9. Kostic S, Kjellin A, Ruth M, et al. Pneumatic dilatation or laparoscopic cardiomyotomy in the management of newly diagnosed idiopathic achalasia. Results of a randomized controlled trial. World J Surg. 2007;31(3):470–8.
10. Borges AA, Lemme EM, Abrahao LJ Jr, et al. Pneumatic dilation versus laparoscopic Heller myotomy for the treatment of achalasia: variables related to a good response. Dis Esophagus. 2014;27(1):18–23.
11. Hamdy E, El Nakeeb A, El Hanfy E, et al. Comparative study between laparoscopic Heller myotomy versus pneumatic dilatation for treatment of early achalasia: a prospective randomized study. J Laparoendosc Adv Surg Tech A. 2015;25(6):460–4.
12. Chrystoja CC, Darling GE, Diamant NE, et al. Achalasia-Specific Quality of life after pneumatic dilation or laparoscopic Heller myotomy with partial fundoplication: a multicenter, randomized clinical trial. Am J Gastroenterol. 2016;111(11):1536–45.

13. Ling TS, Guo HM, Yang T, Peng CY, Zou XP, Shi RH. Effectiveness of peroral endoscopic myotomy in the treatment of achalasia: a pilot trial in Chinese Han population with a minimum of one-year follow-up. J Dig Dis. 2014;15(7):352–8.
14. Zaninotto G, Costantini M, Portale G, et al. Etiology, diagnosis, and treatment of failures after laparoscopic Heller myotomy for achalasia. Ann Surg. 2002;235(2):186–92.
15. Li QL, Yao LQ, Xu XY, et al. Repeat peroral endoscopic myotomy: a salvage option for persistent/recurrent symptoms. Endoscopy. 2016;48(2):134–40.
16. Patti MG, Allaix ME. Recurrent symptoms after Heller myotomy for achalasia: evaluation and treatment. World J Surg. 2015;39(7):1625–30.
17. Fumagalli U, Rosati R, De Pascale S, et al. Repeated surgical or endoscopic myotomy for recurrent dysphagia in patients after previous myotomy for achalasia. J Gastrointest Surg. 2016;20(3):494–9.
18. Jones EL, Meara MP, Schwartz JS, Hazey JW, Perry KA. Gastroesophageal reflux symptoms do not correlate with objective pH testing after peroral endoscopic myotomy. Surg Endosc. 2016;30(3):947–52.
19. Teitelbaum EN, Dunst CM, Reavis KM, Sharata AM, Ward MA, DeMeester SR, Swanström LL. Clinical outcomes five years after POEM for treatment of primary esophageal motility disorders. Surg Endosc. 2018;32:421–7.
20. Duffy PE, Awad ZT, Filipi CJ. The laparoscopic reoperation of failed Heller myotomy. Surg Endosc. 2003;17(7):1046–9.
21. Vigneswaran Y, Yetasook AK, Zhao JC, Denham W, Linn JG, Ujiki MB. Peroral endoscopic myotomy (POEM): feasible as reoperation following Heller myotomy. J Gastrointest Surg. 2014;18(6):1071–6.
22. Gockel I, Junginger T, Eckardt VF. Persistent and recurrent achalasia after Heller myotomy: analysis of different patterns and long-term results of reoperation. Arch Surg. 2007;142(11):1093–7.
23. Loviscek MF, Wright AS, Hinojosa MW, et al. Recurrent dysphagia after Heller myotomy: is esophagectomy always the answer? J Am Coll Surg. 2013;216(4):736–44.
24. Leeuwenburgh I, Scholten P, Alderliesten J, et al. Long-term esophageal cancer risk in patients with primary achalasia: a prospective study. Am J Gastroenterol. 2010;105(10):2144–9.
25. Leeuwenburgh I, Gerrits MM, Capello A, et al. Expression of p53 as predictor for the development of esophageal cancer in achalasia patients. Dis Esophagus. 2010;23(6):506–11.
26. Guardino JM, Vela MF, Connor JT, Richter JE. Pneumatic dilation for the treatment of achalasia in untreated patients and patients with failed Heller myotomy. J Clin Gastroenterol. 2004;38(10):855–60.
27. Kumbhari V, Behary J, Szczesniak M, Zhang T, Cook IJ. Efficacy and safety of pneumatic dilatation for achalasia in the treatment of post-myotomy symptom relapse. Am J Gastroenterol. 2013;108(7):1076–81.
28. Legros L, Ropert A, Brochard C, et al. Long-term results of pneumatic dilatation for relapsing symptoms of achalasia after Heller myotomy. Neurogastroenterol Motil. 2014;26(9):1248–55.
29. Amani MFN, Shirami S, Malekzadeh R, Mikaeli J. Assessment of pneumatic balloon dilation in patients with symptomatic relapse after failed Heller myotomy. Middle East J Dig Dis. 2015;8:57–62.
30. Saleh CM, Ponds FA, Schijven MP, Smout AJ, Bredenoord AJ. Efficacy of pneumodilation in achalasia after failed Heller myotomy. Neurogastroenterol Motil. 2016;28:1741–6.
31. Stewart RD, Hawel J, French D, Bethune D, Ellsmere J. Pneumatic balloon dilation for palliation of recurrent symptoms of achalasia after esophagomyotomy. Surg Endosc. 2018;32:4017–21.
32. Rakita S, Villadolid D, Kalipersad C, Thometz D, Rosemurgy A. Outcomes promote reoperative Heller myotomy for symptoms of achalasia. Surg Endosc. 2007;21(10):1709–14.
33. Wood TW, Ross SB, Ryan CE, et al. Reoperative Heller myotomy: more pain, less gain. Am Surg. 2015;81(6):637–45.
34. Veenstra BR, Goldberg RF, Bowers SP, Thomas M, Hinder RA, Smith CD. Revisional surgery after failed esophagogastric myotomy for achalasia: successful esophageal preservation. Surg Endosc. 2016;30(5):1754–61.

35. Onimaru M, Inoue H, Ikeda H, et al. Peroral endoscopic myotomy is a viable option for failed surgical esophagocardiomyotomy instead of redo surgical Heller myotomy: a single center prospective study. J Am Coll Surg. 2013;217(4):598–605.
36. Kristensen HO, Kirkegard J, Kjaer DW, Mortensen FV, Kunda R, Bjerregaard NC. Long-term outcome of peroral endoscopic myotomy for esophageal achalasia in patients with previous Heller myotomy. Surg Endosc. 2017;31(6):2596–601.
37. Ngamruengphong S, Inoue H, Ujiki MB, Patel LY, Bapaye A, Desai PN, et al. Efficacy and safety of peroral endoscopic myotomy for treatment of achalasia after failed Heller myotomy. Clin Gastroenterol Hepatol. 2017;15(10):1531–1537.e3.
38. Tyberg A, Seewald S, Sharaiha RZ, Martinez G, Desai PA, Kumta NA, et al. A multicenter international registry of redo per-oral endoscopic myotomy (POEM) after failed POEM. Gastrointest Endosc. 2018;85:1208–11.
39. Zhang X, Modayil RJ, Friedel D, Gurram KC, Brathwaite CE, Taylor SI, et al. Per-oral endoscopic myotomy in patients with or without prior Heller's myotomy: comparing long-term outcomes in a large U.S. single-center cohort (with videos). Gastrointest Endosc. 2018;87(4):972–85.
40. Petersen RP, Pellegrini CA. Revisional surgery after Heller myotomy for esophageal achalasia. Surg Laparosc Endosc Percutan Tech. 2010;20(5):321–5.
41. Boeckxstaens GE, Zaninotto G, Richter JE. Achalasia. Lancet. 2014;383(9911):83–93.
42. Costantini M, Salvador R, Capovilla G, Vallese L, Costantini A, Nicoletti L, et al. A thousand and one laparoscopic Heller myotomies for esophageal achalasia: a 25-year experience at a single tertiary center. J Gastrointest Surg. 2019;23:23–35.
43. Finley CJ, Kondra J, Clifton J, Yee J, Finley R. Factors associated with postoperative symptoms after laparoscopic Heller myotomy. Ann Thorac Surg. 2010;89(2):392–6.
44. Campos GM, Vittinghoff E, Rabl C, et al. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. Ann Surg. 2009;249(1):45–57.

41 Laparoscopy or Thoracotomy for Symptomatic Recurrent Paraesophageal Hernia

Miroslav P. Peev and Mark K. Ferguson

Introduction

Since the year 2000 the number of diagnosed and surgically treated paraesophageal hernias has substantially increased. Regardless of the technique used (transthoracic or transabdominal) the number of recurrences has grown so that surgeons started facing a new technically challenging problem—a symptomatic recurrent paraesophageal hernia. The reported rates of recurrence after primary laparoscopic and open repair of paraesophageal hernias range from 2% to 59% [1]. In comparison, when the classic transthoracic approach was used for initial repair, the rate of symptomatic recurrence was approximately 7% in a large case series [2].

The most commonly reported symptoms associated with recurrence include heartburn, regurgitation, dysphagia and/or pain [3]. Despite the large number of reported anatomic recurrences, only 3–6% of those patients will require an operative intervention [4, 5]. The decision to recommend reoperation should be individualized and highly scrutinized by both the patient and the surgeon, especially considering the complexity of the procedure.

The purpose of this chapter is to review the outcomes of thoracotomy versus laparoscopy for management of recurrent symptomatic paraesophageal hiatal hernias.

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Table 41.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with recurrent paraesophageal hernia	Laparoscopic reoperation	Thoracotomy for reoperation	Complications Symptom relief Radiographic success recurrence

Search Strategy

The literature search was performed using PubMed, Science Direct, MEDLINE, Web of Science and Directory of Open Access Journals. We used combinations of the following terms: "paraesophageal hernia", "hiatal hernia", "recurrent", "revisional, "reoperative", "redo repair", "failed repair", "thoracotomy", "laparoscopy", "transthoracic" and "operative repair" (Table 41.1). Only papers published after 2005 were included, and there were no limitations on language. Studies focused on gastroesophageal reflux disease (GERD) and anti-reflux redo surgery were excluded from this review. In some of the selected articles there was a wide variety of data so that we extracted only the data that were relevant for this chapter.

Results

In a retrospective case series that compared redo paraesophageal hiatal hernia repair with primary repair, Kao reported two cohorts: 305 primary repairs as well as 97 revisions [6]. All patients in the revision group with exception of one (Belsey IV) underwent laparoscopic repair. The mean time from the initial repair to the reported symptom recurrence was 48.8 months. Redo paraesophageal hiatal hernia repair had a longer mean operative time (256.4 vs. 190.3 min; $P < 0.0001$) and a higher rate of conversion to open when compared to primary repair (10.3% vs. 0.67%; $P < 0.0001$). The rate of complications in the laparoscopic cohort was as high as 44.7%, with a 30-day readmission rate of 11.7% and a radiographic hernia recurrence evident in 31%. An additional reoperation for symptomatic hernia recurrence was required in 3.1% of the patients (Table 41.2).

Juhasz reported a retrospectively collected series of patients who underwent revisional GERD surgery [7]. From 220 subjects in the study who underwent redo procedures for reflux, only 20% had large recurrent hiatus hernias that were operatively addressed. The symptom free period after the initial operation was 44 months. The choice of approach was individualized based on patient presentation and surgeon preference. In the early period of the study the majority of the reoperative procedures were performed via thoracotomy. However, with increasing experience and utilization of Roux en Y gastric reconstruction as ultimate antireflux surgery, the rate of transabdominal and laparoscopic procedures increased. The 15 reported postoperative complications were not stratified based on the approach used. Additional revision was performed in 3 (6.8%) of the patients from the entire cohort.

Table 41.2 Selected studies investigating thoracic and laparoscopic repair of recurrent symptomatic paraesophageal hernia

			Thoracotomy		Laparoscopy							
Study	Pts	Years	n	Postop complications %	n	Conversion to open %	Postop complications %	Radiographic recurrence %	Symptomatic recurrence %	Mortality %	Grade of evidence	Type of study
Kao [6]	97	2008–2017	1	NR	96	10.3	44.7	31	3.1	0	Low	Retrospective
Juhaszl [7]	44	2003–2009	8	25	23	NR	NR	NR	6.8	0	Low	Retrospective
Brown [8]	24	2011–2016	NA	NA	24	33	20.8	NR	NR	0	Low	Retrospective
Zahiri [10]	46	2004–2016	NA	NA	46	NR	10.9	2.2	2.2	0	Low	Retrospective
Wennergren [9]	34	2009–2013	NA	NA	34	NR	24	20.5	12	0	Low	Retrospective
Haider [11]	52	1993–2004	28	37	19	NR	37	9.6	9.6	1.9	Low	Retrospective

Pts patients, *NR* not reported, *NA* not applicable

Brown defined radiographic recurrence as >2 cm of vertical extension of gastric mucosa above the level of the diaphragm [8]. The authors matched 24 patients who underwent PEH revision with 48 patients who underwent primary repair and compared various postoperative outcomes and quality of life. All redo paraesophageal hiatal hernia repairs were approached laparoscopically. The revision cohort had conversion rate of 33% and required longer operative time (311.5 vs. 249.9 min; P = 0.012) with a higher blood loss (129.4 vs. 49.5 mL; P = 0.038). Postoperative complications were observed in 5 (20.8%) of the patients and there was no operative mortality.

Two other recent case series that compared primary versus revision operations for PEH included only patients approached using transabdominal/laparoscopic approaches [9, 10]. Zahiri included 271 patients undergoing an initial operation and 46 revisions [10]. Similar to previous reports, patients undergoing a recurrent operation required longer operative time (139.1 vs. 112.2 min; $p < 0.001$) as well as greater need for concomitant procedures such as Collis gastroplasty (87.0% vs. 30.2%; $p < 0.001$). Postoperative complications including wound related complications were observed in 10.9% of patients. Two patients (4.4%) required readmission within 30 days of discharge. The patients in the initial repair group reported greater benefit from surgery than the redo group ($p = 0.032$). The majority of patents in the initial (64%) and redo (57%) groups completely discontinued their anti-reflux medications after the procedure.

Wennergren [9] included 34 laparoscopic PEH revisions in their comparative study [9]. Operative times (203 vs. 163 min; $p < 0.001$) and frequency of Collis gastroplasty (24% vs. 1%; $p < 0.0001$) were higher in the revision group. The reported mean hospital LOS for recurrent PEHs was 2 days (range 1–3 days) with 8 (24%) patients requiring readmission. There were total of 7 (20.5%) radiographic and 3 (12%) symptomatic recurrences 4 months after the initial PEH revision.

A retrospective series combined patients who underwent revisional PEH repair through the chest or the abdomen [11]. The authors included 52 patients for the period 1993–2004. More than half of the patients underwent thoracotomy (53.8%), 19 patients (35%) were initially approached laparoscopically, and the rest of the patients in the cohort underwent Nissen or Toupet fundoplication via laparotomy. The preoperatively reported chest pain resolved in 83% of the patients undergoing laparoscopy and in 93% of the patients undergoing thoracotomy. Perioperative complications were reported in 37%, however the authors did not stratify the complications based on the operative approach used. One mortality occurred secondary to herniating of the stomach into the chest with subsequent development of respiratory failure. Five patients (9.6%) developed symptomatic recurrence and three of them were operated again through the chest and the remaining two underwent laparoscopy.

Conclusions and Recommendations

There are no randomized controlled trials that compare thoracotomy to laparoscopy for repair of recurrent symptomatic paraesophageal hernia. The studies in this review are retrospective, have low grade of evidence, and include small numbers of

patients. The available evidence for repair of recurrent PEH is scarce. The results of these two approaches are not distinctly different. We make a weak recommendation for a laparoscopic approach over thoracotomy due to the anticipated higher morbidity of the latter.

Recommendation

- We recommend a laparoscopic approach for initial repair of symptomatic recurrent paraesophageal hiatal hernias (evidence quality low; weak recommendation)

A Personal View of the Data

We think that the decision to operate through the chest or the abdomen, open or minimally invasively should be individualized on a case by case basis. However, what we strongly recommend is a careful assessment of the history and presentation of the patient before and after the initial operation, a review of the details of the initial operation, and, if possible, identify what led to the failure. Based on that information, we believe surgeons should develop an individualized surgical plan and discuss with the patient the benefits, risks and potential outcomes of a redo PEH repair. Most patients we see have already undergone an attempted or failed laparoscopic or open laparotomy approach for redo repair, and thus most of our operations are performed using a transthoracic approach. This approach provides the most successful means for ensuring optimal mobilization of the esophagus, and includes a Belsey fundoplication, which is an excellent way of anchoring the stomach and fundoplication wrap within the abdomen.

References

1. Morrow EH, Oelschlager BK. Laparoscopic paraesophageal hernia repair. Surg Laparosc Endosc Percutan Tech. 2013;23(5):446–8.
2. Skinner DB, Belsey RH. Surgical management of esophageal reflux and hiatus hernia. Long-term results with 1,030 patients. J Thorac Cardiovasc Surg. 1967;53(1):33–54.
3. Lidor AO, Steele KE, Stem M, Fleming RM, Schweitzer MA, Marohn MR. Long-term quality of life and risk factors for recurrence after laparoscopic repair of paraesophageal hernia. JAMA Surg. 2015;150(5):424–31.
4. Anvari M, Allen C. Five-year comprehensive outcomes evaluation in 181 patients after laparoscopic Nissen fundoplication. J Am Coll Surg. 2003;196(1):51–8.
5. Byrne JP, Smithers BM, Nathanson LK, Martin I, Ong HS, Gotley DC. Symptomatic and functional outcome after laparoscopic reoperation for failed antireflux surgery. Br J Surg. 2005;92(8):996–1001.
6. Kao AM, Otero J, Schlosser KA, Marx JE, Prasad T, Colavita PD, et al. One more time: redo paraesophageal hernia repair results in safe, durable outcomes compared with primary repairs. Am Surg. 2018;84(7):1138–45.

7. Juhasz A, Sundaram A, Hoshino M, Lee TH, Mittal SK. Outcomes of surgical management of symptomatic large recurrent hiatus hernia. Surg Endosc. 2012;26(6):1501–8.
8. Brown AM, Nagle R, Pucci MJ, Chojnacki K, Rosato EL, Palazzo F. Perioperative outcomes and quality of life after repair of recurrent hiatal hernia are compromised compared with primary repair. Am Surg. 2019;85(5):556–60.
9. Wennergren J, Levy S, Bower C, Miller M, Borman D, Davenport D, et al. Revisional paraesophageal hernia repair outcomes compare favorably to initial operations. Surg Endosc. 2016;30(9):3854–60.
10. Zahiri HR, Weltz AS, Sibia US, Paranji N, Leydorf SD, Fantry GT, et al. Primary versus redo paraesophageal hiatal hernia repair: a comparative analysis of operative and quality of life outcomes. Surg Endosc. 2017;31(12):5166–74.
11. Haider M, Iqbal A, Salinas V, Karu A, Mittal SK, Filipi CJ. Surgical repair of recurrent hiatal hernia. Hernia. 2006;10(1):13–9.

Part III

Diaphragm

Does Diaphragm Pacing for Bilateral Phrenic Nerve Paralysis Improve Function or Quality of Life?

42

Raymond Onders

Introduction

Bilateral phrenic nerve paralysis leads to bilateral diaphragm paralysis and significant patient symptoms. In compromised patients this may require continuous positive pressure assistance or even tracheostomy and mechanical ventilation (MV). The most common cause of bilateral diaphragm paralysis is cervical spinal cord injury (SCI). In these patients there is no longer a connection between the respiratory control system in the brainstem or volitional control of breathing area in the cerebral cortex with the phrenic motor neurons in the cervical spinal cord. In the cervical SCI population, 50% of patients are discharged on temporary MV. SCI coupled with MV is a catastrophic life changing event that drastically decreases life expectancy along with increasing yearly costs of care by $185,000. For example, a MV dependent 20 year old SCI patient would be expected to live only 10.6 years compared to 34 years for a similarly injured patient not ventilated. The greatest reason for reduced life expectancy is pneumonia [1].

Independent breathing is compromised in SCI patients due to disruption of the signaling pathway, the spinal cord, from the respiratory center in the brain to the diaphragm. In patients with an intact phrenic nerve, the signaling pathway can be bypassed by implanting permanent electrodes to provide direct electrical stimulation to the diaphragm, which is the mechanism of action of diaphragm pacing (DP) (NeuRx DPS, Synapse Biomedical, Oberlin, Ohio). The DP system is implanted via a laparoscopic surgical procedure by placing electrodes into each hemidiaphragm near the phrenic nerve motor point. Each electrode percutaneously exits the body

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and is connected to a four-channel external stimulator. The laparoscopic surgical technique has been well described [2, 3]. In ventilator-dependent SCI patients, DP effectively functions initially as a powered muscle stimulator for treating disuse atrophy and then, once the diaphragm has been sufficiently reconditioned, as a functional electrical stimulator (or breathing pacemaker) to drive respiration and weaning from mechanical ventilation.

Bilateral diaphragm paralysis from SCI is a rare event in the United States with less than 1000 cases annually. Each trauma unit in the US may only see several cases a year, so additional knowledge and skill will be required to change the standard of care for these patients. The DP device is indicated for stable SCI patients with diaphragms that can be stimulated to contract, but who lack control of their diaphragms. If a patient has complete transection of the phrenic nerves or damage to cervical motor neurons, DP would not be indicated unless phrenic nerve reconstruction would to be done, which is addressed in another chapter. In this chapter the present literature on DP results will be reviewed to help overcome the scarcity of experience and improve management of SCI patients with bilateral phrenic nerve paralysis.

Search Strategy

A search of PubMed with the search criteria (diaphragm OR diaphragmatic) AND (pacer OR pacing OR pacemaker) AND ("spinal cord injury" OR SCI) was completed. Studies from 2014 through 2019 were than manually identified from these search parameters, such that the data included subjects with high-level spinal cord injury concordant with the indication for device use. The Kerwin, Onders, and Posluszny reports were identified in this fashion [4–6]. The summary of the Lammertse study was obtained from the authors after the presentation of the abstract at a conference and will be included [7]. A systematic review article by Garara et al. which covered multiple early published studies that consisted of 12 articles from 2006 to 2014 will also be discussed [8]. The initial clinical study data that supported the initial FDA approval will also be presented for historical purposes [9]. The main goal of the intervention of DP is replacement of invasive mechanical ventilation which is summarized in Table 42.1 using the PICO format.

Table 42.1 PICO formatted terms for literature search

Patients	Intervention	Comparison	Outcomes
Spinal cord injured patient with bilateral diaphragm paralysis dependent on mechanical ventilation	Laparoscopic placement of diaphragm pacing electrodes and weaning from mechanical ventilation	Standard of care of chronic tracheostomy mechanical ventilation	Removal from mechanical ventilation, tidal volumes, mortality rate, quality of life

Results

In 2018, Kerwin et al. reported their single center retrospective matched cohort analysis evaluating early use of DP on in-hospital outcomes of patients with acute cervical SCI [4]. The matched cohorts included 40 patients who received DP implants under FDA approved use and 61 matched patients without a DP implant. There were minor demographic differences between the groups in that the DP patients were significantly older (45 ± 16 vs. 39 ± 16 years; p = 0.05) and more likely to be female (28% vs. 11%; p = 0.04). However, there were no differences in the injury severity score or the level of spinal injury. Mean time to implantation was 14 days. Median time to MV liberation after DP implantation was 7 days. Twenty-six DP patients (65%) and 39 patients (64%) in the control group were diagnosed with ventilator-associated pneumonia (VAP) (p = 0.91). The DP patients that developed VAP had significantly fewer vent days as compared to the control patients (24.5 ± 15.2 days vs. 33.2 ± 23.3 days; p = 0.05). Mortality was 15% for the control group compared to 3% for the DP group (p = 0.04). Length of hospital stay was significantly shorter in the DP group: 65 ± 61 vs. 43 ± 24 days for the control and DP groups, respectively (p = 0.03). In this large single institution series of DP implantation for acute cervical SCI, the researchers found that DP implantation was safe and feasible for patients with acute cervical SCI, and that for patients who developed VAP, mean ventilator days were significantly shorter.

Kerwin's group further expanded on the improvement of respiratory mechanics of diaphragm pacing at the Annual meeting of the American Association for the Surgery of Trauma (AAST) in September of 2019 with a presentation and published abstract [10]. They report on 37 patients with DP and 34 matched patients without DP. DP lead to a statistically increase in spontaneous tidal volume compared to no DP (+88 mL vs. −13 mL; 95% CI 46–131 vs. −78 to 58 mL respectively; p = 0.004). More important was that the median time to ventilator liberation after DP was significantly shorter (10 days vs. 29 days; 95% CI 6.5–13.6 vs. 23.1–35.3 days; p < 0.001). They concluded that: "Comprehensive care of acute cervical spinal cord injury patients should include DP implantation".

In 2018, Onders et al. reported on the largest long term results in traumatic SCI. From 2000 to 2017, 92 patients underwent laparoscopic diaphragm mapping and implantation of DP for diaphragm strengthening and ventilator weaning. The age at time of injury ranged from birth to 74 years old (average of 27). Time on MV was an average of 47.5 months (6 days to 25 years with median of 1.58 years). As an indicator of DP success in conditioning the diaphragm in the initial patients implanted [35], the stimulated tidal volume relative to basal requirement (7 cc/kg for males and 5 cc/kg for females) over time of conditioning was examined. Overall, in the first week of DP, there was a gain from 7% below basal requirements to 36%

over basal requirements. A total of 88% of patients (81/92) achieved the minimum of 4 h of pacing. Seventy (76%) patients used DP at least 12 h per day. Fifty-six (60.8%) patients used DP 24 h per day. Five (5.4%) patients had full recovery of volitional breathing with subsequent DP removal. Five (5.4%) patients were not successfully weaned from MV. Median survival was 22.2 years (95% CI 14.0—not reached) with only 31 deaths. Subgroup analysis showed a trend that earlier DP implantation leads to a greater number of patients utilizing DP for 24 h with no need for any MV. The investigators concluded that DP can successfully decrease need for MV in traumatic SCI and that earlier implantation should be considered. A secondary benefit was also reported, that after DP, 21 of 44 patients (48%) with a chronically cuffed tracheostomy no longer needed a cuffed tracheostomy. Seven patients were completely decannulated from tracheostomy because of DP and an early implanted patient completely avoided a tracheostomy. The clinical significance is that chronic cuffed tracheostomy tubes increase the risks of hemorrhage, tracheomalacia, infections, mucous production, pneumonias, granulation tissue, and stenosis [5].

In 2016, Lammertse et al. presented results of a multicenter longitudinal follow-up of DP patients [7]. The independent study was conducted by six Spinal Cord Injury Model Systems (SCIMS) centers and funded by the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR). The aim of the study was to determine the long term outcomes of patients with SCI that were using DP. The study used questionnaire-based patient reported outcomes with data collected for the years 2011–2016 on patients with implants performed 2007–2014. Thirty-one patients, 23 male and 8 female, with mean age of 34 years (range 19–71 years) were enrolled at six SCIMS centers. Neurological level of injury was C1 32%, C2 45%, C3 19%, and C4 3%. Thirty percent had complete SCI and 70% had incomplete SCI. Mean time to implant post-SCI was 4.5 years (range < 1 month to 28 years). Mean follow-up was 3.2 years (range 15 days to 7.4 years). Patients (n = 28) initiated pacing a mean of 2.5 days and a median of 1 day (range 0–7 days) post-electrode placement. Patients achieved pacing for 6 h per day after a median of 7 days (range 0–60 days) and 24 h per day after a median of 5 days (range 0–30 days). Twenty-four (24) patients (86%) were still using DPS (4–24 h; mean 16 h, median 16 h) at the time of the follow-up and 7 patients (25%) were pacing 24 h per day. Four [4] patients (14%) were not pacing due to “medical issues”, including an adverse reaction to pacing, shoulder pain, or need for pressure support via the ventilator. Device-related adverse events included infection issues at the electrode wire exit site (17%), pain with pacing (14%), and electrode wire issues involving hospitalization (13%). From a subjective patient satisfaction standpoint, 95% were happy or very happy with their decision to have DP; 79% were satisfied or very satisfied

with DP; 57% reported improved ability to engage in activities (e.g., air travel, community mobility, conversation, socialization, energy, sex, etc.), although attendant care needs were unchanged in 89%.

Posluszny's 2014 report was similar to Kerwin's in that he focused on early implantation of DP in SCI [6]. Their analysis included 29 patients, 22 of whom were implanted; 7 patients had denervated "dead diaphragms" at surgery. These diaphragms could not be stimulated because of complete destruction of the lower motor neurons from the trauma insult. The average time frame of injury to implant was 3–112 days with a median of 33 days; 72.7% (16 of 22) were completely free of MV in an average of 10.2 days. A subset of patients implanted within 11 days of injury weaned off MV in 5.7 days. Some patients (36%) implanted early after injury had recovery of respiration and were able to wean off of DP. The ability to record dEMG in this SCI population highlighted the potential of electrical stimulation from DP and neuroplasticity of the spinal cord allowing recovery of phrenic nerve function. Also noteworthy was the fact that early identification of those patients with "dead diaphragms" saves significant amounts of time, frustration, and money on futile ventilator weaning and also allows early consideration of the growing use of nerve transfer techniques to allow recovery.

The initial FDA multi-center clinical trial (N = 50) of DP in SCI dependent on tracheostomy MV showed 96% (48/50) of implanted patients were able to breathe for four consecutive hours with DP alone [9]. This was a single arm prospective evaluation. Outcome measures included stimulated tidal volume, use of DP, patient/caregiver satisfaction, and mortality. Fifty-two percent (26/50) were able to replace MV full time. The subjects achieved the primary endpoint of four hours off of MV in a mean of 2.2 months (range 0.2–7.8 months). Patients ranged in age from 18 years to 74 years (mean 36 years). There were 37 males with the majority of injuries resulting from motor vehicle accidents followed by sports injuries. Patients were on MV from 3 months to 27 years prior to DP implant with the average time of injury to implant being 5.6 years. A 1 year psychosocial survey of the effect of DP was completed in 22 subjects. All patients were living at home. Sixty-four percent reported less secretions with 70% of caregivers reporting less suctioning. Seventy-seven percent reported "more normal breathing". Ninety percent of caregivers stated that caring for DP was less work than MV. Ninety-five percent of patients described an increase in mobility and 91% reported more freedom and feelings of independence. Ninety-six percent of patients and 100% of caregivers would recommend DP to other SCI patients. The most common adverse event was capnothorax; carbon dioxide from the abdominal cavity used during laparoscopy tracking into the pleural space for which minimal treatment was required.

Earlier studies of DP were summarized by Garara et al. at the Imperial College Healthcare NHS Trust [8]. After analyzing 12 publications from 2004 to 2014, they concluded that DP was safe and effective. They noted between 40% and 72.7% of patients were completely free of MV after conditioning, excluding case reports. They also recommended earlier implantation since it does not appear to be associated with greater surgical risk and had a higher rate of complete success. They also noted that the most frequent post-operative complication was a capnothorax, which was managed successfully with observation, drainage or aspiration.

When comparing the monthly cost of maintaining a patient at home with a portable ventilator including the cost of long-term equipment replacement/rental, medical, and nursing care, DP is cost effective. Onders et al. described the cost savings of $13,000 monthly for one SCI patient who was successfully weaned off the ventilator to full-time pacing [2].

Pacing allows natural negative pressure ventilation, preferentially aerating the posterior lobes of the lungs and increasing respiratory compliance, and therefore should decrease pneumonia rates in this patient population. Hirshfield et al. analyzed 64 spinal cord patients with chronic respiratory insufficiency in whom 32 were able to receive either a phrenic or diaphragm pacer and 32 who did not [11]. Pacing the diaphragm and allowing negative pressure ventilation decreased respiratory infections from 2 per 100 days to 0 with pacing ($p < 0.001$).

Another report looked at the quality of life of patients with pacing compared to when they were on the ventilator and all patients would recommend pacing to other potential recipients [12]. They found that pacing improved patients' ability to go outside of the home and participate in leisure activities and relationships with others. This study also showed a significant improvement in olfaction and taste with the use of pacing.

The first four articles that were discussed in the results will form the basis for the conclusions and are summarized in Table 42.2. The strength of the evidence is also reported for each article along with conflicts and limitations. The GRADE approach for recommendations also relies on the benefits and downsides of the proposed therapy. Kim Anderson has been at the forefront in the SCI community of what research should be done based on the expressed needs of the patients with SCI. She states the need to be removed from MV is so inherently obvious and should be at the forefront of research that it is not even posed as a research question to patients [13]. Given the little risk or downside of DP and the significant benefit of being removed from a ventilator allows the final recommendation for DP to be strong in all four highlighted articles. The simplicity of confirming device effectiveness adds to the high quality of the evidence for DP. These are large well performed observational studies that are not randomized, but the patients act as their own controls. If the device is turned off, the patient cannot ventilate and has to be returned to MV. This direct cause and effect gives us the confidence to state there is high quality evidence of the positive effect of DP in these studies.

Table 42.2 Relevant reports on mechanically ventilated spinal cord injured patients who were implanted with diaphragm pacing

Author (year)	Type of study, method	Population	Outcome measures	Efficacy results	Safety results	Evidence quality	Conclusions; conflicts; limitations
Kerwin 2018 [4]	Single center, single arm, retrospective, observational, matched cohort	40 implants 61 matched Mean time to implantation of DP 14 days	Hospital length of stay, ICU length of stay, vent days, incidence of VAP and mortality	• The DP patients that developed VAP (26/40) had significantly shorter vent days as compared to the control patients that developed VAP (39/61): 24.5 ± 15.2 days vs. 33.2 ± 23.3 days; p = 0.05	• Mortality significantly higher in the control MV group (15% vs. 3%; p = 0.04) • Length of hospital stay significantly higher in the control MV group (65 ± 61 vs. 43 ± 24 days; p = 0.03)	Moderate	"DPS implantation was safe and feasible", Vent days shorter for patients with VAP; No conflicts of interest reported; Limited to single site

(continued)

Table 42.2 (continued)

Author (year)	Type of study, method	Population	Outcome measures	Efficacy results	Safety results	Evidence quality	Conclusions; conflicts; limitations
Onders 2018 [5]	Single center, single arm, open label retrospective review	N = 92 Mean time on MV = 47.5 months (range 6 days to 25 years)	MV independence; mortality	• 88% (81/92) achieved a minimum of 4 h of DP pacing • 60.8% (56/92) used DP 24 h/day • 5 (5.4%) had full recovery of volitional breathing • 5 (5.4%) were not successfully weaned from MV • Subgroup analysis showed a trend that earlier DP implantation leads to a greater number of patients utilizing DP for 24 h	• Median survival was 22.2 years (95% CI 14.0—not reached) with only 31 deaths • 4/5 (80%) of patients unable to be weaned from MV died a mean of 9.9 months post-injury • In 17 patients with causes of death available, none were attributable to the device.	Moderate	DPS can decrease need for MV; Conflict of interest reported; Limited to single site long term experience

Lammerste 2016 [6]	Six centers, prospective experience report	N = 31 Mean time on MV 4.5 years(range 1 month to 28 years)	Long term outcomes of utilization, questionnaire based patient reported outcomes	• 24/28 pts. (86%) were still using DPS (4–24 h) at the time of the follow-up (mean 16 h, median 16 h) • 7/28 pts. (25%) were pacing 24 h/day • 4/28 pts. (14%) were not pacing due to: "medical issues", adverse reaction to pacing, shoulder pain, or need for pressure support via ventilator	• Infection issues at the electrode wire exit site (17%) • Pain with pacing (14%) • Electrode wire issues involving hospitalization (13%)	Moderate	"DPS is effective and reasonably safe"; No conflicts of interest reported; Manuscript in process
Posluszny 2014 [7]	Ten centers, retrospective analysis	N = 29 22 implanted, 7 non-responsive diaphragms; Patients implanted at median 33 days post injury (range 3–112)	Surgical Selection, MV independence	• 73% (16/22) implanted were free of MV at a mean of 10.2 days after DP • 36% (8/22) had complete recovery of respiration and DPS wires were removed	• 1 patient, withdrawal of care and death • 3 (14%) partial wean and/or use with MV	Moderate	Surgical mapping can immediately identify patients, DP can shorten and in many cases allow for complete MV independence; Conflict of interest reported

MV mechanical ventilation, *ICU* intensive care unit, *VAP* ventilator associated pneumonia, *DP* diaphragm pacing

Conclusions and Recommendations

In conclusion, after over a decade of being approved by the FDA, DP remains underutilized for SCI patients with bilateral phrenic nerve paralysis dependent on MV. A strong recommendation for all SCI patients dependent on MV is warranted. Many patients will be able to have complete weaning from MV. There is strong evidence that DP should be utilized early with significant positive results for this group of patients. If the diaphragm cannot be stimulated because of phrenic nerve injury or death of phrenic motor neurons, the patient can be assessed for intercostal to phrenic nerve transfer. Also, early knowledge of a non-stimulatable diaphragm is confirmation of the inability to wean from MV; long term ventilator management can be immediately begun, which in SCI patients includes high tidal volume ventilation to prevent atelectasis and pneumonias [14, 15]. Timely assessment and implantation can significantly decrease early morbidity, mortality and length of stay which decreases costs.

Recommendations

- All spinal cord injured patients on mechanical ventilation should have their diaphragms assessed for diaphragm pacing and possible diaphragm pacemaker implantation (evidence quality moderate; strong recommendation).
- Diaphragm pacing should be implanted early after spinal cord injury (evidence quality moderate; strong recommendation).

A Personal View of the Data

As part of the team at Case Western Reserve University and University Hospitals Cleveland Medical Center that developed DP technology, I have been involved in use of this technology for over two decades. Recent reports have highlighted the growing benefit of early utilization of DP to wean SCI patients off of the ventilator. This allows earlier transfer to rehabilitation centers to manage the significant other problems of high level quadriplegia. In our current trauma practice, once the initial injury is stabilized, we document if the patient can volitionally move their diaphragm to initiate ventilation. If they can, then standard weaning occurs. If the patient cannot, we go directly to diagnostic laparoscopy to determine if the diaphragm can be stimulated. If the diaphragm can be stimulated, DP is implanted and rapid weaning without tracheostomy begins. It is extremely rewarding to wean a young SCI patient off of MV without a tracheostomy, allowing them verbal communication with family and to begin the rehabilitation process after a life changing injury.

Conflict of Interest Disclosure Dr. Raymond Onders, University Hospitals of Cleveland and Case Western Reserve University School of Medicine have intellectual property rights involved with the diaphragm pacing system and equity in Synapse Biomedical who manufactures the device.

References

1. National Spinal Cord Injury Statistical Center. http://www.spinal cord.uab.edu. Accessed 25 Oct 2019.
2. Onders RP, Ignagni AI, Aiyer H, Mortimer JT. Mapping the phrenic nerve motor point: the key to a successful laparoscopic diaphragm pacing system in the first human series. Surgery. 2004;136:819–26.
3. Onders RP, Ignagni AI, DiMarco AF, Mortimer JT. The learning curve of investigational surgery: lessons learned from the first series of laparoscopic diaphragm pacing for chronic ventilator dependence. Surg Endosc. 2005;19:633–7.
4. Kerwin AJ, Yorkgitis BK, Ebler DJ, Madbak FG, Hsu AT, Crandall ML. Use of diaphragm pacing in the management of acute cervical spinal cord injury. J Trauma Acute Care Surg. 2018;85:928–31.
5. Onders RP, Elmo MJ, Kaplan C, Schilz R, Katirji B, Tinkoff G. Long-term experience with diaphragm pacing for traumatic spinal cord injury: early implantation should be considered. Surgery. 2018;164:705–11.
6. Posluszny JA, Onders R, Kerwin AJ, Weinstein MS, Stein DM, Knight J, Lottenberg L, Cheatham ML, Khansarinia S, Dayal S, Byers PM. Multicenter review of diaphragm pacing in spinal cord injury: Successful not only in weaning from ventilators but also in bridging to independent respiration. J Trauma Acute Care Surg. 2014;76:303–10.
7. Lammertse DS, Charlifue S, Berliner J. Longitudinal follow-up of individuals with implanted diaphragm pacing systems—a multi-center study. https://clinicaltrials.gov/ct2/show/NCT01815554 and in Topics in Spinal Cord Injury Rehabilitation 2016; 23 supplement 1:57–58. Accessed 25 Oct 2019.
8. Garara B, Wood A, Marcus H, Tsang K, Wilson MJ, Khan M. Intramuscular diaphragmatic stimulation for patients with traumatic high cervical injuries and ventilator dependent respiratory failure: a systematic review of safety and effectiveness. Injury. 2016;47:539–44.
9. FDA: HDE H070003. US Food and Drug Administration. NeuRx DPS™, Diaphragm Pacing System. Summary of Safety and Probable Benefit (SSPB). 2008. Retrieved October 15, 2019 from FDA website: https://www.accessdata.fda.gov/cdrh_docs/pdf7/H070003B.pdf.
10. Kerwin AJ, Yorkgitis YD, Mull R, Hsu AT, Madbak FG, Ebler DJ, Skarupa DJ, Shiber J, Crandal ML. Diaphragm pacing improves respiratory mechanics in acute spinal cord injury. Presented at the 78th annual meeting of the American Association for the Surgery of Trauma. Published in the online abstract book accessed on October 15th, 2019 from website: http://www.aast.org/AnnualMeeting/PastAbstracts.aspx.
11. Hirchfield S, Exner G, Luukkaala T, Baer GA. Mechanic ventilation or phrenic nerve stimulation for treatment of spinal cord-induced respiratory insufficiency. Spinal Cord. 2008;46:738–42.
12. Adler D, Gonzalez-Bermejo J, Duguet A, Demoule A, Le Pimpec-Barthes F, Hurbault A, Morelot-Panzine C, Similowski T. Diaphragm pacing restores olfaction in tetraplegia. Eur Respir J. 2009;34:365–70.
13. Anderson K. Targeting recovery: priorities of the spinal cord-injured population. J Neurotrauma. 2004;21:1371–83.
14. Fenton JJ, Warner ML, Lammertse D, Charlifue S, Martinez L, Dannels-McClure A, Kreider S, Pretz C. A comparison of high vs standard tidal volumes in ventilator weaning for individuals with sub-acute spinal cord injuries: a site specific randomized clinical trial. Spinal Cord. 2016;54:234–8.
15. Consortium for Spinal Cord Medicine. Clinical Practice Guidelines: respiratory management following spinal cord injury: a clinical practice guideline for health care professionals. Paralyzed Veterans Am. 2005;28:259–93.

Does Phrenic Nerve Reconstruction for Unilateral Diaphragm Paralysis Improve Function or Quality of Life

43

Matthew R. Kaufman and Thomas Bauer

Introduction

Unilateral diaphragmatic paralysis may result from acute or chronic neural injury along the central or peripheral nerve pathways. The possible location of pathology includes: the cervical spinal cord, the peripheral cervical roots (C3–5), and the phrenic nerve in its cervical, mediastinal, or thoracic segments [1–3]. Symptoms may be mild in some patients, yet a substantial number will present for treatment to correct exertional dyspnea, orthopnea, and sleep disordered breathing [1, 2, 4, 5]. Although there are identifiable traumatic or iatrogenic etiologies in a subset of patients, many idiopathic presentations are subsequently found to result from chronic peripheral compression neuropathies undetectable on current imaging modalities. Electrodiagnostic evaluation of the phrenic nerve and diaphragm performed by experienced physicians can assist in identifying patients whose paralysis may be reversed using microsurgical nerve reconstruction. Magnetic resonance

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imaging of the cervical spinal cord can eliminate the possibility of degenerative cervical spine disease as the underlying etiology.

Unilateral phrenic nerve paralysis is often associated with symptoms that adversely affect function and quality of life. Options for managing symptomatic unilateral phrenic nerve paralysis traditionally include diaphragm plication, although newer modalities such as diaphragm pacing and phrenic nerve reconstruction have recently been introduced. This chapter evaluates the functional outcomes of phrenic nerve reconstruction.

Search Strategy

Following the PICO format, we identified a population of patients with symptomatic unilateral diaphragm paralysis. The intervention was phrenic nerve reconstruction and a comparison was made to no treatment and other surgical treatment options. The target outcomes were symptomatic and functional recovery based on physical functioning surveys, electrodiagnostic testing, and pulmonary function testing (Table 43.1).

The literature search was performed in PUBMED using the following search terms: diaphragmatic paralysis, phrenic nerve injury, diaphragm plication, phrenic nerve reconstruction, and diaphragm pacemaker. A search of the medical literature was performed from 1980 through 2019. Articles pertaining to diaphragm pacemakers for ventilator dependent spinal cord injury were excluded. We identified no randomized controlled trials investigating any of the current surgical treatment options for unilateral diaphragm paralysis.

Results

Patient Selection

Symptomatic unilateral paralysis should be evaluated for surgical treatment after failure of conservative management. The optimal time for intervention is 8–12 months from onset (or thereafter) absent subjective or objective evidence of spontaneous improvement. Diagnostic testing is necessary to determine feasibility of surgical correction, and the most appropriate modality or modalities. Co-morbid conditions, body mass index, and patient age must also be considered in surgical planning.

Table 43.1 PICO formatted terms for literature search

Population	Intervention	Comparison intervention	Outcome measures
Symptomatic unilateral diaphragm paralysis	Phrenic nerve reconstruction	No treatment Diaphragm plication Diaphragm pacemakers	Symptomatic recovery Functional recovery Physical function surveys Electrodiagnostic testing Pulmonary function testing

Results of Intervention for Unilateral Diaphragm Paralysis

Diaphragm Plication

The traditional approach for plication is through a standard posterolateral thoracotomy [6–13]. With the advent of minimally invasive surgery, video-assisted thoracic surgical (VATS) or laparoscopic approaches have slowly replaced open thoracotomies [7, 14, 15]. A retrospective review has demonstrated the VATS approach to achieve similar results as thoracotomy based on pulmonary function tests, dyspnea scores, and functional assessment with shorter length of stay, lower complications rates, and lower mortality rates [10]. Plication should be reserved for those patients with documented diaphragmatic paralysis and significant dyspnea. Morbidly obese patients and those with long-standing paralysis are less likely to benefit from this repair [7]. The accumulated literature supporting plication surgery as a treatment for symptomatic unilateral diaphragm paralysis is comprised of retrospective case series and case reports (Table 43.2).

Phrenic Nerve Reconstruction

Phrenic nerve reconstruction was first reported in 2011 as an application of nerve repair techniques in patients with chronic diaphragmatic paralysis, and in a series of 12 patients there was improvement in diaphragmatic function in 8 of the 9 patients (89%) who could be fully evaluated [16].

In a 2014 cohort analysis comparing results of phrenic nerve reconstruction in 68 patients to both historical cohorts from a meta-analysis of diaphragm plication and a non-surgical group of patients undergoing observation, the investigators demonstrated at least a functional equivalency to plication at 1 year follow-up, and results that were far superior to no treatment (Table 43.3) [17]. In the phrenic nerve surgery group there was a statistically significant improvement in SF-36 quality of life scores. Furthermore, electrodiagnostic recovery, including both a 69% improvement in conduction latency and a motor amplitude increase of 37%, was significant in the phrenic nerve surgery group, indicating recovery of functional activity. This improvement did not occur with plication surgery or in the non-surgical group.

A 2017 review evaluating long term outcomes after phrenic nerve reconstruction in 180 patients found progressive improvement in diaphragmatic recovery with greater than 2 year follow up and a formal program of post-operative rehabilitation (Table 43.4) [18]. This included a 125% increase in diaphragm motor amplitudes, and significant improvement in FEV, FVC, VC, and TLC. Compared to a 28% improvement in SF-36 quality of life scores in the prior cohort study with 1 year follow up, in this study (mean follow up = 2.7 years) there was a statistically significant 67% improvement in SF-36 scores. Approximately 90% of patients experienced a successful outcome (functional diaphragmatic improvement) after treatment.

Early case reports by Brouillette (1986) and Schoeller (2001) detailed successful immediate repair of the phrenic nerve after intra-thoracic nerve injuries due to trauma or tumor resection, respectively [19, 20].

Kaufman et al. (2012) reported on three patients with symptomatic unilateral diaphragm paralysis found to be caused by vascular compression of the phrenic

Table 43.2 Reported outcomes following diaphragm plication

Authors	Pub. year	Study design	Results			Complications
			PFT	Subjective	Other testing	
Freeman [14]	2006	Prospective case series	FVC improved 17% FEV improved 21.4% FRC improved 20.3% TLC improved 16.1%	–	– Mean MRC dyspnea scores significantly improved in the operative cohort	Superficial wound infection (n = 1) DVT (n = 1)
Graham [6]	1990	Retrospective case series	–	– Significant subjective improvement in breathlessness and orthopnea – Mean dyspnea scores significantly improved	– Postoperative chest radiographs showed the plicated diaphragm was lowered to an almost normal position – Significant improvements in spirometric values and lung volumes	None
Freeman [9]	2009	Prospective case series	FVC improved 19% FEV1 improved 23% FRC improved 21% TLC improved 19%	– Significant improvement in daily living activity scores in 90% of patients	– Significant improvement in mean pulmonary spirometry and MRC dyspnea scores in 90% of patients	Pneumonia (n = 2) Atrial fibrillation (n = 2) Prolonged ileus (n = 1)
Groth [11]	2010	Prospective case series	FVC improved 10.3% at 1 month and 3.0% at 1 year. FEV1 improved 12.8% at 1 month and 7.4% at 1 year. FIFmax improved 22.2% at 1 month and 16.2% at 1 year	– Patients experienced symptom improvement, evidenced by a 20-point reduction in SGRQ (respiratory quality-of-life) scores at 1-month and 1-year post-op	– 1 year post-op plicated hemidiaphragm was lower in all patients	Prolonged chest tube drainage (n = 2) Pleural effusion (n = 1) Respiratory failure requiring reintubation (n = 1) Upper gastrointestinal hemorrhage (n = 1) Stroke (n = 1) Urinary tract infection (n = 1) Paroxysmal atrial fibrillation (n = 1)

FVC forced vital capacity, *FEV1* forced expiratory volume during the first second, *FRC* function residual capacity, *TLC* total lung capacity, *MRC* Medical Research Council, *DVT* deep venous thrombosis, *FIFmax* maximum forced inspiratory flow, *SGRQ* St. George's Respiratory Questionnaire

Table 43.3 Outcomes of 92 patients with symptomatic diaphragmatic paralysis treated with phrenic nerve surgical intervention (PS), nonsurgical (NS) care, and diaphragmatic plication (DP) [17]

	Baseline scores	Post-treatment average improvement
FEV_1	PS: 63% ± 14% DP: 60% ± 5% NS: 64% ± 21%	PS: 13% ± 11% ($p < 0.0001$) DP: 17% ± 7% ($p < 0.0001$) NS: 1.7% ± 6% ($p = 0.25$)
FVC	PS: 65% ± 14% DP: 63% ± 6% NS: 67% ± 15%	PS: 14% ± 12% ($p < 0.0001$) DP: 17% ± 14% ($p < 0.0001$) NS: −0.4% ± 4% ($p = 0.4$)
Latency[a]	PS: 10.9 ± 4.1 ms NS: 11.6 ± 4.4 ms	PS: 69% ($p = 0.036$)
Amplitude[b]	PS: 0.24 ± 0.17 mV NS: 0.23 ± 0.15 mV	PS: 37% ($p < 0.0001$)
SF-36[c]	PS: 41% ± 21% NS: 54% ± 18%	PS: 28% ± 20% ($p = 0.004$) NS: 4% ± 8% ($p = 0.16$)

FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity
[a]Latency reference value: 7.0 ± 1.4 ms
[b]Amplitude reference value: 0.75 ± 0.54 mV
[c]SF-36 (Short Form 36) normal score: 100%

Table 43.4 Long-term results of 180 patients treated with phrenic nerve reconstruction for chronic diaphragm paralysis [18]

	Mean baseline scores	Mean post-op scores	% improvement
FEV_1	61%	68%	11% ($p \leq 0.01$)
FVC	63%	67%	6% ($p \leq 0.01$)
VC	67%	73%	9% ($p \leq 0.05$)
TLC	75%	85%	13% ($p \leq 0.01$)
Latency[a]	11.6 ms	9.6 ms	23% ($p \leq 0.005$)
Amplitude[b]	0.118 mV	0.265 mV	125% ($p \leq 0.0001$)
SF-36[c]	39%	65%	66.7% ($p \leq 0.0001$)

FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *VC* vital capacity, *TLC* total lung capacity
[a]Latency reference value: 7.0 ± 1.4 ms
[b]Amplitude reference value: 0.75 ± 0.54 mV
[c]SF-36 (Short Form 36) normal score: 100%

nerve by the transverse cervical artery, and described this phenomenon as "Red Cross Syndrome". All three patients were treated successfully with phrenic nerve reconstruction [1].

Kawashima et al. (2015) evaluated VATS repair of the phrenic nerve in 6 patients using either direct repair or intercostal nerve interposition and demonstrated functional recovery in 5/6 patients [21]. Hoshide and Brown (2017) reported on phrenic nerve reconstruction in a patient with symptomatic unilateral diaphragm paralysis who achieved full functional recovery at 4 years follow up [22].

Limitations to phrenic nerve reconstruction include applicability only to certain patient groups. For example, individuals with uncontrolled diabetes, morbid obesity, and the elderly will not be suitable candidates for this surgical treatment.

Furthermore, an inability to participate in an aggressive program of diaphragm rehabilitation will reduce the likelihood of significant long term recovery. Complications of phrenic nerve surgery reported in the largest series of 180 patients included: seroma (2%), hematoma (2%), pleural effusion (1%), and wound infection (1%). There were no reported mortalities [18].

Although there are no randomized controlled trials investigating phrenic nerve reconstruction, higher quality investigations are not likely to change the outcomes achieved and estimates of the effect reported by the specialty referral centers regularly performing this procedure. Similar to the quality of evidence available for nerve reconstruction to treat other peripheral nerve disorders, the outcomes are reported in large case series by centers with extensive experience. The current literature for phrenic nerve reconstruction is limited, yet the reported large effects in relatively high numbers of patients requires special consideration. Unilateral diaphragm paralysis has traditionally been undertreated, even in symptomatic patients who were previously without an option for functional recovery.

Diaphragm Pacemakers

Diaphragm pacemakers are FDA approved for chronic ventilator dependency and spinal cord injury and have demonstrated efficacy at achieving ventilator weaning [23]. Indications for diaphragm pacemakers have expanded to unilateral or bilateral diaphragmatic dysfunction. In 2014 Onders et al. reported the use of diaphragm pacemakers in 21 patients with diaphragmatic dysfunction (and at least partial preservation of phrenic nerve activity), and demonstrated clinically relevant respiratory improvement in 62% [24]. In order for diaphragm pacemakers to stimulate muscle contraction there must be at least partial residual phrenic nerve integrity. Therefore, application of this treatment for unilateral diaphragm paralysis must be carefully selected based upon preoperative diagnostic testing. Active investigations are evaluating combination therapy using phrenic nerve reconstruction and simultaneous implantation of diaphragm pacemakers to determine if there may be a synergistic effect.

Conclusions and Recommendations

The literature supports surgical treatment for symptomatic unilateral diaphragm paralysis. Functional correction using phrenic nerve reconstruction as first-line treatment may offer symptomatic relief and improved quality of life in select patients. Treatment failures retain the option of pursuing diaphragm plication as a salvage procedure. Plication may also be the only indication when severe, long-standing neuromuscular atrophy has occurred. Diaphragm pacemakers have only begun to be evaluated as functional treatment for unilateral paralysis and anticipated studies may provide evidence regarding the effectiveness of combination treatment.

Recommendations

- Surgical treatment for symptomatic unilateral diaphragmatic paralysis is superior to observation (evidence quality moderate; strong recommendation).
- Phrenic nerve reconstruction for the treatment of symptomatic unilateral diaphragm paralysis is indicated in selected patients who wish to optimize diaphragm function and quality of life (evidence quality moderate; strong recommendation).

A Personal Approach to the Data

Phrenic nerve reconstruction for symptomatic unilateral diaphragm paralysis has expanded the treatment options for this undertreated respiratory disorder and filled a void in offering an effective option for functional recovery. The literature is limited, yet the treatment effect is robust in large case series and a cohort study in demonstrating functional recovery and quality of life improvements. The specialty centers performing this procedure and reporting outcomes, including those of the co-authors, have established and developed the protocols, personnel, and expertise to be able to provide superior care. This includes reliable and consistent preoperative evaluations as the basis for treatment recommendations, properly executed surgical technique, and a specific post-operative rehabilitation regimen.

The value of restoring functional activity to the diaphragm is a priority for many younger patients, and preference will be given to surgical techniques that aim to achieve this outcome versus the static permanency of diaphragm plication. Nonetheless, primary plication surgery in certain subgroups, and also to salvage nerve reconstruction treatment failures, may improve overall treatment success. A surgical treatment algorithm for the management of diaphragmatic paralysis has been published, expanding the treatment options for this condition and assisting in optimizing overall outcomes in this patient population [25].

References

1. Kaufman MR, Willekes LJ, Elkwood AI, et al. Diaphragm paralysis caused by transverse cervical artery compression of the phrenic nerve: the Red Cross syndrome. Clin Neurol Neurosurg. 2012;114(5):502–5.
2. Kaufman MR, Elkwood AI, Aboharb F, et al. Diaphragmatic reinnervation in ventilator-dependent patients with cervical spinal cord injury and concomitant phrenic nerve lesions using simultaneous nerve transfers and implantable neurostimulators. J Reconstr Microsurg. 2015;31(5):391–5.
3. Patterson DL, DeRemee RA, Hunt LW. Severe asthma complicated by bilateral diaphragmatic paralysis attributed to Parsonage-Turner syndrome. Mayo Clin Proc. 1994;69(8):774–8.
4. Steier J, Jolley CJ, Seymour J, Kaul S, Luo YM, Rafferty GF, et al. Sleep-disordered breathing in unilateral diaphragm paralysis or severe weakness. Eur Respir J. 2008;32(6):1479–87.

5. Summerhill EM, El-Sameed YA, Glidden TJ, McCool FD. Monitoring recovery from diaphragm paralysis with ultrasound. Chest. 2008;133(3):737–43.
6. Graham DR, Kaplan D, Evans CC, Hind CR, Donnelly RJ. Diaphragmatic plication for unilateral diaphragmatic paralysis: a 10-year experience. Ann Thorac Surg. 1990;49(2):248–51.
7. Gharagozloo F, McReynolds SD, Snyder L. Thoracoscopic plication of the diaphragm. Surg Endosc. 1995;9(11):1204–6.
8. Van Onna IE, Metz R, Jekel L, Woolley SR, van de Wal HJ. Post cardiac surgery phrenic nerve palsy: value of plication and potential for recovery. Eur J Cardiothorac Surg. 1998;14(2):179–84.
9. Freeman RK, Van Woerkom J, Vyverberg A, Ascioti AJ. Long-term follow-up of the functional and physiologic results of diaphragm plication in adults with unilateral diaphragm paralysis. Ann Thorac Surg. 2009;88(4):1112–7.
10. Hüttl TP, Wichmann MW, Reichart B, Geiger TK, Schildberg FW, Meyer G. Laparoscopic diaphragmatic plication: long-term results of a novel surgical technique for postoperative phrenic nerve palsy. Surg Endosc. 2004;18(3):547–51.
11. Groth SS, Andrade RS. Diaphragm plication for eventration or paralysis: a review of the literature. Ann Thorac Surg. 2010;89(6):S2146–50.
12. Groth SS, Rueth NM, Kast T, D'Cunha J, Kelly RF, Maddaus MA, et al. Laparoscopic diaphragmatic plication for diaphragmatic paralysis and eventration: an objective evaluation of short-term and midterm results. J Thorac Cardiovasc Surg. 2010;139(6):1452–6.
13. Ciccolella DE, Daly BD, Celli BR. Improved diaphragmatic function after surgical plication for unilateral diaphragmatic paralysis. Am Rev Respir Dis. 1992;146(3):797–9.
14. Freeman RK, Wozniak TC, Fitzgerald EB. Functional and physiologic results of video-assisted thoracoscopic diaphragm plication in adult patients with unilateral diaphragm paralysis. Ann Thorac Surg. 2006;81(5):1853–7.
15. Gazala S, Hunt I, Bédard EL. Diaphragmatic plication offers functional improvement in dyspnoea and better pulmonary function with low morbidity. Interact Cardiovasc Thorac Surg. 2012;15(3):505–8.
16. Kaufman MR, Elkwood AI, Rose MI, Patel T, Ashinoff R, Saad A, et al. Reinnervation of the paralyzed diaphragm: application of nerve surgery techniques following unilateral phrenic nerve injury. Chest. 2011;140(1):191–7.
17. Kaufman MR, Elkwood AI, Colicchio AR, CeCe J, Jarrahy R, Willekes LJ, et al. Functional restoration of diaphragmatic paralysis: an evaluation of phrenic nerve reconstruction. Ann Thorac Surg. 2014;97(1):260–6.
18. Kaufman MR, Elkwood AI, Brown D, Cece J, Martins C, Bauer T, et al. Long-term follow-up after phrenic nerve reconstruction for diaphragmatic paralysis: a review of 180 patients. J Reconstr Microsurg. 2017;33(1):63–9.
19. Schoeller T, Ohlbauer M, Wechselberger G, Piza-Katzer H, Margreiter R. Successful immediate phrenic nerve reconstruction during mediastinal tumor resection. J Thorac Cardiovasc Surg. 2001;122(6):1235–7.
20. Brouillette RT, Hahn YS, Noah ZL, Ilbawi MN, Wessel HU. Successful reinnervation of the diaphragm after phrenic nerve transection. J Pediatr Surg. 1986;21(1):63–5.
21. Kawashima S, Kohno T, Fujimori S, Yokomakura N, Ikeda T, Harano T, et al. Phrenic nerve reconstruction in complete video-assisted thoracic surgery. Interact Cardiovasc Thorac Surg. 2015;20(1):54–9.
22. Hoshide R, Brown J. Phrenic nerve decompression for the management of unilateral diaphragmatic paralysis—preoperative evaluation and operative technique. Surg Neurol Int. 2017;8:254.
23. Tedde ML, Vasconcelos Filho P, Hajjar LA, de Almeida JP, Flora GF, Okumura EM, et al. Diaphragmatic pacing stimulation in spinal cord injury: anesthetic and perioperative management. Clinics (Sao Paulo). 2012;67(11):1265–9.
24. Onders RP, Elmo M, Kaplan C, Katirji B, Schilz R. Extended use of diaphragm pacing in patients with unilateral or bilateral diaphragm dysfunction: a new therapeutic option. Surgery. 2014;156(4):776–84.
25. Kaufman M, Bauer T. Surgical treatment of phrenic nerve injury. UpToDate: Wolters Kluwer; 2018. https://www.uptodate.com/contents/surgical-treatment-of-phrenic-nerve-injury. Accessed 2 Oct 2019.

Is Plication for Diaphragmatic Eventration Effective in Improving Lung Function?

44

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Introduction

Diaphragmatic eventration is a rare congenital disorder (incidence <0.05%) that affects the central portion of the diaphragm [1]. It is characterized by a paucity of muscle fibers, while the normal diaphragmatic attachments to the sternum, ribs and spine are not affected [2]. In contrast, diaphragmatic paralysis is an acquired condition in which the muscle fibers might be atrophic, but they are present. Some authors have classified diaphragmatic eventration as congenital or acquired. This is a common misconception, as both pathologies have similar symptoms, physiological impact, and treatment. For this reason, we have chosen to name both diseases "eventration" in this chapter.

Eventration is a diagnosis of exclusion, often asymptomatic in adults, more common in males, and affects predominantly the left hemidiaphragm, although there are cases of right/bilateral involvement reported in the literature. The condition is thought to be caused by abnormal myoblast migration from the third, fourth, and fifth cervical somites into the septum transversum and pleuro-peritoneal membrane [3]. The main symptom that patients experience is dyspnoea, owing to a combination of loss of pulmonary and chest wall compliance and a ventilation/perfusion mismatch [4]. Other non-specific symptoms include epigastric pain, bloating, nausea, and constipation [5]. "Acquired" diaphragm eventration (paralysis) is most

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commonly seen following heart surgery or in pathologies affecting the phrenic nerve such as intrathoracic tumours and neuromuscular disorders. Symptoms are usually worse in children, who sometimes require mechanical ventilation, because they rely more on their diaphragmatic excursion for respiration due to intercostal muscle underdevelopment and a horizontal orientation of the ribs [6].

Surgical repair can be done either open or minimally invasively using a transthoracic or transabdominal approach, and various techniques such as plication, imbrication, and double breasted suturing have been described. Diaphragmatic plication seems to be the most popular method and has the goal to provide symptomatic relief by improving diaphragmatic function; therefore, surgical treatment is reserved exclusively for symptomatic patients [1].

As diaphragmatic dysfunction reduces the compliance of the chest wall, pulmonary function tests (PFTs) can demonstrate a restrictive pattern [4]. Furthermore, the diaphragm plays a critical role in inspiration, therefore measuring the maximum forced inspiratory flow (FIF_{max}) is useful, as is assessing pulmonary function tests (PFTs) in both supine and upright positions (when supine the PFTs decrease between 20% and 50%) [7]. Despite the PFTs often being abnormal in patients with diaphragmatic eventration, these changes are not consistent and do not correlate with the severity of dyspnea.

Surgery for diaphragmatic eventration in children is mostly performed to facilitate weaning off ventilatory support [6], and we have excluded the studies looking at outcomes following plication in this group of patients.

PFTs are useful in monitoring changes after treatment and in providing an objective evaluation of improvement in diaphragm and chest wall function [1]. This chapter reviews the potential benefit of unilateral diaphragm plication in adult patients with unilateral diaphragm eventration in improving lung function tests.

Search Strategy

Electronic searches were performed using the PubMEd, Embase and Cochrane Evidence based medicine databases from 1990 to 2019 and used to identify available data on outcomes after diaphragm plication in adult patients with diaphragmatic eventration published in the English language. The index terms used were "unilateral diaphragm eventration AND plication OR surgery AND outcomes OR quality of life OR physiological changes OR results". Conference abstracts, case reports and studies which included only diaphragmatic paralysis were excluded. The quality of the data was classified using the GRADE system. Table 44.1 shows the PICO terms used to perform the literature search.

Table 44.1 PICO formatted terms for literature search

P(Patients)	I (Intervention)	C (Comparator)	O (Outcome)
Unilateral diaphragm eventration	Plication surgery	Observation	Quality of life, physiologic changes

Results

Most data on outcomes following unilateral diaphragm plication in adults comes from retrospective analyses of case series. Due to the rare nature of this disease, randomized control studies are not feasible, therefore the level of evidence discussed in this chapter is low. Given the myriad of surgical techniques described in the literature, we have divided the results into two sections based on the approach used.

Outcomes After Open Diaphragmatic Plication

In 1992 Ribet et al. [8] published their outcomes after open (thoracotomy) diaphragmatic plication in a cohort of 24 patients over a period of 20 years, including both adults and children, and suggested that one has to be sure the diaphragm is causing the symptoms before performing the procedure (Table 44.2). Out of the 11 adult patients who underwent open diaphragmatic plication, 6 had decreased respiratory function and in 5 cases the post-operative pulmonary function tests were available

Table 44.2 Outcomes after open diaphragmatic plication (thoracotomy)

Author, study type and data collection period	Number of patients	Follow-up period	Pre-operative values	Post-operative values	P value
Ribet [8] retrospective (1968–1988)	11 adults	3 months–18 years	6 patients had decreased respiratory function (no values given)	5 had post-op lung function tests FVC increased by a mean of 20%, FEV1 increased by a mean of 15%	Not given
Calvinho [9] retrospective (1988–2007)	20 adults	4 months–206 months	FEV1% 66.2 ± 15.3 FVC% 70.4 ± 16.0 MRC 2.06 ± 0.97	FEV1% 76.1 ± 20.1 FVC% 78.4 ± 17.3 MRC 1.06 ± 1.14	>0.1 >0.1 0.007
Balci [10] retrospective (2003–2009)	28	12 months	MRC 3.4 ± 0.9 FEV1 1.7 ± 0.6 L	MRC 1.8 ± 0.7 FEV1 2.1 L ± 0.7 L	0.000 0.013
Ali Shah [12] retrospective (2002–2013)	38	6 months	MRC 2.6 ± 0.73 FEV1% 63.5 ± 13.3 FVC% 67.2 ± 14.6	MRC 0.56 ± 0.47 FEV1% 75.2 ± 18.1 FVC% 78.7 ± 12.8	<0.05 <0.05 <0.05
Evman [11] retrospective (2007–2013)	42(23 accordion, 19 double breasted)	12 months	MRC 3 ± 0.6 FEV1% 62 ± 8 FVC% 61 ± 9	MRC 0.9 ± 0.6 FEV1% 76 ± 5 FVC% 76 ± 4	<0.001 No difference between groups

MRC Medical Research Council dyspnea scale, *FEV1* forced expiratory volume in the first second, *FVC* forced vital capacity

and demonstrated an increase in forced vital capacity (FVC) by a mean of 20% and in forced expiratory volume in the first second (FEV1) by a mean of 15%. Interestingly, in 5 cases the diaphragmatic elevation persisted post-operatively, albeit to a lesser extent.

Calvinho et al. [9] retrospectively analyzed outcomes in 20 patients operated between 1988 and 2007 with an average length of follow-up of 59.6 ± 55.1 months. The subjective improvement (dyspnea score) was statistically significant at follow-up (Medical Research Council [MRC] dyspnea scale) improved from a mean of 2.06 ± 0.97 to 1.06 ± 1.14; p = 0.007). Although the PFTs improved post-operatively (FEV1% from 66.2 ± 15.3 to 76.1 ± 20.1 and FVC% from 70.4 ± 16.0 to 78.4 ± 17.3), the differences were not statistically significant. The authors attributed this discrepancy to the small sample size and concluded that subjective improvement is of much more value than the objective data from spirometry.

Balci et al. [10] compared outcomes according to etiology and patch use. In their cohort of 28 patients, 18 cases were secondary to previous operation/disease, 8 were idiopathic, and 2 were post-traumatic. They observed that the patients with a congenital/idiopathic etiology (true eventration) were younger, had a higher diaphragm, were operated sooner after the onset of symptoms, and had better preoperative FEV1 values. In terms of surgical technique, there was no statistically significant difference between open diaphragmatic plication and open diaphragmatic plication and patch. Of note, none of the patients who had the diaphragmatic plication and patch had a post-operative diaphragmatic event; in the plication only group, one patient had an ipsilateral diaphragmatic hernia and one patient developed a recurrence.

Another study by Evman et al. [11] compared mid-term clinical outcomes of open accordion plication vs. open double breasted plication in 42 symptomatic patients with eventration and paralysis. The PFTs and the dyspnea scores (MRC) improved significantly, but there were no statistical differences between the groups. The postoperative increases in FEV1 and FVC were greater than 20% and persisted at 2 years. Although the double breasted technique significantly improved the caudal shift of the diaphragm, this difference did not translate to an increased improvement in pulmonary function tests compared to accordion plication.

Shah et al. [12] retrospectively analyzed 38 patients who underwent surgery for true diaphragmatic eventration over 11 years. They also noted a statistically significant improvement in PFTs and dyspnea score at 6 months post-operatively. Furthermore, they reported a 5.2% 30-day morbidity rate due to surgical emphysema and surgical site infection and a 2.6% 30-day mortality (one patient died due to a fatal arrhythmia).

Outcomes After Minimally Invasive Diaphragmatic Plication

There are only a few studies analyzing outcomes after minimally invasive (VATS or laparoscopy) plication in patients with diaphragmatic eventration. Most are retrospective with the exception of that led by Moroux and colleagues [13], who

Table 44.3 Outcomes after minimally invasive diaphragmatic plication (VATS or laparoscopic)

Author, study type and data collection period	Number of patients	Follow-up period and technique	Pre-operative values	Post-operative values	P value
Moroux et al. [13] prospective (1992–2003)	12	1 year VATs	FVC 1.9 ± 0.8 L FEV1 1.4 ± 0.6 L	FVC 2.47 ± 1.09 L FEV1 1.72 ± 0.8 L	0.0001 0.0006
Groth et al. [14] retrospective (2005–2008)	25	1 year[a] Laparoscopic	SGRQ 59.3 ± 26.8 FVC% 59.2 ± 11.7 FEV1% 55.4 ± 12.9 FIF_{max}% 93.2 ± 34.1	SGRQ 30.8 ± 18.8 FVC% 61.0 ± 10.6 FEV1% 60.9 ± 10.7 FIF_{max}% 115.5 ± 30.9	<0.05 <0.05 <0.05 <0.05
Rombola et al. [15] retrospective (2005–2011)	18	1 year VATS assisted mini-thoracotomy	FVC2.0 ± 0.9 L FEV11.4 ± 0.6 L PEF 5.0 ± 2.0 L PIF 3.4 ± 1.2 L	FVC 2.5 ± 1.1 L FEV1 1.8 ± 0.8 L PEF 5.7 ± 2.0 L PIF 4.0 ± 2.2 L	<0.001 <0.001 0.002 Not significant

FEV1 forced expiratory volume in the first second, *FVC* forced vital capacity, *SGRQ* St. George Respiratory Questionnaire, FIF_{max} maximum forced inspiratory flow, *PEF* peak expiratory flow, *PIF* peak inspiratory flow

[a]Results after excluding data from the patient who resumed smoking

performed VATS plication in 12 patients with unilateral diaphragmatic eventration and prospectively analyzed the results over an 11 year period. Subjective and objective functional improvement as well as radiological improvement were observed in all patients and persisted long term (Table 44.3.).

Groth et al. [14] retrospectively evaluated the short and mid-term results following laparoscopic diaphragmatic plication for symptomatic, unilateral diaphragmatic paralysis and eventration. Their study included 25 patients and showed significant improvement in respiratory quality of life and pulmonary function test results. Unlike other studies, they included the FIFmax in the analysis and found that the improvement 1 year after plication did not reach statistical significance. After investigating the reason behind this discrepancy, they found that one patient resumed smoking after the 1-month postoperative visit. When analyzing the cohort's 1-year PFT data after excluding this patient, they found significant improvements in FVC%, FEV1%, and FIFmax% at 1 year after laparoscopic diaphragmatic plication.

Rombolá and coworkers [15] observed the clinical respiratory and spirometric effects of video-assisted mini-thoracotomy diaphragmatic plication (VAM-TDP) in the treatment of diaphragmatic eventration. Eighteen symptomatic patients were included and significant clinical and spirometric improvement persisted up to 1 year post-operatively. They reported no perioperative mortality, but five of their patients

had postoperative complications (two required non-invasive ventilation, one had a small hepatic hematoma, and two had postoperative ileus).

In summary, both open and minimally invasive approaches yield similar clinical and functional results. The complication rates after open plication are reported as high as 14.3% in one study [10] and 5.2% in another [12], while in minimally invasive plication Groth et al. [14] and Rombola et al. [15] reported that 25% and 27%, respectively, of their cohorts developed a postoperative complication. In contrast, Evman et al. [11] reported no complications in their cohort of 42 patients undergoing open diaphragm plication as did Moroux et al. [13] in their 12 patients who underwent VATS diaphragm plication. The reported complications are similar in all studies and include (but are not limited to) dyspnea, respiratory failure requiring non-invasive ventilation or endotracheal intubation, prolonged drainage, surgical site infections, stroke, and atrial fibrillation. Although the complication rates for minimally invasive diaphragm plication seem to be higher, these results need to be interpreted with care as these studies are retrospective and include different techniques, number of patients, methodology, and reporting.

The post-operative length of stay seems to be similar in both types of approach, ranging between 2 to 15 days across the studies involving open procedures [8–12] and 1 to 15 days in VATs studies [13–15]. However, these results need to be interpreted with caution, as the studies looking into outcomes after open plication involve more patients and have a more variable follow-up period than those studying the outcomes after VATs.

Conclusions and Recommendations

The results of the aforementioned studies should be interpreted with care, as the diagnosis of eventration is often confused with diaphragmatic paralysis. Both open and minimally invasive approaches offer similar clinical and spirometric improvement. However, there is no level 1 evidence comparing the approaches. Diaphragmatic plication is recommended for symptomatic patients with diaphragmatic eventration, as it provides durable improvement in both lung function and symptoms.

Recommendations

- Diaphragmatic plication is indicated in symptomatic patients with diaphragm eventration (evidence quality low; weak recommendation).
- Minimally invasive and open techniques have similar outcomes, thus an approach with which the surgeon is familiar should be adopted (evidence quality low; weak recommendation).

A Personal View of the Data

In our opinion, as with diaphragmatic paralysis, respiratory capacity improvement is likely to occur following repair of eventration at the abdominal-rib cage level in both the operated and contralateral sides, with restoration of synchrony of chest wall movements. These dynamic improvements are not captured by simple spirometry [16]. We prefer a thoracoscopic approach to diaphragmatic plication, as midterm and long term results are similar to other approaches, and the potential for chronic pain is low in our experience. While VATS and laparoscopic approaches have become more popular, a comparative study with open techniques is warranted.

References

1. Groth SS, Andrade RS. Diaphragm plication for eventration or paralysis: a review of the literature. Ann Thorac Surg. 2010;89(6):S2146–50.
2. Christensen P. Eventration of the diaphragm. Thorax. 1959;14:311–9.
3. Schumpelick V, Steinau G, Schluper I, Prescher A. Surgical embryology and anatomy of the diaphragm. Surg Clin North Am. 2000;80(1):213–39.
4. Ridyard JB, Stewart RM. Regional lung function in unilateral diaphragmatic paralysis. Thorax. 1976;31:438–42.
5. Gibson GJ. Diaphragmatic paresis: pathophysiology, clinical features, and investigation. Thorax. 1989;44:960–70.
6. Wu S, Zang N, Zhu J, Pan Z, Wu C. Congenital diaphragmatic eventration in children: 12 years' experience with 177 cases in a single institution. J Pediatr Surg. 2015;50(7):1088–92.
7. Clague HW, Hall DR. Effect of posture on lung volume: airway closure and gas exchange in hemidiaphragmatic paralysis. Thorax. 1979;34:523–6.
8. Ribet M, Linder JL. Plication of the diaphragm for unilateral eventration or paralysis. Eur J Cardiothorac Surg. 1992;6:357–60.
9. Calvinho P, Bastos C, Bernardo JE, Eugenio L, Antunes MJ. Diaphragmmatic eventration: long-term follow-up and results of open chest plication. Eur J Cardiothorac Surg. 2009;36:883–7.
10. Balci AE, Ozyurtkan MO. Clinical and surgical specifications of adult unilateral diaphragmatic eventration according to their aetiology in 28 patients. Importance of using diaphragmatic patch and minimal thoracotomy incision. Eur J Cardiothorac Surg. 2010;37:606–12.
11. Evman S, Tezel C, Vayvada M, Kanbur S, et al. Comparison of mid-term clinical outcomes of different surgical approaches in symptomatic diaphragmatic eventration. Ann Thorac Cardiovasc Surg. 2016;22(4):224–9.
12. Shah SZA, Khan SA, Bilal A, Ahmad M, Muhammad G, Khan K, Khan MA. Eventration of diaphragm in adults: eleven years experience. J Ayub Med Coll Abbottabad. 2014;26(4):459–62.
13. Mouroux J, Venissac N, Leo F, Alifano M, Guillot F. Surgical treatment of diaphragmatic eventration using video-assisted thoracic surgery: a prospective study. Ann Thorac Surg. 2005;79:308–12.
14. Groth SS, Rueth NM, Kast T, D'Cunha J, Kelly RF, Maddaus MA, et al. Laparoscopic diaphragmatic plication for diaphragmatic paralysis and eventration: an objective evaluation of short-term and midterm results. J Thorac Cardiovasc Surg. 2010;139(6):1452–6.
15. Rombolá C, Crespo MG, López PT, Martínez AH, Atance PL, Ramírez AT, Montes JA. Video-assisted minithoracotomy diaphragmatic plication: respiratory effects in adults. Thorac Cardiovasc Surg. 2011;64:647–53.
16. Elshafie G, Acosta J, Aliverti A, Bradley A, Kumar P, Rajesh P, Naidu B. Chest wall mechanics before and after diaphragm plication. J Cardiothorac Surg. 2016;11:25.

Part IV

Airways

Is Long-Term Stenting for Benign Airway Obstruction Effective?

45

Faiz Y. Bhora and Mirza Zain Baig

Introduction

Airway stents are used in a variety of malignant and benign diseases [1–6]. Their use in malignant stenosis has been shown to be effective in multiple studies. Our group has previously reported successful palliation of symptoms and improved survival in patients with malignant airway obstruction who underwent timely airway stenting [7]. Use of airway stents in benign airway stenosis remains the subject of debate and study. Stents are foreign bodies and long term use frequently results in complications ranging from migration, halitosis, granulation tissue formation, stent occlusion, stent fracture, need for reintervention, and rarely stent erosion into adjacent structures. Complication rates are therefore higher in cases of benign obstruction as these patients have a much longer life expectancy. Herein, we explore published literature as well as our own personal clinical experience to evaluate the efficacy of long-term airway stenting for benign airway stenosis.

Search Strategy

We conducted an electronic-based literature search of English language publications to identify data on utility of airway stents in benign airway stenosis and its long-term outcomes (Table 45.1). Databases searched included Ovid Medline,

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Difficult Decisions in Surgery: An Evidence-Based Approach,
https://doi.org/10.1007/978-3-030-47404-1_45

Table 45.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with benign airway obstruction or stenosis	Airway stent	Dilation Ablation	Complications Prognosis Quality of life

Table 45.2 Evidence regarding the use of airway stents

Category of evidence	Quality of evidence
When feasible, endobronchial ablation/repair should be first line therapy for benign airway stenosis	Moderate
Metallic stents, though convenient to deploy, have a number of associated complications	Moderate
Long term use of airway stents is associated with higher number of reinterventions	Moderate
The overall complication rate after metallic airway stent implantation is greater with benign conditions than malignant conditions	Moderate
Long term airway stenting may complicate or preclude surgery	Low

Pubmed, Google Scholar and the Cochrane central register of controlled trials. The following medical subject heading terms, keywords and their combinations were used: "Benign airway obstruction; Benign airway stenosis; Airway Stent; Silicone Stent; Metallic Stent; long term outcomes; complications; prognosis." Only articles that were available as full text articles were included in our review. We also manually searched the reference lists of relevant studies. We restricted ourselves to literature published 2010 through 2019 (Table 45.2).

Results

Several ablative techniques exist that should be utilized as first line treatment for benign tracheobronchial stenosis. These include argon plasma coagulation, bipolar cautery, radiofrequency ablation, and spray cryotherapy [8–10]. Most ablative techniques are combined with either rigid or balloon dilation, or both. Scarlata et al., and Wahidi et al., each reported large patient case series where they experienced success with endobronchial ablative techniques [11, 12]. Our group has also published encouraging results for spray cryotherapy coupled with tracheobronchial dilation in patients with recalcitrant benign tracheal stenosis [13].

When endobronchial ablation is not feasible, however, airway stents can be placed to provide rapid resolution of symptoms or protect a critically narrowed airway to avoid complete occlusion and significant lung atelectasis [14]. This has been validated by multiple studies. Sehgal et al., placed 27 silicone Y stents in 18 subjects with grade 3–4 obstruction and reported relief of symptoms in all of the patients as well as rapid resolution of respiratory failure [5]. Similarly, in another study, 32 stenting procedures were done in 23 patients. Technical success was

described in 96.9% of cases and symptomatic improvement was reported in 90.6% [15]. Our group has also reported successful airway patency with significant improvements in Medical Research Council (MRC) dyspnea scale and Eastern Cooperative Oncology Group (ECOG) score in 50 patients post stenting with no procedure related morbidity and mortality [7].

Silicone Stents

Terra et al., placed 258 silicone stents in 92 patients with benign airway strictures [16]. They demonstrated successful decannulation in 21% of the cases that were deemed inoperable before stenting. Mean follow-up was 37.4 months with granulation tissue formation (22%) and stent migration (5%) being the most common complications.

In another study with less successful outcomes, 50 silicone stents were placed in 19 patients with tracheobronchial stenosis [17]. Successful stent removal was possible in 7 patients. There was no procedure related mortality. Complications included restenosis (33%) and migration (32%).

Gildea et al., have recently described success with the use of patient specific 3D printed silicone stents for benign disease [18]. In their study, these stents were placed in two patients with Wegener's granulomatosis who had not responded to systemic therapy and standard endobronchial techniques. They reported shorter procedure times and general clinical improvement at 1-year follow-up. Similarly, Schweiger et al., have also described symptomatic improvement with the use of customized 3D printed stents in two patients with tracheobronchomalacia [19]. 3D customization of stents, while appealing, is not needed or logistically practical in most cases.

Despite the fact that silicone stents are relatively inexpensive, potentially retrievable, and available in a large number of shapes and sizes, they are more likely to migrate and to interfere with mucociliary clearance [20–23]. The need for rigid bronchoscopy for deployment also precludes their use in a number of patients and limits therapy to operators experienced with this technique [9, 24]. Folch et al. in their review describe a higher rate of migration than for metallic stents and the need for repeated bronchoscopic procedures [25]. They also describe obstruction from accumulated secretions and granulation tissue growth at the proximal and distal ends. In addition, silicone stents carry a risk for potential ignition during endobronchial treatments (i.e., laser therapy).

Metallic Stents

Compared to silicone stents, self expanding metallic stents (SEMS) offer a larger airway lumen due to their greater internal-to-external diameter ratio [23, 24]. They are radio-opaque, allowing easy detection on radiographic films, and have a lower rate of migration [23]. In addition, metallic stents may interfere less with

mucociliary clearance [23]. They also allow for quick and generally easy placement using flexible bronchoscopy, which can be performed under moderate sedation in the ambulatory setting. This has popularized their use in both benign and malignant disease [21, 23].

However, SEMS are associated with higher rates of granulation tissue formation, stent fracture, and bacterial colonization. Vascular and airway erosion are possible rare complication [22, 25]. Also important is the fact that uncovered and partially covered stents tend to undergo neo-epithelialization [23, 25]. Epithelialized stents are difficult or impossible to remove, and removal may cause mucosal tears, bleeding, and re-obstruction [26]. Alazemi et al. described their experience with endoscopic removal of 55 metallic airway stents from 46 patients [26]. Eighty percent of the stents were placed for benign disorders. Sixty-five percent of the patients had high grade airway stenosis with granulation tissue, hence requiring removal of the stents. Thirty-eight percent of removals were complicated by significant airway obstructions from edema and malacia and required re-stenting with silicone stents.

Lunn et al. also demonstrated significant complications with stent removal including re-obstruction requiring re-stenting (14/25), retained stent pieces (7/25), the need for postoperative mechanical ventilation, mucosal tears (4/25), and tension pneumothorax (1/25) [27].

Long Term Use of Airway Stents

Alazemi et al., describe the high number of interventions in patients undergoing airway stenting [26]. Fifty-six percent of the patients required additional interventions to facilitate stent removal. Twenty-nine percent required ablation of granulation tissue with argon plasma coagulation or electrocautery prior to stent removal, and 25% required multiple bronchoscopic sessions. They also report an estimated median total cost of $10,700 per stent removal encounter, which is likely an underestimation. Similarly, Karush et al., described their experience with 220 silicone stents in 40 patients over 13 years [28]. In their cohort, median freedom from reintervention was 104 days. The most common indications for re-intervention included mucus accumulation (60%), migration (28%), and intubation (8%).

In 2005, the US Food and Drug Administration (FDA) released a public health warning against the use of metallic stents in benign airway disease [29, 30, 32]. Reports comparing the outcomes of metallic stents in benign and malignant disease have shown a higher rate of complications in the benign group [6]. This may be due to the fact that patients with benign disease generally live longer and have a longer follow up time during which complications may arise [23, 25].

Chung and colleagues inserted 211 SEMS in 149 patients and observed a significantly greater complication rate in patients with benign disease as compared to those with malignant disease (42.2% vs. 21.1%) [31]. This included a greater rate of granulation tissue formation (19% vs. 10.5%) and stent fracture (16.4% vs. 1.1%). Another case series in which 82 SEMS were placed in 35 patients with benign disease and reported at least one complication in 77% of the patients treated [23].

Based on some of these concerns, the FDA made the following recommendations [32]:

- Metallic stents in patients with benign airway disorders should be used only after thoroughly exploring all other treatment options.
- Metallic stents should not be used as a bridge to other therapies, as removal of metallic stents can result in serious complications.
- If a metallic stent is necessary for a patient, the procedure should be performed by a physician trained or experienced in its deployment.
- If removal of a metallic stent is necessary, then the procedure should be performed by a physician trained or experienced in removing them.

Alazemi and colleagues reported a sharp decrease in the number of referrals for SEMS related complications in the years following the FDA advisory [26]. However, they noted a subsequent rapid increase to levels even higher than those prior to the FDA advisory. This reemergence of SEMS for benign disease may be due to misinterpretation of a few studies. The survival rates in these studies were extremely low for benign disease (51% and 23% at 3 and 6 years respectively). Therefore, these cohorts were essentially behaving more like patients with malignant than benign airway obstruction.

Long Term Airway Stenting May Complicate Surgery

Long term stenting may complicate surgical treatment in some cases, especially when it extends the lesion to greater than 4–5 cm due to granulation tissue formation at each end. Also important is the fact that stenting can cause local inflammation and mucosal injury which may interrupt airway healing after resection and anastomosis [25]. In a small study involving 15 patients who underwent SEMS insertion for benign disease, granulation tissue and stricture formation were noted in areas previously found to be normal before device placement [33]. Of particular interest were three patients who were believed to be candidates for surgical therapy before airway stenting but could no longer proceed due to the changes in the airway induced by the stents. It is therefore important that thoracic surgeons and interventional pulmonologists rule out any surgically resectable disease before proceeding with stent placement.

Conclusions and Recommendations

Stents are an effective treatment for patients with central airway obstruction. They allow for rapid resolution of symptoms. However, depending on the underlying disease, long term complications are common, especially when used for benign obstruction. For the vast majority of patients, nonmalignant subglottic and tracheal stenosis can be managed by endoscopic techniques. Laryngeal suspension and rigid

bronchoscopy are ideal access techniques for benign upper airway stenosis. For refractory and recurrent lesions, open resection and end to end anastomosis is an option, provided the diseased segment is less than 4 cm in length. In situations where stenting is deemed necessary, silicone stents are preferred. Fully covered metallic stents are not advised as first line therapy for benign disease, however, in exceptional cases, they may be utilized for short periods of time at a center experienced in advanced endoscopic airway procedures. We strongly recommend stent insertion and removal to be performed by trained and experienced physicians at specialized centers.

Recommendations

- For the vast majority of patients, benign subglottic and tracheal stenosis can be managed by endoscopic ablative and repair techniques (evidence quality moderate, strong recommendation).
- For recalcitrant lesions, open resection and end to end anastomosis is the preferred option in short segment tracheal stenosis (evidence quality moderate, strong recommendation)
- For benign diseases, silicone stents are preferred (evidence quality moderate, strong recommendation)
- For long term stenting of benign disease, metal stents are not advised (evidence quality moderate, strong recommendation).

A Personal View of the Data

In our experience, the vast majority of benign subglottic and tracheal stenosis can be managed by endoscopic techniques using a combination of ablative modalities, especially spray cryotherapy, coupled with endoscopic balloon dilation. The use of spray cryotherapy is superior to conventional heat-based energy modalities due to less scar tissue formation, decreased reintervention rates, and ability to treat difficult and recalcitrant lesions. In addition, cryotherapy helps in scar remodeling and regeneration of normal tissue [13, 34–36]. Our preferred access for treatment of benign airway stenosis, especially upper airway stenosis, is laryngeal suspension, a technique utilized by some head and neck surgeons but in our opinion very important for thoracic surgeons to be familiar with. The suspension technique opens up the entire airway for intervention below the vocal cords, akin to a strategic attacking chess move. When the need for stenting is felt necessary, silicone stents and/ or T-tubes provide good short-term stenting options. Stenting in such situations should be used to maintain patency and to temporarily remodel the airway following the use of endoscopic ablative techniques. We do not advise the routine use of metal stents, but they are permissible in exceptional situations for about 4 weeks and with subsequent removal. Management of benign airway stenosis should be performed at centers experienced in the full range of endoscopic modalities and with experienced physicians and surgeons experienced in the care of these patients at airway centers of excellence.

References

1. Herth F, Eberhardt R. Airway stent: what is new and what should be discarded. Curr Opin Pulm Med. 2016;22(3):252–6.
2. Lee P, Kupeli E, Mehta A. Airway stents. Clin Chest Med. 2010;31(1):141–50.
3. Al-Ayoubi A, Bhora F. Current readings: the role of stenting in tracheobronchial disease. Semin Thorac Cardiovasc Surg. 2014;26(1):71–5.
4. Casal R. Update in airway stents. Curr Opin Pulm Med. 2010;16(4):321–8.
5. Sehgal I, Dhooria S, Madan K, Pattabhiraman V, Mehta R, Goyal R, et al. Placement of tracheobronchial silicone Y-stents: multicenter experience and systematic review of the literature. Lung India. 2017;34(4):311–7.
6. Ayub A, Al-Ayoubi A, Bhora F. Stents for airway strictures: selection and results. J Thorac Dis. 2017;9(S2):S116–21.
7. Razi S, Lebovics R, Schwartz G, Sancheti M, Belsley S, Connery C, et al. Timely airway stenting improves survival in patients with malignant central airway obstruction. Ann Thorac Surg. 2010;90(4):1088–93.
8. Fernando H, Sherwood J, Krimsky W. Endoscopic therapies and stents for benign airway disorders: where are we, and where are we heading? Ann Thorac Surg. 2010;89(6):S2183.
9. Flannery A, Daneshvar C, Dutau H, Breen D. The art of rigid bronchoscopy and airway stenting. Clin Chest Med. 2018;39(1):149–67.
10. Wright C. Nonoperative endoscopic management of benign tracheobronchial disorders. Thorac Surg Clin. 2018;28(2):243–7.
11. Scarlata S, Graziano P, Lucantoni G, Battistoni P, Batzella S, Dello Jacono R, et al. Endoscopic treatment of primary benign central airway tumors: results from a large consecutive case series and decision-making flow chart to address bronchoscopic excision. Eur J Surg Oncol. 2015;41(10):1437–42.
12. Wahidi M, Unroe M, Adlakha N, Beyea M, Shofer S. The use of electrocautery as the primary ablation modality for malignant and benign airway obstruction. J Thorac Oncol. 2011;6(9):1516–20.
13. Bhora F, Ayub A, Forleiter C, Huang C, Alshehri K, Rehmani S, et al. Treatment of benign tracheal stenosis using endoluminal spray cryotherapy. JAMA Otolaryngol Head Neck Surg. 2016;142(11):1082.
14. Gompelmann D, Eberhardt R, Schuhmann M, Heussel C, Herth F. Self-expanding Y stents in the treatment of central airway stenosis: a retrospective analysis. Ther Adv Respir Dis. 2013;7(5):255–63.
15. Kim J, Shin J, Kim J, Song H, Song S, Park C. Metallic stent placement for the management of tracheal carina strictures and fistulas: technical and clinical outcomes. AJR Am J Roentgenol. 2014;202(4):880–5.
16. Terra R, Bibas B, Minamoto H, Waisberg D, Tamagno M, Tedde M, et al. Decannulation in tracheal stenosis deemed inoperable is possible after long-term airway stenting. Ann Thorac Surg. 2013;95(2):440–4.
17. Jeong B, Um S, Suh G, Chung M, Kwon O, Kim H, et al. Results of interventional bronchoscopy in the management of postoperative tracheobronchial stenosis. J Thorac Cardiovasc Surg. 2012;144(1):217–22.
18. Gildea T, Young B, Machuzak M. Application of 3D printing for patient-specific silicone stents: 1-year follow-up on 2 patients. Respiration. 2018;96(5):488–94.
19. Schweiger T, Gildea T, Prosch H, Lang G, Klepetko W, Hoetzenecker K. Patient-specific, 3-dimensionally engineered silicone Y-stents in tracheobronchomalacia: clinical experience with a novel type of airway stent. J Thorac Cardiovasc Surg. 2018;156(5):2019–21.
20. Saueressig M, Sanches P, Neto A, Moreschi A, Oliveira H, Xavier R. Novel silicone stent to treat tracheobronchial lesions: results of 35 patients. Asian Cardiovasc Thorac Ann. 2010;18(6):521–8.

21. Marchese R, Poidomani G, Paglino G, Crimi C, Lo Nigro C, Argano V. Fully covered self-expandable metal stent in tracheobronchial disorders: clinical experience. Respiration. 2015;89(1):49–56.
22. Shin J. Interventional management of tracheobronchial strictures. World J Radiol. 2010;2(8):323.
23. Fortin M, MacEachern P, Hergott C, Chee A, Dumoulin E, Tremblay A. Self-expandable metallic stents in nonmalignant large airway disease. Can Respir J. 2015;22(4):235–6.
24. Tsakiridis K, Darwiche K, Visouli A, Zarogoulidis P, Machairiotis N, Christofis C, et al. Management of complex benign post-tracheostomy tracheal stenosis with bronchoscopic insertion of silicon tracheal stents, in patients with failed or contraindicated surgical reconstruction of trachea. J Thorac Dis. 2012;4(S1):32–40.
25. Folch E, Keyes C. Airway stents. Ann Cardiothorac Surg. 2018;7(2):273–83.
26. Alazemi S, Lunn W, Majid A, Berkowitz D, Michaud G, Feller-Kopman D, et al. Outcomes, health-care resources use, and costs of endoscopic removal of metallic airway stents. Chest. 2010;138(2):350–6.
27. Lunn W, Feller-Kopman D, Wahidi M, Ashiku S, Thurer R, Ernst A. Endoscopic removal of metallic airway stents. Chest. 2005;127(6):2106–12.
28. Karush J, Seder C, Raman A, Chmielewski G, Liptay M, Warren W, et al. Durability of silicone airway stents in the management of benign central airway obstruction. Lung. 2017;195(5):601–6.
29. Khemasuwan D, Gildea T, Machuzak M. Complex metallic stent removal. J Bronchol Interv Pulmonol. 2014;21(4):358–60.
30. Musani A, Jensen K, Mitchell J, Weyant M, Garces K, Hsia D. Novel use of a percutaneous endoscopic gastrostomy tube fastener for securing silicone tracheal stents in patients with benign proximal airway obstruction. J Bronchol Interv Pulmonol. 2012;19(2):121–5.
31. Chung F, Chen H, Chou C, Yu C, Kuo C, Kuo H, et al. An outcome analysis of self-expandable metallic stents in central airway obstruction: a cohort study. J Cardiothorac Surg. 2011;6(1):46.
32. http://www.jsre.org/info/0801_fda.pdf. Accessed 20 Feb 2020.
33. Gaissert H, Grillo H, Wright C, Donahue D, Wain J, Mathisen D. Complication of benign tracheobronchial strictures by self-expanding metal stents. J Thorac Cardiovasc Surg. 2003;126(3):744–7.
34. Krimsky W, Broussard J, Sarkar S, Harley D. Bronchoscopic spray cryotherapy: assessment of safety and depth of airway injury. J Thorac Cardiovasc Surg. 2010;139(3):781–2.
35. Krimsky W, Rodrigues M, Malayaman N, Sarkar S. Spray cryotherapy for the treatment of glottic and subglottic stenosis. Laryngoscope. 2010;120(3):473–7.
36. Fernando HC, Dekeratry D, Downie G, Finley D, Sullivan V, Sarkar S, et al. Feasibility of spray cryotherapy and balloon dilation for non-malignant strictures of the airway. Eur J Cardiothorac Surg. 2011;40(5):1177–80.

Are Engineered Tissues Useful for Tracheal Reconstruction?

46

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Introduction

Most tracheal disorders requiring resection do not affect the entire length of the trachea. Resection of short tracheal segments was first reported mid twentieth century [1, 2]. Subsequent development of mobilization techniques helped to extend the resectable length up to several centimeters [3]. Reconstruction via primary anastomosis to re-establish a patent airway can therefore be performed safely in the majority of patients referred to a thoracic surgeon [4]. However, in rare cases, neoplasms, iatrogenic injury, and autoimmune disease can involve most of or the entire length of the trachea, creating an unmet clinical need for a suitable replacement. Over the past century, scientists and surgeons have tried to meet this need by exploring synthetic tracheal prosthesis, tracheal transplantation, tracheal replacement with biomaterials, tracheal replacement with autologous tissue, and tissue engineered tracheal grafts [5, 6]. This chapter focuses on outcomes of tissue engineered implants for tracheal reconstruction.

Search Strategy

We searched Pubmed for articles published from January 2000 to September 2019 for the key words "tracheal replacement" or "tracheal substitute" or "tracheal regeneration" or "tracheal tissue engineering" or "tracheal transplantation". We included

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Table 46.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with long-segment tracheal defects not amenable to primary repair	Tissue engineered tracheal reconstruction	Tracheal allotransplantation, autologous tissue reconstruction, bioprosthetic reconstruction	Morbidity and mortality

only studies in which patients underwent circumferential or near-circumferential (>270°) replacement of the trachea (Table 46.1). We excluded animal model and non-clinical studies. We limited our search to publications in English language and excluded abstracts, conference presentations, editorials, and expert opinions. We included reviews in which new patient information was reported and excluded all retracted articles from our analysis.

Results

An initial search using pre-specified criteria identified 2554 articles. After excluding articles that described solely pre-clinical, animal, or non-circumferential repairs this number was reduced to 25. An additional two articles were excluded due to retraction. Among the remaining 23 articles only 5 employed a tissue engineering approach. In contrast, the other 18 articles employed allotransplantation, autologous tissue, or bioprosthetics reconstruction of the trachea, which will be discussed separately. We included two articles that we view with skepticism given revelations of academic misconduct on the part of the senior author [7, 8]. In all of these reports on tracheal reconstruction, publications have been limited to single case reports or case series. To date, there have been no randomized controlled trials or high-powered observational or cohort studies, and the quality of evidence ranges from low to very low.

Tracheal Tissue Engineering

Tissue engineering is an attractive methodology to provide a solution to organ and tissue shortage. Conceptually, tissue engineering most commonly involves the implantation of a biodegradable scaffold seeded with harvested host cells. After culture in a bioreactor or after direct implantation in the host, a population of stem cells within the seeded cells either differentiates into mature cells or recruits and organizes circulating or adjacent host cells [9]. In either case, this process theoretically leads to repopulation of the graft and replacement of the biodegradable scaffold through deposition of a new extracellular matrix.

This methodology has captured public imagination since its description by Langer and Vacanti [10]. In particular, a tissue engineering approach has enormous potential in pediatric populations, as mature grafts may have the ability to

grow with the child into adulthood and spare such patients initial size-mismatch or subsequent reoperation. Tissue engineering has shown some promise in bladder reconstruction and in vascular grafts, but widespread clinical adoption remains limited [11, 12].

Unfortunately, the field of tracheal tissue engineering has been mired by controversy and scientific misconduct. Several reports highlighted the successful clinical translation of a tissue engineering approach [13–15]. However, over the last 5 years it has become clear that the reported success of this technique was overstated and many of the patients who underwent these procedures developed devastating complications [7, 16–19].

In separate reports, two pediatric patients have undergone treatment with tissue engineered tracheal conduits to repair complications of severe congenital airway defects [20–22]. The first patient developed a tracheal aortic fistula as a results of recurrent stenting procedures. For this patient, a suspension of cells isolated from bone-marrow aspirate were used to seed a cadaveric tracheal homograft. The tracheal rings of the graft were also injected with tissue transforming growth factor beta and the entire construct soaked in human recombinant erythropoietin and granulocyte colony stimulating factor prior to implantation [20]. Post-operatively the patient required multiple stenting and bronchoscopic procedures, especially within the first year of implantation; however, the graft remained patent with evidence of a ciliated epithelial cell layer in the last reported follow-up at four years [21].

In 2012, a second pediatric patient with multiple congenital abnormalities of the airway and multiple prior interventions underwent treatment with a tissue engineered tracheal conduit [22]. A decellularized cadaveric tracheal graft was seeded over a period of 48 h in a bioreactor with expanded bone marrow-derived mesenchymal stromal cells as well as autologous respiratory epithelial cell obtained from mucosal biopsies of the nasal septum. The graft was supported by a stent, but without a pedicled tissue buttress. While the initial postoperative course was uncomplicated, the patient deteriorated on post-operative day 15 and suffered a prolonged respiratory arrest secondary to airway collapse. This episode was associated with severe hypoxic brain injury and the patient died shortly thereafter.

Alternatives to Tissue Engineering in Tracheal Repair

Alternative methods of tracheal reconstruction have been reported including tracheal allotransplantation, autologous tissue reconstruction, and bioprosthetic repair. Each methodology is associated with its own unique advantages and drawbacks which are compared to tissue engineering in Table 46.2. It is important to state that treatment with radiotherapy alone remains a viable albeit not ideal alternative for patients with adenoid cystic carcinoma and squamous cell carcinoma of the trachea. To date, there has been no randomized controlled trials or direct comparisons between these various methods and the quality of evidence is low to very low. A brief description of each methodology is provided below.

Table 46.2 Comparison of methodology for tracheal reconstruction

Method	Study	Patients	Outcomes	Mechanism	Advantages	Disadvantages	Quality of evidence
Allo-transplantation	Delaere et al. 2012 [25]	6	Partial graft rejection in 50% of patient. No reported graft related mortality	Heterotopic revascularization of donor trachea prior to implantation as a tracheal conduit	Structural and mechanical properties of native tissue	Weeks of heterotopic revascularization Immunosuppression	Low quality
Autologous tissue reconstruction	Spaggiari et al. 2005 [27]	1	ARDS, graft stenosis	Tubularized autologous tissue with vascular pedicle supported by a stent +/− additional support with harvested costal cartilage	No need for immunosuppression	Technically difficult	Low quality
	Olias et al. 2005 [28]	1	No direct graft related morbidity or mortality		Potentially single day procedure	Lack of mucociliary clearance	
	Fabre et al. 2013 [29]	12	ARDS (58%), brachiocephalic artery rupture (8.3%)		Retains blood supply	Donor site morbidity	
	Zhang et al. 2015 [30]	5	Hemoptysis/30-day mortality (20%)				
	Thomet et al. 2018 [31]	2	No direct graft related morbidity or mortality				
	Kolb et al. 2018 [32]	1	Revision at 2 years to close tracheostomy				

Bioprosthetic reconstruction	Hoffman et al. 2001 [33]	1	Bridge to transplant but patent at explantation	Aortic homograft or acellular dermal matrix implanted as a tubularized conduit generally with a supporting stent	Off-shelf availability	Lack of mucociliary clearance	Low quality
	Davidson et al. 2009 [36]	1	Dehiscence, 30-day mortality		No immunosuppression	No robust blood supply	
	Warts et al. 2010 [37]	6	Long-term stent dependence (83%), graft dehiscence requiring operative revision (50%)				
	Bolton et al. 2017 [39]	1	Required operative revision				
	Martinod et al. 2018 [40]	5	Long term stent dependence (40%), tracheal granuloma (20%), no direct graft related mortality				
Tissue engineering	Macchiarini et al. 2008 [13]	1[a]	Pneumonectomy	Biodegradable scaffold or decellularized donor trachea seeded with autologous stem cells.	No immunosuppression	Difficult to revascularize	Very low quality
	Elliot et al. 2012 [20]	1	Multiple stents		Possibility of growth potential	Ex-vivo cell seeding	
	Elliot et al. 2017 [22]	1	Graft collapse, 30-day mortality				

ARDS acute respiratory distress syndrome

[a]Studies involving additional patients have been retracted, further investigation of outcomes ongoing

Tracheal Allotransplantation

Tracheal allotransplantation has been challenging due to the segmental blood supply of the trachea, which makes a traditional vascular anastomosis and single stage transplant ineffective [23]. Delaere et al. have sought to overcome these issues through a two-stage procedure, in which the donor trachea is implanted in the forearm of the recipient after being wrapped in a fasciocutaneous flap perfused by a radial vascular pedicle [24]. During this time the recipient is placed on immunosuppressants while revascularization occurs through ingrowth of recipient vessels. After sufficient ingrowth, the tracheal allograft along with the perfusing vascular pedicle can be explanted and implanted in the orthotopic position, while the blood supply is reestablished by anastomosis of the pedicle to the superior thyroid artery and internal jugular vein.

Two stage tracheal allotransplantation has been performed in 6 patients to date [17, 24]. The primary complications have been graft rejection leading to partial loss of the allograft in three patients. Over time, the reported technique has evolved to promote donor repopulation of the mucosa and prevent stricture. Eventually, graft-chimerism may be achieved allowing for withdrawal of immunosuppressants [17, 25, 26].

Autologous Tissue Reconstruction

Autologous tissue reconstruction relies on a well perfused pedicled graft which can be tubularized into a neotrachea [27–30]. These grafts may be supported by stenting or through implantation of cartilaginous rings harvested and fashioned from costal cartilage. Fabre et al. reported the largest series using this technique, which included 12 patients [29]. Modified versions of this technique have been utilized by two other independent groups in three additional patients [31, 32] .

The results of autologous repair have been mixed. There is generally a need for at least short-term stenting and it is not possible to regenerate airway epithelium, thus the mucociliary escalator is lost. In the series reported by Fabre et al., 58% developed acute respiratory distress syndrome and two patients were tracheostomy dependent. A possible solution is described by Olias et al., who harvest oral mucosal grafts to line the lumen of their neo-tracheas, which may provide some mucociliary function. Unfortunately, this requires a staged procedure and is associated with donor site morbidity [28].

Bioprosthetic Reconstruction

Between 2001 and 2019, aortic interpositional homografts and acellular dermal matrix have been used in circumferential repairs by 5 different groups of investigators in 14 individual patients [33–39]. The largest study involved 6 patients, in which homografts that were supported internally by a stent and externally by a muscle flap buttress were used to reconstruct the airway in patients with large mucoepidermoid and adenoid cystic carcinomas [35, 37]. Long-term stenting was required in 80% and half encountered major complications such as anastomotic dehiscence, sternal dehiscence, and fungal infection of the graft.

More recently, Martinod et al. have reported tracheal repair in five patients with benign laryngeal tracheal stenosis through aortic homograft reconstruction supported by Nitinol stents and buttressed with strap muscle [38, 40]. Importantly, Martinod preserved the membranous portion of the native trachea in their repair. The authors proposed an "in vivo tissue engineering" mechanism in which retained growth and angiogenic factors within the donor extracellular matrix are released and lead to the migration, proliferation, and differentiation of host cells [38]. In long-term follow-up ranging from 9 months to 7 years all patients remain alive and three have had stents removed.

Conclusions and Recommendations

Tissue engineered tracheal grafts have been associated with significant mortality and morbidity in translation to clinical practice. When possible, primary tracheal resection and reconstruction is the safest form of repair. In rare cases of tracheal pathology that precludes primary repair, allotransplantation, autologous tissue reconstruction, and bioprosthetic repair are viable options and associated with less morbidity and mortality than tissue engineered approaches. The overall quality of evidence remains low and is based on limited case series and case reports.

Recommendation

- We recommend against the use of tissue engineered trachea for tracheal reconstruction (quality of evidence low; strong recommendation).

A Personal View of the Data

Attempts to replace lost human tissue with synthetic material have been made since the early days of medicine and surgery. In some applications, such as heart valve or joint prostheses, this approach has been very successful. However, three inherent characteristics of the native trachea make it a particularly challenging application: (1) it is in contact with the outside world; (2) it requires excellent blood supply; and (3) it resists the native universal proclivity of most tissues to close a space or orifice. In areas where implanted grafts or devices come in contact with the outside world, colonization and subsequent infection are major limiting factors. Once colonized, a biofilm establishes itself that provides a constant source of reinfection and necessitates graft removal in most cases. Tissue engineering, the concept of creating a living graft that fully integrates in the host similar to a donor organ, could theoretically solve this problem and enable the host's immune system together with the graft's inherent barrier function to protect the implant and maintain intricate mechanical properties [10]. In order to do so, any tissue graft of relevant scale would have to be perfused by the recipient's cardiovascular system. However, to date, no tissue

engineering approach has enabled the formation of perfusable tissue, i.e. tissue with intact vasculature [41]. In fact, NASA is currently conducting a Centennial Challenge to increase awareness of this unmet need, and supports research to generate a 1 × 1 cm sized section of perfusable living tissue [42]. As surgeons we learned that transplantation of a living tissue graft thicker than 0.2 mm will require an immediate blood supply or lead to devastating failure. We also learned that implanting a foreign material without tissue coverage and in contact with the outside world will lead to failure. Unfortunately, until technologies are developed that enable the formation of viable, mature (barrier and mechanical stability), and perfusable tissue grafts, we have no option but to continue to use established techniques to treat patients with tracheal disorders.

References

1. Belsey R. Resection and reconstruction of the intrathoracic trachea. Br J Surg. 1950;38:200–5.
2. Deslauriers J. Birth of airway surgery and evolution over the past fifty years. Thorac Surg Clin. 2018;28:109–15.
3. Grillo HC. Surgery of the trachea. Curr Probl Surg. 1970;7(7):3–59.
4. Grillo HC. Notes on the windpipe. Ann Thorac Surg. 1989;47:9–26.
5. Grillo HC. Tracheal replacement: a critical review. Ann Thorac Surg. 2002;73:1995–2004.
6. Udelsman B, Mathisen DJ, Ott HC. A reassessment of tracheal substitutes—a systematic review. Ann Cardiothorac Surg. 2018;7:175–82.
7. Cyranoski D. Investigations launched into artificial tracheas. Nature. 2014;516:16–7.
8. Delaere PR, Van Raemdonck D. The trachea: the first tissue-engineered organ? J Thorac Cardiovasc Surg. 2014;147:1128–32.
9. Roh JD, Sawh-Martinez R, Brennan MP, et al. Tissue-engineered vascular grafts transform into mature blood vessels via an inflammation-mediated process of vascular remodeling. Proc Natl Acad Sci U S A. 2010;107:4669–74.
10. Langer R, Vacanti JP. Tissue engineering. Science. 1993;260:920–6.
11. Adamowicz J, Pokrywczynska M, Van Breda SV, Kloskowski T, Drewa T. Concise review: tissue engineering of urinary bladder; we still have a long way to go? Stem Cells Transl Med. 2017;6:2033–43.
12. Udelsman BV, Maxfield MW, Breuer CK. Tissue engineering of blood vessels in cardiovascular disease: moving towards clinical translation. Heart. 2013;99:454–60.
13. Macchiarini P, Jungebluth P, Go T, et al. Clinical transplantation of a tissue-engineered airway. Lancet. 2008;372:2023–30.
14. Jungebluth P, Alici E, Baiguera S, et al. Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. Lancet. 2011;378:1997–2004.
15. Gonfiotti A, Jaus MO, Barale D, et al. The first tissue-engineered airway transplantation: 5-year follow-up results. Lancet. 2014;383:238–44.
16. Vogel G. Trachea transplants test the limits. Science. 2013;340:266–8.
17. Delaere P, Van Raemdonck D. Tracheal replacement. J Thorac Dis. 2016;8:S186–96.
18. Heckscher S, Carlberg I, Gahmberg C. Karolinska Institutet and the Macchiarini case. 2016. https://news.ki.se/sites/default/files/migrate/karolinska_institutet_and_the_macchiarini_case_summary_in_english_and_swedish.pdf. Accessed 12 Feb 2020.
19. Molins L. Patient follow-up after tissue-engineered airway transplantation. Lancet. 2019;393:1099.
20. Elliott MJ, De Coppi P, Speggiorin S, et al. Stem-cell-based, tissue engineered tracheal replacement in a child: a 2-year follow-up study. Lancet. 2012;380:994–1000.

21. Hamilton NJ, Kanani M, Roebuck DJ, et al. Tissue-engineered tracheal replacement in a child: a 4-year follow-up study. Am J Transplant. 2015;15:2750–7.
22. Elliott MJ, Butler CR, Varanou-Jenkins A, et al. Tracheal replacement therapy with a stem cell-seeded graft: lessons from compassionate use application of a GMP-compliant tissue-engineered medicine. Stem Cells Transl Med. 2017;6:1458–64.
23. Delaere P, Van Raemdonck D, Vranckx J. Tracheal transplantation. Intensive Care Med. 2019;45:391–3.
24. Delaere P, Vranckx J, Verleden G, De Leyn P, Van Raemdonck D, Leuven Tracheal Transplant Group. Tracheal allotransplantation after withdrawal of immunosuppressive therapy. N Engl J Med. 2010;362:138–45.
25. Delaere PR, Vranckx JJ, Meulemans J, et al. Learning curve in tracheal allotransplantation. Am J Transplant. 2012;12:2538–45.
26. Delaere PR, Vranckx JJ, Den Hondt M, Leuven Tracheal Transplant Group. Tracheal allograft after withdrawal of immunosuppressive therapy. N Engl J Med. 2014;370:1568–70.
27. Spaggiari L, Calabrese LS, D'Aiuto M, et al. Successful subtotal tracheal replacement (using a skin/omental graft) for dehiscence after a resection for thyroid cancer. J Thorac Cardiovasc Surg. 2005;129:1455–6.
28. Olias J, Millan G, da Costa D. Circumferential tracheal reconstruction for the functional treatment of airway compromise. Laryngoscope. 2005;115:159–61.
29. Fabre D, Kolb F, Fadel E, et al. Successful tracheal replacement in humans using autologous tissues: an 8-year experience. Ann Thorac Surg. 2013;96:1146–55.
30. Zhang S, Liu Z. Airway reconstruction with autologous pulmonary tissue flap and an elastic metallic stent. World J Surg. 2015;39:1981–5.
31. Thomet C, Modarressi A, Ruegg EM, Dulguerov P, Pittet-Cuenod B. Long-segment tracheal reconstruction with free radial forearm flap reinforced by rib cartilage. Ann Plast Surg. 2018;80:525–8.
32. Kolb F, Simon F, Gaudin R, et al. 4-Year follow-up in a child with a total autologous tracheal replacement. N Engl J Med. 2018;378:1355–7.
33. Hoffman TM, Gaynor JW, Bridges ND, Paridon SM, Spray TL. Aortic homograft interposition for management of complete tracheal anastomotic disruption after heart-lung transplantation. J Thorac Cardiovasc Surg. 2001;121:587–8.
34. Azorin JF, Bertin F, Martinod E, Laskar M. Tracheal replacement with an aortic autograft. Eur J Cardiothorac Surg. 2006;29:261–3.
35. Wurtz A, Porte H, Conti M, et al. Tracheal replacement with aortic allografts. N Engl J Med. 2006;355:1938–40.
36. Davidson MB, Mustafa K, Girdwood RW. Tracheal replacement with an aortic homograft. Ann Thorac Surg. 2009;88:1006–8.
37. Wurtz A, Porte H, Conti M, et al. Surgical technique and results of tracheal and carinal replacement with aortic allografts for salivary gland-type carcinoma. J Thorac Cardiovasc Surg. 2010;140:387–93 e2.
38. Martinod E, Paquet J, Dutau H, et al. In vivo tissue engineering of human airways. Ann Thorac Surg. 2017;103:1631–40.
39. Bolton WD, Ben-Or S, Hale AL, Stephenson JE. Reconstruction of a long-segment tracheal defect using an alloderm conduit. Innovations (Phila). 2017;12:137–9.
40. Martinod E, Chouahnia K, Radu DM, et al. Feasibility of bioengineered tracheal and bronchial reconstruction using stented aortic matrices. JAMA. 2018;319:2212–22.
41. Delaere P, Lerut T, Van Raemdonck D. Tracheal transplantation: state of the art and key role of blood supply in its success. Thorac Surg Clin. 2018;28:337–45.
42. STMD: Centennial Challenges. 2019. https://www.nasa.gov/directorates/spacetech/centennial_challenges/vascular_tissue.html. Accessed 2 Nov 2019.

Management of Positive Margins After Resection of Primary Tracheal Malignancies

47

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Introduction

Like all cancer operations, the success of tracheal resection for malignancy is measured by its completeness. An in-depth pathological characterization of the most common primary tracheal tumors demonstrated that positive margins, lymphatic invasion and tumor extension into the thyroid gland in squamous cell carcinoma (SCC) and positive margins, extramural disease, perineural invasion and positive lymph nodes in adenoid cystic carcinoma (ACC) predicted poor long-term prognosis [1, 2]. The presence of positive margins on frozen section requires removal of additional tissue and real-time examination of new margins with additional resection until cancer-free margins are achieved, if possible. Superseding this principle, however, is the central tenet of tracheal surgery—airway reconstruction must be completed as a low tension, well-vascularized anastomosis. Anatomic features of the trachea, such as its finite length, segmental blood supply, and need to function as a semi-rigid conduit between two relatively fixed points, limit the amount of trachea that can be safely resected and reconstructed. In the hands of an experienced airway surgeon, on average one-half the length of the upper trachea (~4.5 cm) can be excised while leaving enough native trachea for safe reconstruction [3].

Well-differentiated indolent primary tracheal tumors such as ACC have a propensity for circumferential or longitudinal submucosal extension beyond the gross tumor borders, which results in a high rate of positive surgical margins and late recurrence after tracheal resection [4, 5]. In ACC, particular attention should be paid to the *type* of positive margin, since grossly positive tracheal margins negatively

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impact survival within 5 years whereas microscopically positive tracheal margins negatively impact survival only after 15 years [1]. In these cases, positive resection margin status must be balanced with the ability to perform a tension-free anastomosis. Here we review and discuss the literature regarding the management of positive margins after resection of primary tracheal tumors, with an emphasis on SCC and ACC, as the rarity of more low-grade tracheal malignancies such as mucoepidermoid carcinoma and carcinoid has precluded their evaluation in a data-driven manner.

Search Strategy

To identify the highest quality literature addressing the optimal management of positive margins during the resection of primary tracheal tumors, we performed a PubMed search of English language publications with abstracts involving human subjects from 1999 to 2019. Select high-impact studies published prior to 1999 were included if they were frequently cited by recent literature. Search terms included "primary tracheal tumor" AND "resection" AND ("positive margins" OR "incomplete resection" OR "adjuvant therapy") (Table 47.1). References from topical reviews published within the last 2 years were mined for relevant studies that were missed by our database search. Case reports and editorials were excluded to isolate higher quality data. The resulting original research publications were critically assessed and classified using the GRADE system.

Results

Description of Published Data

The gold standard for treatment of tracheal tumors is complete resection, which provides superior long-term survival and functional outcomes compared to definitive radiation [6]. Because under-treatment of these infrequently encountered tumors can be as high 32%, patients should undergo a multidisciplinary evaluation at a major center before concluding that a patient has unresectable disease [7]. Good survival and disease progression outcomes have been described with the addition of adjuvant radiation therapy (RT) after complete or incomplete tracheal resection, but the data is not robust. Available data are derived largely from institutional series and retrospective analyses that suffer from inherent selection bias (Table 47.2) [8–16].

Table 47.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcome)
Primary tracheal tumors (e.g. SCC, ACC)	Adjuvant radiation or chemotherapy	Surgery alone	Survival Recurrence Complications

SCC squamous cell carcinoma, *ACC* adenoid cystic carcinoma

Table 47.2 Key studies examining outcomes after resection of primary tracheal tumors

Study	Patients (N)	Treatment	Results	Finding(s)	Quality of Evidence
Regnard et al. [11]	Primary tracheal tumors = 208 – SCC = 94 – ACC = 65 – Adenocarcinoma = 4 – Carcinoid = 9 – MEC = 4	R0 vs R1/R2 resections Postoperative chemo/RT	SCC 5-year OS: – R0 = 55% – R1/R2 = 25% ($p < 0.02$) ACC 5-year OS: – R0 = 82% – R1/R2 = 63% ($p < 0.20$) Positive margins – ACC = 38% – SCC = 26% R1/R0 SCC 5-year OS – No-RT = 0% – +RT = 47% ($p < 0.05$)	Higher survival for higher grade tumors, and likely ACCs, after complete resection. RT improves survival for R1/R2, but not R0, resections of SCC, but not ACC	Medium
Gaissert et al. [8]	ACC/SCC = 270	Unresected = 79 – Tumor length (67%) – Regional extent (24%) – Distant metastasis (7%) – Other (2%) Resected = 191 – + airway margins (40%) – + LNs (19.4%)	ACC 5-Year OS – Unresected = 33% – Resected = 52% 10-Year OS – Unresected = 10% – Resected = 29% SCC 5-Year OS – Unresected = 7.3% – Resected = 39% 10-Year OS – Unresected = 4.9% – Resected = 18% Long-term survival associations – Complete resection ($p < 0.05$) – Negative airway margins ($p < 0.05$) ACC ($p < 0.001$)	Locoregional involvement determines resectability. Resection improves survival, particularly with R0 resection and ACC tumors	Medium

(continued)

Table 47.2 (continued)

Study	Patients (N)	Treatment	Results	Finding(s)	Quality of Evidence
Webb et al. [10]	Primary tracheal tumors = 74 patients	Surgery only = 10 (6 SCC, 1 ACC, 3 other) Surgery + RT = 11 (4 SCC, 6 ACC, 1 other)	Kaplan-Meier plot OS p = 0.159 Kaplan-Meier plot DSS p = 0.111 ACC had better outcomes	Insufficient N to show significant benefit of adjuvant RT Authors continue to recommend adjuvant RT	Low
Honings et al. [13]	Tracheal malignancies = 308 – SCC 52.9% – ACC 7.1%	No intervention = 103 Surgery only = 34 RT only = 156	5-Year OS – No surgery = 15% – Surgery = 51% 10-Year OS – No surgery = 6% – Surgery = 33% (p < 0.0001)	Broaden use of skilled tracheal resection	Low
Xie et al. [15]	Primary tracheal tumors (resectable and unresectable) = 156	Surgery only (matched-pair) = 48 Surgery + RT = 48	Surgery only – Median survival = 42 months – 5-Year OS = 43.9% Surgery + RT – Median survival = 91 months 5-Year OS = 55.7% (p = 0.132) SCC subset – 5-Year OS: 58.2% (RT) vs 6.7% (no-RT)	Due to study limitations, authors suggest RT for tracheal cancers	Low
Chen et al. [14]	Resected ACC of trachea = 48	R0 no-RT = 11 R1, R2 = 37 – No-RT = 13 – + RT = 24 (12 + chemo)	R0 vs R1/R2 = no difference R1/R2 alone – DFS = 62 months – OS = 78 months R1/R2 + RT – DFS = 92 months (p = 0.027) – OS = 125 months (p = 0.004) R1/R2 + RT ± chemo – DFS p = 0.390 – OS p = 0.646	Adjuvant RT for R1/R2 No survival benefit with chemo after adjuvant RT	Medium

Yusuf et al. [16]	NCI database of primary tracheal tumors + resection = 549 – SCC = 234 – ACC = 180	Adjuvant RT = 300 (55%)	RT was not associated with OS ($p > 0.05$) Positive margins more likely to have received RT (OR 1.80, CI 1.06–3.07) ACC more likely to have received RT	No appreciated benefit from adjuvant RT for resected primary tracheal tumors	Medium
Hogerle et al. [12]	ACC of trachea = 38	Surgery only = 7 Surgery + RT = 13 – R0 = 9 – R1 = 10 – R2 = 1 – All R1/R2 received RT RT only = 18	5-Year OS – Surgery only = 100% – Surgery + RT = 84% – RT only = 100% 10-Year OS – Surgery only = 80% – Surgery + RT = 84% – RT only = 83% No difference in OS between R0 and R1/R2	Good OS achieved with RT in case of R1/R2 resections. Cannot comment on R1/R2 ± RT since all incomplete resections received RT	Low
Maziak et al. [9]	ACC of trachea = 38	Surgery only = 6 Surgery + RT = 26 RT only = 6	Median OS – R0 = 210 months – R1/R2 = 120 months	Adjuvant RT appeared to favorably influence outcomes	Low

ACC adenoid cystic carcinoma, *MEC* mucoepidermoid carcinoma, *NCI* National Cancer Institute, *OS* overall survival, *RT* radiation therapy, *SCC* squamous cell carcinoma

Several studies span long time periods such that improvements in surgical technique, perioperative care and radiation regimens need to be considered. In addition, many studies fail to assess the effect of adjuvant RT across different histologies (ACC versus SCC) and resection margin status (R0, R1, R2).

Historical Base of Knowledge

Several key early studies provided the first look at long-term results for patients with resected primary tracheal tumors. These studies challenged the assumption that an R0 resection was required and introduced the idea that postoperative RT could help achieve local control and prolong survival. The summary of their findings are listed here:

- In patients with SCC, positive lymph nodes or invasive tumor at the margin was associated with decreased survival compared to negative lymph nodes and negative or *in situ* disease at the margin [4, 5, 8].
- In patients with ACC, positive margins or positive lymph nodes appeared to have little effect on survival [4, 5, 8].
- Postoperative RT was recommended for patients in whom surgical margins were close, when microscopic tumor was found at the margin or in the lymph nodes, or in patients with ACC since this histologic type extends for long distances along the nerves and submucosa [4, 5, 8–11].
- Most patients with SCC would likely undergo adjuvant RT given the close margins inherent in tracheal surgery [4, 5, 8, 10, 11].

Recent Retrospective Analyses

Out of 38 English-language papers found from 1999 to 2019 using search terms "primary tracheal tumor" AND "resection" AND ("positive margins" OR "incomplete resection" OR "adjuvant therapy") on Pubmed, 12 were deemed appropriate as part of this review. Due to the limited number of studies addressing this topic, we included five papers published before 1999 that were recurrently referenced in recent reports. Most recent studies are retrospective and continue to show superior outcomes in patients who undergo surgical resection as the primary mode of therapy. Comparable survival outcomes between patients who undergo resection and patients who undergo resection with adjuvant RT indicate that adjuvant RT can provide "rescue" to patients with positive margins.

In a study of 20 patients with ACC who underwent resection from a single institution in Germany from 1991 to 2017 [12], 45% of patients had R0 resections and 55% of patients had incomplete (R1, R2) resections. Adjuvant RT was administered to all patients who had incomplete resections and to two patients who had R0 resections but close margins. Survival between patients who underwent surgery alone versus patients who underwent surgery and adjuvant RT was comparable (5-year

survival 100% versus 84%; 10-year survival 80% versus 84%). At 10 years, none of the patients who underwent surgery or surgery and radiation had local progression, and the incidence of distant disease progression was 35–40%. The authors also found no survival difference between complete and incomplete resections; however, the effect of adjuvant RT on patients with positive margins could not be examined as all patients with incomplete resections received RT.

In a retrospective epidemiological study looking at all patients with primary tracheal cancer in the Netherlands Cancer Registry between 1989 and 2002, 11.6% of 312 patients underwent surgical resection as primary treatment and two-thirds of these patients were given postoperative RT. Surgery provided a significant increase in overall survival at 5- and 10-years compared to patients who underwent no treatment or radiotherapy alone. Because adjuvant RT was used selectively in patients based on tumor stage and surgical margin status, outcome differences between patients who received postoperative RT and surgery alone were not possible to determine [13].

In a retrospective analysis of 48 patients who underwent surgery for ACC from four institutions in China from 1995 to 2012 [14], 11 had R0 resections and required no further therapy, 24 had incomplete resections and underwent adjuvant RT, and 13 had incomplete resections and did not undergo further therapy. Half of the patients (12/24) who had incomplete resections and underwent adjuvant RT also received adjuvant chemotherapy. There was no significant difference in survival between patients who had complete versus incomplete resections (median overall survival 121 versus 119 months, $p = 0.829$; median disease-free survival 98 versus 84 months, $p = 0.683$). In patients with incomplete resections, adjuvant RT significantly improved median disease-free survival (92 versus 62 months, $p = 0.027$) and median overall survival (125 versus 78 months, $p = 0.004$). The outcomes of patients with incomplete resections and adjuvant RT were comparable to patients who underwent complete resections. The addition of chemotherapy to the adjuvant regimen did not impact survival.

An Attempt to Utilize Big Data

Two large database studies employed statistical methods to compensate for selection bias and address the question of whether adjuvant RT improves survival of patients with primary tracheal tumors. Matched-pair analysis of the Surveillance, Epidemiology and End Results (SEER) database from 1988 to 2007 was performed using 48 patient pairs matched for type of surgery, disease extent, histology and gender [15]. There was a non-significant increase in median survival and overall survival among the 48 patients who underwent surgery and adjuvant RT compared to control patients who underwent surgery alone. Of note, 44 of the 48 patients undergoing surgery in each group underwent “subtotal” resection, defined as “local tumor destruction” or “local tumor excision” or “simple or partial surgical removal” or “debulking”. In subset analyses, adjuvant RT conferred a significant survival advantage in patients with SCC (5-year survival 58.2% versus 6.7%; $p = 0.0003$).

There was no information about the resection margin status in this study. Propensity-score matching of 549 patients in the National Cancer Database from 2004 to 2014 who underwent resection of primary tracheal tumors with or without adjuvant RT found that adjuvant RT was not associated with increased survival and that patients with ACC histology and positive margins were significantly more likely to have received postoperative RT [16].

Conclusions and Recommendations

There are no prospective, randomized trials concerning the management of SCC and ACC of the trachea. When making recommendations, we consider that (A) complete resection is limited by anastomotic tension and (B) adjuvant RT to the tracheal anastomosis can be done safely. As it stands, the data show that adjuvant RT may increase, but does not appear to decrease, survival among patients with positive margins. Given the tumor biology, constraints of the operation, and risk for long-term recurrence, we recommend that adjuvant RT should be given to patients with primary tracheal tumors after incomplete resection or in the presence of high-risk pathological features such as lymphatic or perineural invasion, extra-capsular extension, or advanced tumor stage. In addition, adjuvant RT can be considered in patients with complete resection and ACC or SCC histology.

Recommendation

- Adjuvant RT should be given after incomplete resection of primary tracheal tumors or in the presence of high-risk pathological features such as lymphatic or perineural invasion, extra-capsular extension, or advanced tumor stage (evidence quality moderate; strong recommendation).

A Personal View of the Data

Complete R0 resection is the gold standard treatment for primary tracheal tumors, and airway surgeons should be well-versed in techniques allowing for extended resection of the trachea when needed. In patients with positive margins after maximal safe tracheal resection, the available data is exclusively retrospective, but suggests that adjuvant RT provides a survival benefit, especially for patients with higher-grade cancers such as SCC. ACCs, while more indolent, do tend to recur late and may also benefit from adjuvant therapy, although the available data is mixed. High-risk pathological features that question the completeness of surgical resection should prompt consideration of adjuvant RT to maximize local control. There is no evidence that adjuvant chemotherapy provides benefit. Randomized prospective studies to support these clinical recommendations with more certainty will remain difficult to perform given the rarity of primary tracheal tumors.

References

1. Honings J, Gaissert HA, Weinberg AC, Mark EJ, Wright CD, Wain JC, Mathisen DJ. Prognostic value of pathologic characteristics and resection margins in tracheal adenoid cystic carcinoma. Eur J Cardiothorac Surg. 2010;37(6):1438–44.
2. Honings J, Gaissert HA, Ruangchira-Urai R, Wain JC, Wright CD, Mathisen DJ, Mark EJ. Pathologic characteristics of resected squamous cell carcinoma of the trachea: prognostic factors based on an analysis of 59 cases. Virchows Arch. 2009;455(5):423–9.
3. Mulliken JB, Grillo HC. The limits of tracheal resection with primary anastomosis: further anatomical studies in man. J Thorac Cardiovasc Surg. 1968;55(3):418–21.
4. Grillo HC. Tracheal tumors: surgical management. Ann Thorac Surg. 1978;26(2):112–25.
5. Grillo HC, Mathisen DJ. Primary tracheal tumors: treatment and results. Ann Thorac Surg. 1990;49(1):69–77.
6. Gaissert HA, Honings J, Gokhale M. Treatment of tracheal tumors. Semin Thorac Cardiovasc Surg. 2009;21(3):290–5.
7. Honings J, Gaissert HA, Verhagen AF, van Dijck JA, van der Heijden HF, van Die L, Bussink J, Kaanders JH, Marres HA. Undertreatment of tracheal carcinoma: multidisciplinary audit of epidemiologic data. Ann Surg Oncol. 2009;16(2):246–53.
8. Gaissert HA, Grillo HC, Shadmehr MB, Wright CD, Gokhale M, Wain JC, Mathisen DJ. Long-term survival after resection of primary adenoid cystic and squamous cell carcinoma of the trachea and carina. Ann Thorac Surg. 2004;78(6):1889–96.
9. Maziak DE, Todd TR, Keshavjee SH, Winton TL, Van Nostrand P, Pearson FG. Adenoid cystic carcinoma of the airway: thirty-two-year experience. J Thorac Cardiovasc Surg. 1996;112(6):1522–31.
10. Webb BD, Walsh GL, Roberts DB, Sturgis EM. Primary tracheal malignant neoplasms: the University of Texas MD Anderson Cancer Center experience. J Am Coll Surg. 2006;202(2):237–46.
11. Regnard JF, Fourquier P, Levasseur P. Results and prognostic factors in resections of primary tracheal tumors: a multicenter retrospective study. The French Society of Cardiovascular Surgery. J Thorac Cardiovasc Surg. 1996;111(4):808–13.
12. Hogerle BA, Lasitschka F, Muley T, Bougatf N, Herfarth K, Adeberg S, Eichhorn M, Debus J, Winter H, Rieken S, et al. Primary adenoid cystic carcinoma of the trachea: clinical outcome of 38 patients after interdisciplinary treatment in a single institution. Radiat Oncol. 2019;14(1):117.
13. Honings J, van Dijck JA, Verhagen AF, van der Heijden HF, Marres HA. Incidence and treatment of tracheal cancer: a nationwide study in the Netherlands. Ann Surg Oncol. 2007;14(2):968–76.
14. Chen F, Huang M, Xu Y, Li T, Xie K, Zhang L, Cheng D, Liu L, Che G, Hou M, et al. Primary tracheal adenoid cystic carcinoma: adjuvant treatment outcome. Int J Clin Oncol. 2015;20(4):686–92.
15. Xie L, Fan M, Sheets NC, Chen RC, Jiang GL, Marks LB. The use of radiation therapy appears to improve outcome in patients with malignant primary tracheal tumors: a SEER-based analysis. Int J Radiat Oncol Biol Phys. 2012;84(2):464–70.
16. Yusuf M, Gaskins J, Trawick E, Tennant P, Bumpous J, van Berkel V, Fox M, Dunlap N. Effects of adjuvant radiation therapy on survival for patients with resected primary tracheal carcinoma: an analysis of the National Cancer Database. Jpn J Clin Oncol. 2019;49(7):628–38.

Optimal Management of Posttransplant Bronchial Stenosis: Stenting or Reoperation

48

Lucas Hoyos Mejia and Andres Varela de Ugarte

Introduction

Airway complication (AC) is a significant cause of morbidity and mortality after pulmonary transplantation. The rate of related mortality is 2–4%, and as recently reported by Hayanga et al. [1], the presence of AC is associated with an almost three-fold increased risk of death and a more than 30% reduction in long-term survival. Moreover, *AC leads to increased costs*, more significant morbidity, and decreased quality of life [2]. The reported incidence of AC varies greatly, mostly because of the lack of a standardized classification system, ranging from 1.6% to 33%. However, recent publications report institutional rates of 11–14.5% [3–5], while Hayanga et al. [1] reported a data base analysis with a rate of 1.4%. Most experts agree that the rate of AC is currently around 15%. Bronchial stenosis is the most common AC with an incidence between 1.6% and 32% [6–10]. This chapter explores treatment options for this condition.

Search Strategy

A literature search of English language publications from 1990 to 2018 was used to identity published data on AC after lung transplant focused on airway stenosis and therapy alternatives. Databases searched were PubMed, Embase, Science Citation Index/Social Sciences, Citation Index, and Cochrane Evidence Based Medicine. Terms used in the search were: lung transplantation; bronchoscopy; airway stenting; bronchial stenting; bronchial stenosis; anastomotic complications; silicone stents; self-expandable metallic stents (Table 48.1). Only articles relevant to the original

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Difficult Decisions in Surgery: An Evidence-Based Approach,
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Table 48.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Lung transplant with symptomatic bronchial stenosis	Balloon dilation	No treatment	Symptom relief Morbidity Mortality
Lung transplant with symptomatic bronchial stenosis	Metal stenting	No treatment	Symptom relief Morbidity Mortality
Lung transplant with symptomatic bronchial stenosis	Silicon stenting	No treatment OR other treatments	Symptom relief Morbidity Mortality
Lung transplant with symptomatic bronchial stenosis	Surgery	No treatment OR other treatments	Symptom relief Morbidity Mortality

question were included on this analysis. However, there are no randomized, controlled trials examining this issue, and the best available evidence is from case series and expert opinion. Twenty observational retrospective series and four review articles were included in our analysis. The data was classified using the GRADE system.

Results

Background

Two patterns of bronchial stenosis have been described. The most common is central airway stenosis (CAS), located at the anastomotic line or within 2 cm of it, with an estimated incidence of 12–40% [9, 10]. The second pattern is non-anastomotic related stenosis called distal anastomosis stenosis (DAS), which develops distally to the suture line and can extend to segmental and subsegmental bronchi, with an incidence 2–4% [11, 12]. A common DAS involves the bronchus intermedius, of which the most devastating form is Vanishing Bronchus Intermedius Syndrome (VBIS), which can lead to complete stenosis of the airway. It occurs in about 2% of patients and is associated with high morbidity and mortality with a mean survival of 25 months after diagnosis [11].

Although bronchial stenosis may occur without an underlying cause, some risk factors are well known, such as extensive necrosis, dehiscence, infection, and bacterial infection, especially *Actinomyces* and *Pseudomonas aeruginosa* [9]. As for fungus, *Aspergillus species* [7, 9, 13] are the most frequently encountered. The surgical technique of telescoping the anastomosis increases the risk of bronchial stenosis [14, 15]. Early rejection recently has been described as a risk factor [8, 9, 11], as has the use of sirolimus for immunosuppression. A summary of factors thought to be related to AC is listed in Table 48.2 [1, 5, 13, 16–23].

Because of the variety and complexity of the AC, none of the classification systems presented in the past provided an integrated schema or were universally accepted [4, 9, 24–26]. Recent efforts of the ISHTL workgroup to tackle this

Table 48.2 Risk factors for airway complications

Group	Risk factor	Comments	Author, year (reference)
Donor factors	Height mismatch	Probably more related to bronchus diameter than the TLC itself Donor over 170 cm	Van de Wauwer (2007) [16] Yserbyt (2015) [5]
	Smoking history	No information regarding the amount	Hayanga (2016) [1]
	Prolong MV	Over 50 h of MV	Van de Wauwer (2007) [16]
	CMV infection	Mismatching	Hayanga (2016) [1]
Recipient factors	PGD G3	Recent evidence supports the conjunction of hypoxemia and high ventilation pressure needed, rather than PGD itself [7]	Ruttman (2005) [17]
	Acute rejection	Within the first year of transplant	Castleberry (2013) [18]
	Prolong MV	Questions regarding duration, plateaus, and PEEP pressure still unanswered	Alvarez (2001) [19]
	Age	Over 54 years of age, cumulative risk Hazard ratio 1.08 per year	Yserbyt (2015) [5]
	Gender	Male greater risk than female	Hayanga (2016) [1]
	Laterality	Right side	Yserbyt (2015) [5]
	Infections	Preoperative: Colonization with *Aspergillus fumigatus* or *Pseudomonas cepacia* Postoperative: Any infection during first 3 months *Haemophilus* spp. *Aspergillus* spp.	De Pablo (2005) [20] Herrera (2001) [21] Yserbyt (2015) [5] Felton (2012) [13]
	In hospital treatment	Pretransplant ICU care Posttransplant in hospital treatment	Hayanga (2016) [1]
	Diagnosis	COPD—recent reports suggest emphysema patients are not at increased risk IPF—controversial as a risk factor Diagnoses other than COPD and IPF are strongly supported as a risk factor	Van de Wauwer (2007) [16] Hayanga (2016) [1]
	Sirolimus		King-Biggs (2003) [22] Groetzner (2004) [23]

TLC total lung capacity, *MV* mechanical ventilation, *ICU* intensive care unit, *COPD* chronic obstructive pulmonary disease, *IPF* idiopathic pulmonary fibrosis

Modified after: Varela A, Hoyos L, Romero A, Campo-Cañaveral JL, Crowley S. Management of bronchial complications after lung transplantation and sequelae. Thorac Surg Clin. 2018;28:365–75 [29]

Table 48.3 ISHLT adult and pediatric airway complications after lung transplantation (proposed grading system)

Necrosis and Ischemia (I)	Location	(a) Perianastomosis—within 1 cm of the anastomosis
		(b) Extending >1 cm from anastomosis to major airway ()
		(c) Extending >1 cm from anastomosis into lobar or segmental
	Extent	(a) <50% circumferential
		(b) >50–100% circumferential
		(a) <50% circumferential necrosis
		(b) >50–100% circumferential necrosis
Dehiscence (D)	Location	(a) Cartilaginous
		(b) Membranous
		(c) Both
	Extent	(a) 0–25% of circumference
		(b) >25–50% circumference
		(c) >50–75% circumference
		(d) >75% circumference
Stenosis (S)	Location	(a) Anastomosis
		(b) Anastomosis plus lobar/segmental
		(c) Lobar or segmental only
	Extent	(a) 0–25% of reduction in cross-sectional area
		(b) >25–50% of reduction in cross-sectional area
		(c) >50% but <100% of reduction in cross-sectional area
		(d) 100% obstruction
Malacia (M)	Location	(a) Perianastomotica—within 1 cm of the anastomosis
		(b) Diffuse—involving the anastomosis and extending beyond 1 cm

Crespo MM, Mccarthy DP, Hopkins PM, Clark SC, Budev M, Bermudez CA, et al. ISHLT Consensus Statement on adult and pediatric airway complications after lung transplantation: Definitions, grading system, and therapeutics. J Heart Lung Transplant. 2019;37:548–63 [27]

problem resulted in a grading scheme intended to provide a unified system of assessment and measurement that allows for a standardized description of endoscopic changes as the airways evolve through the early and late stages of healing [27] (Table 48.3). The findings are categorized based on bronchoscopic findings within the first 2 weeks after lung transplant and the trajectory of changes over time.

Treatment Strategies

Dilation

Bronchial stenosis is defined as a fixed reduction in the caliber of the airway. When stenosis occurs at an anastomosis, it is based on the caliber of the distal airway to differentiate a pathologic stenosis from a simple size mismatch between donor and recipient airways. The narrowing usually presents between 2 to 9 months after

transplant [28] but could happen even years later. Asymptomatic patients are frequently diagnosed during a surveillance bronchoscopy. Symptomatic patients may present with dyspnea, cough, wheezing, postobstructive pneumonia, or declining flow rates on spirometry [6, 28, 29]. Flexible bronchoscopy is the gold standard for diagnosis. CT can achieve additional information about the exact location, length of the structure, and the patency of the distal airway with multiplanar reconstruction, which is useful for intervention planning [7, 30]. Asymptomatic and mild bronchial stenosis can be managed conservatively with radiological and endoscopic follow-up. Patients with lumen narrowing >50% or who have clinical symptoms are considered as having a severe narrowing, and multidisciplinary evaluation for treatment is recommended.

Despite the high prevalence of this complication, there have been no randomized, controlled trials examining the treatment of post-transplant stenosis, and the best available evidence is from case series and expert opinion. Here we present some of the alternative therapies available and their primary indications (Table 48.4) [9, 10, 14, 15, 19, 31–42].

Often the initial step in management can be accomplished by endoscopic balloon bronchoplasty, with a rigid scope, or using a bougie. Balloon bronchoplasty is, by far, the most common procedure and it is recommended as the first option [9, 14, 32,

Table 48.4 Bronchial stenosis incidence and endobronchial treatment options

Author	Year	Pt	RA	BS	%	Type	BD	Stent	TYPE	SX%
Colquhoun [31]	1994	67	75	5	6,7	1 CAS 4 DAS	N/A	3	Silicon	N/A
Alvarez [19]	2001	101	151	4	2,6	CAS	2	1	Metal	N/A
Chhajed [32]	2001	312	N/A	31		CAS	31	26	Metal	100
Burns [33]	2002	431	N/A	13		CAS	13	13	Metal	100
De Gracia [34]	2006	152	284	10	3,5	6 DAS 4 CAS	10	5	Metal	86
Kapoor [35]	2007	25	N/A	15		CAS	N/A	22	Metal	85
Murthy [15]	2007	272	N/A	67		N/A	29	13	Not stated	N/A
Thistlethwaite [9]	2008	240	348	22	6,3	17 CAS 5 DAS	11	22	Silicon	90
Gottlieb [36]	2009	706	1275	65	5,1	N/A	N/A	65	Metal	80
Dutau [37]	2009	117	221	15	6,8	CAS	N/A	15	Silicon	100
Samano [14]	2009	71	107	4	3,7	CAS	2	4	Metal	100
Lischke [38]	2010	80	110	7	6,4	CAS	7	6	PDS	100
Fernandez-Bussy [39]	2011	223	345	52	15,1	CAS	2	47	Covered metal	100
Sundset [40]	2012	279	470	35	7,4	N/A	6	27	Silicon	100
Redmond [10]	2013	N/A	N/A	22		CAS	N/A	22	Metal	N/A
Abdel-Rahman [41]	2013	435	503	60	11,9	CAS	N/A	60	Metal	95
Mazzetta [42]	2019	160	310	22	7,1	CAS	22	9	Silicon	100

Pt number of patients, *RA* number of at risk anastomoses, *BS* bronchial stenosis, *CAS* central airway stenosis, *DAS* distal airway stenosis, *N/A* no data, *BD* bronchial dilation or balloon dilation, *SX%* percent of patients with symptom relief after therapy, *PDS* polydioxanone

34, 39, 42, 44], particularly in the presence of inflamed tissue prior to the development of a fibrotic strictures [35, 43]. It is a quick and safe method that can be performed with flexible bronchoscopy under conscious sedation. An excellent palliative outcome, notably in mild stenosis, is characterized by immediate improvement of symptoms in the majority of patients. Moreover, up to 26% of lung transplant recipients with airway stenosis may not need a stent placement following balloon dilation [13, 14, 32], although in most cases more than one procedure is needed, with the recommendation of at least two attempts prior to considering stent placement [32, 34, 42]. Other endobronchial techniques such as cryoablation, electrocautery, or laser can be performed individually or added to the balloon technique, particularly in the presence of scar tissue. Patients are often selected for various treatment approaches based on the appearance and location of the airway stenosis, as well as local availability of techniques and expertise [6, 27, 29].

Stenting

Stent placement is reserved for severe and refractory stenosis, (i.e., if more than two dilations a month are needed, with clear symptomatic improvement). This technique has been traditionally related to a rate of complications as high as 50% [31, 32, 35, 41].

Several stenting techniques are available. Self-expanding metallic stents (SEMS) were historically more frequently used in this kind of patient, but the FDA published a health advisory in 2005 discouraging their use in benign airway disorders because of the high rate of complications, especially their tendency to induce granulation tissue formation and their difficulty of removal [33, 37, 40]. Nevertheless, recent studies have demonstrated their long term safety [41]. SEMS can be placed under conscious sedation using flexible bronchoscopy and provide immediate relief and functional improvement in a high percentage of patients. Furthermore, the larger internal to external diameter ratio makes them less likely to migrate and reduces mucus plugging.

However, complications related to SEMS are not uncommon. Bacterial and fungal colonization have been described in a high percentage of patients [7, 11, 15, 37], but their main problem is the formation of granulation tissue, which may lead to re-stenosis and makes them difficult to remove. Granulation tissue develops over the ends of the stent and incorporates the stent within the airway wall 3–6 weeks after stent placement. Thus, stents should be removed or exchanged before becoming incorporated into the mucosa [10, 28]. In addition, erosion of airways, fracture due to metal fatigue, and fatal hemoptysis due to bronchovascular fistulas have also been described [10, 15, 28, 44], although these complications have decreased with newer generations of SEMS.

Silicone stents are currently preferred for management of nonmalignant airway stenosis. Some advantages include the ease of deployment, their flexibility, the ability to be modified and customized, and lower rates of granulation tissue formation, which makes them easier to remove. Their placement requires the use of rigid bronchoscopy under general anesthesia, and complications include their tendency to migrate (which is often the main drawback of this type of stent), obstruction by

secretions due to their thick walls and narrow lumens, and less commonly, granulation tissue formation [9, 10, 28, 37, 41].

Hybrid stents have also been described for use in airway complications in lung transplant patients. Gildea et al. published their experience with the Polyflex stent (Boston scientific; Boston, MA), a self-expanding silicone stent, in 12 lung transplant recipients with anastomotic stenosis. However, the results were less than desirable, with a migration rate of 100% [45].

Biodegradable stents have been recently introduced into practice. Polydioxanone (PDS) stents have shown to be well tolerated by tracheobronchial mucosa, are able to maintain airway patency for 6 weeks, and completely degrade within 15 weeks after placement. A pilot study published by Lischke described outcomes of 20 biodegradable stents implanted in 6 patients with posttransplant bronchial anastomosic stenosis. There were no complications related to the procedure, but four patients needed multiple stenting due to anastomotic re-stenosis with a median time of 5 months to re-stenting. They conclude that biodegradable stents are a safe and reliable alternative to classic stents [38].

To date, there are no randomized trials to conclude which stent is the best in these patients. All stents are associated with a high rate of complications, and their use should be reserved for refractory cases in which other procedures have failed [6, 7, 29].

Surgery

In recalcitrant cases in which endoscopic interventions have failed, surgery may be required. Experts agree that surgical strategies depend on the location and extent of stenosis, and preservation of lung parenchyma should be the primary goal to guarantee proper pulmonary function and quality of life [6, 29].

Nonanastomotic stenosis extending to lobar bronchi represents the most difficult challenge. In these instances, reconstruction may be technically challenging, and sleeve lobectomies are often required. In contrast, most of the published literature regarding central stenosis agrees that segmental resection of the stenotic area followed by end-to-end re-anastomosis is the preferred method [21, 46–48]. The use of a vascularized flap in either instance is still not well established, but should be considered, as suggested by both Paulson and Camargo (Table 48.5) [12, 46, 49].

Table 48.5 Surgical treatment of bronchial stenosis

Author	Year	Pts	Bronchial stenoses	Type	Prior intervention	Surgical intervention	Flap coverage	Mortality
Camargo [46]	2008	251	4	CAS	Balloon dilation	2 SL 2 BS	Mediastinal fat	0
Marulli [47]	2007	154	3	DAS	Balloon dilation	1 bilobectomy 1 BS	None	0
Schafers [49]	1994	121	5	CAS	Not stated	2 lobectomy 1 BS 2 RT	None	0

Pts number of patients transplanted, *CAS* central airway stenosis, *DAS* distal airway stenosis, *SL* sleeve lobectomy, *BS* bronchial sleeve resection, *RT* re-transplantation

Other approaches, such as pneumonectomy or retransplantation, have been described with acceptable outcomes [12, 46–48]. Furthermore, all the procedures are very challenging in these patients because of immunosuppression treatment and poor functional status.

Conclusions and Recommendations

Post-transplant bronchial stenosisis associated with high postoperative morbidity and mortality, prolonged hospital stay, and increased hospital costs. Since most of the available evidence for treatment comes from observational studies, mainly retrospective analyses, it is still debatable not only which endoscopic technique should be preferred, but also whether an endoscopic or surgical treatment leads to better results or to more complications. Asymptomatic patients with limited central stenosis can be kept under close monitoring. Symptomatic patients may benefit from interventions under a multidisciplinary team approach. Based on current evidence, dilation via balloon bronchoplasty, with or without scar tissue resection by an energy device, is the safest and most effective first-line intervention. Stenting can be considered in the presence of refractory stenoses in patients whose symptoms recur after balloon dilation. Furthermore, although there is no evidence of superiority among stent alternatives, many groups prefer silicon stents. Finally, surgery should be the last option for the management of AC, especially bronchial stenosis. Careful consideration of the patient's characteristics, including stenosis location and extent, is mandatory before attempting repair. No evidence is available regarding the best surgical options.

Recommendations

- Balloon bronchoplasty is the most effective first-line intervention for bronchial stenosis after transplantation (evidence quality low, weak recommendation).
- Stenting of post-transplant bronchial stenosis can be considered in patients who fail balloon bronchoplasty (evidence quality low, weak recommendation).
- Surgical resection of bronchial stenosis may be considered in patients who have failed conservative therapy (evidence quality low, weak recommendation).

A Personal View of the Data

AC has a significant negative impact on the quality of life of patients after transplantation. Strategies to deal with these pathologies are evolving, and results are far from acceptable. For bronchial stenosis, our unit assesses only symptomatic patients using a multidisciplinary approach. The first step is always balloon dilation.

Concomitant tissue resection, either with laser or cryotherapy, is only considered in selected patient in the setting of failed dilations. Stenting is generally avoided except for severely ill patients and as a last resort due to the high rate of complications. Surgery is reserved for patients with rapidly progressive disease or recalcitrant stenoses, and the type of intervention is individualized base on each case.

References

1. Hayanga JWA, Aboagye JK, Shigemura N, Hayanga HK, Murphy E, Khaghani A, et al. Airway complications after lung transplantation: contemporary survival and outcomes. J Heart Lung Transplant. 2017;35(10):1206–11.
2. Weder W, Inci I, Korom S, Kestenholz PB, Hillinger S, Eich C, et al. Airway complications after lung transplantation: risk factors, prevention and outcome. Eur J Cardiothorac Surg. 2009;35(2):293–8.
3. Shofer SL, Wahidi MM, Davis WA, Palmer SM, Hartwig MG, Lu Y, Snyder LD. Significance of and risk factors for the development of central airway stenosis after lung transplantation. Am J Transplant. 2013;13(2):383–9.
4. Dutau H, Vandemoortele T, Laroumagne S, Gomez C, Boussaud V. A new endoscopic standardized grading system for macroscopic central airway complications following lung transplantation : the MDS classification. Eur J Cardiothorac Surg. 2014;45(2):e33–8.
5. Yserbyt J, Dooms C, Vos R, Dupont LJ. Anastomotic airway complications after lung transplantation : risk factors, treatment modalities and outcome — a single-centre experience. Eur J Cardiothorac Surg. 2016;49:1–8.
6. Machuzak M, Santacruz JF. Airway complications after lung transplantation. Thorac Surg Clin. 2017;25(1):55–75.
7. Santacruz JF, Mehta AC. Airway complications and management after lung transplantation: ischemia, dehiscence, and stenosis. Proc Am Thorac Soc. 2009;6(1):79–93.
8. Moreno P, Alvarez A, Algar FJ, Cano JR, Espinosa D, Cerezo F, et al. Incidence, management and clinical outcomes of patients with airway complications following lung transplantation. Eur J Cardiothorac Surg. 2008;34(6):1198–205.
9. Thistlethwaite PA, Yung G, Kemp A, Osbourne S, Jamieson SW, Channick C, et al. Airway stenoses after lung transplantation: incidence, management, and outcome. J Thorac Cardiovasc Surg. 2008;136(6):1569–75.
10. Redmond J, Diamond J, Dunn J, Cohen GS, Soliman AMS. Rigid bronchoscopic management of complications related to endobronchial stents after lung transplantation. Ann Otol Rhinol Laryngol. 2013;122(3):183–9.
11. Hasegawa T, Iacono AT, Orons PD, Yousem SA. Segmental nonanastomotic bronchial stenosis after lung transplantation. Ann Thorac Surg. 2000;69(4):1020–4.
12. Paulson EC, Singhal S, Kucharczuk JC, Sterman DH, Kaiser LR, Marshall MB. Bronchial sleeve resection for posttransplant stricture. Ann Thorac Surg. 2003;76(6):2075–6.
13. Felton TW, Roberts SA, Isalska B, Brennan S, Philips A, Whiteside S, et al. Isolation of Aspergillus species from the airway of lung transplant recipients is associated with excess mortality. J Infect. 2012;65(4):350–6.
14. Samano MN, Minamoto H, Junqueira JJM, Yamaçake KGR, Gomes HAP, Mariani AW, et al. Bronchial complications following lung transplantation. Transplant Proc. 2009;41(3):921–6.
15. Murthy SC, Blackstone EH, Gildea TR, Gonzalez-Stawinski GV, Feng J, Budev M, et al. Impact of anastomotic airway complications after lung transplantation. Ann Thorac Surg. 2007;84(2):401–9.
16. Van De Wauwer C, Van Raemdonck D, Verleden GM, Dupont L, De Leyn P, Coosemans W, et al. Risk factors for airway complications within the first year after lung transplantation. Eur J Cardiothorac Surg. 2007;31(4):703–10.

17. Ruttmann E, Ulmer H, Marchese M, Dunst K, Geltner C, Margreiter R, et al. Evaluation of factors damaging the bronchial wall in lung transplantation. J Heart Lung Transplant. 2005;24(3):275–81.
18. Castleberry AW, Worni M, Kuchibhatla M, Lin SS, Snyder LD, Shofer SL, et al. A comparative analysis of bronchial stricture after lung transplantation in recipients with and without early acute rejection. Ann Thorac Surg. 2013;96(3):1008–18.
19. Alvarez A, Algar J, Santos F, Lama R, Aranda JL, Baamonde C, et al. Airway complications after lung transplantation: a review of 151 anastomoses. Eur J Cardiothorac Surg. 2001;19(4):381–7.
20. de Pablo A, López S, Ussetti P, Carreño MC, Laporta R, López García-Gallo C, Ferreiro MJ. Lung transplant therapy for suppurative diseases. Arch Bronconeumol. 2005;41(5):255–9.
21. Herrera JM, McNeil KD, Higgins RS, Coulden RA, Flower CD, Nashef SA, et al. Airway complications after lung transplantation: treatment and long-term outcome. Ann Thorac Surg. 2001;71(3):989–93.
22. King-Biggs MB, Dunitz JM, Park SJ, Kay Savik S, Hertz MI. Airway anastomotic dehiscence associated with use of sirolimus immediately after lung transplantation. Transplantation. 2003;75(9):1437–43.
23. Groetzner J, Kur F, Spelsberg F, Behr J, Frey L, Bittmann I, et al. Airway anastomosis complications in de novo lung transplantation with sirolimus-based immunosuppression. J Heart Lung Transplant. 2004;23(5):632–8.
24. Shennib H, Massard G. Airway complications in lung transplantation. Ann Thorac Surg. 1994;57:506–11.
25. Couraud L, Nashef SA, Nicolini P, et al. Classification of airway anastomotic healing. Eur J Cardiothorac Surg. 1992;6:496–7.
26. Chhajed PN, Tamm M, Glanville AR. Role of flexible bronchoscopy in lung transplantation. Semin Respir Crit Care Med. 2004;25(4):413–23.
27. Crespo MM, Mccarthy DP, Hopkins PM, Clark SC, Budev M, Bermudez CA, et al. ISHLT Consensus Statement on adult and pediatric airway complications after lung transplantation: definitions, grading system, and therapeutics. J Heart Lung Transplant. 2019;37:548–63.
28. Puchalski J, Lee HJ, Sterman DH. Airway complications following lung transplantation. Clin Chest Med. 2011;32(2):357–66.
29. Varela A, Hoyos L, Romero A, Campo-Cañaveral JL, Crowley S. Management of bronchial complications after lung transplantation and sequelae. Thorac Surg Clin. 2018;28:365–75.
30. Habre C, Soccal PM, Triponez F, Aubert J-D, Krueger T, Martin SP, Gariani J, Pache J-C, Lador F, Montet X, Hachulla A-L. Radiological findings of complications after lung transplantation. Insights Imaging. 2018;9(5):709–19.
31. Colquhoun IW, Gascoigne AD, Au J, Corrins PA, Hilton CJ, Dark JH. Airway complications after pulmonary transplantation. Ann Thorac Surg. 1994;57(1):141–5.
32. Chhajed PN, Malouf MA, Tamm M, Glanville AR. Ultraflex stents for the management of airway complications in lung transplant recipients. Respirology. 2003;8(1):59–64.
33. Burns KEA, Orons PD, Dauber JH, Grgurich WF, Stitt LW, Raghu S, et al. Endobronchial metallic stent placement for airway complications after lung transplantation: longitudinal results. Ann Thorac Surg. 2002;74:1934–41.
34. De Gracia J, Culebras M, Álvarez A, Catalán E, De la Rosa D, Maestre J, et al. Bronchoscopic balloon dilatation in the management of bronchial stenosis following lung transplantation. Respir Med. 2007;101(1):27–33.
35. Kapoor BS, May B, Panu N, Kowalik K, Hunter DW. Endobronchial stent placement for the lung transplantation. J Vasc Interv Radiol. 2019;18:629–32.
36. Gottlieb J, Fuehner T, Dierich M, Wiesner O, Simon AR, Welte T. Are metallic stents really safe? A long-term analysis in lung transplant recipients. Eur Respir J. 2009;34(6):1417–22.
37. Dutau H, Cavailles A, Sakr L, Badier M, Gaubert JY, Boniface S, et al. A retrospective study of silicone stent placement for management of anastomotic airway complications in lung transplant recipients: short- and long-term outcomes. J Heart Lung Transplant. 2010;29(6):658–64.

38. Lischke R, Pozniak J, Vondrys D, Elliott MJ. Novel biodegradable stents in the treatment of bronchial stenosis after lung transplantation. Eur J Cardiothorac Surg. 2011;40(3):619–24.
39. Fernández-Bussy S, Majid A, Caviedes I, Akindipe O, Baz M, Jantz M. Treatment of airway complications following lung transplantation. Arch Bronconeumol. 2011;47(3):128–33.
40. Sundset A, Lund B, Hansen G, Bjørtuft Ø, Kongerud J, Geiran OR. Airway complications after lung transplantation: long-term outcome of silicone stenting. Respiration. 2012;83(3):245–52.
41. Abdel-Rahman N, Kramer MR, Saute M, Raviv Y, Fruchter O. Metallic stents for airway complications after lung transplantation. Eur J Cardiothorac Surg. 2014;45:854–8.
42. Mazzetta A, Porzio M, Riou M, Coiffard B, Olland A, et al. Patients treated for central airway stenosis after lung transplantation have persistent airflow limitation. Ann Transplant. 2019;24:84–92.
43. Mulligan MS. Endoscopic management of airway complications after lung transplantation. Chest Surg Clin N Am. 2001;11(4):907–15.
44. Fernandez-Bussy S, Akindipe O, Kulkarni V, Swafford W, Baz M, Jantz MA. Clinical experience with a new removable tracheobronchial stent in the management of airway complications after lung transplantation. J Heart Lung Transplant. 2009;28(7):683–8.
45. Gildea TR, Murthy SC, Sahoo D, Mason DP, Mehta AC. Performance of a self-expanding silicone stent in palliation of benign airway conditions. Chest. 2006;130(5):1419–23.
46. de Jesus Peixoto Camargo J, Camargo SM, Machuca TN, Perin FA, Schio SM, Felicetti JC. Surgical maneuvers for the management of bronchial complications in lung transplantation. Eur J Cardiothorac Surg. 2008;34(6):1206–9.
47. Marulli G, Loy M, Rizzardi G, Calabrese F, Feltracco P, Sartori F, et al. Surgical treatment of posttransplant bronchial stenoses: case reports. Transplant Proc. 2007;39(6):1973–5.
48. Schrijver IT, Luijk B, Meijer RCA, de Heer LM. Successful treatment of bronchial stenosis after lung transplantation. Interact Cardiovasc Thorac Surg. 2017;24(6):980–1.
49. Schäfers HJ, Schäfer CM, Zink C, Haverich A, Borst HG. Surgical treatment of airway complications after lung transplantation. J Thorac Cardiovasc Surg. 1994;107(6):1476–80.

Part V

Pleura and Pleural Spaces

Is tPA/DNase Effective in the Management of Pleural Empyema?

49

Andrew R. Brownlee and Mark K. Ferguson

Introduction

Empyema affects approximately 65,000 individuals in the United States annually, costing an estimated $500 million with a mortality of 15% [1, 2]. It is a dynamic process that gradually transitions from exudative through fibrinopurulent to an organized phase, with overlap among phases. The goals of treatment are drainage of the pleural space, eradication of infection, and re-expansion of the lung. The treatment of empyema traditionally involves antibiotics and pleural drainage, with surgery reserved for cases of inadequate pleural drainage, failure of lung reexpansion, or severe or persistent sepsis. Timely and effective treatment is desirable, as treatment delay or failure results in increased morbidity and mortality [3]. Early small studies suggested that fibrinolytics (streptokinase) were a safe and potentially effective alternative to surgery in treating empyema [4–7]. The first large multicenter trial (MIST1), however, showed that streptokinase had no benefit in the treatment of empyema and this finding has since been supported with further studies [8].

Despite these initial failures, optimism persisted that the theoretical benefit of fibrinolytics could be realized in a clinical setting [9, 10]. This prompted a study of alternate fibrinolytic agents including the combination of tissue plasminogen activator (tPA) and deoxyribonuclease (DNase) [11, 12].

In this chapter, we discuss the current state of the literature regarding the efficacy of tPA and DNase in the treatment of pleural empyema.

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Table 49.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with pleural empyema	tPA-DNase	Thoracostomy tube alone, surgery	Pleural opacification, LOS, morbidity, mortality, need for delayed surgery

tPA tissue plasminogen activator, *DNase* deoxyribonucleic acid, *LOS* length of stay

Search Strategy

A literature search of English language publications from 1985 to 2019 was used to identify published papers on the use of tPA and DNase in the treatment of empyema. Databases and engines searched were PubMed, Cochrane Evidence Based Medicine, and Google Scholar. The terms used were "empyema and fibrinolytics", "empyema and tPA and DNase", "treatment of empyema", "tPA and DNase versus surgery for empyema", "fibrinolytics versus surgery for empyema". Articles were included if they specifically addressed the use of tPA and DNase in the treatment of empyema. One randomized controlled trial and four retrospective reviews were included (Table 49.1).

Results

Combined t-PA and DNase vs Monotherapy and Placebo

In a double blinded randomized controlled trial, Rahman et al. randomized 210 patients to 4 study arms: double placebo, intrapleural tPA and DNase, tPA and placebo, and DNase and placebo. Patients diagnosed with empyema had a thoracostomy tube placed and received the fibrinolytic or placebo shortly thereafter. The primary outcome was change in pleural opacity on the chest radiograph at 7 days. Secondary outcomes were referral for surgery, length of hospital stay, and adverse events. They found a statistically significant decrease in pleural opacity in the tPA-DNase group compared to the placebo group which was not observed with tPA alone or DNase alone. There was a decreased frequency of referral to surgery at 3 months in the tPA-DNase group compared to the placebo group, but there was a higher referral rate in the DNase only group. The tPA-DNase group had a decreased hospital stay compared to placebo only [12].

Combined tPA-DNase After Failed Thoracostomy Drainage

Piccolo et al. sought to determine if tPA-DNase was effective when used after failed thoracostomy drainage and antibiotics. Appropriateness of tPA-DNase and failure

were 'determined by the attending physicians'. This was determined most often after >24 h of thoracostomy drainage. Of the 107 patients treated, 92.3% did not need surgical intervention. The authors noted increased pleural fluid drainage and improved radiographic appearance of the hemithorax following rescue therapy with tPA-DNase [13].

Majid et al. performed a single center retrospective review of their experience. They identified 73 patients who received tPA-DNase after failure of thoracostomy and antibiotics. Failure was 'determined by the attending physicians'. Their treatment was 90.4% effective, and 80.8% of treatments were effective with less than 6 doses [14].

Fibrinolytics vs Surgery

The majority of studies comparing intrapleural fibrinolytics to surgery were performed in the era prior to the widespread use of tPA-DNase and therefore offer little insight into the current role of early surgery in the treatment of empyema. A meta-analysis of eight randomized controlled trials evaluating studies that compared early surgical vs non-surgical treatment of empyema found that there was no difference in mortality, and that VATS specifically may reduce length of stay compared to thoracostomy and fibrinolytics alone. This meta-analysis examined six studies examining a pediatric population and two involving adults. None of the studies used tPA-DNase [15].

Predicting Failure of tPA-DNase Therapy

In a study of 84 patients who received tPA-DNase for empyema, failure of treatment occurred in one third of patients. Predictors of failure included the presence of pleural thickening, the presence of a lung abscess or necrotizing pneumonia, elevated pleural protein, and the presence of loculations [16].

Complications of tPA-DNase Therapy

The complications related to tPA-DNase administration are minimal. The most common complication is intrapleural hemorrage. This occurs in 0–5.7% of cases. In the studies reviewed, cessation of intrapleural tPA-DNase was sufficient to stop bleeding in all cases (Tables 49.2 and 49.3) [12–14, 17, 18].

Table 49.2 Summary of studies investigating the use of tPA and DNase in the treatment of pleural empyema

Study	Study type	Patients	Interventions	LOS	Mortality	Findings	Treatment success rate (no surgical intervention)
Rahman et al. [12]	Randomized controlled	201	t-PA-DNase vs t-PA vs DNase vs placebo	Decreased stay in tPA-DNase vs placebo (−6.7d p = 0.0006)	8% vs 8% vs 4% vs 13% in tPA-DNase, tPA, placebo, DNase groups respectively (p = 0.37)	Decreased LOS, decreased pleural opacity, decreased surgical referral	96.0%
Piccolo et al. [13]	Retrospective review	107	tPA-DNase		2.80%	Improved pleural opacity, decreased C-reactive protein, increased fluid drainage (250 ml–>2475 ml/24 h)	92.3%
Majid et al. [14]	Retrospective review	73	tPA-DNase		2.70%	Increased fluid drainage (295 ml–>1102 ml/24 h)	90.7%
Bishwakarma et al. [18]	Retrospective review	39	tPA-DNase		7%	Concomitant administration appears effective	85.0%
Innabi et al. [17]	Retrospective review	17	tPA-DNase		0%	No intrapleural bleeding, chest pain	93.0%

tPA tissue plasminogen activator, *DNase* deoxyribonucleic acid, *LOS* length of stay

Table 49.3 Evidence and associated grade for the use of tPA and DNase in the treatment of empyema

Proposed advantage of use of tPA-DNase	Quality of evidence
tPA-Dnase decreases pleural opacification when compared to thoracostomy only	High
tPA-DNase reduces the need for delayed surgery compared to thoracostomy tube alone	High
tPA-DNase reduces LOS compared to thoracostomy alone	Moderate

tPA tissue plasminogen activator, *DNase* deoxyribonucleic acid, *LOS* length of stay

Conclusions and Recommendations

The use of tPA-DNase reduces pleural opacification and the need for delayed surgical intervention when compared to single agent fibrinolysis or tube thoracostomy alone. What is not clear from the current literature is how tPA-DNase compares to early surgical intervention. When a diagnosis of empyema is made, a thoracostomy tube should be placed if not already present. We recommend that if a thoracostomy tube alone does not result in satisfactory drainage of the pleural space, either surgery or tPA-DNase is a safe and effective remedy.

Recommendation

- If a thoracostomy tube alone does not result in satisfactory drainage of the pleural space, either surgery or tPA-DNase is a safe and effective remedy (evidence quality moderate, strong recommendation).

A Personal View of the Data

The treatment of pleural empyema requires an individualized approach. Much of the current data favors tPA-DNase use as it reduces delayed surgical intervention when compared to other fibrinolytics and no fibrinolytics. Although this is an important finding, it is not the question that thoracic surgeons are most commonly faced with. We currently don't have sufficient studies to guide our decision about which patients should undergo early surgical intervention vs tPA-DNase. In our institution, patients who have multiple co-morbidities and poor performance status who are at higher risk for complications with surgery and general anesthesia are recommended to receive tPA-DNase. Younger, healthier patients with good performance status are recommended to undergo early surgical intervention. In general, we favor early surgical intervention for any patient who can tolerate it safely and has failed antibiotics and thoracostomy tube drainage.

References

1. Farjah F, Symons RG, Krishnadasan B, Wood DE, Flum DR. Management of pleural space infections: a population-based analysis. J Thorac Cardiovasc Surg. 2006;133(2):346–51.
2. Ferguson AD, Prescott RJ, Selkon JB, Watson D, Swinburn CR. The clinical course and management of thoracic empyema. QJM. 2006;89(4):285–9.
3. Dienemann HC, Hoffman H, Detterbeck FC. Chest surgery. New York: Springer; 2015.
4. Moulton JS, Benkert RE, Weisiger KH, Chambers JA. Treatment of complicated pleural fluid collections with image-guided drainage and intracavitary urokinase. Chest. 1995;108(5):1252–9.
5. Talib SH, Verma GR, Arshad M, Tayade BO, Rafeeque A. Utility of intrapleural streptokinase in management of chronic empyemas. J Assoc Physicians India. 2003;51:464–8.
6. Diacon AH, Theron J, Schuurmans MM, Van de Wal BW, Bolliger CT. Intrapleural streptokinase for empyema and complicated parapneumonic effusions. Am J Respir. 2004;170(1):49–53.
7. Davies RJ, Traill ZC, Gleeson FV. Randomised controlled trial of intrapleural streptokinase in community acquired pleural infection. Thorax. 1997;52(5):416–21.
8. Maskell NA, Davies CW, Nunn AJ, Hedley EL, Gleeson FV, Miller R, et al. First Multicenter Intrapleural Sepsis Trial (MIST1) Group. U.K. Controlled trial of intrapleural streptokinase for pleural infection. N Engl J Med. 2005;352(9):865–74.
9. Tokuda Y, Matsushima D, Stein GH, Miyagi S. Intrapleural fibrinolytic agents for empyema and complicated parapneumonic effusions: a meta-analysis. Chest. 2006;129(3):783–90.
10. Heffner JE. Multicenter trials of treatment for empyema—after all these years. N Engl J Med. 2005;352(9):926–8.
11. Zhu Z, Hawthorne ML, Guo Y, Drake W, Bilaceroglu S, Misra HL, et al. Tissue plasminogen activator combined with human recombinant deoxyribonuclease is effective therapy for empyema in a rabbit model. Chest. 2006;129(6):1577–83.
12. Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med. 2011;365(6):518–26.
13. Piccolo F, Pitman N, Bhatnagar R, Popowicz N, Smith NA, Brockway B. Intrapleural tissue plasminogen activator and deoxyribonuclease for pleural infection. An effective and safe alternative to surgery. Ann Am Thorac Soc. 2014;11(9):1419–25.
14. Majid A, Kheir F, Folch A, Fernandez-Bussy S, Chatterji S, Maskey A. Concurrent intrapleural instillation of tissue plasminogen activator and DNase for pleural infection. A single center experience. Ann Am Thorac Soc. 2016;13(9):1512–8.
15. Redden MD, Chin TY, van Driel ML. Surgical versus non-surgical management for pleural empyema. Cochrane Library. 2020. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010651.pub2/full. Accessed 12 Feb 2020.
16. Khemasuwan D, Sorensen J, Griffin DC. Predictive variables for failure in administration of intrapleural tissue plasminogen activator/deoxyribonuclease in patients with complicated parapneumonic effusions/empyema. Chest. 2018;154(3):550–6.
17. Innabi A, Surana A, Alzghoul B, Meena N. Rethinking the doses of tissue intrapleural therapy for complicated pleural effusion and empyema. Cureus. 2018;10(2):2214.
18. Bishwakarma R, Shah S, Frank L, Zhang W, Sharma G, Nishi SP. Mixing it up: coadministration of tPA/DNase in complicated parapneumonic pleural effusions and empyema. J Bronchology Interv Pulmonol. 2017;24(1):40–7.

VATS vs Open Management of Pleural Empyema

50

Brian Mitzman

Introduction

Pleural empyema is a common problem known to all thoracic surgeons. With an increased incidence in western countries [1–3] along with more widely adopted minimally invasive techniques, the best approach for decortication is constantly debated. Although minimally invasive procedures have evolved and are accepted for many other thoracic surgical procedures [4], there is still no consensus on the best approach for empyema. Treatment options vary from just antibiotics and chest tube drainage to total decortication via thoracotomy. While there is no standard algorithm, decision making includes analysis of the stage of empyema, current clinical status, and overall evaluation of the patient's ability to tolerate an operation. The clinical, pathologic, and pleural fluid analyses are now organized into a fairly accepted system the three stages of empyema; uncomplicated/simple, complicated/fibrinopurulent, and complicated/organized [5, 6]. As stage I empyemas often do not require formal decortication and resolve with drainage, many of the subsequent studies in this review evaluate only Stage II or III patients. Whether minimally invasive approaches to decortication are feasible in more complex empyemas and provide adequate results when compared with thoracotomy remains a debated topic.

Search Strategy

A MEDLINE search of the MeSH database was performed based on PICO elements using subheadings from the term "empyema, pleura." These included "Empyema, Pleural/mortality" OR "empyema, pleural/therapy" OR "empyema, pleural/

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Table 50.1 PICO formatted terms for literature search

P (patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with pleural empyema	Open decortication	VATS decortication	Mortality Procedure success Postoperative morbidity Costs Conversion rate

surgery." Additional articles were included from Pubmed describing surgical management of pleural empyema. A cut off of 1999 was used so that only articles from the last 20 years utilizing most current techniques and technology in thoracoscopy would be analyzed. A specific focus was placed on recent additions to the literature in the last 5 years. Results were limited to adults, humans, and papers published in the English language (Table 50.1).

Results

The initial search yielded 63 results after excluding case reports and very small case series. After evaluating each manuscript and focusing on the more recent (within 10 years) observational studies and database analyses with larger cohorts, ten main studies were used in developing these recommendations (Table 50.2).

VATS vs Thoracotomy: Current Consensus

Guidelines for the management of pleural empyema were created by the American College of Chest Physicians (ACCP) [7] in 2000 and the British Thoracic Society (BTS) in 2003 [8]. The surgical approach was not evaluated by the BTS guidelines, however, and there was limited evidence supporting VATS in the ACCP guidelines as it was a fairly new technique at the time.

Over the last 5 years however, several international organizations developed consensus guidelines to help better guide the thoracic community. In 2015, the EACTS released an expert consensus on management of pleural empyema [9]. When specifically evaluating Stage II empyema, the working group concluded that based on large non-randomized trials, data supported VATS as a useful and beneficial first approach (Class I recommendation, Level B evidence). Without providing a specific grade of evidence, they concluded that for chronic Stage III empyema, VATS could be as effective as open thoracotomy when performed by experienced high volume centers, albeit the conversion rate being high (up to 62% based on evaluated literature).

In 2017, the AATS convened an Empyema Guidelines Working Group [10]. The authors concluded that for Stage II acute empyema, a VATS approach was reasonable, with limited evidence (Class IIA recommendation, Level B evidence). The major determinants of approach were the ability for the patient to tolerate one lung

Table 50.2 Recent studies evaluating vats for the treatment of pleural empyema

Study	Type of study	Year	Approach	Number of patients	Operating Time (min)	Conversion	Chest tube duration (days)	Post operative length of stay (days)	Postop morbidity	Procedure success	Mortality	Quality of evidence
Towe [18]	Database	2019	Open	4435	114 (82–158)	–	–	13 (9–20)	45.3%	–	3.7%	Moderate
			VATS	2281	85 (60–118)	14.2%[a]	–	11.5 (8–17)	35.4%	–	2.8%	
Semenkovich [23]	Database	2018	Open	1219	–	–	–	15 (10–21)	–	96.0%	6.8%	Low
			VATS	1313	–	–	–	12 (9–19)	–	97.0%	5.4%	
Reichert [17]	SCRR	2018	Open	107	160 (53–386)	–	6 (1–17)	12 (2–193)	57.0%	97.2%	6.5%	Moderate
			VATS	110	140 (41–385)	4.50%	6 (2–22)	10 (3–230)	52.4%	95.5%	9.5%	
Reichert [19]	SCRR	2017	VATS 2011–2012	43	170.1 (41–378)	4.70%	6 (2–16)	13.9 (4–45)	51.2%	93.1%	4.9%	Moderate
			VATS 2013–2015	84	141.6 (43–385)	3.60%	7 (2–22)	20.3 (3–230)	46.9%	94.1%	11.1%	
Jagelavicius [21]	SCRR	2017	VATS	71	82 ± 26	25.30%	5 (3–35)	11 (9–17)	19.7%	88.7%	1.4%	Low
Hajjar [22]	SCRR	2016	Open (Stage III)	12	222.4 ± 52.0	–	15.9 ± 8.2	21.8 ± 16.4	32.4%	–	4.0%	Low
			VATS (Stage II)	26	122.5 ± 45.2	0%	7.2 ± 3.4	8.5 ± 3.9	41.3%	–	0.0%	
			VATS (Stage III)	25	103.9 ± 24.3	32.4%[b]	7.8 ± 3.3	9.7 ± 4.1	67.7%	–	0.0%	
Stefani [15]	SCRR	2013	Open	57	162 (80–225)	–	5.0 (2–40)	8.4 (3–44)	32.0%	98.0%	1.0%	Low
			VATS	40	146 (90–210)	59%[b]	4.4 (2–12)	8.3 (3–30)	12.5%	100.0%	0.0%	
Muhammad [20]	SCRR	2012	Open	24	137.4 ± 27.0	–	8.9 ± 2.6	8.9 ± 2.6	–	100.0%	0.0%	Moderate
			VATS	25	84.7 ± 24.0	8%	7.8 ± 4.6	7.8 ± 4.6	–	92.0%	0.0%	
Tong [14]	SCRR	2010	Open	94	155	–	9.7 ± 10.1	10	–	89.4%	16.1%	Low
			VATS	326	97	11.40%	7.0 ± 13.7	7	–	92.3%	7.6%	
Chan [13]	SCRR	2007	Open	36	228	–	8.5 ± 4.4	21 ± 14.2	25.0%		0.0%	Moderate
			VATS	41	150	0.00%	7.9 ± 5.7	16 ± 16.5	21.9%		0.0%	

VATS video-assisted thoracoscopic surgery, *SCRR* single center retrospective review

[a]Only available on data from 2014–2016

[b]All patients in study initially attempted VATS

ventilation and the predicted technical success of the decortication (full evacuation and lung expansion). Conversion to thoracotomy was recommended if those two goals could not be met. Specific guidelines for approach were not given for Stage III chronic empyema, but the authors state that VATS can be considered if the overall goals of reexpansion can be met.

To date, there are still no randomized trials of VATS versus open thoracotomy for decortication. This leads to substantial selection bias when trying to evaluate perioperative outcomes based on technique for decortication. Many studies compare Stage II empyema VATS with Stage III empyema open decortication without utilizing an intention to treat model. Therefore, the length of stay and perioperative morbidity may not truly be less in the VATS group. Finally, in analyses that include upfront thoracotomy, that selection bias precludes us from knowing if VATS could have been successful in those patients. Fortunately, many of these studies use similar definitions and outcomes for analysis. By evaluating these studies as a whole, we can develop some generalizable algorithms with less bias.

A Cochrane review was updated in 2017 evaluating surgical vs non surgical management of pleural empyema [11]. Three main outcomes were evaluated: mortality, length of stay, and post procedural complications. Unfortunately, VATS and thoracotomy were each independently compared against tube thoracostomy, and not against each other. It is still useful to take into account this data in our overall analysis.

Procedure Success

In 2003, Roberts reported his experience with patients who underwent initial VATS decortication [12]. There was a 61.6% conversion rate to thoracotomy. While he did not specifically classify the stages of empyema, 65.0% were considered "simple parapneumonic." It is important to note that this report is from the early days of VATS, and even the high conversion rate is still commendable for this time period. Chan et al. evaluated 77 consecutive patients at 2 University of Hong Kong hospitals in 2007 [13]. Based on histopathologic findings and intraoperative findings, the authors determined 75% of the patients were Stage III, with the remainder Stage II. The VATS group had 41 patients, none of whom experienced conversion to thoracotomy. The overall success rate was reported 100%. This was determined subjectively however, and primarily by the opinion of the operating surgeon. Operative time was significantly shorter in the VATS group (2.5 ± 0.96 vs 3.8 ± 1.4 h, $p < 0.001$), and there were no statistically significant differences in radiologic improvement on CXR, mean time return to work, or perceived improvement in exercise tolerance.

Tong et al published the results for 420 empyema patients in 2010. There was an 11.4% conversion rate from VATS to thoracotomy. Decision making for initial approach was by surgeon preference, although this is a high volume VATS center with 326 of the patients in the VATS cohort. While this study was not broken down by stage, the authors report that VATS is appropriate for all stages of empyema, as long as there was a willingness to convert to thoracotomy if adequate results aren't achieved in the OR [14]. Operative time was substantially longer for an open

approach (155 min vs 97 min; $p < 0.001$), but the open group had procedures such as muscle flap performed in addition to the decortication in more than two-thirds of the patients.

Despite advances in technical expertise, there is still significant variability in rates of conversion from VATS to open thoracotomy for decortication. In 2013, Stefani et al. reported a 59% conversion rate in 97 patients, while in 2014 Chung et al. reported 1 conversion and 2 recurrences in a series of 128 VATS decorticications [15, 16].

Reichert et al. reported their more recent data in 2018 from a major academic center hospital in Germany. Specifically evaluating Stage III empyema, 127 patients underwent VATS decortication. The overall conversion rate was 3.9% during the entire time period. 6.3% of patients required re-do interventions for recurrent empyema after initial VATS [17].

The largest analysis of pulmonary decortication was a recently published STS General Thoracic Surgery Database review [18]. A total of 7316 patients were evaluated for VATS vs open thoracotomy of whom 4435 underwent a VATS approach. The conversion rate data was only available since 2014, and of 1496 VATS patients, 14.2% were converted. The operative time was lower in the VATS group (112.0 min vs 82.0 min, $p < 0.001$). There was no objective way to assess true procedural success in this dataset except for evaluating postoperative complications and length of stay, as more granular data is not available in this dataset. Length of stay was higher in the thoracotomy group (8.0 vs 7.0 days, $p < 0.0001$), as was prolonged length of stay, defined as greater than 19 days (11.9% vs 8.2%, $p < 0.0001$). The reason for the extended stay cannot be evaluated with the provided data. The thoracotomy group had a higher rate of postoperative events (45.3% vs 35.4%, $p < 0.0001$), most of which were pulmonary related. These complications are not necessarily correlated with 'procedural success' however, since these patients may still have had adequate clearance of their infection and expansion of the lung. While the groups were fairly well matched, there is no way to assess the stage of empyema.

The general consensus among all of these manuscripts is that the 'procedural success' is highly subjective, and is based on the surgeon's personal thoughts on appropriate lung reexpansion and technical ability performing VATS.

Mortality

As with all outcomes in this analysis, it is difficult to study mortality comparing VATS and open thoracotomy, as these are all retrospective studies that are not well matched. Thirty day mortality ranged from 0% to 18% for both open and VATS [12–28]. A single retrospective study showed better mortality in VATS decortication (7.5% vs 16.1%, $p = 0.02$) [14]. Recent systematic reviews and meta-analyses report decortication mortality to range from 1% to 19% [9, 24, 25]. Rather than the approach chosen, mortality appears to be related to time to operative intervention, preoperative clinical status, and technical success of the decortication. In the Cochrane review from 2017, there were no deaths in a single study evaluated for

thoracotomy subanalysis. There was one death in a total of 46 patients evaluated from 2 studies [11]. The STS Database review reported an operative mortality of 3.7% for open, and 2.8% for VATS (p = 0.026). Again, disease severity was not available for analysis and is a major confounder in this statistic [18].

Postoperative Morbidity

Decreased blood loss and OR time are common in patients undergoing VATS treatment of empyema, along with decreased air leak, pain, and ventilator requirements [14, 17, 20, 22]. These outcomes will generally lead to a shorter chest tube duration, and subsequently a shorter length of stay [13–15, 17–20, 22, 23]. In studies that provided specific complication categories, renal failure rates and cardiac complications were similar for VATS and open approaches [14, 17, 18].

There are few studies that include cost in analysis of pulmonary decortication, and none that directly compare VATS to open thoracotomy in the same institutional setting. Thourani et al. performed a cost-effectiveness analysis of 77 patients diagnosed with empyema undergoing various treatment modalities [27]. Seventeen patients underwent open decortication, with mean hospital charges of $34,771 ± 2,456. While this was more expensive than those who successfully underwent image directed catheters (23,354.93 ± 2430.23) or tube thoracostomy (25,534.72 ± 4,285.64), it was substantially cheaper than patients who failed those two less invasive therapies (55,609.32 ± 3078.03 and 43,168.63 ± 1000.34, respectively).

Robotic Approach

With the advent of robotic technology and its increased use over the past several years, there have been anecdotes of robotic pulmonary decortications being successfully performed. An additional Pubmed search was performed specifically for any case series or controlled trial evaluating the use of robotics for decortication. The literature was quite sparse. While there are a handful of case reports of robotic decortications [29–31], at this point caution must be exercised due to the lack of information. The general tenants of decortication should apply—if the empyema cannot be completely evacuated with complete expansion of the lung during a robotic decortication, then conversion to thoracotomy is appropriate.

Conclusions and Recommendations

VATS is an appropriate first line surgical therapy for thoracic empyema regardless of stage. A low threshold for early conversion to thoracotomy is important, as complete evacuation and expansion are the primary outcomes required for low morbidity and mortality. Factors related to likely need for conversion are Stage III empyema

and prolonged time from initiation of symptoms to surgical treatment. VATS appears to have improved perioperative outcomes when compared to thoracotomy, but only if the decortication is completed successfully.

Recommendation

- Patients with empyema should undergo a minimally invasive decortication as first line surgical therapy (evidence quality low, weak recommendation).

A Personal View of the Data

My personal view is that decortication should involve a step-wise approach. There is no harm in attempting the operation in a minimally invasive manner. I have often been surprised at my ability to decorticate some patients via VATS, even when the preoperative imaging shows chronic thickened pleura. Early conversion to thoracotomy is key, and one must remain realistic as to his or her ability to perform a complete decortication with 100% lung re-expansion. It is inappropriate to spend 4 h doing VATS, just to convert for the last 20% of the operation. If one is technically experienced in robotics but not VATS (as many surgeons are in the current era), it is reasonable to attempt a robotic decortication, although I have not seen any significant benefit in robotics to VATS for the average surgeon skilled in both techniques for these cases.

As reviewed above, morbidity and mortality should be similar as long as a complete decortication is accomplished. Increased length of stay and perioperative complications are generally associated with incomplete reexpansion, regardless of technique.

References

1. Burgos J, Falco V, Pahissa A. The increasing incidence of empyema. Curr Opin Pulm Med. 2013;19:350–6.
2. Grijalva CG, Zhu Y, Pekka Nuorti J, Griffin MR. Emergence of parapneumonic empyema in the USA. Thorax. 2011;66(8):663–8.
3. Farjah F, Symons RG, Krishnadasan B, Wood DE, Flum DR. Management of pleural space infections: a population- based analysis. J Thorac Cardiovasc Surg. 2007;133:346–51.
4. Onaitis MW, Petersen RP, Balderson SS, et al. Thoracoscopic lobectomy is a safe and versatile procedure: experience with 500 consecutive patients. Ann Surg. 2006;244:420–5.
5. Andrews NC, Parker EF, Shaw RR, Wilson NJ, Webb WR. Management of nontuberculous empyema. Am Rev Respir Dis. 1962;85:935–6.
6. Light RW. A new classification of parapneumonic effusions and empyema. Chest. 1995;108:299–301.
7. Colice GL, Curtis A, Deslauriers J. Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. Chest. 2000;118:1158–71.

8. Davies CW, Gleeson FV, Davies RJ, BTS Pleural Disease Group. BTS guidelines for the management of pleural infection. Thorax. 2003;58(Suppl II):ii18–28.
9. Scarci M, Abah U, Solli P, et al. EACTS expert consensus statement for surgical management of pleural empyema. Eur J Cardiothorac Surg. 2015;48:642–53.
10. Shen KR, Bribriesco A, Crabtree T, et al. The American Association for Thoracic Surgery consensus guidelines for the management of empyema. J Thorac Cardiovasc Surg. 2017;153:e129–46.
11. Redden MD, Chin TY, van Driel ML. Surgical versus non-surgical management for pleural empyema. Cochrane Database Syst Rev. 2017;3:CD010651.
12. Roberts JR. Minimally invasive surgery in the treatment of empyema: intraoperative decision making. Ann Thorac Surg. 2003;76:225–30.
13. Chan DTL, Siho ADL, Chan S, et al. Surgical treatment for empyema thoracis: is video-assisted thoracic surgery "better" than thoracotomy? Ann Thorac Surg. 2007;84:225–31.
14. Tong BC, Hanna J, Toloza EM, et al. Outcomes of video-assisted thoracoscopic decortication. Ann Thorac Surg. 2010;89:220–5.
15. Stefani A, Aramini B, Casa GD, et al. Preoperative predictors of successful surgical treatment in the management of parapneumonic empyema. Ann Thorac Surg. 2013;96:1812–9.
16. Chung JH, Lee SH, Kim KT, et al. Optimal timing of thoracoscopic drainage and decortication for empyema. Ann Thorac Surg. 2014;97:224–9.
17. Reichert M, Posentrup B, Hecker A, et al. Thoracotomy versus video-assisted thoracoscopic surgery (VATS) in stage III empyema – an analysis of 217 consecutive patients. Surg Endosc. 2018;32:2664–75.
18. Towe CW, Carr SR, Donahue JM, et al. Morbidity and 30-day mortality after decortication for parapneumonic empyema and pleural effusion among patients in the Society of Thoracic Surgeons' General Thoracic Surgery Database. J Thorac Cardiovasc Surg. 2019;157:1288–97.
19. Reichert M, Posentrup B, Hecker A. Lung decortication in phase III pleural empyema by video-assisted thoracoscopic surgery (VATS) – results of a learning curve study. J Thorac Dis. 2018;10:4311–20.
20. Muhammad MI. Management of complicated parapneumonic effusion and empyema using different treatment modalities. Asian Cardiovasc Thorac Ann. 2012;20(2):177–81.
21. Jagelavicius Z, Jovaisas V, Mataciunas M, et al. Preoperative predictors of conversion in thoracoscopic surgery for pleural empyema. Eur J Cardiothoracic Surg. 2017;52:70–5.
22. Hajjar WM, Ahmed I, Al-Nassar SA, et al. Video-assisted thoracoscopic decortication for the management of late stage pleural empyema, is it feasible? Ann Thorac Med. 2016;1:71–8.
23. Semenkovich TR, Olsen MA, Puri V, et al. Current state of empyema management. Ann Thorac Surg. 2018;105:1589–96.
24. Molnar TF. Current surgical treatment of thoracic empyema in adults. Eur J Cardiothorac Surg. 2007;32:422–30.
25. Taylor MD, Kozower BD. Surgical spectrum in the management of empyemas. Thorac Surg Clin. 2012;22:431–40.
26. Scarci M, Zahid I, Bille A, et al. Is video-assisted thoracoscopic surgery the best treatment for paediatric pleural empyema? Interact Cardiovasc Thorac Surg. 2011;13:70–6.
27. Thourani VH, Brady KM, Mansour KA, et al. Evaluation of treatment modalities for thoracic empyema. Ann Thorac Surg. 1998;66:1121–7.
28. Wait MA, Sharma S, Hohn J, et al. A randomized trial of empyema therapy. Chest. 1997;111:1548–51.
29. Jett GK. Robotic-assisted total decortication of right lung for fibrothorax. CTSNet. June 2018. https://doi.org/10.25373/ctsnet.6609419.
30. Margolis M, Meyer M, Tempesta B, et al. Robotic pulmonary decortication. June 2013. https://meetings.ismics.org/abstracts/2012/EP68.cgi. Accessed 03 Oct 2019.
31. Khan AZ, et al. Robotic thoracic surgery in inflammatory and infective diseases. Ann Cardiothorac Surg. 2019;8(2):241–9.

Indwelling Pleural Catheters Versus Talc Pleurodesis for Recurrent Symptomatic Malignant Pleural Effusions

51

Clinton T. Morgan, Daniel P. McCarthy, and Malcolm M. DeCamp

Introduction

Malignant pleural effusions can destroy quality of life in patients with advanced cancer and thoracic surgeons should be prepared to direct the palliative management of this condition. Although asymptomatic effusions can be safely observed, the majority of patients with malignant pleural effusions will develop symptoms that necessitate intervention [1]. Dyspnea is the most common complaint, often accompanied by constitutional symptoms such as weight loss, anorexia, and fatigue [2]. The goal of therapy is palliation. Quality of life is enhanced by alleviating symptoms and reducing interactions with the healthcare system, while minimizing treatment-related complications [3]. This balance is especially relevant considering the mean life expectancy is approximately 4 months [4]. Understanding and educating patients regarding expectations for symptomatic improvement, length of hospital stay, need for additional treatments and potential complications is critical for shared decision-making. In this chapter, we evaluate the use of indwelling pleural catheters versus pleurodesis for the management of symptomatic malignant pleural effusions.

Search Strategy

We used the PICO (Population, Intervention, Comparator, and Outcomes) format to focus our investigation into the management of symptomatic malignant pleural effusions (Table 51.1). One of the most frequent challenges is selecting the optimal

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Table 51.1 PICO formatted terms for literature search

	Patients	Intervention	Comparator	Outcomes
Factors	Symptomatic malignant pleural effusion	Indwelling pleural catheter	Talc pleurodesis	Dyspnea, length of stay, treatment failure, adverse events

intervention. We therefore formulated the following PICO question: In patients with symptomatic malignant pleural effusion, is indwelling pleural catheter or pleurodesis recommended? Relevant publications were identified using PubMed database Mesh terms: ((“Pleural Effusion, Malignant/drug therapy”[Mesh] OR “Pleural Effusion, Malignant/prevention and control”[Mesh] OR “Pleural Effusion, Malignant/surgery”[Mesh] OR “Pleural Effusion, Malignant/therapy”[Mesh]) AND “Pleural Effusion, Malignant”[Mesh]) AND (“Pleurodesis/therapeutic use”[Mesh] OR “Pleurodesis/therapy”[Mesh]) AND (Clinical Trial[type])) to identify relevant primary literature. We limited our search results to clinical trials and retrospective studies published in English from 2010 through 2019. Relevant societal guidelines were used to identify additional relevant literature publications meeting our criteria [2, 5]. Our search yielded four randomized controlled trials and two large retrospective series (Table 51.2) that were evaluated using the GRADE system (Table 51.3) to assess quality of evidence and provide strength weighted recommendations.

Results

The identified articles were used to assess the comparative outcomes in our PICO analysis. We focused on the outcomes for improvement in dyspnea, hospital length of stay, need for additional interventions, and adverse events between the two treatments.

Dyspnea

Improvement in dyspnea was evaluated in all four of the randomized controlled trials. Boshuizen et al. conducted a multi-center randomized controlled trial comparing talc pleurodesis (TP) to indwelling pleural catheters (IPC) in patients with recurrent malignant pleural effusions from 2011 to 2013 [6]. Their primary outcome of interest was dyspnea, assessed with a modified Borg Scale (MBS) [7]. Secondary endpoints included number of hospital visits, pleural re-interventions, length of hospital stay, and time to treatment failure. They excluded patients previously treated with talc pleurodesis or indwelling pleural catheters, and patients with impaired immunity or thrombocytopenia (platelets $<50 \times 10^9$/L). Patients underwent thoracentesis upon registration and were randomized to talc pleurodesis or indwelling pleural catheter in a 1:1 ratio if recurrence occurred within 6 months. Notably, indwelling pleural catheters were placed on an outpatient basis. Patients

Table 51.2 Summary of evidence for IPC vs TP in patients with symptomatic malignant pleural effusions

Author, year, (study type)	Number of patients	Primary outcome	Dyspnea vs baseline	Dyspnea vs TP	LOS vs TP	Reinterventions vs TP	Adverse events vs TP
Boshuizen et al. (2017) (RCT)	94	Dyspnea	Significantly improved	No significant difference	Significantly fewer	Significantly fewer	No significant difference
Thomas et al. (2017) (RCT)	146	Hospital days	Significantly improved	No significant different	Significantly fewer	Significantly fewer	n/a
Davies et al. (2012) (RCT)	106	Dyspnea	Significantly improved	No significant difference	Significantly fewer	Significantly fewer	No significant difference[a]
Demmy et al. (2012) (RCT)	57	"Success"[b]	Significantly improved	Significantly improved[c]	n/a	n/a	n/a
Freeman et al. (2013) (retrospective cohort)	60	n/a	n/a	n/a	Significantly fewer	No significant difference	n/a
Hunt et al. (2012) (retrospective)	109	n/a	n/a	n/a	Significantly fewer	No significant difference	No significant difference

IPC indwelling pleural catheter, *TP* talc pleurodesis, *RCT* randomized control trial

[a]No significant difference in serious adverse events

[b]Success was defined as achievement of several predetermined criteria 30 days after treatment: (1) alive; (2) no effusion recurrence; (3) lung reexpansion of 90% or greater after effusion drainage; (4) completion of intervention by 2 weeks

[c]This improvement was driven by a subgroup of patients with "poor expansion" (i.e. trapped lung)

Table 51.3 Grading of recommendations for IPC vs TP in patients with symptomatic malignant pleural effusions

Outcome of interest	Quality of evidence	Recommendation	Strength of recommendation
Dyspnea	Low to moderate	IPC and TP are equally appropriate and efficacious for relief of dyspnea[a]	Strong
LOS	Low to moderate	IPC is recommended	Weak
Reinterventions	Low to moderate	IPC is recommended	Weak
Adverse events	Low to moderate	IPC and TP have similar serious adverse event rates and are equally appropriate	Weak

[a]If there is evidence of "trapped" lung, we recommend IPC placement

randomized to talc pleurodesis were admitted and treated according the Dutch guidelines for malignant pleural effusion management [8]. Ninety-four patients were enrolled and randomized in a balanced fashion. Thirty-five patients died within 6 weeks of enrollment. Thirty-one and forty patients were eligible for per-protocol and intention to treat analyses, respectively. Compared to dyspnea scores at enrollment, the authors noted a statistically significant improvement in dyspnea in both treatment arms at 6 weeks. They compared dyspnea scores for talc pleurodesis versus tunneled pleural catheter and found a significant mean improvement in modified Borg Scale of 2.2 and 1.5 points for TP and IPC respectively at rest. During exercise, MBS results were 1.3 vs 1.7 MBS points for TP and IPC, respectively ($p < 0.01$ in all four cases). Taken together, there was no statistically significant difference comparing dyspnea scores of the IPC versus the TP groups.

Davies et al. conducted a multi-center randomized controlled trial (Second Therapeutic Intervention in Malignant Pleural Effusion Trial [TIME-2]) comparing indwelling pleural catheter to talc [9]. They enrolled 106 patients between April 2007 and February 2011. The main outcome of the study was improvement in dyspnea. Patients underwent indwelling pleural catheter placement on an outpatient basis. Patients randomized to talc pleurodesis were admitted for chest tube placement and talc slurry pleurodesis. The authors assessed daily dyspnea scores using a 100-mm line visual analog scale (VAS) of dyspnea (0 mm represents no dyspnea, 100 mm represents maximal dyspnea, and 10 mm represents minimal clinically significant difference). The authors found that dyspnea improved in both groups, but there was no significant difference in improvement between treatment arms [mean VAS dyspnea score 24.7 vs 24.4 in the indwelling pleural catheter group (baseline mean VAS 62) versus the talc pleurodesis group (baseline mean VAS 55)] in the first 42 days. At 6 months, there was a significant improvement in dyspnea in the indwelling pleural catheter group (-14.0 mm, $p = 0.01$), compared to the talc pleurodesis group.

Demmy et al. conducted a multi-institutional prospective, randomized trial comparing indwelling pleural catheters with talc pleurodesis [10]. Between October 2002 and December 2004, they randomized 57 patients with unilateral malignant

pleural effusion requiring pleurodesis or ongoing drainage to either indwelling pleural catheter placement or talc slurry pleurodesis. Their primary objective was to compare the proportion of patients that "maintained successful treatment" 30 days after intervention. They defined "success" as achievement of several predetermined criteria: (1) alive; (2) no effusion recurrence; (3) lung re-expansion of 90% or greater after effusion drainage; and (4) completion of intervention by 2 weeks based on removal of the chest tube (inserted for pleurodesis) or proper function of the tunneled pleural catheter. They found no significant difference in the original overall combined success rate for tunneled pleural catheter (62%) versus talc pleurodesis (46%), p = 0.290. The authors found that tunneled pleural catheter patients had improved dyspnea indices compared to the talc pleurodesis patients (8.5 vs 6.1; p = 0.047). Notably, this benefit was driven by a subgroup of patients with "poor expansion," i.e. patients with trapped lung.

Thomas et al. conducted a multi-center randomized controlled trial comparing indwelling pleural catheters versus talc slurry pleurodesis in 146 patients with symptomatic malignant pleural effusions enrolled between July 2012 and October 2014 [11]. The primary endpoint was the total number of days spent in the hospital from procedure (indwelling pleural catheter placement or talc pleurodesis) to death or to 12 months. Secondary outcomes included additional pleural interventions, dyspnea, and adverse events. Thomas et al. used the visual analog scale (VAS) of breathlessness to assess dyspnea and found improvements (14.5 mm; 95% CI, 8.4–20.7 and 17.4 mm; 95% CI, 11.1–23.7) for the indwelling pleural catheter (baseline mean VAS 50 mm vs 64.5 mm post-procedure day 1) and talc pleurodesis (baseline mean VAS 52.2 mm vs 69.7 mm post-procedure day 1) groups, respectively. There was no difference in the magnitude of improvement between the treatment groups.

In summary, dyspnea improved with either indwelling pleural catheter or talc pleurodesis in all four of the randomized controlled trials [6, 9–11]. Notably, there was no statistical difference in the degree of dyspnea improvement between the two treatments in three of the trials. Taken together, these results suggest that either indwelling pleural catheter placement or talc pleurodesis is appropriate treatment for alleviation of dyspnea in patients with recurrent malignant pleural effusion. Importantly, while three of the trials found no significant difference in dyspnea scores between indwelling pleural catheter and talc pleurodesis groups, Demmy et al. found improved dyspnea scores in the indwelling pleural catheter group [10]. This result was likely driven by a subset of patient's with trapped lung and highlights the importance of applying patient specific clinical knowledge in selecting the most appropriate therapy.

Number of Hospital Days

Limiting the time spent in the hospital is an essential goal in the care of patients with malignant pleural effusions. Three of the randomized controlled trials and two retrospective studies addressed this issue.

Boshuizen et al. found the median hospitalization days since randomization to indwelling pleural catheter or talc pleurodesis (7 days vs 2 days, p = 0.0016) was lower in the indwelling pleural catheter group [6]. The number of hospital admissions per patient was 1.6 days vs 1.0 days (p = 0.0035) for the talc pleurodesis and indwelling pleural catheter groups, respectively.

Similarly, Davies et al. also noted a significant difference in length of initial hospitalization between the groups, with a median of 0 and 4 days for the indwelling pleural catheter versus talc pleurodesis groups (mean difference −3.5 days, 95% CI, −4.8—1.5 days; p < 0.001), respectively [9]. In both of these studies, indwelling pleural catheter placement was performed on an outpatient basis and this was likely a major contributor to the difference in length of stay.

In their randomized controlled trial, Thomas et al. found that indwelling pleural catheter placement significantly reduced the number of total hospital days attributable to pleural effusion or treatment complications [11] (median, 1 day [IQR 1–3] versus 4 days [IQR, 3–6], p = 0.001). The median days in hospital for the initial admission was also shorter for indwelling pleural catheter placement than the pleurodesis group (1 day [IQR 1–2] versus 3 days [IQR 3–4], p < 0.001). Indwelling catheters were placed on an outpatient or overnight stay basis. After the initial admission, there was no significant difference in the number of effusion-related hospital days in the indwelling catheter group versus the talc pleurodesis group (median, 0 days [IQR 0–1] versus 0 days [IQR 0–0.5], p = 0.08), respectively.

Two retrospective analyses evaluated length of stay for indwelling pleural catheter placement versus talc pleurodesis. Freeman et al. performed a retrospective propensity-matched cohort comparison of pleurodesis versus indwelling pleural catheter placement in patients undergoing diagnostic thoracoscopy for malignancy [12]. They identified 60 patients with recurrent symptomatic pleural effusion suspected to be malignant who had undergone thoracoscopic exploration after at least two non-diagnostic thoracenteses. They used propensity matching to compare patients who received talc pleurodesis versus patients who received tunneled pleural catheters. Mean length of hospitalization was shorter for the indwelling pleural catheters versus talc pleurodesis (3 ± 2 [range 1–8] versus 6 ± 4 [range 4–13], p < 0.0017). Hunt et al. performed a retrospective chart review of 109 consecutive patients with malignant pleural effusion patients treated with either tunneled pleural catheter (54%) or VATS talc pleurodesis (46%) between 2005 and 2011 [13]. The authors found that the tunneled pleural catheter group's overall length of stay was shorter than the VATS talc pleurodesis group (mean 7 days, mode 1 day versus mean 8 days, mode 4 days; p = 0.006).

Taken together, indwelling pleural catheter placement is clearly associated with shorter length of stay. This is driven, in large part, by placement of the catheters in an outpatient or overnight stay setting. By contrast, inpatient management is typically performed for talc pleurodesis and thoracostomy tube management. Three prospective randomized trials and two large retrospective studies showed a significant reduction in hospital days (approximately 3–7 days) which we would consider a relatively large effect with respect to the life-expectancy. This makes outpatient

placement of an indwelling pleural catheter an attractive option for patients desiring to limit days in the hospital.

Reinterventions

It is also important to consider the burden of additional interventions related to treatment failure for each modality. One useful proxy for treatment failure is pleural re-intervention. Three of the randomized controlled trials and both of the retrospective reviews compared the need for re-intervention between tunneled pleural catheter and talc pleurodesis.

Thomas et al. noted that significantly fewer patients in the indwelling pleural catheter group required additional pleural interventions for ipsilateral fluid drainage (n = 3, 4.1%) versus talc pleurodesis group (n = 16, 22.5%, p = 0.001) [11]. Failure was diagnosed if additional ipsilateral fluid drainage procedures were needed for symptom relief. Boshuizen et al. found that the mean number of re-interventions was higher for the talc pleurodesis group (0.53 vs 0.21, p = 0.05), but an equal number of patients had at least one re-intervention (15 vs 7, p = 0.09) [6]. Time to re-intervention was significantly longer for the indwelling pleural catheter group (p = 0.045). Davies et al. found that 22% of patients in the talc pleurodesis group required additional pleural procedures versus 6% of the indwelling pleural catheter group (odds ratio 0.21; 95% CI, 0.04–0.86; p = 0.03) [9]. In their retrospective propensity-matched cohort comparison, Freeman et al. found rates of reintervention were equal for talc pleurodesis (10%) and indwelling pleural catheter placement (10%, p = 1.0) [12]. The retrospective cohort analysis by Hunt et al. found that the tunneled pleural catheter group underwent significantly fewer reinterventions for recurrent pleural effusions than the VATS talc group (2% vs 16%, p = 0.01) [13].

Results of three randomized controlled trials and one of two retrospective analyses suggest a lower rate of re-intervention after placement of an indwelling pleural catheter compared to talc pleurodesis. Taken together, these data suggest a reproducible, clinically significant decrease in the rates of reintervention for indwelling pleural catheter versus talc pleurodesis.

Adverse Events

Adverse events are a significant factor to consider as they can prolong the duration of hospitalization and/or require additional interventions. Three of the randomized controlled trials and one of the retrospective studies evaluated adverse events. Davies et al. found that 21 of 52 (40%) patients in the indwelling catheter group experienced adverse events versus 7 of 54 (13%) in the talc pleurodesis group (OR, 4.70; 95% CI, 1.75–12.60; p = 0.002), but no significant difference in serious adverse events (17% in the indwelling pleural catheter group vs 9% in the talc group [OR 2.1; 95% CI 0.57–7.71; p = 0.26]) [9]. The adverse events included serious and non-serious pleural infection, cellulitis, pleural loculations requiring fibrinolytics,

catheter site metastases, and catheter blockage, as well as less common adverse events. Thomas et al. reported serious adverse events in one patient (1%) in the indwelling pleural catheter group and 3 patients (4%) in the talc pleurodesis group [11]. Twenty-two patients (30%) in the indwelling pleural catheter group and 13 patients (18%) in the talc group experienced an adverse event. Procedure related pain and worsening dyspnea were the most common adverse events. Boshuizen et al. reported no difference in the rate of adverse events between patients in the indwelling pleural catheter versus the talc pleurodesis groups (16% vs 19%), respectively [6]. These included pain, dyspnea, infection, cardiovascular events, and general malaise. Finally, in their retrospective analysis, Hunt et al. found no significant difference in complication rates between tunneled pleural catheters and VATS talc pleurodesis groups (5% versus 8%, $p = 0.41$) [13].

In combination, the results of these studies suggest no significant difference in serious adverse events after indwelling pleural catheter placement versus talc pleurodesis.

Conclusions and Recommendations

The GRADE system was used to assess the quality of evidence and provide strength weighted recommendations for use of indwelling pleural catheters versus talc pleurodesis for patients with symptomatic malignant pleural effusions (Table 51.3). For patients with recurrent symptomatic malignant pleural effusions, placement of an indwelling pleural catheter or talc pleurodesis is equally appropriate and efficacious for the relief of dyspnea. The risk of adverse events in these patients is similar between the two interventions. In patients who experience a recurrent symptomatic malignant pleural effusions after intrapleural therapy, indwelling pleural catheter placement is superior to talc pleurodesis for number of hospital days and need for reinterventions.

Recommendations

- For patients with recurrent symptomatic malignant pleural effusions, placement of an indwelling pleural catheter or talc pleurodesis is equally appropriate and efficacious for the relief of dyspnea (moderate quality of evidence, strong recommendation).
- For patients with recurrent symptomatic malignant pleural effusions, indwelling pleural catheter placement is superior to talc pleurodesis for number of hospital days and need for reinterventions (low quality of evidence, weak recommendation).

A Personal View of the Data

Indwelling pleural catheters and talc pleurodesis are equivalent in reducing dyspnea from malignant pleural effusions. Thus surgeons can individualize the treatment decision to the patient and care delivery system.

Some factors may still favor pleurodesis over indwelling pleural catheters. For example, patients may lack the manual dexterity to drain their catheters independently. Practical considerations, such as the presence of an existing temporary pleural drain or institutional care protocols, may reduce the real-world advantage of reduced hospital days. Finally, some patients may require thoracoscopy to confirm the diagnosis or obtain additional tissue for molecular studies, thus reducing the outpatient advantage of pleural catheters.

Other factors might heighten the secondary benefits of indwelling pleural catheters. Reintervention rates and downstream hospital admissions are particularly important for patients who live far from their healthcare providers. The possibility of entrapped lung, which reduces the effectiveness of pleurodesis, may motivate placement of an indwelling pleural catheter to avoid the need for initial thoracentesis or the risk of failure due to lung entrapment. The subgroup analysis by Demmy et al. suggests that pleural catheters may be the preferred approach for patients with trapped lung [10]. The recently published, multidisciplinary clinical practice guidelines also favored IPC's in the setting of documented trapped lung [5].

Ultimately, a hybrid approach to malignant pleural effusion may prove the most reliable, effective strategy. The IPC Plus trial recently demonstrated superiority in achieving pleurodesis at 35 days using a tunneled catheter plus talc slurry versus tunneled catheter alone (43% vs. 23%, $p = 0.008$) [14]. This hybrid approach maintains the benefits of tunneled pleural catheters while minimizing the inconvenience and risk of a long-term catheter. With several proven treatment options available, surgeons are empowered to tailor the palliative approach to each patient.

References

1. Chernow B, Sahn SA. Carcinomatous involvement of the pleural: an analysis of 96 patients. Am J Med. 1977;63:695–702.
2. Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ, BTS Pleural Disease Guideline Group. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65(Suppl 2):ii32–40.
3. Ost DE, Niu J, Zhao H, Grosu H, Giordano SH. Quality gaps and comparative effectiveness of management strategies for recurrent malignant pleural effusions. Chest. 2018;153:438–52.
4. Burrows CM, Mathews WC, Colt HG. Predicting survival in patients with recurrent symptomatic malignant pleural effusions: an assessment of the prognostic values of physiologic, morphologic, and quality of life measures of extent of disease. Chest. 2000;117(1):73–8.
5. Feller-Kopman DJ, Reddy CB, DeCamp MM, Diekemper RL, Gould MK, Henry T, Iyer NP, Lee YCG, Lewis SZ, Maskell NA, Rahman NM, Sterman DH, Wahidi MM, Balekian AA. Management of malignant pleural effusions. An official ATS/STS/STR clinical practice guideline. Am J Respir Crit Care Med. 2018;198(7):839–49.

6. Boshuizen RC, Vd Noort V, Burgers JA, Herder GJM, Hashemi SMS, Hiltermann TJN, Kunst PW, Stigt JA, van den Heuvel MM. A randomized controlled trial comparing indwelling pleural catheters with talc pleurodesis (NVALT-14). Lung Cancer. 2017;108:9–14.
7. Boshuizen RC, Vincent AD, van den Heuvel MM. Comparison of modified Borg scale and visual analog scale dyspnea scores in predicting re-intervention after drainage of malignant pleural effusion. Support Care Cancer. 2013;21(11):3109–16.
8. Boshuizen R, Vincent A, Kunst P, Burgers S, van den Heuvel M. A Dutch web-survey on management of malignant pleural effusions. Eur Respir J. 2011;38:p3560.
9. Davies HE, Mishra EK, Kahan BC, Wrightson JM, Stanton AE, Guhan A, Davies CW, Grayez J, Harrison R, Prasad A, Crosthwaite N, Lee YC, Davies RJ, Miller RF, Rahman NM. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: The TIME2 randomized controlled trial. JAMA. 2012;307(22):2383–9.
10. Demmy TL, Gu L, Burkhalter JE, Toloza EM, D'Amico TA, Sutherland S, Wang X, Archer L, Veit LJ, Kohman L, Cancer and Leukemia Group B. Optimal management of malignant pleural effusions (results of CALGB 30102). J Natl Compr Cancer Netw. 2012;10(8):975–82.
11. Thomas R, Fysh ETH, Smith NA, Lee P, Kwan BCH, Yap E, Horwood FC, Piccolo F, Lam DCL, Garske LA, Shrestha R, Kosky C, Read CA, Murray K, Lee YCG. Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: the AMPLE randomized clinical trial. JAMA. 2017;318(19):1903–12.
12. Freeman RK, Ascioti AJ, Mahidhara RS. A propensity-matched comparison of pleurodesis or tunneled pleural catheter in patients undergoing diagnostic thoracoscopy for malignancy. Ann Thorac Surg. 2013;96(1):259–63.
13. Hunt BM, Farivar AS, Vallières E, Louie BE, Aye RW, Flores EE, Gorden JA. Thoracoscopic talc versus tunneled pleural catheters for palliation of malignant pleural effusions. Ann Thorac Surg. 2012;94(4):1053–7.
14. Bhatnagar R, Keenan EK, Morley AJ, Kahan BC, Stanton AE, Haris M, Harrison RN, Mustafa RA, Bishop LJ, Ahmed L, West A, Holme J, Evison M, Munavvar M, Sivasothy P, Herre J, Cooper D, Roberts M, Guhan A, Hooper C, Walters J, Saba TS, Chakrabarti B, Gunatilake S, Psallidas I, Walker SP, Bibby AC, Smith S, Stadon LJ, Zahan-Evans NJ, YCG L, Harvey JE, Rahman NM, Miller RF, Maskell NA. Outpatient talc administration by indwelling pleural catheter for malignant effusion. N Engl J Med. 2018;378(14):1313–22.

Quality of Life: Extended Pleurectomy/Decortication vs Extrapleural Pneumonectomy

52

Kimberly J. Song and Andrea S. Wolf

Introduction

Malignant pleural mesothelioma is a rare malignancy strongly linked to history of asbestos exposure. Treatment of this disease remains difficult due to its aggressive nature and the tendency for nearly all patients to recur. Current treatment strategies are multimodal, with surgical options ranging from palliative drainage of effusion to radical debulking, and serious consideration is given to patient age, performance status, and histology before pursuing extended pleurectomy/decortication (EPD) or extrapleural pneumonectomy (EPP). While data suggest that surgical treatment is an independent determinant of increased survival [1], the deadliness of this disease and the morbidity of surgery mandates a treatment strategy that maximizes the patient's quality of life (QOL). The choice of EPD vs EPP remains controversial partly due to the limited availability of high-quality evidence. A dearth of data from prospective or randomized controlled trials comparing the two leaves us to extrapolate from retrospective registries, single procedure multicenter studies, and small cohort series, including those from our own institution [2, 3]. Here, we review the available data pertaining to patient reported post-operative QOL.

Search Strategy

The MEDLINE electronic database was searched for articles from the years 1995–2019 using the keywords "mesothelioma," "surgery," and "quality of life," supplemented by review of the reference lists from these articles (Table 52.1). The

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majority of studies were published after the year 2000, and a total of 240 papers written in English were identified. Retrospective studies, prospective studies, and randomized trials were included. Studies that did not discuss quality of life after surgical therapy were excluded, as were those that reported findings in the lung cancer population without presenting mesothelioma-specific data. Thirteen papers meeting these criteria were identified and used for the final analysis (Tables 52.2 and 52.3).

Table 52.1 PICO formatted terms for literature search

P (population)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with leural mesothelioma	Radical surgical debulking via extended pleurectomy/ decortication	Radical surgical debulking via extrapleural pneumonectomy	Postoperative short and long-term physical and mental quality of life

Table 52.2 Studies regarding quality of life after extrapleural pneumonectomy

Reference	Study design, time period	Population	Duration of follow-up	Physical QOL findings	Mental QOL findings
Weder (2007) [4]	Prospective multi-center 2000–2003	n = 45; all histologies	6 months	Modified RSCL physical symptom and activity scores return to near-baseline by 6 months	Modified RSCL psychological scores were most affected; overall QOL improved but did not return to baseline
Ambrogi (2009, 2012) [5, 6]	Prospective single center 1997–2007	n = 29; all histologies	Up to 3 years	Karnofsky scores improved at 3 months but returned to baseline by 24 months; SF-36 physical domains improved at 3 months but all fell back to baseline or worse by 24 months; SGRQ symptom and activity scores improved at 3 months but worsened progressively thereafter	SF-36 mental domains and SGRQ mood scores improved at 3 months but worsened progressively thereafter

Table 52.2 (continued)

Reference	Study design, time period	Population	Duration of follow-up	Physical QOL findings	Mental QOL findings
Alvarez (2009) [7]	Prospective single center 2004–2007	n = 16; stage I–II epithelioid	12 months	ECOG scores slightly declined after 6 months; Karnofsky scores slightly improved from 6 to 12 months; patients who did not have surgery had stable scores	N/A
Treasure (2011) [8]	RCT multi center 2005–2008	n = 12; all histologies	24 months	Median EORTC QLQ-C30 and LC13 scores were lower in the EPP group vs no surgery group	

QOL quality of life, *RSCL* Rotterdam symptom checklist, *SF-36* short form 36, *SGRQ* St George Respiratory Questionnaire, *ECOG* Eastern Cooperative Oncology Group, *EORTC* European Organisation for Research and Treatment of Cancer

Table 52.3 Studies regarding quality of life after extended pleurectomy/decortication

Reference	Study design, time period	Population	Duration of follow-up	Physical QOL findings	Mental QOL findings
Burkholder (2015) [11], Mollberg (2012) [12]	Prospective multi center 2010–2011	n = 36; epithelioid or biphasic	8 months	EORTC QLQ-C30 physical scores did not change for WHO PS 0; all physical scores improved for PS 1–2	EORTC QLQ-C30 mental scores did not change for WHO PS 0 except for improvement in emotional functioning; all mental scores improved for PS 1–2
Soysal (1997) [13]	Retrospective single center 1974–1992	n = 100; all histologies	6 months	Dyspnea and cough improved in all patients presenting with these symptoms; chest pain improved in 85% of patients	N/A

(continued)

Table 52.3 (continued)

Reference	Study design, time period	Population	Duration of follow-up	Physical QOL findings	Mental QOL findings
Martin-Ucar (2001) [14]	Prospective single center 1997–2001	n = 51; all histologies; early stage excluded	12 months	MRC Dyspnea Scores improved significantly in dyspnea and pain at 6 weeks and 3 months	N/A
Tanaka (2017, 2019) [15, 16]	Prospective single center 2013–2016	n = 16; no histology information provided	12 months	SF-36 physical components initially decreased but returned to baseline	SF-36 mental components initially decreased but returned to baseline
Vigneswaran (2018) [17]	Prospective single center 2008–2015	n = 114; all histologies	11 months	EORTC QLQ-C30 overall health decreased at 1 month but later improved in all groups; physical functioning, appetite and pain improved significantly at 7–8 months	EORTC QLQ-C30 emotional functioning showed significant early improvement; insomnia improved significantly at 7–8 months

QOL quality of life, *EORTC* European Organisation for Research and Treatment of Cancer, *WHO* World Health Organization, *PS* performance status, *MRC* Medical Research Council, *SF-36* short form 36

Results

Quality of Life After EPP

Weder et al. studied self-reported QOL measures for 45 patients after neoadjuvant chemotherapy, EPP, and possible adjuvant radiation and showed that certain activity scores and physical symptoms including fatigue, dyspnea, and chest pain decreased from baseline in the first few months after surgery but returned by 6 months [4]. Psychological distress, the most significantly impaired measure, subsequently returned to near-baseline levels but overall self-reported QOL did not.

Ambrogi and colleagues used multiple tools to evaluate QOL in 29 patients. While the SF-36 improved in all mental and physical health aspects at 3 months, only the physical components remained above baseline at 12 months. By 24 months, all components were at or below baseline [5, 6]. Similarly, for the St. George

Respiratory Questionnaire, results showed initial improvement that worsened progressively through the rest of the study. Karnofsky scores also initially improved from baseline, but this improvement did not last.

In a small prospective study by Alvarez et al. comparing outcomes in patients undergoing EPP with adjuvant chemoradiation (n = 16/34) vs. definitive chemoradiation alone, those completing trimodality therapy had Eastern Cooperative Oncology Group (ECOG) and Karnofsky scores of 1 and 74, respectively, at 6 months and 0.8 and 82 at 12 months [7]. Patients in the non-surgery cohort had ECOG and Karnofsky scores of 1.7 and 46 at both time points. Without the baseline scores being reported for either cohort, it is difficult to determine whether bias in selection of fitter patients for the surgical cohort confounded these results.

In the Mesothelioma and Radical Surgery (MARS) feasibility trial, Treasure and co-investigators randomized patients to receive induction chemotherapy, EPP, and hemithoracic radiation or chemotherapy. The group reported lower median European Organization for Research and Treatment of Cancer (EORTC) Quality of Life in Cancer (QLQ-C30) and lung cancer-specific LC13 scores in the EPP group, though none of the differences was statistically significant [8]. While it was a laudable effort to attempt a prospective randomized controlled trial addressing the role of EPP, the study had numerous issues limiting conclusions that could be drawn from its results, including less than 50% of registered patients being randomized, high EPP mortality (12.5%, compared to reports in the literature of 3.2–6%) [9], and lack of data regarding time interval between start of chemotherapy and EPP [10].

Quality of Life After EPD

Investigators from the University of Chicago followed EORTC QLQ-C30 scores in patients undergoing EPD with or without neoadjuvant chemotherapy and compared the data according to their baseline World Health Organization Performance Status (WHO PS). [11, 12] Those with PS 0 (no activity restrictions) had no significant change from baseline in nearly all measures including global health QOL, functioning scores, or symptom scores. Emotional functioning scores improved through 8 months. When grouped together, patients with baseline PS 1 (restricted with strenuous activity) and PS 2 (ambulatory and active at least 50% of waking hours) showed improvement through 8 months. Importantly, there was variation in the chemotherapy regimens used in these patients. For example, in the first series of 36 patients, 3 received cisplatin or carboplatinum with pemetrexed as induction (3/36; 8% of the total) or as adjuvant (30/36; 78%) therapy [11].

Soysal et al. assessed baseline physical symptoms in 100 patients undergoing EPD or partial pleurectomy and found that 100% of those with cough or dyspnea had either improvement or relief by 6 months [13]. The majority (n = 60/71; 85%) of those experiencing chest pain also reported improvement. As in other studies, the population in this study was heterogeneous, with 56% receiving what the authors termed “complete pleurectomy/decortication” and the remainder having gross residual tumor with removal of significant amounts of pleura “from the standpoint

of palliation." Adjuvant treatment administration was also variable, with 24% receiving chemotherapy, 31% receiving radiation, and 20% receiving both.

Martin-Ucar et al. used the Medical Research Council Dyspnea Score to measure changes from baseline pain and dyspnea in 51 patients with later-stage disease after EPD [14]. Significant improvement was evident at 6 weeks and again at 3 months. Epithelial cell type and absence of weight loss were predictors for maintained symptomatic control.

Tanaka et al. used the SF-36 to assess QOL through 1 year after EPD with or without preoperative chemotherapy in 16 patients with mostly stage I disease [15, 16]. Although exercise capacity was significantly diminished in the immediate postoperative period, the decrease improved by 1 year and scores reached near-preoperative values. This was associated with changes in pulmonary function. While FEV1 and FVC initially decreased and did not recover fully, there was a subsequent significant improvement in FVC over time. All aspects of physical and mental functioning remained at or recovered to baseline levels by 1 year.

Vigneswaran et al. administered the EORTC QLQ-C30 to 114 patients through 11 months after EPD, and found that patients with PS 1-2, non-epithelioid histology, and large tumor volume demonstrated an initial decrease but then improvement over time in overall QOL, physical and social functioning, lack of appetite, pain, and insomnia [17].

Published findings of both physiologic and QOL outcomes after EPD are further obscured by the lack of a standardized definition for this procedure. Various series have included a mix of patients undergoing partial, extended and palliative pleurectomy, resulting in a heterogeneous population and potentially confounded analyses. Rice et al. administered a survey to 62 surgeons actively performing "pleurectomy/decortication" procedures for mesothelioma and found wide variation in their definitions. For example, resection with intent to remove all macroscopic tumor including diaphragm and pericardium was termed "pleurectomy/decortication" by 40%, but was also referred to as "total pleurectomy" (39%), "radical pleurectomy/decortication" (11%), "palliative debulking" (3.4%), and "partial pleurectomy" (3.4%). Resection with curative intent excluding diaphragm and pericardium was termed "radical pleurectomy/decortication" by 64%, but also "total pleurectomy" (19%) and "pleurectomy/decortication" (5%). Furthermore, respondents showed inconsistency even in their definitions of procedural goals: 72% of respondents defined "pleurectomy/decortication" as removal of all gross visceral and parietal tumor with the objective of clearing macroscopic disease but 26% defined it as removal of visceral and parietal tumor for palliation with the intent of an R2 resection [18].

EPP vs. EPD

When considering either operation for surgical resection in a patient with malignant pleural mesothelioma, careful assessment of patient physiologic reserve is warranted, including a full cardiopulmonary workup. It has been suggested that patients undergoing EPP may benefit from having a predicted postoperative FEV1 of at least

1.2 L [19], considering the added morbidity of diaphragmatic and pericardial resection. In fact, despite the likelihood that EPP is more often performed on candidates with lower operative risk, EPD has been associated with much lower perioperative mortality and possibly increased long-term survival [9, 20].

There are few studies directly comparing QOL after EPD vs. EPP, and only one that directly compared subjective patient reports rather than physical findings. Rena et al. followed responses to the EORTC QLQ-C30 at 6 and 12 months for 77 patients undergoing EPD or EPP, and while both groups showed significant decline from baseline in all components at 6 months, there was a more pronounced effect in the EPP group [21]. While the EPD group improved to baseline levels by 12 months, the EPP cohort did not.

A meta-analysis by Schwartz et al. included many of the studies mentioned above, ultimately extracting a total of 659 distinct mesothelioma patients. While acknowledging that the majority of the data was of low quality, the authors drew the following conclusions: QOL was diminished after either EPP or EPD for at least 6 months after surgery, but it was worse for EPP patients across both physical and social measures. This analysis was limited by the relatively small amount of available data and the variable nature by which QOL was measured in each study [3].

Conclusions and Recommendations

The majority of published data regarding quality of life after EPD or EPP comes from small, single center observational studies from which it is difficult to draw broadly applicable conclusions. There is only one attempted randomized controlled trial and it failed to accrue adequate sample size to draw meaningful conclusions. Quality is further hindered by lack of available long-term follow up and heterogeneity among procedures performed in retrospective series. Controversy persists whether EPD or EPP is the best therapeutic surgical option in the multimodality treatment of malignant pleural mesothelioma but QOL is a parameter that is being given appropriately increased attention and appears to favor EPD. Negative effects on quality of life may be more permanent after EPP, while improvements are short-lived. While the negative impacts of EPD may be less pronounced, it remains unclear whether QOL improves to baseline. More data is needed to determine the feasibility and timeline of full recovery.

We recommend that, to best preserve quality of life, EPD is favored over EPP when pursuing surgical treatment options.

Recommendation

- To best preserve quality of life, EPD is favored over EPP when pursuing surgical treatment for pleural mesothelioma (evidence quality low; weak recommendation).

A Personal View of the Data

In our practice, we follow the tenet that less is more with regard to surgery for malignant pleural mesothelioma, and opt for EPD whenever possible [22]. Local recurrence rates are high, and preservation of lung parenchyma, pericardium, and diaphragm may leave patients with greater physiologic reserve to withstand adjuvant treatment and enjoy maximal quality of life.

References

1. Taioli E, Wolf AS, Camacho-Rivera M, et al. Determinants of survival in malignant pleural mesothelioma: a Surveillance, Epidemiology, and End Results (SEER) study of 14,228 patients. PLoS One. 2015;10(12):e0145039.
2. Schwartz RM, Watson A, Wolf A, Flores R, Taioli E. The impact of surgical approach on quality of life for pleural malignant mesothelioma. Ann Transl Med. 2017;5(11):230.
3. Schwartz RM, Lieberman-Cribbin W, Wolf A, Flores RM, Taioli E. Systematic review of quality of life following pleurectomy decortication and extrapleural pneumonectomy for malignant pleural mesothelioma. BMC Cancer. 2018;18(1):1188.
4. Weder W, Stahel RA, Bernhard J, et al. Multicenter trial of neo-adjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. Ann Oncol. 2007;18(7):1196–202.
5. Ambrogi V, Mineo D, Gatti A, Pompeo E, Mineo TC. Symptomatic and quality of life changes after extrapleural pneumonectomy for malignant pleural mesothelioma. J Surg Oncol. 2009;100(3):199–204.
6. Ambrogi V, Baldi A, Schillaci O, Mineo TC. Clinical impact of extrapleural pneumonectomy for malignant pleural mesothelioma. Ann Surg Oncol. 2012;19(5):1692–9.
7. Alvarez JM, Hasani A, Segal A, et al. Bilateral thoracoscopy, mediastinoscopy and laparoscopy, in addition to CT, MRI and PET imaging, are essential to correctly stage and treat patients with mesothelioma prior to trimodality therapy. ANZ J Surg. 2009;79(10):734–8.
8. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extrapleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol. 2011;12(8):763–72.
9. Taioli E, Wolf AS, Flores RM. Meta-analysis of survival after pleurectomy decortication versus extrapleural pneumonectomy in mesothelioma. Ann Thorac Surg. 2015;99(2):472–80.
10. Weder W, Stahel RA, Baas P, et al. The MARS feasibility trial: conclusions not supported by data. Lancet Oncol. 2011;12(12):1093–4.
11. Burkholder D, Hadi D, Kunnavakkam R, et al. Effects of extended pleurectomy and decortication on quality of life and pulmonary function in patients with malignant pleural mesothelioma. Ann Thorac Surg. 2015;99(5):1775–80.
12. Mollberg NM, Vigneswaran Y, Kindler HL, et al. Quality of life after radical pleurectomy decortication for malignant pleural mesothelioma. Ann Thorac Surg. 2012;94(4):1086–92.
13. Soysal O, Karaoglanoglu N, Demiracan S, et al. Pleurectomy/decortication for palliation in malignant pleural mesothelioma: results of surgery. Eur J Cardiothorac Surg. 1997;11(2):210–3.
14. Martin-Ucar AE, Edwards JG, Rengajaran A, Muller S, Waller DA. Palliative surgical debulking in malignant mesothelioma. Predictors of survival and symptom control. Eur J Cardiothorac Surg. 2001;20(6):1117–21.
15. Tanaka T, Morishita S, Hashimoto M, et al. Physical function and health-related quality of life in patients undergoing surgical treatment for malignant pleural mesothelioma. Support Care Cancer. 2017;25(8):2569–75.

16. Tanaka T, Morishita S, Hashimoto M, et al. Physical function and health-related quality of life in the convalescent phase in surgically treated patients with malignant pleural mesothelioma. Support Care Cancer. 2019;27(11):4107–13.
17. Vigneswaran WT, Kircheva DY, Rodrigues AE, et al. Influence of pleurectomy and decortication in health-related quality of life among patients with malignant pleural mesothelioma. World J Surg. 2018;42(4):1036–45.
18. Rice D, Rusch V, Pass H, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group. J Thorac Oncol. 2011;6(8):1304–12.
19. Wolf AS, Daniel J, Sugarbaker DJ. Surgical techniques for multimodality treatment of malignant pleural mesothelioma: extrapleural pneumonectomy and pleurectomy/decortication. Semin Thorac Cardiovasc Surg. 2009;21(2):132–48.
20. Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. J Thorac Cardiovasc Surg. 2008;135(3):620–6, 626.e621–623.
21. Rena O, Casadio C. Extrapleural pneumonectomy for early stage malignant pleural mesothelioma: a harmful procedure. Lung Cancer. 2012;77(1):151–5.
22. Wolf AS, Flores RM. Mesothelioma: live to fight another day. J Thorac Cardiovasc Surg. 2018;155(4):1855–6.

Part VI

Mediastinum

Does Thymectomy Improve Outcomes in Patients with Nonthymomatous Myasthenia Gravis?

53

Richard Dubois and Joshua Sonett

Introduction

Myasthenia gravis (MG) is a rare autoimmune disorder affecting approximately 7.77 per 100,000 population. The symptoms of MG can vary from weakness of the proximal appendicular muscles to the bulbar and ocular musculature and can have an insidious or more rapid onset [1, 2]. Though there are still questions regarding the origins of MG, the etiology of the process appears to stem from autoantibodies against the acetylcholine receptor at the neuromuscular junction, resulting in a decreased availability of these receptors [2].

Thymectomy for nonthymomatous MG has been utilized as one method of treatment for many years. Early insights prompted a long legacy of various investigations into the role of thymectomy in MG [3–8]. Given that, until recently, many of the studies examining the treatment of MG have been observational or retrospective, there remains speculation regarding the best approach for treating non-thymomatous MG and in whom it would be beneficial. In this chapter, we depict the effects of thymectomy in patients with nonthymomatous MG as compared to medical management alone.

Search Strategy

A literature search was conducted for articles only in English published between the years 1999 and 2019 using PubMed (Table 53.1). Literature searches included "thymectomy AND myasthenia gravis," "thymectomy," thymectomy AND nonthymomatous myasthenia gravis" and "minimally-invasive thymectomy AND

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Table 53.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with myasthenia gravis	Thymectomy	Conventional medical treatment	Complete remission, improved symptomatology

myasthenia gravis," "myasthenia gravis AND treatment." The results of the literature search (Table 53.2) included one prospective, randomized-controlled trial [9] and a companion follow-up study [10], and five retrospective, observational, or single-armed prospective studies [11–15].

Results

MGTX Trial

In 2006, 67 different medical centers across 18 countries began enrollment for a prospective, randomized, rater-blinded trial known as the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX trial) [9]. As the name suggests, this trial randomized patients with acetylcholine receptor antibody positive, nonthymomatous MG to standard transsternal thymectomy plus prednisone therapy or prednisone therapy alone, with the dual primary outcomes being time-weighted average Quantitative Myasthenia Gravis (QMG) score (a physician-rated scoring system which takes into account multiple variables including diplopia, facial muscle weakness, extremity weakness, and vital capacity) and time-weighted average prednisone dose at 36 months. Between September 2006 and November 2012, 126 patients were randomized in a 1:1 fashion.

In the patients who received both prednisone and thymectomy, there was a significantly lower time-weighted average QMG score at 3 years compared to patients receiving prednisone alone (6.15 vs 8.99; $p < 0.001$) [9]. This difference in QMG score was true for both patients with disease onset before 40 years of age and those with disease onset after 40 years of age. The thymectomy group also had a lower time-weighted average prednisone dose at 3 years compared to the prednisone-only group (44 mg vs 60 mg; $p < 0.001$). In addition to a significant improvement in the primary outcomes, the thymectomy group out-performed the prednisone-only group in hospitalization after randomization (9% vs 37%; $p < 0.001$) and the mean cumulative number of hospital days (8.4 days vs 19.2 days; $p = 0.09$). Thymectomy patients also had a higher minimal manifestation status (no symptoms or functional limitations from MG, but possibly some weakness in some muscle groups) at 3 years (67% vs 47%; $p = 0.008$) and had lower use of azathioprine (17% vs 48%, $p < 0.001$). Furthermore, thymectomy appeared to not contribute any significant morbidity or mortality to the patients in the surgical group.

Table 53.2 Results of Literature Search

Study	Patients	Intervention	Trial design	Outcome	Quality of evidence
Wolfe (2016) [9]	Prednisone: 60 Prednisone + thymectomy: 66	Transsternal thymectomy + prednisone vs prednisone alone	Multi-centered, rater-blinded, randomized control trial	Improved time-weighted, average QMG score, lower time-weighted, average prednisone dose at 3 years in thymectomy group	High
Wolfe (2019) [10]	Prednisone: 24 Prednisone + thymectomy: 26	Transsternal thymectomy + prednisone vs prednisone alone	Follow up study at 5 years of a multi-centered, rater-blinded, randomized control trial	Improved time-weighted, average QMG score, lower time-weighted, average prednisone dose at 5 years in thymectomy group	High
Popescu (2002) [11]	Thoracoscopic thymectomy: 25	Thoracoscopic thymectomy	Observational	Surgical outcomes: 0 mortality and 1 minor morbidity. Early improvement in MG symptoms	Low
Zieliński (2007) [12]	Transcervical-subxiphoid-videothoracoscopic thymectomy: 100	Transcervical-subxiphoid-videothoracoscopic thymectomy	Single-center, single-arm, prospective	32% complete remission at 2 years, no mortality, 15% morbidity	Low
Rückert (2008) [13]	Robotic thymectomy: 106	Robotic thymectomy	Single-center, single-arm, prospective	Complete stable remission in >40% of both thymomatous and nonthymomatous, 0 mortality, 2% morbidity	Low
Tomulescu (2011) [14]	Thoracoscopic unilateral extended thymectomy: 134	Thoracoscopic unilateral extended thymectomy	Portion of data was gathered retrospectively and the rest was collected prospectively	Complete stable remission in 61% of patients, no post operative mortality, 5% morbidity	Low
Rückert (2011) [15]	Robotic thymectomy: 74 Thoracoscopic thymectomy: 79	Robotic thymectomy vs thoracoscopic thymectomy	Retrospective cohort study	Similar operative time, conversion rate, morbidity. Cumulative complete remission rate significantly better in robotic group (39.25% vs 20.3%, $p = 0.01$)	Moderate

A follow-up to the MGTX study in 2019 examined the outcomes of 50 (26 thymectomy plus prednisone and 24 prednisone only) patients from the trial at 5 years [10]. In line with the first iteration of the study, the thymectomy plus prednisone group had significantly lower time-weighted, average QMG scores (5.47 vs 9.34, $p = 0.0007$) and lower time-weighted, average prednisone dose (24 mg vs 48 mg, $p = 0.002$) at 5 years. Minimal manifestation status and azathioprine use were also improved in the thymectomy group compared to those patients that received prednisone alone.

The MGTX trial was the first prospective, randomized controlled trial set out to investigate whether a true benefit existed for thymectomy in patients with nonthymomatous MG. Despite the small sample size, the study showed significant improvements in metrics pertaining to not only medication need but also quality of life for patients undergoing thymectomy for MG. Patients who underwent thymectomy not only had better symptomatology, but required less medication to achieve it. Furthermore, this trial proved that transsternal thymectomy for MG can be performed with a superior treatment-related complication profile compared to medical therapy alone [9].

The Approach

Since the origins of thymectomy, significant debate has existed regarding the optimal surgical approach. In 1977, Jaretzki et al. demonstrated that small rests of extra-anatomic thymic tissue were present in some patients and strongly advocated for maximal resection via a combined transsternal and transcervical approach [16]. In a subsequent narrative in 1997, Jaretzki analyzed several approaches to thymectomy and concluded "the evidence indicates that there is a direct relationship between the extent of thymic resection and the results for any given severity of illness and length of post-operative follow-up…the more aggressive the resection, the higher the remission rate." [17] With maximal thymectomy becoming the standard of care, questions lingered regarding how this could be achieved via a less invasive approach.

Popescu described one of the first reports of thoracoscopic thymectomy in a series of 25 patients [11]. In their left-sided thoracoscopic approach, they had no conversions to open thymectomy, an average hospital length of stay of 2 days, no mortality, and only one minor morbidity (right sided pneumothorax). More variations of a thoracoscopic approach soon followed with report of a transcervical-subxiphoid-videothoracoscopic approach involving three separate access points to achieve maximal thymectomy [12]. Results of this hybrid approach were promising in some regards, with an 18% complete remission rate at 1 year and 32% at 2 years. Ectopic thymic tissue was identified in 71% of patients. However, the study noted a 15% morbidity rate, with complications including superior vena cava laceration in 1, post-operative bleeding necessitating conversion in 2, and two minor wound complications.

In an effort to maintain the concept of maximal thymectomy yet reduce the morbidity of an open or hybrid approach, additional studies looked at unilateral

video-assisted thoracoscopy (VATS) or robotic approaches to thymectomy [13–15, 18]. Rückert published a series of 106 patients undergoing robot-assisted thymectomy, with a complete stable remission rate of greater than 40% in both thymomatous and non-thymomatous MG. They reported no mortality and a 2% morbidity incidence (one bleeding complication and one phrenic nerve injury) [13]. In 2011, a 10-year experience of thoracoscopic unilateral extended thymectomy showed a 61% complete stable remission rate with a median time to complete stable remission of 18 months, no post-operative mortality, and 5% post-operative morbidity [14]. A comparison of VATS and robotic assisted thymectomy showed that robotic and VATS thymectomy had similar operative times (187 min vs 198 min), similar conversion rates (1.4% vs 1.3%), and similar post-operative morbidity (2.7% vs 2.5%) [15].

Subtypes

The classification and staging of MG is an ongoing endeavor of the research community. While acetylcholine receptor antibodies are the most widely known and studied biomarkers for MG, muscle-specific kinase (MuSK) antibody and lipoprotein receptor-related protein 4 (LRP4) have begun to draw attention as methods for defining certain subgroups of MG. Furthermore, the natural history and treatment algorithms of ocular MG and seronegative MG differ from that of early-onset, antibody positive disease and thus warrant a separate subgroup.

Since the completion of the MGTX trial, there is now strong evidence that acetylcholine receptor antibody positive MG patients between 18 and 65 years of age have a clear and consistent benefit of thymectomy [9, 10]. Not only did these patients have significant improvements in clinical metrics such as decreased average daily dose of prednisone and fewer subsequent hospitalizations compared to the medically managed arm, but there were statistically significant improvements in quality of life metrics at both 3- and 5-year follow-up. Furthermore, treatment-related complications were not statistically significant between the two groups.

Although approximately 85% of patients with ocular MG will go on to developed generalized MG, there is no strong, high quality evidence that thymectomy in these patients prevents generalization or results in remission [19, 20]. Despite the lack strong of evidence, thymectomy remains a reasonable therapy in patients with ocular MG who have failed medical therapy and have acetylcholine receptor antibodies [19, 20].

Myasthenia patients with MuSK antibodies, LRP4 antibodies, and those without detectable acetylcholine receptor antibodies (seronegative) are three additional subgroups in which the role of thymectomy is less clear. Approximately 1–3% of all patients with MG are LRP4 antibody positive and typically have mild to moderate symptoms [20, 21]. MuSK positive MG tends to have a worse symptom response to medical therapy than other subgroups and typically does not manifest with ocular MG [22, 23]. Ultimately, patients with LRP4 and MuSK positive myasthenia gravis tend to have normal thymic pathology and, although there is little data regarding

thymectomy in these subgroups, the data available suggests no response to surgical therapy [20, 23]. Furthermore, there is insufficient high quality evidence for the use of thymectomy in patients with seronegative disease [20]. On the other hand, contrary to MuSK and LRP4 positive MG, patients with seronegative MG may be considered for thymectomy if they do not respond to medical therapy and/or if the side effects of immunosuppressive therapy are not tolerated [24].

Conclusions and Recommendations

A summary of the surgical approach to myasthenia gravis is provided in Table 53.3. Since the completion of the MGTX trial, we now have strong evidence that thymectomy is beneficial in patients 18–65 years of age with acetylcholine receptor positive disease [9, 10]. This benefit is manifested in clinical metrics and in improved quality of life [9, 10]. There is no high quality evidence to suggest that patients with ocular or seronegative MG will benefit from thymectomy, however consensus guidelines maintain thymectomy is reasonable in select patients in these two subgroups who have features of generalized disease and are refractory or intolerant of medical therapy [20, 24]. Contrary to this, there appears to be no conclusive data that patients with LRP4 and MuSK MG benefit from thymectomy, thus resection is not recommended in these two subgroups [20, 23]. The optimal surgical approach for thymectomy has been the subject of many recent studies, and minimally-invasive approaches yield similar results compared to the open techniques previously described [11–15, 18]. As long as the tenets of maximal thymectomy are adhered to, safely removing as much mediastinal and cervical peri-thymic tissue and fat while protecting the phrenic and recurrent laryngeal nerves, a minimally invasive approach is advised and is now standard of care [25].

Table 53.3 Myasthenia gravis subgroups and role for thymectomy

Subgroup	Antibody	Age of Onset	Treatment
Early onset	Acetylcholine receptor	<50 years	Thymectomy
Late onset	Acetylcholine receptor	>50 years	Thymectomy for 50–65 years
Seronegative	None detected	Any age	No high quality evidence for routine thymectomy[a]
Ocular	Variable	Any age	No high quality evidence for routine thymectomy[a]
Muscle-specific kinase	MuSK antibody	Any age	Thymectomy not recommended
LRP4	LRP4	Any age	Thymectomy not recommended

[a]Consensus recommendations reserve thymectomy in these groups for those patients who are refractory to or intolerant of medical therapy and/or show similarities to early-onset, generalized MG

Recommendations

- Thymectomy is recommended for acetylcholine receptor positive myasthenia gravis in patients 18–65 years of age (evidence quality high, strong recommendation).
- There is no benefit of thymectomy for patients with ocular and seronegative myasthenia gravis; thymectomy is reasonable in such patients who have failed or cannot tolerate medical therapy (evidence quality low, weak recommendation).
- Thymectomy is not recommended in patients with LRP4 and MuSK positive MG (evidence quality low, weak recommendation).
- Minimally invasive approaches to maximal thymectomy are recommended as noninferior to transsternal approaches (evidence quality low, weak recommendation).

A Personal View of the Data

Based on the MGTX trial, we know that patients between the ages of 18–65 years who are acetylcholine receptor antibody positive benefit from thymectomy, thus these patients should be offered thymectomy as a part of their treatment. Minimally invasive extended maximal thymectomy should be offered to all of these patients. Patients who are acetylcholine receptor antibody positive and above 65 years of age with good functional status can be counseled on the risks and possible benefits of thymectomy, keeping in mind that the high quality evidence does not extend to this patient population. Furthermore, I discuss thymectomy with my patients with ocular and seronegative myasthenia gravis with symptoms that are poorly controlled or refractory to medical therapy. To date, there is no evidence to support any benefit of thymectomy in patients with MuSK or LRP4 antibodies and, thus, thymectomy is not recommended to this cohort.

References

1. Wilks S. On cerebritis, hysteria and bulbar paralysis, as illustrative of arrest of function of the cerebrospinal centres. Guys Hosp Rep. 1877;22:7–55.
2. Cooper JD. History of thymectomy for myasthenia gravis. Thorac Surg Clin. 2019;29(2):151–8.
3. Weigert C. II. Pathologisch-anatomischer Beitrag zur Erb'schen Krankheit (Myasthenia gravis). 1901.
4. Bell ET. Tumors of the thymus in myasthenia gravis. J Nerv Ment Dis. 1917;45(130)
5. Blalock A, Harvey AM, Ford FR, Lilienthal JL. The treatment of myasthenia gravis by removal of the thymus gland: preliminary report. JAMA. 1941;117(18):1529–33.
6. Perlo VP, Poskanzer DC, Schwab RS, Viets HR, Osserman KE, Genkins G. Myasthenia gravis: evaluation of treatment in 1,355 patients. Neurology. 1966;16(5):431.
7. Kirschner PA, Osserman KE, Kark AE. Studies in myasthenia gravis: transcervical total thymectomy. JAMA. 1969;209(6):906–10.

8. Buckingham JM, Howard FM Jr, Bernatz PE, Payne WS, Harrison EG Jr, O'Brien PC, Weiland LH. The value of thymectomy in myasthenia gravis: a computer-assisted matched study. Ann Surg. 1976;184(4):453.
9. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, et al. Randomized trial of thymectomy in myasthenia gravis. NEJM. 2016;375(6):511–22.
10. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, et al. Long-term effect of thymectomy plus prednisone versus prednisone alone in patients with non-thymomatous myasthenia gravis: 2-year extension of the MGTX randomised trial. Lancet Neurol. 2019;18(3):259–68.
11. Popescu I, Tomulescu V, Ion V, Tulbure D. Thymectomy by thoracoscopic approach in myasthenia gravis. Surg Endosc. 2002;16(4):679–84.
12. Zieliński M, Hauer Ł, Kużdżał J, Sośnicki W, Harazda M, Pankowski J, Nabialek T, Szlubowski A. Technique of the transcervical-subxiphoid-videothoracoscopic maximal thymectomy. J Minim Access Surg. 2007;3(4):168.
13. Rückert JC, Ismail M, Swierzy M, Sobel H, Rogalla P, Meisel A, Wernecke KD, Rückert RI, Müller JM. Thoracoscopic thymectomy with the da Vinci robotic system for myasthenia gravis. Ann N Y Acad Sci. 2008;1132(1):329–35.
14. Tomulescu V, Sgarbura O, Stanescu C, Valciu C, Campeanu A, Herlea V, Popescu I. Ten-year results of thoracoscopic unilateral extended thymectomy performed in nonthymomatous myasthenia gravis. Ann Surg. 2011;254(5):761–6.
15. Rückert JC, Swierzy M, Ismail M. Comparison of robotic and nonrobotic thoracoscopic thymectomy: a cohort study. J Thorac Cardiovasc Surg. 2011;141(3):673–7.
16. Jaretzki A III, Bethea M, Wolff M, Olarte MR, Lovelace RE, Penn AS, Rowland L. A rational approach to total thymectomy in the treatment of myasthenia gravis. Ann Thorac Surg. 1977;24(2):120–30.
17. Jaretzki A. Thymectomy for myasthenia gravis: analysis of the controversies regarding technique and results. Neurology. 1997;48(Suppl 5):52S–63S.
18. Singh G, Glotzbach J, Costa J, Gorenstein L, Ginsburg M, Sonett JR. Minimally invasive radical thymectomy. Ann Cardiothorac Surg. 2016;5(1):59.
19. Kerty E, Elsais A, Argov Z, Evoli A, Gilhus NE. EFNS/ENS Guidelines for the treatment of ocular myasthenia. Eur J Neurol. 2014;21(5):687–93.
20. Gilhus NE. Myasthenia gravis. NEJM. 2016;375(26):2570–81.
21. Bacchi S, Kramer P, Chalk C. Autoantibodies to low-density lipoprotein receptor-related protein 4 in double seronegative myasthenia gravis: a systematic review. Can J Neurol Sci. 2018;45(1):62–7.
22. Guptill JT, Sanders DB, Evoli A. Anti-MuSK antibody myasthenia gravis: clinical findings and response to treatment in two large cohorts. Muscle Nerve. 2011;44(1):36–40.
23. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol. 2015;14(10):1023–36.
24. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, Kuntz N, Massey JM, Melms A, Murai H, Nicolle M, Palace J, Richman DP, Verschuuren J, Narayanaswami P. International consensus guidance for management of myasthenia gravis: executive summary. Neurology. 2016;87(4):419–25.
25. Sonnet JR, Jaretzki A III. Thymectomy for nonthymomatous myasthenia gravis. A critical review. Ann N Y Acad Sci. 2008;1132:315–28.

Magnetic Resonance Imaging for Evaluation of Suspected Encapsulated Thymoma

54

Wenhan Weng and Xiao Li

Introduction

Thymoma is a relatively rare malignancy characterized by indolent growth manifesting mainly with local extension [1]. Usually, thymoma is asymptomatic and is discovered incidentally during imaging performed for other reasons. All thymomas should be resected due to their malignant potential and complete resection is an important factor in the treatment of thymomas [2]. However, reports of rates of unnecessary or nontherapeutic thymectomy ranging from 22% to 68% [3, 4] emphasize the value of accurately diagnosing thymic lesions preoperatively. Furthermore, the preoperative assessment of the Masaoka stage which determines the treatment strategy for thymomas mandates more accurate imaging [5].

Computed tomography (CT) is generally the first choice and standard modality for diagnostic imaging of the thymus. Encapsulated thymomas typically appear as spherical or ovoid soft tissue lesions. They are well marginated and outlined by adjacent mediastinal fat [6]. However, partial or complete absence of fat planes around the tumor does not indicate the presence of an invasive thymoma [7]. In fact, sometimes thymic hyperplasia can be mistaken for an early stage thymoma. There is no reliable characteristic on CT that distinguishes an encapsulated thymoma from other entities including early invasive thymoma or thymic hyperplasia [4].

Magnetic resonance imaging (MRI) is another modality that is gaining increasing importance in thoracic imaging. It is a substitute for CT for those patients with iodine allergy or renal failure, with the advantage of contrast resolution and lack of need for iodine-based intravenous contrast [8]. The role of MRI for staging thymoma continues to expand [9], and it also has potential use for distinguishing between early thymoma and thymic hyperplasia [10]. This chapter will focus on the MRI evaluation of suspected encapsulated thymoma.

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Table 54.1 PICO formatted terms used for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with thymoma or thymic hyperplasia	MRI	None or any other examinations	MRI findings Diagnostic accuracy

Search Strategy

An English-language literature search of the PubMed was performed with the combination of following keywords in query: ((thymus) OR (thymic gland) OR (thymic epithelial tumor) OR (thymoma) OR (thymic hyperplasia)) AND ((magnetic resonance) OR (magnetic resonance imaging) OR (MR) OR (MRI)). The publishing time of article was limited to 2000–2019. In addition, current guidelines and major thoracic surgical text books were reviewed and references of included publications were screened for additional evidence. There were 1052 results returned in total, and 55 related publications regarding MRI differentiation of early stage thymoma or non-invasive thymoma or low risk thymoma were finally included for review (Table 54.1).

Results

We identified few studies comparing MRI and CT scan directly to evaluate the diagnosis and staging of suspected encapsulated thymomas. However, some evidence could be collected for informing further investigations of this subject.

Differentiation of Thymoma from Benign Thymic Conditions

The differentiation of thymoma from benign thymic conditions (thymic cyst and hyperplasia) is critical in the evaluation for surgical treatment. The differentiation between thymoma and thymic carcinoma is especially complicated, and CT is considered the imaging technique of choice currently. Thymoma is seen as a focal soft tissue mass on CT scan, whereas thymic hyperplasia shows a diffuse symmetrically enlarged gland [6].

Nevertheless, CT has limitations in differentiating thymic hyperplasia from thymoma in some conditions. Thymic lymphoid hyperplasia may display as a focal soft tissue mass; in contrast, thymoma may demonstrate diffuse enlargement in both lobes [11]. In these cases, CT results in indeterminate findings, whereas chemical shift MRI can diagnose thymic hyperplasia by detecting fatty infiltration within the thymus and is useful in its differentiation from neoplastic processes [12, 13].

Inaoka et al. reported a series of 41 patients consisting of 23 thymic hyperplasia and 18 thymic neoplasm, in which all patients with hyperplastic thymus showed an apparent decrease in the signal intensity of the thymus at opposed-phase (OP) images in contrast to in-phase (IP) images, while none of the patients with thymic

tumors showed a decrease in signal intensity at opposed-phase images [13]. Similar results were reported by Priola et al. and Tuan et al., demonstrating significantly higher accuracy with MRI than that with CT in differentiating thymoma from non-thymomatous abnormalities in both qualitative and quantitative assessments [11, 14].

Radiodensity in CT scan and chemical shift ratio [CSR] in MRI were generally used quantitatively in assessments of thymic tissue. A CSR of 1.0 is generally regarded as being indicative of neoplasm. However, some recent reports showed that even a normal thymus in an adult can occasionally have a CSR of about 1.0 or greater [15, 16]. So the interpretation of the CSR should never be made in isolation of other signal-related and morphologic features of the lesion, to avoid misinterpretation and unnecessary thymectomy.

Differentiation Between Early Stage and Advanced Stage Thymoma by MRI

In general, irregular contours, cystic or necrotic components, and heterogeneous enhancement are the featured characteristics on MRI of advanced thymic tumor, especially for thymic carcinomas [17, 18]. Diffusion weighted MR imaging (DWI) has been utilized to differentiate malignant from benign lesions in other organs. This technique creates contrast within an image based on diffusivity of water molecules within the tissues. It has been used in evaluation of thymic epithelial tumors (TETs) recently, and the apparent diffusion coefficient (ADC) value was assessed to identify early stage thymoma [19, 20]. The ADC values of early stage thymomas are significantly higher than those of advanced stage tumors [19]. A similar result was reported by Priola et al. [20] with findings based on a higher proportion of type B3 tumors in the advanced stage group. Thus, it has been argued that it is pathological features, but not Masaoka stage, that determines the differences in DWI in thymic tumors [21]. In conclusion, it still controversial whether DWI is reliable for differentiating early stage thymoma from more invasive tumors.

In 2017, Li et al. [22] introduced the introvaxel incoherent motion (IVIM) scheme, based on DWI, for the evaluation of TETs, and the slow diffusion coefficient (D) value was found to be more effective than the ADC value in differentiating between early and advanced stage TETs. A decrease in D value was detected in advanced TETs according to their results.

In addition to DWI, dynamic MRI and cine MRI have also been applied in assessment of thymomas in recent years. In dynamic MRI, the peak time of time intensity curve (TIC) was used as the index for differentiating stages. A significant difference was found between early stage and stage III; the peak time of TIC shifted toward a delayed area as the stage of thymoma advanced [23]. It was also reported that cine MRI might be able to better evaluate the tumor invasion to adjacent structures. Thus, MRI has the potential for preoperative identification of advanced stage thymomas [24].

Differentiation Among Histologic Subtypes by MRI

The WHO pathological classification correlates to some extent with Masaoka stage and prognosis of thymoma, although there is no unequivocal correlation between them. The proportion of invasive thymomas increases from WHO type A to type B3 thymomas, and the prognosis gets worse as the subtype moves from type A to type B3 [25–27]. Many studies categorize different histologic subtypes of thymoma into low risk (WHO types A-B1) and high risk (WHO types B2/B3) [18, 28]. The high-risk thymomas display irregular shape and contour more often than low-risk tumors on CT scan. There are also significant differences in the internal architecture seen on chest CT comparing high- and low-risk groups [28]. However, the findings are currently of limited value in differentiating the various histologic subtypes of thymomas.

Routine and dynamic contrast agent-enhanced MRI has similar accuracy to CT in differentiating low-risk from high-risk thymic epithelial tumors [17, 18]. In a manner similar to differentiating of early stage thymoma from more advanced stages, the ADC value in DWI can add some accuracy in differentiation between low-risk and high-risk histologic subtypes of thymoma [19, 20, 22, 29]. The ADC value is higher in low-risk thymomas than that of high-risk thymoma. Similarly, the D value in IVIM DWI introduced by Li et al. [22] has higher efficacy than ADC in differentiating between low-risk and high-risk tumors, because the D value reflects pure molecular diffusion more accurately. The limitations of MRI in differentiation among specific histologic subtypes are similar to those of CT. It cannot accurately determine specific subtypes within the WHO classification.

Conclusions and Recommendations

Significantly higher accuracy is consistently reported in the literature for MRI than for CT in differentiating thymoma from nonthymomatous abnormalities. We recommend routine use of MRI for differentiating encapsulated thymoma from benign thymic conditions, although the evidence quality is moderate. There is no obvious advantage for MRI over CT in differentiating between early and advanced stage TETs. CT is still the standard imaging modality for thymomas. However, MRI may supplement CT in providing further information on anatomic details of invasion when present, which may assist in surgical planning. Hence, we recommend MRI for assessing possibly invasive thymomas. Both MRI and CT have similar accuracy in differentiating low-risk from high-risk thymic epithelial tumors. However, neither of them can differentiate histologic subtypes accurately. So we do not recommend using MRI to differentiate among histologic subtypes of thymoma.

Recommendations

- We recommend routine use of MRI for differentiating encapsulated thymoma from benign thymic benign conditions (evidence quality low, weak recommendation).
- We recommend MRI for differentiating between early and advanced stage thymic epithelial tumors (evidence quality low, weak recommendation).
- We do not recommend using MRI to differentiate among histologic subtypes of thymoma (evidence quality low, weak recommendation).

A Personal View of the Data

Our personal view is that preoperative evaluation of suspected thymomas should be as accurate as possible in supporting decisions regarding surgery, as complete resection is the most important prognostic factor for survival from thymomas. CT scan is still the standard radiological imaging for preoperative evaluation and clinical staging. However, it has obvious limitations in differentiating thymoma from nonthymoma abnormalities, and it cannot provide much details about transcapsular invasion. Meanwhile, a growing body of literature in this area agrees that MRI is technically diversified compared with CT, which may be promising for further investigation in the evaluation of thymoma. Various parameters in MRI offer opportunities in seeking a suitable index of invasion status. We are using MRI more often to evaluate thymic malignancies before surgery and to make surgical plans. We look forward to novel research in this area to improve our clinical practice.

References

1. Detterbeck FC, Zeeshan A. Thymoma: current diagnosis and treatment. Chin Med J. 2013;126:2186–91.
2. Rea F, Marulli G, Girardi R, Bortolotti L, Favaretto A, Galligioni A, et al. Long-term survival and prognostic factors in thymic epithelial tumours. Eur J Cardiothorac Surg. 2004;26:412–8.
3. Kent MS, Wang T, Gangadharan SP, Whyte RI. What is the prevalence of a "nontherapeutic" thymectomy? Ann Thorac Surg. 2014;97:276–82.
4. Ackman JB, Verzosa S, Kovach AE, et al. High rate of unnecessary thymectomy and its cause: can computed tomography distinguish thymoma, lymphoma, thymic hyperplasia, and thymic cysts? Eur J Radiol. 2015;84:524–33.
5. Detterbeck FC, Nicholson AG, Kondo K, Van Schil P, Moran C. The Masaoka-Koga stage classification for thymic malignancies: clarification and definition of terms. J Thorac Oncol. 2011;6(7 Suppl 3):S1710–6.
6. Marom EM. Imaging thymoma. J Thorac Oncol. 2010;5:S296–303.
7. Tomiyama N, Muller NL, Ellis SJ, et al. Invasive and noninvasive thymoma: distinctive CT features. J Comput Assist Tomogr. 2001;25:388–93.
8. Marom EM. Advances in thymoma imaging. J Thorac Imaging. 2013;28:69–83.
9. Carter BW, Lichtenberger JP, Benveniste MF. MR imaging of thymic epithelial neoplasms. Top Magn Reson Imaging. 2018;27:65–71.

10. McInnis MC, Flores EJ, Shepard JO, et al. Pitfalls in the imaging and interpretation of benign thymic lesions: how thymic MRI can help. AJR Am J Roentgenol. 2016;206:W1–8.
11. Tuan PA, Vien MV, Dong HV, et al. The value of CT and MRI for determining thymoma in patients with myasthenia gravis. Cancer Control. 2019;26:1–10.
12. Takahashi K, Inaoka T, Murakami N, et al. Characterization of the normal and hyperplastic thymus on chemical-shift MR imaging. Am J Roentgenol. 2003;180:1265–9.
13. Inaoka T, Takahashi K, Mineta M, et al. Thymic hyperplasia and thymus gland tumors: differentiation with chemical shift MR imaging. Radiology. 2007;243:869–76.
14. Priola AM, Priola SM, Gned D, et al. Comparison of CT and chemical-shift MRI for differentiating thymoma from non-thymomatous conditions in myasthenia gravis: value of qualitative and quantitative assessment. Clin Radiol. 2016;71:e157–69.
15. Ackman JB, Mino-Kenudson M, Morse CR. Nonsuppressing normal thymus on chemical shift magnetic resonance imaging in a young woman. J Thorac Imaging. 2012;27:W196–8.
16. Priola AM, Priola SM, Ciccone G, et al. Differentiation of rebound and lymphoid thymic hyperplasia from anterior mediastinal tumors with dual echo chemical-shift MR imaging in adulthood: reliability of the chemical-shift ratio and signal intensity index. Radiology. 2015;274:238–49.
17. Inoue A, Tomiyama N, Fujimoto K, et al. MR imaging of thymic epithelial tumors: correlation with World Health Organization classification. Radiat Med. 2006;24:171–81.
18. Sadohara J, Fujimoto K, Muller NL, et al. Thymic epithelial tumors: comparison of CT and MR imaging findings of low risk thymomas, high-risk thymomas, and thymic carcinomas. Eur J Radiol. 2006;60:70–9.
19. Abdel Razek AA, Khairy M, Nada N. Diffusion-weighted MR imaging in thymic epithelial tumors: correlation with World Health Organization classification and clinical staging. Radiology. 2014;273:268–75.
20. Priola A, Priola S, Giraudo M, Gned D, Fornari A, Ferrero B, Ducco L, Veltri A. Diffusion-weighted magnetic resonance imaging of thymoma: ability of the Apparent Diffusion Coefficient in predicting the World Health Organization (WHO) classification and the Masaoka-Koga staging system and its prognostic significance on disease free survival. Eur Radiol. 2015;26:2126–38.
21. Priola A, Priola S. Usefulness of diffusion-weighted MR imaging in predicting masaoka-koga clinical staging of thymic epithelial tumors by using the apparent diffusion coefficient. Radiology. 2015;274:936–7.
22. Li GF, Duan SJ, Yan LF, et al. Intravoxel incoherent motion diffusion-weighted MR imaging parameters predict pathological classification in thymic epithelial tumors. Oncotarget. 2017;8:44579–92.
23. Sakai S, Murayama S, Soeda H, et al. Differential diagnosis between thymoma and non-thymoma by dynamic MR imaging. Acta Radiol. 2002;43:262–8.
24. Ried M, Hnevkovsky S, Neu R, et al. Impact of surgical evaluation of additional cine magnetic resonance imaging for advanced thymoma with infiltration of adjacent structures: the thoracic surgeon's view. Thorac Cardiovasc Surg. 2016;65(3):244–9.
25. Kim DJ, Yang WI, Choi SS, et al. Prognostic and clinical relevance of the World Health Organization Schema for the Classification of Thymic Epithelial Tumors. Chest. 2005;3:755–61.
26. Rena O, Papalia E, Maggi G, et al. World Health Organization histologic classification: an independent prognostic factor in resected thymomas. Lung Cancer. 2005;50:59–66.
27. Venuta F, Rendina EA, Guerrera F, et al. Does the World Health Organization histological classification predict outcomes after thymomectomy? Results of a multicentre study on 750 patients. Eur J Cardiothorac Surg. 2015;48:48–54.
28. Ozawa Y, Hara M, Shimohira M, et al. Associations between computed tomography features of thymomas and their pathological classification. Acta Radiol. 2016;57:1318–25.
29. Usuda K, Maeda S, Motono N, et al. Diffusion weighted imaging can distinguish benign from malignant mediastinal tumors and mass lesions: comparison with positron emission tomography. Asian Pacific J Cancer Prevent. 2015;16:6469.

Robotic vs. Thoracoscopic Thymectomy for Thymoma

55

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Introduction

The desire for a minimally invasive approach for thymectomy has a long history, with the first report of a transcervical approach published in 1912 by Sauerbach. Sternotomy was popularized by Blalock in the late 1930s and 1940s, and became the standard approach, especially for patients with a thymic mass [1]. Development of thoracoscopy in the 1990s led to interest in this technique for thymectomy with the first cases of thoracoscopic thymectomy being reported in 1993 [2, 3]. However, while it has been more widely adopted for pulmonary resection, video assisted thoracic surgery (VATS) for anterior mediastinal cases such as thymectomy remains challenging due to the much smaller working space within the anterior mediastinum, even with CO_2 insufflation. The development of robotic surgery with instruments that allow increased degrees of freedom, along with three-dimensional visualization, seemed well suited for minimally invasive surgery within the mediastinum. As such, robotic assisted thymectomy has been popular among thoracic surgeons, even among those perform VATS for their pulmonary resections, and the utilization of robotic approaches has increased with time [4]. The robot is not without disadvantages, namely increased costs and a lack of haptic feedback. For encapsulated thymomas, it is not clear whether robotic assistance offers a measureable advantage over VATS. This question is discussed below according to the GRADE methodology.

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Table 55.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with encapsulated thymoma	Robotic resection	VATS resection	Survival Quality of life Cost Length of stay Recurrence

Search Strategy

The primary comparator is VATS vs. robotic thymectomy for encapsulated thymoma (Table 55.1). The search strategy utilized PubMed with the following search terms: ((thymectomy) AND (VATS OR thoracoscopic OR Video-assisted) AND (robotic OR robot OR Robotic-assisted)) AND (RCT OR randomized OR randomized-controlled). Given the absence of any randomized controlled trials, the same search terms were used but without (RCT OR randomized OR randomized-controlled). This search for period 1990–2019 returned 93 studies, of which only five explicitly compared robotic and VATS approaches, and only four did so specifically for thymoma. Studies were limited to English language only. Review articles were not considered for primary analysis, but references lists were utilized to identify any other relevant studies.

Results

The search strategy yielded no randomized controlled trials. There were several cohort studies that served as the basis for the comparisons. The key outcomes of interest were short-term outcomes, long-term outcomes, and costs. Procedural outcomes included mortality, major morbidity and more specifically pulmonary complications, minor complications, length of stay, chest tube output and duration, readmission, resection margin, conversion to open, and pain. Long-term outcomes were overall survival, disease specific survival, and recurrence. There was significant heterogeneity within the results, with multiple studies including patients with encapsulated thymoma, non-encapsulated thymoma, and thymic carcinoma. Other studies looked at myasthenia gravis (MG) and thus included thymomatous and non-thymomatous MG patients. Most studies focused primarily on short-term outcomes including intra-operative measures, post-operative complications, and length of stay. The results of the primary studies used in the analyses are summarized in Table 55.2 [4–9].

Short-Term Outcomes

The largest study was a propensity matched analysis of the National Cancer Data Base (NCDB) published in 2019 that compared 2558 patients who underwent either

Table 55.2 Summary of studies utilized in the primary analysis

Author	Type	N	Mortality	LOS (days)	EBL (mL)	CT output and duration	Complications	Margin	Cost ($)	OR time (min)	Readmission	Conversion	OS
Kamel et al. (2019) [4]	Retrospective cohort, propensity matched (moderate)	580 (280 VATS, 300 Robotic)	1%	Robotic: 4 VATS: 4	N/A	N/A	N/A	R1 resection Robotic: 28% VATS: 23%	N/A	N/A	Robotic: 2% VATS: 2%	**Robotic: 11% VATS: 23%**	Robotic: 93% VATS: 94%
Sehitogullari et al. (2019) [5]	Retrospective cohort, institutional (low)	45 (24 VATS, 21 Robotic)	0%	**Robotic: 4.1 VATS: 5.3**	Robotic 68.4 VATS 92.6	**Robotic: 210 mL, 3 days VATS: 325 mL, 5 days**	Robotic: 11% VATS: 11%	N/A	N/A	**Robotic:76 VATS: 106**	ND	N/A	N/A
Qian et al. (2017) [6]	Retrospective cohort, institutional (low)	86 (VATS 35, Robotic 51)	0%	**Robotic: 4.3 VATS: 5.5**	Robotic: 77.5 VATS: 127	**Robotic: 352 mL, 2.9 days VATS: 613.9 mL, 3.8 days**	0%	N/A	N/A	Robotic: 95 VATS: 79	N/A	Robotic: 0% VATS: 0%	Robotic: 100% VATS: 100%
Rowse et al. (2015) [8]	Retrospective cohort, institutional (low)	54 (VATS 45, Robotic 11)	0%	Robotic: 2.1 VATS: 1.5	**Robotic: 160 VATS: 65**	N/A	Robotic: 9% VATS: 16%	N/A	N/A	**Robotic: 178 VATS: 102**	N/A	Robotic: 0% VATS: 0%	N/A
Ye et al. (2013) [7]	Retrospective cohort, institutional (low)	45 (25 VATS, 21 Robotic)	N/A	**Robotic: 3.7 VATS: 6.7**	Robotic: 58.6 VATS: 86.8	**Robotic: 1.1 days VATS: 3.6 days**	Robotic 4.7% VATS: 4%	N/A	**Robotic: 8662 VATS: 6097**	Robotic: 96 VATS 104	N/A	Robotic: 0% VATS: 4%	N/A
Ruckert et al. (2011) [9]	Retrospective cohort, institutional (low)	154 (VATS 79, Robotic 74)	N/A	N/A	N/A	N/A	Robotic: 2.7% VATS: 2.5%	N/A		**Robotic: 198 VATS: 187**	N/A	Robotic: 1.3 VATS: 1.4%	N/A

Bold represents statistical significance

open (1978), VATS (280), or robotic (300) thymectomy for thymoma [4]. This paper was not limited to encapsulated thymoma, and in 21% of VATS patients and 17% of robotic patients the tumor invaded either the surrounding tissue or an adjacent organ, while 15% of VATS and 10% of robotic patients had thymic carcinoma. In their propensity matched analysis of 197 patients in each group, there was no difference in 30 day or 90 mortality rates between VATS and robotic approaches, which was excellent in both groups at 1%. There was no difference in length of stay or readmission. The only significant difference between the groups was that the conversion rate to open was lower in the robotic group (11% vs. 23%).

Other direct comparisons between robotic and VATS include several small single institutional retrospective cohort studies. A paper by Sehitogullari et al. compared 24 VATS patients with 21 robotic patients [5]. Short term outcomes showed decreased average chest tube drainage amount and chest tube duration for robotic compared to VATS (210 mL, 3 days vs. 325 mL, 5 days), and decreased length of stay, likely related to chest tube duration (robotic 4.1 days vs. VATS 5.3 days).

Two similar studies, both from the Shanghai Chest Hospital, also showed lower chest tube output, shorter chest tube duration, and a shorter length of stay for a robotic vs. VATS approach [6, 7]. The more recent of these two publications found that overall operative time for robotic was slightly longer at 95 min vs. 79 min, but this was not significant and included robotic set up. They did show that over their series, robotic set up time decreased significantly over time, and the overall operative time excluding set up favored a robotic approach (71 min vs. 79 min), but again this was not statistically significant [6].

In contrast to these studies, a case series from the Mayo Clinic comparing 45 VATS thymectomies to 11 robotic thymectomies found that robotic procedures had a longer OR time (178 min vs. 102 min) and increased EBL (160 mL vs. 65 mL) compared with VATS [8]. In this study length of stay was similar (1.5 days for VATS vs. 2.1 days for robotic). The VATS group had more post-operative complications (16% vs. 9%) although that difference was not statistically significant. Of note, the complications in the VATS group included phrenic nerve injury (3 patients), pericarditis (2 patients), pleural effusion (1 patient), and atrial fibrillation (1 patient), with one patient with phrenic nerve palsy requiring reoperation. In the robotic group, the only post-operative complication was one patient with urinary retention requiring catheterization. In this series, only 48% of patients had thymoma, and of these, only 67% were encapsulated. It is also not clear from the results if the pathologies were equally distributed between the approaches.

The largest institutional series of VATS vs. robotic thymectomy was a German study that compared 79 VATS to 74 robotic patients undergoing thymectomy for MG with only 11% overall having a thymoma (14.8% robotic vs. 7.6% of VATS patients) [9]. They demonstrated slightly shorter OR times for robotic thymectomy with no difference in conversion to open (1.4% robotic vs. 1.3% VATS) and no difference in complication rates (2.7% for robotic vs. 2.5% for VATS). They did not look at length of stay.

The only study to examine cost was done by Ye et al. and found that the robotic approach was more expensive, with average hospital costs of $8662 for robotic

compared to $6097 for VATS [7]. No North American studies compared costs, and the methods in the Ye study do not describe in detail what specific factors were accounted for in cost. Reduction in length of stay was generally cited in North American studies as being a significant cost saver for any procedure, and based on specific payor models, has been shown to lead to an overall cost savings, despite higher procedural costs often associated with the robot. The Ye paper however, may be a more objective and realistic assessment, at least in this author's opinion, as the "cost" savings associated with a decreased LOS are often not the hard dollar costs of having a patient in the hospital, but the charges or payments received for an average DRG, averaged out over the length of stay. Thus, when a length of stay is shortened, and a new patient can fill that bed, the "cost savings" are the realized revenue from filling that bed with a new patient, and not a true reduction in cost.

Oncologic and Long Term Outcomes

There was no significant difference in long term or oncologic outcomes in any of the papers. In the large NCDB analysis, which does not include data on recurrence, overall survival was excellent in both groups (robotic 93% vs. VATS 94%) and was not significantly different [4]. Short term oncologic outcomes were also similar, with no difference in R0 resection rates or lymph node retrieval. The study by Qian et al. showed 100% overall survival for both groups with mean follow up of 420 and 701 days respectively for robotic and VATS [6].

Conclusions and Recommendations

The majority of the data comparing approaches for thymectomy compare minimally invasive to open techniques. Specific comparisons between VATS and robotic thymectomy for thymoma are limited to small institutional case series and one larger retrospective database analysis. Thus the quality of these papers is low to moderate at best. The populations are heterogeneous, including patients with myasthenia gravis, non-encapsulated thymomas, and thymic carcinoma. For oncologic outcomes, including resection status, recurrence, and overall survival, none of the studies showed any significant difference between a VATS and robotic approach. The largest study, which included a large portion of patients with non-encapsulated disease, showed a difference only in conversion rate but in no other short term outcomes. The several smaller institutional studies, in contrast, all showed a shorter length of stay for a robotic approach, save for the Mayo series which showed no difference, largely driven by shorter chest tube duration, but no difference in conversion rates. There was also increased cost associated with a robotic approach in one of the single institution studies. Given these findings, my recommendation is that robotic thymectomy is favored over thoracoscopic thymectomy for encapsulated thymomas based largely on decreased length of stay and chest tube duration. There is no evidence to support a recommendation in favor of a robotic approach over a VATS approach based on oncologic or long term data.

Recommendations

- For patients with encapsulated thymoma, a robotic approach is recommended over a VATS approach for better acute outcomes (evidence quality low, weak recommendation).
- Robotic and VATS approaches for encapsulated thymoma are similar with respect to long term outcomes (evidence quality low, no recommendation).

A Personal View of the Data

The excellent oncologic prognosis for encapsulated thymoma overall means it will be essentially impossible to show any significant difference with respect to these long term outcomes based on the surgical approach. The available evidence suggests a small but real improvement in length of stay and chest tube duration. It is my opinion that the true advantage to a robotic approach for encapsulated thymoma is the development of this skill set for the more complex mediastinal tumors one may encounter. The large propensity matched analysis from the NCDB showed a significant reduction in conversion rate. Importantly, this was the most heterogeneous population with a significant proportion of larger, non-encapsulated tumors, and thymic carcinoma. For these more complex resections, the technical limitations of standard thoracoscopy become more apparent. In these circumstances, having a robotic skill set will allow more surgeons to resect these tumors using a minimally invasive approach. With that caveat, the robotic approach remains more expensive, and for many surgeons, when facing larger tumors with invasion into surrounding structures, an open approach will still be the correct choice.

References

1. Shrager JB. Extended transcervical thymectomy: the ultimate minimally invasive approach. Ann Thorac Surg. 2010;89(6):S2128–34.
2. Coosemans W, Lerut TE, Van Raemdonck DE. Thoracoscopic surgery: the Belgian experience. Ann Thorac Surg. 1993;56(3):721–30.
3. Sugarbaker DJ. Thoracoscopy in the management of anterior mediastinal masses. Ann Thorac Surg. 1993;56(3):653–6.
4. Kamel MK, Villena-Vargas J, Rahouma M, Lee B, Harrison S, Stiles BM, Abdelrahman AM, Altorki NK, Port JL. National trends and perioperative outcomes of robotic resection of thymic tumours in the United States: a propensity matching comparison with open and video-assisted thoracoscopic approaches. Eur J Cardiothorac Surg. 2019;56(4):762–9.
5. Sehitogullari A, Nasır A, Anbar R, Erdem K, Bilgin C. Comparison of perioperative outcomes of videothoracoscopy and robotic surgical techniques in thymoma. Asian J Surg. 2020;43(1):244–50.
6. Qian L, Chen X, Huang J, Lin H, Mao F, Zhao X, Luo Q, Ding Z. A comparison of three approaches for the treatment of early-stage thymomas: robot-assisted thoracic surgery, video-assisted thoracic surgery, and median sternotomy. J Thorac Dis. 2017;9(7):1997–2005.

7. Ye B, Tantai JC, Li W, Ge XX, Feng J, Cheng M, Zhao H. Video-assisted thoracoscopic surgery versus robotic-assisted thoracoscopic surgery in the surgical treatment of Masaoka stage I thymoma. World J Surg Oncol. 2013;11:157.
8. Rowse PG, Roden AC, Corl FM, Allen MS, Cassivi SD, Nichols FC, Shen KR, Wigle DA, Blackmon SH. Minimally invasive thymectomy: the Mayo Clinic experience. Ann Cardiothorac Surg. 2015;4(6):519–26.
9. Ruckert JC, Swierzy M, Ismail M. Comparison of robotic and nonrobotic thoracoscopic thymectomy: a cohort study. J Thorac Cardiovasc Surg. 2011;141(3):673–7.

VATS for Resection of Mediastinal Parathyroid Adenomas

56

Yuqin Cao and Hecheng Li

Introduction

Parathyroid adenoma is the main cause of primary hyperparathyroidism (PHPT), which is usually first suspected because of the finding of hypercalcemia. Parathyroid surgery is recommended as a definitive therapy for PHPT patients presenting with nephrolithiasis, bone fractures, symptomatic hypercalcemia, or other symptoms.

The prevalence of ectopic parathyroid adenoma (EPA) outside the cervical region is approximately 20% in unexplored patients with PHPT [1–3], but can be as high as 66% in re-operative patients [4, 5]. The mediastinum is a common location for EPA, hence the resection of mediastinal parathyroid adenoma is in high demand. Based on growing experience with minimally invasive mediastinal surgery, a series of minimally invasive EPA resections was first published in 1994 [6]. However, due to the lack of well-designed clinical trials, the feasibility and efficacy of minimally invasive resection for EPA remain controversial. In this chapter, we discuss the therapeutic effect, rate of incomplete resection, cost, length of stay, and quality of life in patients with mediastinal parathyroid adenomas receiving minimally invasive resection compared with those receiving sternotomy or thoracotomy.

Search Strategy

A literature search of PubMed (MEDLINE), EMBASE and the Cochrane Library was conducted for articles published in English during 2009–2019 using the search terms "parathyroid adenoma" AND ("VATS" OR "video assisted thoracoscopic surgery" OR "minimally invasive"). Due to the lack of high-quality evidence, only one

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Table 56.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with mediastinal parathyroid adenomas	Minimally invasive resection	Sternotomy or thoracotomy	Therapeutic effect, incomplete resection, cost, length of stay, quality of life

cohort study and ten case series were included (Table 56.1). Several single case reports were also reviewed for additional information. The quality of evidence was classified using the GRADE system.

Results

Pre-operative Imaging Modalities

Incomplete excision of parathyroid adenoma is the most common cause of persistent PHPT [7]. As a result, EPA can comprise up to 66% of missed adenomas in failed initial parathyroidectomies [3–5]. Pre-operative imaging is essential for anatomical localization of the glands and their relationship to nearby structures, either for primary or re-operative settings. In addition, precise localization helps to identify candidates for minimally invasive procedures [3].

Sestamibi scintigraphy using the ^{99m}Tc radiotracer is recommended for localizing parathyroid adenomas [8], especially for those patients with elevated serum calcium and parathyroid hormone (PTH) levels who fail to demonstrate abnormality in ultrasound and contrast enhanced computed tomography (CT) of neck and thorax [9, 10].

For the sake of comprehensive planning of the surgical procedure, CT or magnetic resonance imaging (MRI) scan should be performed to accurately identify the location of adenomas and potential abnormal anatomical structures. For example, Nakada et al. reported a case of successful video-assisted resection of a retroesophageal parathyroid adenoma with an aberrant right subclavian artery owing to the three-dimensional CT performed preoperatively [11].

Amer et al. [12] and Adachi et al. [13] utilized methylene blue (MB) to identify mediastinal parathyroid adenomas intraoperatively. The intravenous injection of MB immediately before the intervention proved to be a useful technique to ensure sufficient surgical margins, but the dose of MB they had used varied from 0.5 to 4 mg/kg and so has not yet been standardized.

Comparison of Different Surgical Approaches

Most parathyroid adenomas located in the upper mediastinum can be resected by a cervical approach. For the adenomas not accessible from a standard cervical incision, median sternotomy and thoracotomy used to be advocated for safe and

successful parathyroidectomy [14]. To deal with the postoperative pain, prolonged hospital stay, and high complications rates, video-assisted thoracoscopic surgery (VATS) for ectopic mediastinal parathyroid adenoma was first described by Prinz et al. in 1994 [6]. More recently, robotic-assisted thoracic surgery (RATS) has also been introduced to refine the dissection and optimize the view for performing mediastinal parathyroidectomy [15].

Du et al. conducted a cohort study to compare the therapeutic efficacy of VATS with open surgery in the treatment of mediastinal parathyroid tumors. Among 21 patients included, 9 cases were treated with VATS while 13 cases were treated with open surgery, and the pathology confirmed the diagnosis of EPA in 16 cases. In contrast to conventional open surgery, the cost of VATS was relatively higher (22,456 ± 652 vs. 15,122 ± 451 RMB, $p < 0.05$). However, VATS was superior to open surgery in terms of shorter operation time (68 ± 22 vs. 90 ± 35 min, $p < 0.05$), less blood loss (55 ± 15 vs. 105 ± 35 mL, $p < 0.05$), shorter post-operative hospital stay (3.5 ± 1.5 vs. 5.5 ± 2.5 day, $p < 0.05$), and quicker removal of drainage tube (2.5 ± 1.5 vs. 4.5 ± 2.5 days, $p < 0.05$) [16]. Additionally, the case series reported by Nagano et al. indicated that the single-incision subxiphoid approach, without going through the intercostal space, reduced the frequency of post-thoracotomy pain syndrome and revealed superior aesthetic outcomes [17].

Several case series of RATS demonstrated similar clinical results as VATS for the resection of mediastinal parathyroid adenomas, but suggested added benefits of optimized visualization, dexterity, and ability to suture [18–20].

No mortality was reported in the cited studies, indicating the safety of minimally invasive surgery for mediastinal parathyroid adenomas. However, four conversions to thoracotomy or sternotomy were described due to bleeding or failure to remove the tumor during thoracoscopy [12, 14, 16, 21].

Peri-operative Hormone Monitoring

A majority of patients with parathyroid adenomas demonstrate an elevated level of PTH, which can lead to nephrolithiasis, low bone mineral density, nephrocalcinosis, kidney stones, or other clinical manifestations [22–25]. The goal of parathyroid surgery is the removal of parathyroid adenomas and thereby the cure of biochemical abnormalities.

Ward et al. [20] and Medbery et al. [26] performed intraoperative PTH monitoring and an appropriate decline in PTH levels was observed in all patients shortly after the removal of ectopic mediastinal parathyroid adenomas.

Conclusions and Recommendations

The quality of evidence and clinical outcomes of the cited literatures are outlined in Table 56.2. Minimally invasive surgery, either VATS or RATS, is a safe and feasible procedure for the resection of mediastinal parathyroid adenomas. However, only

Table 56.2 Summary of studies reviewed and the quality of evidence

Author (year)	Study type (evidence quality)	Preoperative localization (%)	Number of patients	Surgical approach	Conversion to open surgery, number (%)	Operation time, min[a]	LOS, days[a]	Cure rate, %	Mortality, %	Complications, number (%)
Nagano et al. (2019) [17]	Case series (low)	MIBI (100) CT (100)	5	VATS	0	134 (57–255)	4 (2–8)	100	0	0
Isaacs et al. (2019) [14]	Case series (low)	MIBI/SPECT (100) 4D-CT (78)	9	VATS	1 (11)	101 (60–160)	1.7 (1–4)	89	0	1 (11)
Scott et al. (2019) [19]	Case series (low)	MIBI (38) CT (75)	8	RATS	0	109 (76–186)	1.1 (1–2)	100	0	0
Du et al. (2017) [16]	Cohort study (moderate)	MIBI (NR) CT/MRI (100)	9	VATS	1 (11)	68 (NR)	3.5 (NR)	89	0	NR
			13	Open	/	90 (NR)	5.5 (NR)	100	0	NR
Ward et al. (2017) [20]	Case series (low)	MIBI (100) CT (100)	5	RATS	0	NR	1.4 (1–3)	100	0	0
Amer et al. (2015) [12]	Case series (low)	MIBI (57) CT (100)	7	VATS	1 (14)	NR	2 (1–7)	86	0	0
Lu et al. (2014) [27]	Case series (low)	MIBI (100) CT (100)	12	VATS	0	155 (80–292)	5.9 (4–8)	92	0	6 (50)
Wei et al. (2011) [28]	Case series (low)	MIBI (100) CT (100)	15	VATS	0	NR	3.3 (NR)	87	0	NR
Iihara et al. (2011) [29]	Case series (low)	MIBI (100) CT (100)	8	VATS	0	152 (56–258)	NR	50	0	0

Van Dessel et al. (2011) [18]	Case series (low)	MIBI (100) CT (100)	2	RATS	0	74 (65–82)	3 (3–3)	100	0	0
Randone et al. (2010) [30]	Case series (low)	MIBI (100) CT (77) MRI (54)	13	VATS	1 (8)	92 (50–240)	4.7 (2–15)	77	0	2 (15)

NR not reported, *MIBI* ^{99m}Tc-sestamibi scintigraphy, *CT* computed tomography, *SPECT* single-photon emission CT, *MRI* magnetic resonance imaging, *VATS* video-assisted thoracoscopic surgery, *RATS* robotic-assisted thoracic surgery, *LOS* length of stay

[a]Values are expressed as mean (range)

one cohort study shows moderate evidence of the superiority of VATS over open surgery. Regardless of which surgical approach is used, pre-operative imaging localization of glands and peri-operative monitoring of PTH are important for a complete resection and thereby cure of parathyroid adenoma.

Recommendations

- Video assisted thoracic surgery is recommended as a first line approach for the resection of mediastinal parathyroid adenoma (evidence quality moderate; strong recommendation).
- Pre-operative ^{99m}Tc-sestamibi scintigraphy is recommended to localize the parathyroid adenomas precisely (evidence quality low; weak recommendation).
- Intraoperative measurement of serum PTH is recommended to confirm successful removal of the adenoma (evidence quality low; weak recommendation).

A Personal View of the Data

According to my personal experience, mediastinal parathyroid adenoma is relatively rare and heterogeneous, and is more frequently initially assessed by endocrine surgeons or medical endocrinologists. However, the diagnosis and management of ectopic mediastinal parathyroid adenomas require the combined efforts of a multidisciplinary team (MDT). For those patients who meet the indications of mediastinal parathyroidectomy, minimally invasive procedures, either VATS or RATS, should be performed by experienced thoracic surgeons. Viewing the lack of high-quality evidence, it is not possible to provide strong recommendations, and well designed prospective clinical trials should be brought into practice in the future to compare different surgical approaches for mediastinal parathyroid adenoma resection.

References

1. Phitayakorn R, McHenry CR. Incidence and location of ectopic abnormal parathyroid glands. Am J Surg. 2006;191:418–23.
2. Roy M, Mazeh H, Chen H, Sippel RS. Incidence and localization of ectopic parathyroid adenomas in previously unexplored patients. World J Surg. 2013;37:102–6.
3. Parikh AM, Suliburk JW, Morón FE. Imaging localization and surgical approach in the management of ectopic parathyroid adenomas. Endocr Pract. 2018;24(6):589–98.
4. Silberfein EJ, Bao R, Lopez A, Grubbs EG, Lee JE, Evans DB, Perrier ND. Reoperative parathyroidectomy: location of missed glands based on a contemporary nomenclature system. Arch Surg. 2010;145:1065–8.
5. Duke WS, Vernon HM, Terris DJ. Reoperative parathyroidectomy: overly descended superior adenoma. Otolaryngol Head Neck Surg. 2016;154:268–71.

6. Prinz RA, Lonchyna V, Carnaille B, Wurtz A, Proye C. Thoracoscopic excision of enlarged mediastinal parathyroid glands. Surgery. 1994;116(6):999–1005.
7. Udelsman R. Approach to the patient with persistent or recurrent primary hyperparathyroidism. J Clin Endocrinol Metab. 2011;96(10):2950–8.
8. Dienemann H. Rare mediastinal tumors. J Thorac Oncol. 2011;6(Suppl 2):S240–1.
9. Fatimi SH, Inam H, Chagan FK, Choudry UK. Management of mediastinal parathyroid adenoma via minimally invasive thoracoscopic surgery: case report. Int J Surg Case Rep. 2017;40:120–3.
10. Naik D, Jebasingh KF, Ramprasath, Roy GB, Paul MJ. Video assisted thoracoscopic surgery (VATS) for excision of an ectopic anterior mediastinal intra-thymic parathyroid adenoma. J Clin Diagn Res. 2016;10(6):PD22–4.
11. Nakada T, Akiba T, Inagaki T, Marushima H, Morikawa T, Ohki T. A case of a retroesophageal parathyroid adenoma with an aberrant right subclavian artery: a potential surgical pitfall. Ann Thorac Cardiovasc Surg. 2014;20(Suppl):786–9.
12. Amer K, Khan AZ, Rew D, Lagattolla N, Singh N. Video assisted thoracoscopic excision of mediastinal ectopic parathyroid adenomas: a UK regional experience. Ann Cardiothorac Surg. 2015;4(6):527–34.
13. Adachi Y, Nakamura H, Taniguchi Y, Miwa K, Fujioka S, Haruki T. Thoracoscopic resection with intraoperative use of methylene blue to localize mediastinal parathyroid adenomas. Gen Thorac Cardiovasc Surg. 2012;60(3):168–70.
14. Isaacs KE, Belete S, Miller BJ, Di Marco AN, Kirby S, Barwick T, Tolley NS, Anderson JR, Palazzo FF. Video-assisted thoracoscopic surgery for ectopic mediastinal parathyroid adenoma. BJS Open. 2019;3:743–9. https://doi.org/10.1002/bjs5.50207.
15. Bodner J, Profanter C, Prommegger R, Greiner A, Margreiter R, Schmid T. Mediastinal parathyroidectomy with the da Vinci robot: presentation of a new technique. J Thorac Cardiovasc Surg. 2004;127(6):1831–2.
16. Du H, Shi M, Zhu L, et al. Comparison of video-assisted thoracic surgery with open surgery in the treatment of ectopic mediastinal parathyroid tumors. J Thorac Dis. 2017;9(12):5171–5.
17. Nagano H, Suda T, Ishizawa H, et al. Video-assisted thoracoscopic surgery for ectopic mediastinal parathyroid tumor: subxiphoid and lateral thoracic approach. J Thorac Dis. 2019;11(7):2932–8.
18. Van Dessel E, Hendriks JM, Lauwers P, Ysebaert D, Ruyssers N Jr, Van Schil PE. Mediastinal parathyroidectomy with the da Vinci robot. Innovations (Phila). 2011;6(4):262–4.
19. Scott BB, Maxfield MW, Hamaguchi R, Wilson JL, Kent MS, Gangadharan SP. Robot-assisted thoracoscopic mediastinal parathyroidectomy: a single surgeon case series. J Laparoendosc Adv Surg Tech A. 2019;29(12):1561–4. https://doi.org/10.1089/lap.2019.0266.
20. Ward AF, Lee T, Ogilvie JB, et al. Robot-assisted complete thymectomy for mediastinal ectopic parathyroid adenomas in primary hyperparathyroidism. J Robot Surg. 2017;11(2):163–9.
21. Randone B, Costi R, Scatton O, et al. Thoracoscopic removal of mediastinal parathyroid glands: a critical appraisal of an emerging technique. Ann Surg. 2010;251(4):717–21.
22. Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. N Engl J Med. 1999;341(17):1249–55.
23. Yu N, Leese GP, Smith D, Donnan PT. The natural history of treated and untreated primary hyperparathyroidism: the parathyroid epidemiology and audit research study. QJM. 2011;104(6):513–21.
24. Rubin MR, Bilezikian JP, McMahon DJ, et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab. 2008;93(9):3462–70.
25. Assadipour Y, Zhou H, Kuo EJ, Haigh PI, Adams AL, Yeh MW. End-organ effects of primary hyperparathyroidism: a population-based study. Surgery. 2019;165(1):99–104.
26. Medbery RL, Winters A, Chen AY, Rogers TE, Force SD. VATS resection of large ectopic posterior mediastinal cystic parathyroid adenoma. Ann Thorac Surg. 2019;108(5):e301–2. pii: S0003-4975(19)30510-7. https://doi.org/10.1016/j.athoracsur.2019.03.029.

27. Lu HI, Chou FF, Chi SY, Huang SC. Thoracoscopic removal of hypertrophic mediastinal parathyroid glands in recurrent secondary hyperparathyroidism. World J Surg. 2015;39(2):400–9.
28. Wei B, Inabnet W, Lee JA, Sonett JR. Optimizing the minimally invasive approach to mediastinal parathyroid adenomas. Ann Thorac Surg. 2011;92(3):1012–7.
29. Iihara M, Suzuki R, Kawamata A, Horiuchi K, Okamoto T. Thoracoscopic removal of mediastinal parathyroid lesions: selection of surgical approach and pitfalls of preoperative and intraoperative localization. World J Surg. 2012;36(6):1327–34.
30. Randone B, Costi R, Scatton O, et al. Thoracoscopic removal of mediastinal parathyroid glands: a critical appraisal of an emerging technique. Ann Surg. 2010;251(4):717–21.

Thymectomy in the Setting of Pleural Metastasis

57

Stephan Adamour Soder and Moishe Liberman

Introduction

Thymic epithelial tumors (TETs) are extremely rare, with an overall incidence of 0.13 per 100,000 person-years [1]. Most cases are diagnosed with localized disease (stage I–III), however, initial presentation of these tumors with non-contiguous pleural spreading occurs in 7–11% of patients [2, 3]. Furthermore, after a curative intent surgical resection for stage I–III tumors, recurrence is reported in 10% to 30% of patients [4–6], and the pleura represents the most frequent site of recurrence. Pleural recurrence is seen in 46–80% of recurrences [4, 7–10].

Complete resection is the mainstay of treatment for patients with TETs and represents the most important determinant of long-term survival [2, 5, 11]. Although disease with pleural spreading makes it very difficult to perform an *en bloc* resection, metastatic disease confined to the chest still allows the potential for complete resection. The slow-growing behavior of thymomas and the common presentation in middle-aged patients who are otherwise healthy has encouraged different modalities of surgical treatment in order to achieve complete resection and the best disease control in Masaoka IVA TETs.

Pleural involvement varies greatly, from a single implant to diffuse and invasive patterns mimicking mesothelioma. Local pleurectomy, complete parietal pleurectomy, parietal and visceral pleurectomy, lung, diaphragm, phrenic nerve and vascular resections, extrapleural pneumonectomy (EPP), and resections combined with hyperthermic intrapleural perfusions have been employed in these patients. Multimodality treatments using chemotherapy and radiation therapy, before or after

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pleural resection, are often used, however the best approach has still not been clarified.

In this chapter, we review published data regarding surgical treatment of TETs with pleural involvement, focusing mainly on the initial presentation (*de novo* Masaoka IVA) disease, analysing the level of evidence and outcomes of published studies.

Search Strategy

We performed a MEDLINE, EMBASE and Cochrane literature search for studies published 2000–2019. We used the following keyword terms to identify relevant literature: "thymic tumors", "thymoma", "thymic carcinoma", "advanced thymoma", "thymectomy", "pleural metastasis", "pleurectomy", "extrapleural pneumonectomy" and "pleural chemoperfusion". Abstracts were read and excluded if they did not meet the goals of the chapter. The reference lists of reviewed manuscripts were also reviewed to identify additional literature relevant to the chapter. The search was limited to articles published in the English language. Papers addressing only treatment of pleural relapses, without patients with pleural metastasis at initial presentation (*de novo* Masaoka IVA), were excluded. Case reports were not included in this review. The PICO search criteria are summarized in Table 57.1.

Results

Twenty-one studies met search criteria. Due to rarity of this disease, there are no randomized clinical trials evaluating the treatment of TETs with pleural metastases and this probably will never be possible. Most studies consist of retrospective analyses of single-center experiences, with small numbers of patients and varying selection criteria, treatments employed, and results obtained, whose heterogeneity makes it difficult to draw conclusions. Considering these limitations, national and international associations such as the International Thymic Malignancies Interest Group (ITMIG), European Society of Thoracic Surgery (ESTS), and Japanese Association for Research on the Thymus (JART) have recently collected data in multi-institutional databases, allowing for larger cohorts and providing more robust results.

Table 57.1 PICO formatted terms for literature search

Patients	Intervention	Comparator	Outcomes
TETs with pleural involvement (Masaoka IVA)	Surgical resection	Other treatments (without surgical resection)	Overall survival Disease-free survival Perioperative morbidity Mortality

TETs thymic epithelial tumors

TETs may initially present with pleural metastasis (de novo Masaoka IVA) while other patients experience pleural relapses after thymic resection. The intrinsic biological differences of these two groups must be taken into consideration when analyzing the literature. Heterogeneity also extends to the type of treatment offered, based on the extent of disease, ranging from local pleurectomy in cases of minor parietal pleural involvement, to extrapleural pneumonectomy.

Tables 57.2 and 57.3 summarize the studies evaluating surgical resection for TETs with pleural involvement, highlighting the proportion of patients with initial Masaoka IVA or recurrences, rate of thymic carcinomas, EPPs, multimodality treatment employed, rate of complete resection and oncological outcomes [12–26].

Historical Results

Kondo and Monden [2] published a multi-institutional retrospective review of 1320 patients with TETs in all Masaoka stages, treated in Japan between 1990–1994. Resectability rate for Masaoka stage IVA thymomas was 42%, and recurrence rate for completely resected Masaoka stage IV thymomas was 34%. The 5-year survival of stage IVA and IVB thymomas and stage IV thymic carcinoma were 70.6%, 52.8% and 37.6%, respectively. In stage III and IV thymoma, the importance of complete resection was emphasized, however, even subtotal resection was associated with improved survival compared to inoperable groups, with 5-year survival rates for complete resection, subtotal resection and inoperable groups of 92.2%, 64.4% and 35.6%, respectively. On the other hand, in thymic carcinoma (stages III and IV), the 5-year survival rates after complete resection, subtotal resection and inoperable groups were 66.9%, 30.1% and 24.2%, with significant difference between the first group and the others, without significant difference between subtotal resection and inoperable groups.

Kim et al. [12] prospectively evaluated the feasibility and outcomes of multimodality treatment in 22 patients with stage III and IV proven thymoma that were deemed unresectable. Major response after induction chemotherapy was observed in 77% of patients and they achieved a 76% complete resection rate. The overall and progression-free survival rates at 5 years were 95% and 77%, respectively.

Results of EPP

Results of EPP for stage IVA thymoma were addressed by Wright [13] in 5 patients. There were no surgical mortalities but one patient had a cardiac tamponade. After reaching high rates of complete resection, they observed a 60% recurrence rate, with a median survival of 86 months and an overall 5-year survival of 75%.

Fabre et al. [19] reviewed results of 17 patients who underwent EPP (53% at initial presentation). Multimodality treatment was used in 82% of the cohort. Major complications were observed in 47% of the cases, including a 23% broncho-pleural

Table 57.2 Studies adressing pleural resection without chemoperfusion for thymic malignances with pleural involvement

Author, year	n	Study design (period)	Population	n thymoma/ TC	n de novo IVA/ recurrences	n stage IVA/IVB	EPP—n (%)	Completeness of resection—R0 or CMR	MMT before surgery	MMT after surgery
Kim (2004) [12]	11	Single-center, prospective	Stage III–IV thymomas submitted to multimodal treatment regimen	11/0	10/1	10/1	NA	CMR 76% of all cohort (21 patients)	100% ChT (protocol)	RT and ChT for all patients (protocol)
Wright (2006) [13]	5	Single-center, retrospective (1972–2006)	Stage IVA thymomas submitted to EPP	5/0	3/2	5/0	5/5 (100%)	R0 60%/CMR 100%	40% ChT; 20% ChT + RT	40% ChT; 20% RT; 40% ChT + RT
Huang (2007) [14]	18	Single-center, retrospective (1996–2006)	Stage IVA thymomas submitted to resection	18/0	18/0	18/0	4/18 (22.2%)	CMR 67%	94% ChT; 6% ChT + RT	28% ChT; 22% RT; 17% Brachytherapy
Ishikawa (2009) [15]	11	Single-center, retrospective (1988–2006)	Stage IVA-IVB thymomas submitted to multimodality treatment	11/0	10/1	9/2	4/12 (33.3%)	NA	73% ChT	36% ChT; 54% RT
Yano (2009) [16]	21	Single-center, retrospective (1994–2008)	Stage IVA thymomas submitted to resection	21/0	21/0	17/4	0 (0%)	CMR 71%	1% ChT; 5% RT; 66% steroid pulse therapy	95% RT
Cardillo (2010) [17]	27	Single-center, retrospective (1991–2007)	TETs stage III–IVA submitted to resection	NR	27/0	27/0	0 (0%)	NA	48% ChT	100% RT
Okereke (2010) [18]	15	Single-center, retrospective (1989–2009)	Stage I-IVA thymomas submitted to resection	15/0	15/0	15/0	6/15 (40%)	CMR 100%	47% ChT; 13% RT	27% RT; 13% ChT
Fabre (2011) [19]	17	Single-center, retrospective (1970–2009)	Stage IVA thymomas submitted to EPP	17/0	9/8	17/0	17/17 (100%)	R0 65%/CMR 100%	No	12% ChT; 6% RT; 12% ChT + RT

Rena (2012) [20]	18	Single-center, retrospective (1998–2008)	Stage IVA thymomas submitted to surgery	18/0	18/0	18/0	1/16 (6%)	CMR 62.5%	100% ChT	100% RT
Okuda (2014) [21]	136	Multicenter, retrospective (1991–2010)	TETs with pleural dissemination submitted to thymectomy and pleural resection	136/0	136/0	118/18	8/136 (5.9%)	CMR 35%	NA	32% ChT; 45% RT; 12% ChT + RT
Murakawa (2015) [22]	13	Single-center, retrospective (1991–2012)	TETs with pleural dissemination submitted to resection	13/0	7/6	13/0	2/13 (15.4%)	CMR 100%	15% ChT; 7% RT	
Bölükbas (2015) [23]	9	Single-center, retrospective (2000–2012)	Stage IVA TETs submitted to resection	8/1	9/0	8/1	0 (0%)	CMR 88,9%	33% ChT	44% RT; 33% ChT + RT
Hamaji (2015) [24]	110	Multicenter, retrospective (1988–2010)	Stage IV thymomas	110/0	NA	NA	NA	CMR 51.8%	Reported 52.7% RT	Reported 7.3% RT
Moser (2017) [25]	152	Multicenter, retrospective (1977–2014—90% since 2001)	Thymoma and TC with pleural involvement (de novo IVA or recurrent)	135/17	107/45	152/0	40/152 (26.5%)	R0 77%/CMR 89%	48% ChT; 4% RT; 2% ChT + RT	7% ChT; 35% RT; 10% ChT + RT
Kaba (2018) [26]	39	Single-center, retrospective analysis/ prospective database (2002–2015)	Thymoma and TC with pleural involvement (de novo IVA or recurrent)	30/9	26/13	39/0	3/39 (7.7%)	NA	25/39 (64.1%)—non specified	33% ChT; 20% RT; 36% ChT + RT

TET thymic epithelial tumor, *TC* thymic carcinoma, *EPP* extrapleural pneumonectomy, *R0* complete resection with microscopically negative margins, *CMR* complete macroscopic resection, *MMT* multimodality therapy, *ChT* chemotherapy, *RT* radiation therapy

Table 57.3 Studies adressing pleural resection without chemoperfusion for thymic malignances with pleural involvement—outcomes

Author, year	PO morbidity	30-days PO mortality	Median follow-up in months [range]	RR, 5-year DFS or FFR (%)	Median survival in months	3-Year OS—%	5-Year OS—%	10-Year OS—%	Favorable prognostic factors for OS	Quality of evidence
Kim (2004) [12]	NA	0%	50.3	5-year DFS 77%	NA	NA	95	NA		Moderate
Wright (2006) [13]	20%	0%	NA	RR 60%	86	NA	75	50		Low
Huang (2007) [14]	39%	0%	32 [1–130]	5-year DFS 90%	Not reached	91	78	65		Moderate
Ishikawa (2009) [15]	NA	0%	112	5-year FFR EPP group: 75% at both 5 and 10 years; non EPP-group: 16% and 0%	NA	NA	81	70		Low
Yano (2009) [16]	19%	0%	NA [2–142]	5-year DFS 13.3%	NA	87.5	73	37.6		Moderate
Cardillo (2010) [17]	NA	0%	77 for entire cohort	NA	NA	NA	NA	28.2		Low
Okereke (2010) [18]	NA	6.7%	Mean 66	NA	NA	NA	88	50		Low
Fabre (2011) [19]	43%	30-day: 18% 90-day: 29%	59 [1–262]	Excluding 90-day mortality, RR 17%	76	70	60	30		Moderate
Rena (2012) [20]	25%	0%	Mean 82	RR: 68.7%/5-year FFR: 58%	78–86	NA	85	53	MCR	Low

Okuda (2014) [21]	NA	NA	52	NA	NA	NA	IVA: 86.7/IVB: 67.8	NA	MCR and number of pleural implants ≤10	Moderate
Murakawa (2015) [22]	NA	8%	31.6	5-year FFR 33%	NA	NA	92.3	NA		Low
Bölükbas (2015) [23]	22%	11%	Mean 41	RR 22%	NA	NA	75 in resectable group	NA		Very low
Hamaji (2015) [24]	NA	NA	44	NA	NA	NA	66.8	35.3		Low
Moser (2017) [25]	43%	1%	52	5-year DFS: 44.9%/5-year FFR 43%	NA	91	87.2	62.7	Thymoma and complete resection (R0)	Moderate
Kaba (2018) [26]	31%	2.6% (1/3 EPP)	NA	NA	132	93	93	56		Low

Abbreviations: *TC* thymic carcinoma, *EPP* extrapleural pneumonectomy, *CMR* complete macroscopic resection, *MMT* multimodality treatment, *PO* post-operative, *NA* non available, *ChT* chemotherapy, *RT* radiation therapy, *RR* recurrence rate, *DFS* disease-free survival, *FFR* freedom from recurrence, *OS* overall survival

fistulae rate. The 30 and 90-day mortality was 17.6% and 29.4%, respectively. The overall 5- and 10-year survivals were 60% and 30%, respectively, with recurrence occurring in two patients (26 and 87 months).

Huang et al. [14] evaluated results of 18 patients with Masaoka stage IVA thymomas. All patients received preoperative chemotherapy. They performed four EPPs and reached a 67% rate of complete macroscopic resection (CMR), without perioperative mortality. With a median follow-up of 32 months, they reported 3-, 5- and 10-year overall survivals of 91%, 78% and 65%, respectively.

Ishikawa et al. [15] performed 4 EPPs (2 in recurrent disease) in 11 patients with stage IVA thymoma. Induction chemotherapy was administered in most patients, with an overall response rate of 75%. Postoperative radiotherapy was indicated for incompletely resected tumors or residual disease. Mortality at 30 days was 0% and overall survival rates were 81% at 5 years and 70% at 10 years. Local recurrence-free survival was 75% at both 5 and 10 years for the EPP group and 16% and 0%, respectively, for the non-EPP group ($p = 0.06$).

Prognostic Factors

Complete resection was shown to be a positive prognostic factor in different series. Yano et al. [16] reported long-term outcomes of 21 surgically treated patients, with an overall survival at 3, 5 and 10 years of 87.5%, 73.1% and 37.6%, respectively. Resected patients experienced better prognosis than patients without resection ($p = 0.0006$) and relapses were less frequent in patients who underwent total resection than in patients who underwent subtotal resection ($p = 0.009$).

Rena et al. [20] described a multimodal approach to stage IVA thymomas at initial presentation, this consisted of induction chemotherapy, surgery only for responders to induction and postoperative mediastinal radiation therapy. Most patients (88.9%) were considered responders and underwent surgery, with CMR rate of 62.5%. All patients with incomplete resection progressed and 50% of those who achieved complete resection relapsed. Overall survival at 5- and 10-year was 85% and 53%. Disease-specific survival was significantly better in patients with complete resection than those with incomplete resection; 10-year survivals were 52% vs 0%, respectively ($p = 0.048$).

Murakawa et al. [22] evaluated outcomes of 13 patients, including 2 EPPs performed in *de novo* cases, achieving CMR rate of 100%. Overall and recurrence-free survival at 5 years were 92.3% and 33.3%, respectively.

In an analysis of surgical exploration in patients with clinical stage IVA thymic malignancies, Bölükbas et al. [23] detected intraoperatively non-resectable disease in 4 patients and lymph node metastasis in 5 patients (upstaging to Masaoka IVB). Five-year survival for the resectable group was 75% and unresectability was independently associated with worse survival (HR 7.8; $p = 0.019$).

Information from Large Databases

Analysis from large databases have contributed more robust evidence regarding oncological outcomes of this rare disease. In 2014, Okuda et al. [21] published a retrospective analysis of 32 centers that participated in the JART Database. There were 136 patients with thymoma with pleural dissemination treated surgically (118 had stage IVA and 18 stage IVB). Only 8 patients underwent EPP (5.9%). Reported CMR of entire cohort was 33.8% and the number of pleural nodules was correlated with resectability ($p = 0.0016$). Patients with 10 or fewer pleural nodules had a better prognosis than those with 11 or more ($p = 0.0057$) and cases in which CMR was obtained had a better prognosis than those with residual tumor ($p = 0.0037$). The 5-year survival of patients with stage IVA thymomas was 86.7%, while for those undergoing EPP was 70%.

In 2015, Hamaji and Burt [24] published a review of the Surveillance, Epidemiology, and End Results (SEER) database, identifying patients with stage IV thymoma ($n = 282$). Of this population, 110 patients underwent surgical resection, with a complete resection rate of 51.8%. The 5- and 10-year OS for surgical patients was 66.8% and 35.3%, respectively, and for nonsurgical patients was 26.4% and 18.9%, respectively ($p < 0.001$). Patients who underwent complete resection did not have OS or cancer specific survival (CSS) statistically different from those patients who underwent incomplete resection.

Using a task force from the European Society of Thoracic Surgery (ESTS) Thymic Working Group, Moser et al. [25] published a retrospective analysis of 152 patients with thymic malignancies (45 with recurrent disease—scenario 1—and 107 with *de novo* stage IVA—scenario 2). Forty EPPs were performed—8 in scenario 1 (18.2% of cases) and 32 in scenario 2 (29.9% of cases), achieving R0 resection in 91% and 71% of cases in scenarios 1 and 2, respectively. Overall survival at 5 and 10-years was 87.2% and 62.7%, respectively. There were statistically significant differences in OS at 3, 5 and 10 years between primary pleural surgery and surgery for pleural recurrence, and between complete (R0) and incomplete resections. Calculation of OS, DFS, cancer specific survival (CSS) and freedom from recurrence (FFR) for thymomas and thymic carcinomas (TCs) revealed statistically significant differences in all analyses favoring thymoma over TC. At multivariable analysis, TCs had a negative effect on OS compared to thymomas [HR 6.506; $p = 0.002$], CSS and FFR. After multivariable analysis only in patients with complete resection, a negative impact on OS was observed in male sex [HR 3.176; $p = 0.025$], TC [HR 3.988; $p = 0.013$] and primary pleural surgery compared with surgery for pleural recurrence [HR 4.132; $p = 0.040$].

Recently, Kaba et al. [26] published a single-institutional review of 39 patients with stage IVA malignancies (30 patients with thymoma and 9 with TC) undergoing surgical resection, 66% of patients had *de novo* disease. Three EPPs were performed, with 33% perioperative mortality (0% for all other procedures). Overall 3, 5 and 10 year survival rates were 93%, 93% and 56% for entire cohort, and 90%, 90% and 72% for primary pleural surgeries, respectively.

Hyperthermic Perfusion

Looking to enhance locoregional control in a large cavity, hyperthermic intrathoracic perfusion chemotherapy (HITHOC) has been administered in addition to resection of thymoma metastases. Refaely et al. [27] analysed an institutional experience of 15 patients with stage IVA thymic malignancies (9 with *de novo* disease) receiving HITHOC. After achieving R0 and CMR rates of 67% and 80%, respectively, 5-year overall survival was 55% for the entire cohort and 70% for thymoma patients. In a large series of HITHOC for pleural malignancies, Kodama et al. [28] described results of 12 patients with stage IV TETs, including 16% EPPs. Freedom from recurrence at 5-year was 65% and overall survival at 5 and 10 years was 91.7% and 73.3%, respectively. However, results of HITHOC for thymic carcinoma have been disappointing. Yellin et al. [29] evaluated outcomes of 35 stage IVA patients (31 with thymoma and 4 with TC) undergoing surgical resection and HITHOC. Median survival for *de novo* thymomas, recurrent thymomas and thymic carcinomas was 184, 140 and 34 months respectively, with overall survival for the three groups being 81%, 67% and 0% at 5 years and 73%, 56% and 0%, respectively.

HITHOC is a promising therapy for reaching better local control of disease, with a low mortality rate and without significant toxicity. However, comparative studies addressing efficacy of these therapies over resection alone are not available. Studies evaluating use of hyperthermic intrapleural chemoperfusions for thymic malignancies with pleural involvement are summarized in Table 57.4 [27–32].

Conclusions and Recommendations

Even though there are no prospective, controlled studies comparing surgical to non-surgical treatment of TETs with pleural dissemination, the best available data suggest that surgical resection, when feasible, offers better disease control and long-term survival compared to non-surgical approaches. The most important prognostic factor in studies evaluating thymoma and thymic carcinoma with pleural metastasis is complete resection. The goal of resection should be complete macroscopic and microscopic resection (R0). EPP is associated with high postoperative morbidity and mortality, however, in patients with significant pleural and pulmonary involvement it is often the only option to achieve an R0 resection.

The number of pleural implants has been correlated with prognosis [33]. The presence of more than ten implants is associated with worse outcomes in de novo Masaoka IVA patients [21] as well as in those with recurrent disease [30]. These findings could be explained by a less aggressive tumor nature and, theoretically, by a higher probability of achieving a complete resection. However, this should not discourage resection in patients with more voluminous, but resectable, disease. Subtotal resection in thymoma patients may still have a benefit compared to inoperable patients, and this is confirmed with data from a large retrospective database [2]. However, subtotal resection was not demonstrated to be beneficial in TCs, and only complete resection has a prognostic value in this population.

Table 57.4 Studies adressing pleural resection WITH chemoperfusion for thymic malignances with pleural involvement

Reference	n	Study design (period)	Population	n thymoma/ TC	n de novo IVA/ recurrences	n stage IVA/ IVB	EPP—n (%)	Chemoperfusion regimen	Completeness of resection—R0 or CMR	MMT before surgery	MMT after surgery
Refaely (2001) [27]	15	Single-center, retrospective (1995–2000)	Stage IVA thymic malignancies	10/4	9/6	15/0	1/15 (6.7%)	Cisplatin 100 mg/m^2—variable in some patients	R0 67%/CMR 80%	53% ChT	No
Belcher (2011) [30]	6	Single-center, retrospective (2007–2010)	Stage IVA thymoma submitted to induction chemotherapy, surgery and pleural irrigation	6/0	3/3	6/0	0 (0%)	Sterile water and povidone-iodine	NA	100% ChT	No
Kodama (2013) [28]	12	Single-center, retrospective (1989–2010)	Thymoma malignancies with pleural involvement treated with HPC	12/0	4/6	11/1	2/12 (16.7%)	Cisplatin (50–100 mg/chest cavity) or carboplatin (450 mg/chest cavity)	NA	NA	NA
Yellin (2013) [29]	35	Single-center, retrospective (1995–2012)	Stage IVA TETs with pleural involvement (de novo or recurrent)	31/4	21/14	35/0	1/35 (2.8%)	Cisplatin and doxorrubicin for thymoma (only cisplatin for TC). Redo HPCP in 7 patients (total: 44 procedures)	Thymomas R0: 45%/CMR 87%/TC R0: 25%/CMR 50%	ChT not used as induction. RT used in pleural relapses	Adjuvant ChT for patients with pleural R2 resection. Adjuvant RT for patients with R1-R2 resection of mediastinal component

(continued)

Table 57.4 (continued)

Reference	n	Study design (period)	Population	n thymoma/ TC	n de novo IVA/ recurrences	n stage IVA/ IVB	EPP—n (%)	Chemoperfusion regimen	Completeness of resection—R0 or CMR	MMT before surgery	MMT after surgery
Yu (2013) [31]	4	Single-center, retrospective (2008–2010)	Thymoma malignancies with pleural involvement treated with HPC	4/0	2/2	NR	0/4	Cisplatin 100 mg/m^2	NA	NA	100% RT
Ried (2014) [32]	13	Single-center, retrospective (2000–2012)	Thymomas IVA submitted to resection and HITHOC	12/1	10/3	13/0	1/13 (7.7)%	In 69% of cases (cisplatin 100–150 mg/m^2)	CMR 92%	68% of entire cohort	46% ChT; 8% ChT + RT
Reference	**PO morbidity**		**30-days PO mortality—%**	**Median follow-up in months [range]**	**RR, 5-year DFS or FFR (%)**	**Median survival in months**		**3-Year OS—%**	**5-Year OS—%**	**10-Year OS—%**	**Quality of evidence**
Refaely (2001) [27]	33% early/13.3% late		0	34 [7–70]	NA	NA		70% for entire group/90% for thymomas	55% for entire group/70% for thymomas	NA	Low
Belcher (2011) [30]	28.6%		0	19 [1–32]	RR 16%				NA	NA	Low
Kodama (2013) [28]	NA		0	68	5-year FFR 64.8%	Not reached		91.7	91.7	73.3	Low

Yellin (2013) [29]	27%	90-day: 2.5	62 [3–202]	Progression-free survival: de novo IVA 61% (10-year 43%)/ recurrent disease: 48% (10-year 18%)	De novo IVA: 184/Recurrent disease: 140/ Thymic carcinoma: 34	NA	De novo IVA: 81/Recurrent disease: 67/ Thymic carcinoma: 0	De novo IVA: 73/ Recurrent disease: 56/ Thymic carcinoma: 0	Moderate
Yu (2013) [31]	25%	0	1–4 years	RR 0%	NA	NA	Not reached	Not reached	Very low
Ried (2014) [32]	Severe complications: 13.6%	0	Mean 29 months	RR 30.7%	20	NA	NA	NA	Low

Abbreviations: *TC* thymic carcinoma, *EPP* extrapleural pneumonectomy, *CMR* complete macroscopic resection, *MMT* multimodality treatment, *PO* post-operative, *NA* non available, *ChT* chemotherapy, *RT* radiation therapy, *RR* recurrence rate, *DFS* disease-free survival, *FFR* freedom from recurrence, *OS* overall survival

Recommendations

- Patients with thymoma with pleural dissemination without extrathoracic metastases should be offered surgical resection if an R0 resection is feasible (quality of evidence moderate, strong recommendation).
- Subtotal resection is controversial for thymoma patients and no conclusions can be made regarding benefits of subtotal resection versus non-surgical approaches.
- In thymic carcinoma patients, debulking surgery is not recommended (quality of evidence low, weak recommendation).

A Personal View of the Data

Initial presentation of TETs with pleural dissemination is rare and there are scarce data with insufficient information to define the best treatment protocol. However, these patients are often young, otherwise healthy, and usually fit for surgery. We evaluate these patients with a multidisciplinary team which should include medical oncologists, radiation oncologists, radiologists and thoracic surgeons. The presence of associated diseases, including myasthenia gravis, is taken into consideration, and patient status and medical conditions are optimized pre-operatively. When confronted by resectable disease in a patient amenable to surgery, we perform a radical thymectomy and pleural resection aiming to achieve an R0 resection. Incisions, approaches, and magnitude of resection are dictated by disease extent and location.

References

1. Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol. 2010;5(10 Suppl 4):S260–5.
2. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg. 2003;76(3):878–84.
3. Ruffini E, Detterbeck F, Van Raemdonck D, Rocco G, Thomas P, Weder W, et al. Tumours of the thymus: a cohort study of prognostic factors from the European Society of Thoracic Surgeons database. Eur J Cardiothorac Surg. 2014;46(3):361–8.
4. Regnard JF, Magdeleinat P, Dromer C, Dulmet E, De Montpreville V, Levi JF, et al. Prognostic factors and long-term results after thymoma resection: a series of 307 patients. J Thorac Cardiovasc Surg. 1996;112(2):376–84.
5. Blumberg D, Port JL, Weksler B, Delgado R, Rosai J, Bains MS, et al. Thymoma: a multivariate analysis of factors predicting survival. Ann Thorac Surg. 1995;60(4):908–14.
6. Maggi G, Casadio C, Cavallo A, Cianci R, Molinatti M, Ruffini E. Thymoma: results of 241 operated cases. Ann Thorac Surg. 1991;51(1):152–6.
7. Wright CD, Wain JC, Wong DR, Donahue DM, Gaissert HA, Grillo HC, et al. Predictors of recurrence in thymic tumors: importance of invasion, World Health Organization histology, and size. J Thorac Cardiovasc Surg. 2005;130(5):1413–21.
8. Utsumi T, Shiono H, Matsumura A, Maeda H, Ohta M, Tada H, et al. Stage III thymoma: relationship of local invasion to recurrence. J Thorac Cardiovasc Surg. 2008;136(6):1481–5.

9. Margaritora S, Cesario A, Cusumano G, Lococo F, Porziella V, Meacci E, et al. Single-centre 40-year results of redo operation for recurrent thymomas. Eur J Cardiothorac Surg. 2011;40(4):894–900.
10. Ruffini E, Filosso PL, Oliaro A. The role of surgery in recurrent thymic tumors. Thorac Surg Clin. 2009;19(1):121–31.
11. Venuta F, Anile M, Diso D, Vitolo D, Rendina EA, De Giacomo T, et al. Thymoma and thymic carcinoma. Eur J Cardiothorac Surg. 2010;37(1):13–25.
12. Kim ES, Putnam JB, Komaki R, Walsh GL, Ro JY, Shin HJ, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. Lung Cancer. 2004;44(3):369–79.
13. Wright CD. Pleuropneumonectomy for the treatment of Masaoka Stage IVA thymoma. Ann Thorac Surg. 2006;82(4):1234–9.
14. Huang J, Rizk NP, Travis WD, Seshan VE, Bains MS, Dycoco J, et al. Feasibility of multimodality therapy including extended resections in stage IVA thymoma. J Thorac Cardiovasc Surg. 2007;134(6):1477–84.
15. Ishikawa Y, Matsuguma H, Nakahara R, Suzuki H, Ui A, Kondo T, et al. Multimodality therapy for patients with invasive thymoma disseminated into the pleural cavity: the potential role of extrapleural pneumonectomy. Ann Thorac Surg. 2009;88(3):952–7.
16. Yano M, Sasaki H, Yukiue H, Kawano O, Okuda K, Hikosaka Y, et al. Thymoma with dissemination: efficacy of macroscopic total resection of disseminated nodules. World J Surg. 2009;33(7):1425–31.
17. Cardillo G, Carleo F, Giunti R, Lopergolo MG, Salvadori L, De Massimi AR, et al. Predictors of survival in patients with locally advanced thymoma and thymic carcinoma (Masaoka stages III and IVa). Eur J Cardiothorac Surg. 2010;37(4):819–23.
18. Okereke IC, Kesler KA, Morad MH, Mi D, Rieger KM, Birdas TJ, et al. Prognostic indicators after surgery for thymoma. Ann Thorac Surg. 2010;89(4):1071–9.
19. Fabre D, Fadel E, Mussot S, Mercier O, Petkova B, Besse B, et al. Long-term outcome of pleuropneumonectomy for Masaoka stage IVa thymoma. Eur J Cardiothorac Surg. 2011;39(5):e133–8.
20. Rena O, Mineo TC, Casadio C. Multimodal treatment for stage IVA thymoma: a proposable strategy. Lung Cancer. 2012;76(1):89–92.
21. Okuda K, Yano M, Yoshino I, Okumura M, Higashiyama M, Suzuki K, et al. Thymoma patients with pleural dissemination: nationwide retrospective study of 136 cases in Japan. Ann Thorac Surg. 2014;97(5):1743–8.
22. Murakawa T, Karasaki T, Kitano K, Nagayama K, Nitadori JI, Anraku M, et al. Invasive thymoma disseminated into the pleural cavity: mid-term results of surgical resection. Eur J Cardiothorac Surg. 2015;47(3):567–72.
23. Bölükbas S, Eberlein M, Oguzhan S, Schirren M, Sponholz S, Schirren J. Extended thymectomy including lung-sparing pleurectomy for the treatment of thymic malignancies with pleural spread. Thorac Cardiovasc Surg. 2015;63(3):217–22.
24. Hamaji M, Burt BM. Long-term outcomes of surgical and nonsurgical management of stage IV thymoma: a population-based analysis of 282 patients. Semin Thorac Cardiovasc Surg. 2015;27(1):1–3.
25. Moser B, Fadel E, Fabre D, Keshavjee S, de Perrot M, Thomas P, et al. Surgical therapy of thymic tumours with pleural involvement: an ESTS Thymic Working Group Project. Eur J Cardiothorac Surg. 2017;52(2):346–55.
26. Kaba E, Ozkan B, Erus S, Duman S, Cimenoglu B, Toker A. Role of surgery in the treatment of Masaoka stage IVa thymoma. Ann Thorac Cardiovasc Surg. 2018;24(1):6–12.
27. Refaely Y, Simansky DA, Paley M, Gottfried M, Yellin A. Resection and perfusion thermochemotherapy: a new approach for the treatment of thymic malignancies with pleural spread. Ann Thorac Surg. 2001;72(2):366–70.

28. Kodama K, Higashiyama M, Okami J, Tokunaga T, Fujiwara A, Imamura F, et al. Cytoreductive surgery and post-operative heated pleural chemotherapy for the management of pleural surface malignancy. Int J Hyperth. 2013;29(7):653–62.
29. Yellin A, Simansky DA, Ben-Avi R, Perelman M, Zeitlin N, Refaely Y, et al. Resection and heated pleural chemoperfusion in patients with thymic epithelial malignant disease and pleural spread: a single-institution experience. J Thorac Cardiovasc Surg. 2013;145(1):83–9.
30. Belcher E, Hardwick T, Lal R, Marshall S, Spicer J, Lang-Lazdunski L. Induction chemotherapy, cytoreductive surgery and intraoperative hyperthermic pleural irrigation in patients with stage IVA thymoma. Interact Cardiovasc Thorac Surg. 2011;12(5):744–8.
31. Yu L, Jing Y, Ma S, Li F, Zhang YF. Cytoreductive surgery combined with hyperthermic intrapleural chemotherapy to treat thymoma or thymic carcinoma with pleural dissemination. Onco Targets Ther. 2013;6:517–21.
32. Ried M, Potzger T, Sziklavari Z, Diez C, Neu R, Schalke B, et al. Extended surgical resections of advanced thymoma Masaoka stages III and IVa facilitate outcome. Thorac Cardiovasc Surg. 2014;62(2):161–8.
33. Yano M, Sasaki H, Moriyama S, Hikosaka Y, Yokota K, Masaoka A, et al. Number of recurrent lesions is a prognostic factor in recurrent thymoma. Interact Cardiovasc Thorac Surg. 2011;13(1):21–4.

Sympathectomy for Malignant Ventricular Arrhythmias

58

Vignesh Raman and David H. Harpole Jr

Introduction

The autonomic nervous system has long been implicated in arrhythmogenesis. Sympathetic discharge can trigger arrhythmias by causing afterdepolarizations and maintain a pro-arrhythmic state by promoting dispersion [1]. Cardiac sympathetic denervation (CSD) has been reported as successful therapy primarily in patients with long QT syndrome (LQTS) to mitigate symptoms like syncope and decrease internal cardiac defibrillator (ICD) discharge [2–4]. Similarly, CSD has been successfully used in another channelopathy, catecholaminergic polymorphic ventricular tachycardia (CPVT), to mitigate symptoms and ICD shocks [2, 5].

The mechanisms explaining the success of CSD have been well described with animal models [5, 6]. CSD increases the threshold for ventricular fibrillation (VF) and raises refractoriness, thereby decreasing the probability of VF after surgery. It improves the capacity of coronary artery dilation, which enhances its use in patients with cardiomyopathy especially of ischemic etiology. CSD preserves cardiac contractility. Since CSD does not entirely obliterate ventricular catecholamines, it does not result in postdenervation supersensitivity. The preganglionic denervation achieved by CSD prevents reinnervation, which increases the probability of durable freedom from arrhythmia and intervention.

While the use of CSD has been described in reducing ICD shocks and symptoms in patients with channelopathies like LQTS or CPVT, it is increasingly used in patients with refractory ventricular arrhythmias (VA) due to other causes like cardiomyopathy, arrhythmogenic right ventricle, and idiopathic ventricular fibrillation. However, the evidence supporting its use in these situations is limited. In this chapter, we focus on the use of CSD in patients with refractory VA.

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Table 58.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with refractory ventricular arrhythmia	Cardiac sympathetic denervation	Maximum medical therapy and catheter ablation	Freedom from ventricular arrhythmia

Search Strategy

Our search strategy is summarized in the Table 58.1 based on PICO formatting. Initially, the following search terms were applied on PubMed and Google Scholar to identify the earliest and most cited articles: "sympathectomy", "cardiac sympathetic denervation", "arrhythmia". For the results section of the chapter, the same search terms were applied but during the period of January 2009 through September 2019 to identify only the most relatively recent studies.

Results

Observational Studies

No prospective, randomized trials were identified evaluating the role of CSD in patients with refractory VA. Most studies included patients due to one of the following reasons: (1) continued VA despite maximal pharmacotherapy (beta blockade) and catheter ablation or (2) poor tolerance for pharmacotherapy or unsuitable anatomy (e.g., multiple foci of automatic activity or circuits arising from interventricular septum, papillary muscles, juxta-coronary regions) for catheter ablation [7].

The observational studies evaluating CSD in patients with refractory VA are summarized in Table 58.2 [7–13]. The primary outcome reported in most studies is freedom from VA following surgery, with many studies quantifying the decrease in arrhythmic events as well. The largest study, by Vaseghi and colleagues, was reported in 2014 [12]. In this study, 41 patients with cardiomyopathy and refractory VA underwent CSD that was either left-sided or bilateral. A total of 48% of patients with bilateral CSD experienced freedom from VA following surgery while 30% experienced freedom from VA in the left CSD group. In their total cohort, 90% of patients experienced a reduction in ICD shocks.

In 2014, Hofferberth and coworkers described their experience performing left CSD in 24 patients with refractory VA due to multiple etiologies including channelopathy [11]. They found that 55% of patients experienced freedom from VA and 73% marked reduction in arrhythmia burden following surgery at a median follow-up of 28 months. Coleman and colleagues reported the outcomes of 27 patients who underwent left CSD in patients with non-LQTS syndromes that predispose to VA [10]. A total of 18 of 22 symptomatic patients (82%) experienced complete freedom from VA following surgery at a follow-up of 14 months. Four other studies each reported their experience of less than 10 patients undergoing CSD, with a 56–100% freedom from VA reported [7–9, 13].

Table 58.2 Summary of data from observational studies evaluating the role of cardiac sympathetic denervation (CSD) in the treatment of ventricular arrhythmias (VA)

Author	Year of publication	Total cohort (number)	Reason for surgery	Laterality (left vs. bilateral)	Patients with freedom from arrhythmia (n, %)	Major complications from surgery
Bourke et al. [8]	2010	9	VA refractory to ablation	Left	5 (56%)	None
Ajijola et al. [9]	2012	6	VA refractory to ablation	Bilateral	4 (67%)	None
Coleman et al. [10]	2012	27 (22 symptomatic)	Non-QT VA-causing syndrome	Left	18 (82%)	None
Hofferberth et al. [11]	2014	24	Refractory VA (cohort includes QT syndrome patients)	Left	12 (55%)	None
Vaseghi et al. [12]	2014	41	CM and refractory VA	Left in 14 and 27 bilateral	4 (30%) left and 13 (48%) bilateral	Hemothorax requiring reoperation (n = 1)
Richardson et al. [7]	2018	7	VA refractory to ablation	Bilateral in 6 and left in 1	7 (100%)	None
Assis et al. [13]	2019	8	ARVC with refractory VA	Bilateral	5 (63%)	None

NR not reported, *QT* QTc interval, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *CA* cardiomyopathy

Complications of CSD

CSD is a generally safe operation that can be performed using video assisted thoracic surgery (VATS). No perioperative mortality attributable to the operation has been reported. The only major complication identified in observational studies is hemothorax, with one patient requiring reoperation for evacuation of a hemothorax within 24 h of the index operation [12]. Minor complications include pneumothorax and generally self-limited ptosis. Chronic complications include hyperalgesia of chest and back and changes in sweating [12].

Extent of CSD

There are no studies comparing the extent of CSD in patients with refractory VA. However, most studies report resection of the sympathetic ganglia from T2 to T4–5 in addition to excision of the lower third to half of the stellate ganglion [10, 12, 14]. The lateral nerves of Kuntz, if present, are also removed. While some older studies report preservation of the stellate ganglion to prevent iatrogenic Horner syndrome, most modern series report resection of the inferior part of the ganglion, which mitigates arrhythmogenesis from the stellate ganglion while also minimizing the risk of Horner syndrome because ocular fibers generally cross in the superior half of the ganglion.

Left vs. Bilateral CSD

Both left and bilateral CSD have been described in the treatment of refractory VA. The only study that included both techniques, cited above, found that 30% of patients had freedom from VA after left CSD and 48% after bilateral CSD [12]. However, the study included heterogeneous patients and small groups. Bilateral CSD offers theoretical advantages over left CSD [1]. The right stellate ganglion does innervate the ventricles and its denervation should decrease the arrhythmogenicity of the ventricles [2]. Denervation of one stellate ganglion may lead to hypertrophy of the contralateral ganglia and result in continued arrhythmogenesis. For these reasons, we perform bilateral CSD in our patients with refractory VA.

Conclusions and Recommendations

There is neither high nor moderate quality evidence evaluating the role of CSD in patients with refractory VA. However, based on low quality evidence, we recommend that patients who continue to experience significant VA despite maximal medical therapy and catheter ablation and those who cannot tolerate or are not amenable for ablation and pharmacotherapy be considered for bilateral CSD. They should undergo multidisciplinary evaluation at a center with advanced electrophysiology,

cardiac intensive care, and thoracic surgery capabilities. Our recommendation is further supported by observational studies and our experience suggesting that bilateral CSD is a safe operation with a negligible incidence of major complications.

Recommendation

- We recommend the use of bilateral cardiac sympathetic denervation in patients with ventricular arrhythmia either refractory to maximal pharmacotherapy and catheter ablation or not amenable for ablation and poorly tolerant of pharmacotherapy (evidence quality low, weak recommendation).

A Personal View of the Data

Although thoracic surgeons have been performing VATS sympathectomies for more than two decades for hyperhidrosis palmaris and other disorders, it has become more useful for patients with refractory ventricular dysrhythmias. We have performed more than 20 in the last 5 years with excellent postoperative control and minimal morbidity. If possible, patients should have a left stellate ganglion block prior to operation to verify utility of a sympathectomy. The procedure even can be performed safely on patients with refractory VT having ventricular assist devices. Although the data are scant, we prefer bilateral VATS sympathectomy for more complete cardiac denervation. A prospective multi-institutional database should be designed for collection of more evidence.

References

1. Bradfield JS, Ajijola OA, Vaseghi M, Shivkumar K. Mechanisms and management of refractory ventricular arrhythmias in the age of autonomic modulation. Heart Rhythm. 2018;15(8):1252–60.
2. Olde Nordkamp LRA, Driessen AHG, Odero A, Blom NA, Koolbergen DR, Schwartz PJ, et al. Left cardiac sympathetic denervation in the Netherlands for the treatment of inherited arrhythmia syndromes. Neth Heart J. 2014;22(4):160–6.
3. Schwartz PJ, Priori SG, Cerrone M, Spazzolini C, Odero A, Napolitano C, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. Circulation. 2004;109(15):1826–33.
4. Li J, Wang L, Wang J. Video-assisted thoracoscopic sympathectomy for congenital long QT syndromes. Pacing Clin Electrophysiol. 2003;26(4p1):870–3.
5. Wilde AAM, Bhuiyan ZA, Crotti L, Facchini M, De Ferrari GM, Paul T, et al. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. NEJM. 2008;358(19):2024–9.
6. Schwartz PJ. Cardiac sympathetic denervation to prevent life-threatening arrhythmias. Nat Rev Cardiol. 2014;11(6):346–53.
7. Richardson T, Lugo R, Saavedra P, Crossley G, Clair W, Shen S, et al. Cardiac sympathectomy for the management of ventricular arrhythmias refractory to catheter ablation. Heart Rhythm. 2018;15(1):56–62.

8. Bourke T, Vaseghi M, Michowitz Y, Sankhla V, Shah M, Swapna N, Boyle NG, Mahajan A, Narasimhan C, Lokhandwala Y, Shivkumar K. Neuraxial modulation for refractory ventricular arrhythmias: value of thoracic epidural anesthesia and surgical left cardiac sympathetic denervation. Circulation. 2010;121(21):2255–62.
9. Ajijola OA, Lellouche N, Bourke T, Tung R, Ahn S, Mahajan A, et al. Bilateral cardiac sympathetic denervation for the management of electrical storm. J Am Coll Cardiol. 2012;59(1):91–2.
10. Coleman MA, Bos JM, Johnson JN, Owen HJ, Deschamps C, Moir C, et al. Videoscopic left cardiac sympathetic denervation for patients with recurrent ventricular fibrillation/malignant ventricular arrhythmia syndromes besides congenital long-QT syndrome. Circ Arrhythm Electrophysiol. 2012;5(4):782–8.
11. Hofferberth SC, Cecchin F, Loberman D, Fynn-Thompson F. Left thoracoscopic sympathectomy for cardiac denervation in patients with life-threatening ventricular arrhythmias. J Thorac Cardiovasc Surg. 2014;147(1):404–11.
12. Vaseghi M, Gima J, Kanaan C, Ajijola OA, Marmureanu A, Mahajan A, et al. Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: intermediate and long-term follow-up. Heart Rhythm. 2014;11(3):360–6.
13. Assis FR, Krishnan A, Zhou X, James CA, Murray B, Tichnell C, Berger R, Calkins H, Tandri H, Mandal K. Cardiac sympathectomy for refractory ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy. Heart Rhythm. 2019;16:1003–10.
14. Atallah J, Fynn-Thompson F, Cecchin F, DiBardino DJ, Walsh EP, Berul CI. Video-assisted thoracoscopic cardiac denervation: a potential novel therapeutic option for children with intractable ventricular arrhythmias. Ann Thorac Surg. 2008;86(5):1620–5.

The Extent of Surgery for Palmar Hyperhidrosis

59

Shane P. Smith and Eric Vallières

Introduction

Idiopathic palmar hyperhidrosis is a debilitating disease with a prevalence of up to 3% in the US population [1]. It is a cause of social anxiety and a boundary to both social and professional development [2]. Endoscopic thoracic sympathectomy (ETS) offers a permanent solution in contrast to temporizing medical therapies [3, 4]. The extent of surgery for palmar hyperhidrosis, namely which level(s) of the thoracic sympathetic chain are to be interrupted, by which method, and using which surgical access remain subjects of debate. The details of the procedure performed have an effect on the outcomes associated with ETS including patient satisfaction, morbidity, compensatory hyperhidrosis (CH), and quality of life (QOL).

Search Strategy

A literature search of English language publications from 2000–2019 was used to identify data on the extent of surgery for palmar hyperhidrosis (Table 59.1). Databases searched included: PubMed, Cochrane Evidence Based Medicine, and Ovid. Terms used in the literature search were "hyperhidrosis, palmar/surgery," "hyperhidrosis, palms/surgery," "hyperhidrosis, palmar/ surgery extent," "hyperhidrosis, palms/ surgery extent," AND ("intraoperative complications" OR "perioperative complications" OR "postoperative complications"), "compensatory hyperhidrosis," "compensatory sweating," and "quality of life." Articles were excluded if they did not subcategorize hyperhidrosis based on the palmar location. Four randomized clinical trials, five prospective cohort studies, one retrospective

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Table 59.1 PICO formatted terms for literature search

Population	Intervention	Comparison	Outcome
Patients with predominant palmar hyperhidrosis	Endoscopic thoracic surgery	• Location of interruption of the sympathetic chain: R2–5 • Method of interruption: clip ligation, sympathotomy, sympathectomy • Number of ports	• Freedom from sweating • Complications • Quality of life

review, one expert consensus, one systematic review, and one meta-analysis were included in our analysis. The data was classified using the GRADE system.

Results

Location of Interruption of the Sympathetic Chain

The level of thoracic chain interruption has been a topic of debate in ETS for palmar hyperhidrosis. Levels are described in two methods: the thoracic spinal level of the ganglion (T) or the ribs at which the interruption was performed below or on (R). Typical levels of destruction include levels T2–4 or R2–R4 [4]. For purposes of uniformity we will use the R descriptor for location of interruption. Some reports that use T nomenclature will interrupt at more than one rib and this will be clarified by conversion to R nomenclature within this text. Levels of interruption most common to the literature include R2–R4 singly and a combination of these levels.

Overall immediate success rate is reported as being greater than 93% for studies pertaining to ETS involving interruptions from R2 to R5 and combinations of these levels (Table 59.2) [3, 5–12]. The major differences noted when comparing these levels of interruption relate to the rates and severity of postoperative compensatory sweating (CH) as a result of the sympathetic chain disruption.

R2 involvement in a sympathectomy has typically been favored for the selectivity of the palms. However, there is an associated increased rate of CH with R2 targeting. Sang et al. performed a systematic review of the literature and found an increased rate of CH in patients with R2 involved in their sympathectomy when compared to those that did not include R2 [5]. In comparison, Yazbek et al. in two separate randomized clinical trials demonstrated a higher immediate success rate, lower CH, and greater quality of life for R2/R3 ETS as compared to R3/R4 [6, 7].

Of note, the Society of Thoracic Surgeons (STS) expert consensus promotes R3 or R4 levels for palmar hyperhidrosis for the best success rate and lowest CH levels [8]. This has been supported by randomized clinical trials and a meta-analysis [9–11].

Quality of life after ETS is a time dependent variable. Throughout the literature that compares ETS levels of interruption, those operations including R2 had the best satisfaction with the longest follow up time of 20 months [6]. However, in a non-comparison study, Horslen et al. reported an 86% improvement in quality of life at a median follow up of 60 months for ETS at R3/R4 [3].

Table 59.2 Levels of interruption of the sympathetic chain and outcomes

First author, year, reference	Study type (Level of evidence)	Interruption level	Patients	Immediate success rate	Surgical morbidity	Rate of compensatory hyperhidrosis (CH)	Follow up time	Quality of life
Yazbek (2009) [6]	Randomized clinical trial (Moderate)	R2,3 vs R3,4	59	100% R2,3 97% R3,4	CH	67% R2, 93% R3 (less severe)	20 months (mean)	R2,3 > R3,4 at 20 months
Liu (2009) [10]	Randomized clinical trial (Moderate)	R3 vs R4	141	100% R3 94% R4	CH	77% R3, 56% R4	18 months (mean)	R4 > R3 at 18 months
Li (2008) [9]	Randomized clinical trial (Moderate)	R3 vs R2–R4	56	100% for both	CH	Severe: 10% R2–R4, 3% R3	12 months (mean)	R3 > R2–R4
Yazbek (2005) [7]	Randomized clinical trial (Moderate)	R2,3 vs R3,4	60	100% R2,3 97% R3,4	CH	86% R2, 90% R3 (less severe)	6 months (mean)	R2,3 = R2,4 at 6 months
Sugimura (2009) [12]	Prospective cohort (Low)	R2 R2–3 R3–4	535	96% for all groups as a whole	CH, PTX, SVC Tear, Horner's Syndrome	Severe: 15% R2, 24% R2–3, 8% R3–4	10.4 months (mean)	Excellent satisfaction R2 74%, R2–3 62%, R3–4 85%
Zhang (2017) [11]	Meta-analysis (Moderate)	R3 vs R4	1195	No statistical difference R3 vs R4	CH, Dry hands R3 > R4, Gustatory sweating R3 > R4	R3 > R4 (significant heterogeneity)	Variety	No statistical difference R3 vs R4
Sang (2017) [5]	Systematic review (Moderate)	R2 R2–3 R2–4 R2–5 R3 R4 R3–4	Not reported	95–100% for all groups	CH, Horner's syndrome avoidable if limited to R3 and/or R4, CH R2-involved groups > R2-free	R2 involved groups 57% R2 free groups 29%	Not reported	Not reported
Horslen (2018) [3]	Prospective cohort (Low)	R3–4	54	93%	CH	84%	60 months (median)	86% reported improvement
Cerfolio (2011) [8]	Expert consensus (Moderate)	R2 R2–3 R2–4 R2–5 R3 R4 R3–4	3760 (Total)	>94%, R3 or R4 with the highest rates	CH, PTX, Horner's Syndrome, Permanent Bradycardia	R3 > R4	6–40 months (variety)	Not reported

PTX pneumothorax

Method of Interruption

There are a variety of modalities utilized in ETS to interrupt the sympathetic chain. In the treatment of palmar hyperhidrosis the method of interruption is a consideration in the extent of surgery. Methods typically utilized include clip ligation of the chain, sympathotomy with thermal cut, and sympathectomy in which a section of the chain is actually removed. Benefits of clip ligation include the potential for early reversibility of the procedure if the patient suffers from severe CH and/or decreased quality of life [4]. However, the aspect of reversibility has been questioned as reliable in patients who undergo ETS with clip ligation. It has been reported that clip removal is successful in reversing approximately half of patients who undergo surgery to remove clips [12]. However, high quality data is lacking from the literature, and success has mostly been limited to clip removal within the first 2 weeks following the initial procedure [13].

Cheng et al. presented a retrospective chart review comparing all three methods of interruption with a mean follow up time of 5 years, in which they found lower rates of CH with clip ligation. Higher morbidity and Horner's Syndrome was documented after sympathotomy and sympathectomy [14]. Panhofer et al. reflected the findings of Cheng et al. in a prospective cohort study comparing clip ligation to diathermic cut (Table 59.3). This study showed a higher rate of morbidity with cut, as well as more pneumothoraces, compared to clip ligation, along with a lower rate of CH in the clip ligation group [15].

Number of Ports

ETS is typically performed using video assisted thoracic surgery (VATS) techniques. The procedure itself does not involve complex dissection or resection of large amounts of tissue, so minimally invasive techniques have been pursued. Techniques have been described using from one to three working ports [4, 8]. Fewer ports tend to offer less injury to the chest wall and therefore a less painful recovery, but with the risk of limited surgical mobility and a greater potential for complications [16].

The literature provides few comparison studies of the number of ports used in ETS (Table 59.4). Ibrahim et al. compared a single port method to multiple ports in a prospective cohort and reported excellent success with both methods, but a higher incidence of pneumothorax and a lower rate of CH in the multiple port technique [17]. In another prospective cohort study, Murphy et al. compare a single to the use of two ports and they again reflect a significantly higher rate of pneumothorax in the multiple method without a statistically significant difference in CH [18].

Conclusions and Recommendations

Endoscopic thoracic sympathectomy is an overall successful technique in the treatment of palmar hyperhidrosis. The extent of the surgery performed is of debate, with the goal of providing a high success rate with lasting quality of life and

Table 59.3 Method of interruption of the sympathetic chain

Author, year, reference	Study type (Level of evidence)	Methods compared	Patients	Immediate success rate	Surgical morbidity	Rate of compensatory hyperhidrosis (CH)	Mean follow up time	Quality of life
Cheng (2015) [14]	Retrospective chart review (Very low)	Sympathotomy, Sympathectomy, Clip ligation	210	85% overall, $p > 0.05$ between groups	Horner's Syndrome: 1% (Sympathotomy and Sympathectomy), CH	Sympathotomy (72%) Sympathectomy (77%) Clip ligation (68%) $p > 0.05$ between groups	5 years	76% overall $p > 0.05$ between groups
Panhofer (2014) [15]	Prospective cohort (Low)	Clip ligation, Diathermic cut	37	85% clip ligation, 91% Diathermic cut	Pneumothorax: 2.6% clip ligation, 3.3% diathermic cut	Clip ligation 7.9% Diathermic cut 11% $p = 0.479$	12 months	No significant difference in improvement $p = 0.127$

Table 59.4 Number of ports used for treating hyperhidrosis

First author, year, reference	Study type (Level of evidence)	Methods compared	Number of patients	Immediate success rate	Surgical morbidity	Rate of compensatory hyperhidrosis (CH)	Mean follow up time	Quality of life
Ibrahim (2014) [17]	Prospective cohort (Low)	Single port, multiple ports	71	100%	PTX: 2.8% Single port, 5.7% multiple ports, $p > 0.05$	22% Single port, 20% multiple ports, $p > 0.05$	1 year	Not assessed
Murphy (2006) [18]	Prospective cohort (Low)	Single port, two ports	46	75%	PTX: 7.7% Single port, 15.8% two ports $p < 0.05$	31% Single port, 29% two port	25 months (median)	Single port > two port

PTX pneumothorax

minimal postoperative morbidity. In assessing the body of literature, the extent of surgery can be subdivided into level of sympathetic chain interruption, method of interruption, and number of ports used.

The strongest quality of data is available for the level at which the sympathetic chain is interrupted. The R2 level may be more specific for palmar hyperhidrosis, but the R3 and/or R4 levels provide just as high success rates with less CH. A lower quality of data is available regarding the method of interruption and number of ports. In the studies available, clip ligation provides a satisfactory initial success rate and long lasting quality of life with less CH and the possibility of reversal when performed early following the initial procedure. In regards to ports, less pain and morbidity are associated with smaller numbers of ports. However, more prospective randomized studies would significantly add to the literature and aid in a more supported consensus regarding method of interruption and number of ports.

Recommendations

- We recommend VATS targeting R3 and/or R4 for management of palmar hyperhidrosis (high quality evidence, strong recommendation).
- We recommend clip ligation of the sympathetic chain rather than sympathotomy or sympathectomy for management of hyperhidrosis (low quality of evidence, weak recommendation).
- A single or double port technique is recommended for VATS sympathotomy (low quality of evidence, weak recommendation).

A Personal View of the Data

Our personal approach to patients suffering from predominately palmar hyperhidrosis is bilateral isolation of the T3 sympathetic nerve ganglion by VATS placement of two 5-mm titanium hemoclips below ribs 3 and 4 (R3–4). We use hemoclips and do not transect to allow for the possibility of reversal. We use a double 5 mm port technique. Our results have been studied internally and published. The benefits are maintained long term and, after surgery, the resultant quality of life is preferred even when affected by variable degrees of CH [3].

References

1. Strutton DR, Kowalski JW, Pharm D, Glaser DA, Stang PE. US prevalence of hyperhidrosis and impact on individuals with axillary hyperhidrosis: results from a national survey. J Am Acad Dermatol. 2004;51(2):241–8. https://doi.org/10.1016/j.jaad.2003.12.040.
2. Milanez de Campos JR, Kauffman P, de Campos Werebe E, et al. Quality of life, before and after thoracic sympathectomy: report on 378 operated patients. Ann Thorac Surg. 2003;76(3):886–91. https://doi.org/10.1016/S0003-4975(03)00895-6.
3. Horslen LC, Wilshire CL, Louie BE, Vallières E. Long-term impact of endoscopic thoracic sympathectomy for primary palmar hyperhidrosis. Ann Thorac Surg. 2018;106(4):1008–12. https://doi.org/10.1016/j.athoracsur.2018.04.063.

4. Vallières E. Endoscopic upper thoracic sympathectomy. Neurosurg Clin N Am. 2001;12(2):321–7.
5. Sang HW, Li GL, Xiong P, Zhu MC, Zhu M. Optimal targeting of sympathetic chain levels for treatment of palmar hyperhidrosis: an updated systematic review. Surg Endosc. 2017;31(11):4357–69. https://doi.org/10.1007/s00464-017-5508-y.
6. Yazbek G, Wolosker N, Kauffman P, de Campos JRM, Puech-Leão P, Jatene FB. Twenty months of evolution following sympathectomy on patients with palmar hyperhidrosis: sympathectomy at the T3 level is better than at the T2 level. Clinics. 2009;64(8):743–9. https://doi.org/10.1590/S1807-59322009000800006.
7. Yazbek G, Wolosker N, Milanez De Campos JR, Kauffman P, Ishy A, Puech-Leão P. Palmar hyperhidrosis – which is the best level of denervation using video-assisted thoracoscopic sympathectomy: T2 or T3 ganglion? J Vasc Surg. 2005;42(2):281–5. https://doi.org/10.1016/j.jvs.2005.03.041.
8. Cerfolio RJ, De Campos JRM, Bryant AS, et al. The Society of Thoracic Surgeons expert consensus for the surgical treatment of hyperhidrosis. Ann Thorac Surg. 2011;91(5):1642–8. https://doi.org/10.1016/j.athoracsur.2011.01.105.
9. Li X, Tu YR, Lin M, Lai FC, Chen JF, Dai ZJ. Endoscopic thoracic sympathectomy for palmar hyperhidrosis: a randomized control trial comparing T3 and T2-4 ablation. Ann Thorac Surg. 2008;85(5):1747–51. https://doi.org/10.1016/j.athoracsur.2008.01.060.
10. Liu Y, Yang J, Liu J, et al. Surgical treatment of primary palmar hyperhidrosis: a prospective randomized study comparing T3 and T4 sympathicotomy. Eur J Cardiothorac Surg. 2009;35(3):398–402. https://doi.org/10.1016/j.ejcts.2008.10.048.
11. Zhang W, Wei Y, Jiang H, Xu J, Yu D. T3 versus T4 thoracoscopic sympathicotomy for palmar hyperhidrosis: a meta-analysis and system review. J Surg Res. 2017;218:124–31. https://doi.org/10.1016/j.jss.2017.05.063.
12. Sugimura H, Spratt EH, Compeau CG, Kattail D, Shargall Y. Thoracoscopic sympathetic clipping for hyperhidrosis: long-term results and reversibility. J Thorac Cardiovasc Surg. 2009;137(6):1370–8. https://doi.org/10.1016/j.jtcvs.2009.01.008.
13. Hynes CF, Yamaguchi S, Bond CD, Blair Marshall M. Reversal of sympathetic interruption by removal of clips. Ann Thorac Surg. 2015;99(3):1020–3. https://doi.org/10.1016/j.athoracsur.2014.10.062.
14. Cheng A, Johnsen H, Chang MY. Patient satisfaction after thoracoscopic sympathectomy for palmar hyperhidrosis: do method and level matter? Perm J. 2015;19(4):29–31. https://doi.org/10.7812/TPP/15-040.
15. Panhofer P, Ringhofer C, Gleiss A, et al. Quality of life after sympathetic surgery at the T4 ganglion for primary hyperhidrosis: clip application versus diathermic cut. Int J Surg. 2014;12(12):1478–83. https://doi.org/10.1016/j.ijsu.2014.11.018.
16. Chen Y, Ye W, Yang W, et al. Uniportal versus biportal video-assisted thoracoscopic sympathectomy for palmar hyperhidrosis. Chin Med J. 2009;122(5):1525–8.
17. Ibrahim M, Allam A. Comparing two methods of thoracoscopic sympathectomy for palmar hyperhidrosis. JAAPA. 2014;27(9):1–4. https://doi.org/10.1097/01.JAA.0000453237.17130.6b.
18. Murphy MO, Ghosh J, Khwaja N, et al. Upper dorsal endoscopic thoracic sympathectomy: a comparison of one- and two-port ablation techniques. Eur J Cardiothorac Surg. 2006;30:223–7. https://doi.org/10.1016/j.ejcts.2006.04.016.

Part VII

Chest Wall

Synthetic Versus Biologic Reconstruction of Bony Chest Wall Defects

60

Onkar Khullar and Felix Fernandez

Introduction

Chest wall reconstruction is a challenging thoracic operation for even the most seasoned surgeon, particularly when bony defects are present. Iatrogenic defects are typically the result of resection of the chest wall for a number of conditions, including neoplasms, congenital defects, radiation injuries, and complicated infections. Larger defects of the chest wall can lead to skeletal instability, altered respiratory mechanics, and significant cosmetic defects. Reconstruction of these large defects of the chest wall can present an arduous challenge and often require prosthetic materials to fill.

Overall, the objectives of chest wall reconstruction include restoration of skeletal integrity, protection of underlying structures, and providing a good cosmetic result. A variety of materials exist for skeletal reconstruction and are promoted for reconstruction, including rigid versus non-rigid materials, permeable versus non-permeable materials, patches/meshes versus rib/sternal plates/bars, and synthetic versus biologic materials [1]. The ideal prosthetic material would have the following properties: rigid enough to abolish paradoxical chest wall motion; malleable enough to allow for appropriate contouring; physically and chemically inert; allows for tissue in-growth; radiolucent; sterile and resistant to infection; inexpensive. Unfortunately, no material exists that meets all such criteria.

Complications after chest wall reconstruction are frequent, with rates reported as high as 20–60%. Common complications include poor wound healing, seromas, infectious complications, pulmonary complications, and respiratory compromise. Other important postoperative outcomes include chronic pain, quality of life (QOL)

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concerns, and poor cosmetic results. When compared with synthetic materials, biologic reconstruction materials have the theoretical advantage of being more resistant to infectious complications and may require less frequent removal. On the other hand, non-rigid biologic materials are ultimately reabsorbed after some degree of tissue infiltration and regrowth. This may result in less chest wall stability, potentially resulting in greater respiratory compromise and worse cosmetic outcomes. The purpose of this review is to compare outcomes and results from reconstruction with biologic materials versus synthetic materials.

Search Strategy

We examined the literature on chest wall reconstruction for iatrogenic bony chest wall defects comparing reconstruction with biologic material versus synthetic material, with a focus on postoperative complications, mesh removal rates, QOL outcomes, and cosmetic outcomes (Table 60.1). A literature search of English language publications over a 10 year period from 2009 to 2019 was used to identify published data on prosthetic chest wall reconstruction of bony chest wall defects. Database searched included PubMed, Embase, and Cochrane Evidence Based Medicine. Terms used in the search were "prosthetic chest wall reconstruction", "synthetic chest wall reconstruction", and "biologic chest wall reconstruction". No randomized control trials or prospective cohort studies were identified. Five retrospective cohort studies and 19 cases series were included in our analysis. Analysis was limited to studies reporting immediate postoperative outcomes from reconstruction. Case reports were excluded from the analysis. Studies where outcomes related to reconstruction were not reported were also excluded. Results were classified using the GRADE system. As can be ascertained from Table 60.2, the literature in regards to this topic is limited to case series of varying sizes and a few retrospective cohort analyses with limited comparative analyses.

Results

To date, there have been no high-quality randomized clinical trials comparing one prosthetic material to another. As a result, the choice of material used is often based on institutional availability and cost, surgeon preference, and anecdotal evidence (Table 60.2) [2–21, 23–28]. Below, we will review what literature is currently available.

Table 60.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Pts with iatrogenic chest wall defects	Reconstruction with biological material	Reconstruction with synthetic materials	Complications, quality of life, prosthesis removal

Table 60.2 Summary of published literature for chest wall reconstruction

Author (year)	N[a]	Reconstruction material utilized	Overall complications	Wound infection	Seroma formation	Prosthesis removal	Perioperative mortality	Study design (Quality of evidence)
Synthetic								
Galbis Caravajal et al. (2009) [2]	11	PTFE patch, polypropylene mesh	18%	NR	NR	18%	0%	Case-series (Low)
Daigeler et al. (2009) [3]	62	Polypropylene mesh	42%	15.2%	NR	6.5%	5.4%	Case-series (Low)
Aghajanzadeh et al. (2010) [4]	60	Polypropylene mesh (n = 40), methylmethacrylate/mesh (n = 20)	36%	5%	3%	NR	3.3%	Case-series (Low)
Noble et al. (2010) [5]	17	Methylmethacrylate and polypropylene mesh sandwich	NR	0%	5.9%	0%	0%	Case-series (Low)
Girotti et al. (2011) [6]	101	Synthetic mesh (n = 52), synthetic rigid "shield" (n = 27), synthetic "rib-like" prosthesis (n = 22)	22.7%	12.8%	NR	6.9%	0.9%	Retrospective cohort study (Low)
Fabre et al. (2012) [7]	24	Titanium rib plates with vicryl mesh or PTFE patch	NR	4.2%	8.3%	0%	0%	Case-series (Low)
Berthet et al. (2012) [8]	31	Titanium rib plates with PTFE mesh	16%	9.7%	0%	3.2%	6.4%	Case-series (Low)
Huang et al. (2015)[b] [9]	23	Expanded PTFE patch (n = 18), polypropylene mesh (n = 4), felt (n = 1)	60.9%	8.7% (all with PTFE)	21.7% (all with PTFE)	8.7% (all with PTFE)	0%	Retrospective cohort study (Low)
Aghajanzadeh et al. (2015) [10]	43	Methylmethacrylate and polypropylene mesh sandwich	NR	7%	9.3%	2.3%	2.3%	Case-series (Low)

(continued)

Table 60.2 (continued)

Author (year)	N[a]	Reconstruction material utilized	Overall complications	Wound infection	Seroma formation	Prosthesis removal	Perioperative mortality	Study design (Quality of evidence)
Yang et al. (2015) [11]	27	Titanium mesh	14.8%	0%	7.4%	0%	0%	Case-series (Low)
Khalil et al. (2016) [12]	71	Polypropylene mesh, methyl methacrylate, titanium plates	NR	2.8%	0%	0%	0%	Case-series (Low)
Foroulis et al. (2016) [13]	20	Methylmethacrylate and polypropylene mesh sandwich	20%	0%	0%	0%	0%	Case-series (Low)
Biologic								
Ge et al. (2010) [14]	10	AlloDerm or Flex HD human dermal matrix	40%	10%	30%	0%	0%	Case-series (Low)
Lin et al. (2012) [15]	5	Permacol porcine dermal matrix	40%	0%	20%	0%	0%	Case-series (Low)
Barua et al. (2012) [16]	6[c]	Permacol porcine dermal matrix, Veritas collagen matrix	33.3%	0%	0%	0%	16.7%	Case-series (Low)
Dell'Amore et al. (2012) [17]	4	Sternal allograft	0%	0%	0%	0%	0%	Case-series (Low)
Guillen et al. (2017) [18]	8	L-Lactic acid and glycolic acid copolymer bioabsorbable plates	0%	0%	0%	0%	0%	Case-series (Low)
Schmidt et al. (2016) [19]	6	Permacol porcine dermal matrix	0%	0%	0%	0%	0%	Case-series (Low)
Khalil et al. (2018) [20]	8	Strattice bovine dermal matrix	0%	0%	0%	0%	0%	Case-series (Low)

D'Amico et al. (2018) [21]	11	Protexa porcine dermal matrix	45%	27%	0%	0%	0%	Case-series (Low)
Synthetic and biologic								
Rocco et al. (2014) [22]	46	"New materials" (titanium plates, cryopreserved grafts, and acellular collagen matrices, n = 21) "Conventional materials" (PTFE and methyl methacrylate, n = 21) Combination (n = 4)	16%	8.1%	NR	4.6%	0%	Retrospective cohort study (Low)
George et al. (2014) [23]	21	XCM biologic porcine dermis tissue matrix with (10) or without (11) rib plates	14.3%	14.3% (all with Synthes rib plates)	0%	14.3% (all with Synthes rib plates)	0%	Case-series (Low)
Spicer et al. (2016)[d] [24]	427	Biologic (n = 111) Synthetic (n = 316)	24%[e]	2.8%	NR	0%	1%	Retrospective cohort study (Moderate)
Azoury et al. (2016) [25]	59	Biologic (n = 10) Synthetic (n = 22) Biologic/synthetic combination (n = 27)	24.7%	8.6% (n = 5 in synthetic only, n = 2 combo)	1.2%	0%	6.8% (all in synthetic alone group)	Retrospective cohort study (Moderate)

NR not reported, *PTFE* polytetrafluoroethylene. AlloDerm: Allergan, Madisan, NJ; Flex HD: Ethicon, Bridgewater, NJ; Permacol: Covidien, Mansfield, MA; Veritas: Synovis, St Paul, MN; XCM: Depuy Synthes, Oberdorf, Switzerland; Protexa: Teconss, Giaveno, Italy; Synthes Titanium System: Depuy Synthes, Oberdorf, Switzerland

[a]Number of patients reconstructed with synthetic or biologic prosthesis. Patients treated without reconstruction or with autologous tissue flaps only not included

[b]14 patients in this study were reconstructed with autologous tissue and are not included here

[c]Number of chest wall reconstructions, total sample size of case series was 44 including soft tissue reconstructions

[d]A variety of reconstruction materials were used including biologic, synthetic, flexible, and rigid

[e]Only pulmonary complications were reported

Woven meshes and patches such as polypropylene and polytetrafluoroethylene are easy to use, non-absorbable, and provide uniform tensile strength. However, as they are synthetic they may be more prone to infection, which typically requires removal of the prosthesis. More recent case series report infection rates ranging from 5% to 15%, with similar rates of prosthesis removal [2–4, 6, 9, 22]. Similarly, seroma rates were between 3% and 22%, however this was highly dependent on perioperative technique and typically did not require removal of the prosthetic if infection was absent.

Recent studies of newer titanium plates have shown promising results, however in the majority of cases these are used along as a rigid scaffold along with a biologic or synthetic mesh with similar infection rates to more traditional synthetic materials alone [7, 8, 12, 22]. Interestingly, Yang et al. published a series of 27 patients reconstructed with a titanium mesh, and reported no wound infections or chest wall instability [11]. While these results are promising, this was a small retrospective series and additional study of this mesh is needed.

Biologic meshes are typically made from allograft or homograft tissue that has been decellularized, leaving only a collagen matrix. These meshes promote new collagen deposition and tissue ingrowth, as opposed to scarring which is seen with synthetic meshes. Anecdotally they are often utilized in infected fields. The majority of studies examining the use of biologic materials are limited to small case series. Infection rates ranged from 0% to 27% [14–21]. Despite this, however, most of these series reported that the prosthesis could be salvaged without removal.

For example, Schmidt et al., in a series of 6 patients reconstructed with a porcine decellularized dermis matrix, reported no infectious complications and good to excellent chest wall stability measured by the surgeon's impression and evidence of structural changes on CT scan [19]. D'Amico et al., in a series of 11 patients with chest wall resection for sarcoma, reported a wound complication rate (hematoma and infection) of 27%, though none required implant removal [21]. Similar to the Schmidt series, they found good long-term chest wall stability and integrity on CT scan at 2 years after surgery.

Quality of life after chest wall reconstruction with either synthetic or biologic materials has been studied only by a few authors and the endpoints have not been standardized. Compared to patients undergoing lung resection without the need for chest wall resection, those who underwent lung resection combined with chest wall resection and reconstruction experienced similar quality of life (pain, fatigue, dyspnea) and overall lung function [26]. Long-term outcomes appear to be more strongly related to preoperative status than the extent of chest wall resection required for treating lung cancer and the type of reconstruction necessary [27]. Treatment of chest wall tumors with resection and reconstruction results in long-term quality of life results similar to that in the general population [28].

We identified three retrospective cohort studies which directly compare biologic and synthetic prosthetics, and are summarized in Table 60.3 [22, 24, 25]. One such study from Spicer et al., compared outcomes after reconstruction with absorbable (Vicryl and biologic, n = 111) and non-absorbable (synthetic, n = 316) meshes [24]. On multivariable analysis, they found no difference in pulmonary complications

Table 60.3 Studies comparing synthetic and biologic prosthetic chest wall reconstruction materials

Author (year)	Conclusions
Rocco et al. (2014) [22]	Combined use of synthetic and biologic materials associated with increased risk of local wound complications (p = 0.032; OR not reported). No difference identified between synthetic alone versus biologic alone
Spicer et al. (2016) [24]	No difference identified in infection rates between biologic and synthetic mesh (p = 0.477, OR not reported), or pulmonary complications (OR = 1.47, 95% CI 0.86–2.53, p = 0.155)
Azoury et al. (2016) [25]	No difference identified in incidence of chest wall/wound complications between synthetic, biologic or combination biologic inlay with synthetic onlay mesh groups (31.8%, 10%, 22.2% respectively, p = 0.47)

(OR = 1.47, 95% confidence interval 0.86–2.53, p = 0.155) or wound infection rates (p = 0.477, OR not reported). It should be noted that in their study, they found a remarkably low overall wound infection rate of 2.8% (n = 12), and had no explants due to infected mesh, regardless of material used.

Azoury et al. reported similar results and found no difference in incidence of chest wall/wound complications between synthetic, biologic or combination biologic inlay with synthetic onlay mesh groups (31.8%, 10%, 22.2% respectively, p = 0.47) [25]. They concluded that combined use of both materials provides the dual advantages of tissue ingrowth and revascularization from the acellular dermal matrix along with the structural durability of a synthetic mesh, although they acknowledged that larger sample sizes were needed to make definitive conclusions.

Rocco et al. in 2014 reported a case series examining the use of vacuum assisted closure as well as comparing what they refer to as "new materials" (titanium plates, cryopreserved grafts, and acellular collagen matrices} with conventional materials (polytetrafluoroethylene and methyl methacrylate) [22]. Twenty-one patients were treated with new materials, 21 with conventional materials, and 4 with both. Interestingly, the authors found no difference in local wound complications between these two cohorts when only a single material was used. However, in a multivariable regression, the use of both materials together was associated with higher rates of wound complications (OR not reported, p = 0.032). These results are difficult to interpret given only 4 patients in the combined materials cohort.

There is no comparative QOL data between biologic and synthetic materials. Future study will require prospective comparative studies including well-validated QOL endpoints, in addition to measuring clinical outcomes.

Conclusions and Recommendations

In summary, the current literature in regards to utilization of synthetic vs. biologic prosthesis for reconstruction of bony chest wall defects is limited to single institution retrospective cases series, and a few retrospective cohort studies. Only three studies directly compare postoperative outcomes between synthetic and biologic

prostheses, specifically in regards to infectious wound complications. These few retrospective series are limited by selection bias given the study design, there does not appear to be a significant difference in regards to wound complications or rates of prosthesis removal. There may be increased risk of local wound complications when a combination of synthetic and prosthetic materials is used, however the data is limited and conclusive statements cannot be made. There is little data in regards to QOL or cosmesis.

Based on this review of the literature, many surgeons will prefer to use a biologic prosthesis in a contaminated field. In the absence of an infected, contaminated field, a synthetic prosthesis should be used with likely equivalent rates of infectious complications and rates of prosthesis removal, and lower costs. Recommendations regarding postoperative QOL and cosmesis cannot be made at this time.

Recommendations

- A synthetic prosthesis is recommended as the best overall choice for chest wall reconstruction (evidence quality low, weak recommendation).
- A biologic prosthesis is recommended for chest wall reconstruction in a contaminated field (evidence quality low, weak recommendation).

A Personal View of the Data

Reconstruction of iatrogenic bony chest wall defects is a difficult challenge for even the most seasoned surgeon. If a prosthetic material is needed for reconstruction, our preference is to utilize synthetic mesh material in most situations. The available case series show that infectious rates with synthetic materials are relatively low, with low rates of mesh removal. The added advantage of structural integrity and lower cost make synthetic materials, such as PTFE, our preference in the absence of an infected field. When a rigid prosthetic is needed our typical practice is to use methyl methacrylate “sandwiched” in Vicryl mesh, however newer titanium materials show considerable promise and warrant further study. In the presence of an infected field, our preference is to utilize a biologic prosthesis. Further recommendations and future study will require prospective, randomized trials with clearly defined endpoints for complications, cosmesis, and quality of life.

References

1. Khullar OV, Fernandez FG. Prosthetic reconstruction of the chest wall. Thorac Surg Clin. 2017;27(2):201–8.
2. Galbis Caravajal JM, Yeste Sanchez L, Fuster Diana CA, Guijarro Jorge R, Fernandez Ortiz P, Deaville PJ. Sternal resection and reconstruction after malignant tumours. Clin Transl Oncol. 2009;11(2):91–5.

3. Daigeler A, Druecke D, Hakimi M, et al. Reconstruction of the thoracic wall-long-term follow-up including pulmonary function tests. Langenbecks Arch Surg. 2009;394(4):705–15.
4. Aghajanzadeh M, Alavy A, Taskindost M, Pourrasouly Z, Aghajanzadeh G, Massahnia S. Results of chest wall resection and reconstruction in 162 patients with benign and malignant chest wall disease. J Thorac Dis. 2010;2(2):81–5.
5. Noble J, Sirohi B, Ashley S, Ladas G, Smith I. Sternal/para-sternal resection for parasternal local recurrence in breast cancer. Breast. 2010;19(5):350–4.
6. Girotti P, Leo F, Bravi F, et al. The "rib-like" technique for surgical treatment of sternal tumors: lessons learned from 101 consecutive cases. Ann Thorac Surg. 2011;92(4):1208–16.
7. Fabre D, El Batti S, Singhal S, et al. A paradigm shift for sternal reconstruction using a novel titanium rib bridge system following oncological resections. Eur J Cardiothorac Surg. 2012;42(6):965–70.
8. Berthet JP, Wihlm JM, Canaud L, et al. The combination of polytetrafluoroethylene mesh and titanium rib implants: an innovative process for reconstructing large full thickness chest wall defects. Eur J Cardiothorac Surg. 2012;42(3):444–53.
9. Huang H, Kitano K, Nagayama K, et al. Results of bony chest wall reconstruction with expanded polytetrafluoroethylene soft tissue patch. Ann Thorac Cardiovasc Surg. 2015;21(2):119–24.
10. Aghajanzadeh M, Alavi A, Aghajanzadeh G, Ebrahimi H, Jahromi SK, Massahnia S. Reconstruction of chest wall using a two-layer prolene mesh and bone cement sandwich. Indian J Surg. 2015;77(1):39–43.
11. Yang H, Tantai J, Zhao H. Clinical experience with titanium mesh in reconstruction of massive chest wall defects following oncological resection. J Thorac Dis. 2015;7(7):1227–34.
12. Khalil HH, Malahias MN, Balasubramanian B, et al. Multidisciplinary oncoplastic approach reduces infection in chest wall resection and reconstruction for malignant chest wall tumors. Plast Reconstr Surg Glob Open. 2016;4(7):e809.
13. Foroulis CN, Kleontas AD, Tagarakis G, et al. Massive chest wall resection and reconstruction for malignant disease. Onco Targets Ther. 2016;9:2349–58.
14. Ge PS, Imai TA, Aboulian A, Van Natta TL. The use of human acellular dermal matrix for chest wall reconstruction. Ann Thorac Surg. 2010;90(6):1799–804.
15. Lin SR, Kastenberg ZJ, Bruzoni M, Albanese CT, Dutta S. Chest wall reconstruction using implantable cross-linked porcine dermal collagen matrix (Permacol). J Pediatr Surg. 2012;47(7):1472–5.
16. Barua A, Catton JA, Socci L, et al. Initial experience with the use of biological implants for soft tissue and chest wall reconstruction in thoracic surgery. Ann Thorac Surg. 2012;94(5):1701–5.
17. Dell'Amore A, Cassanelli N, Dolci G, Stella F. An alternative technique for anterior chest wall reconstruction: the sternal allograft transplantation. Interact Cardiovasc Thorac Surg. 2012;15(6):944–7.
18. Guillen G, Garcia L, Marhuenda C, et al. Thoracic wall reconstruction with bioabsorbable plates in pediatric malignant thoracic wall tumors. J Pediatr Surg. 2017;52(3):377–81.
19. Schmidt J, Redwan B, Koesek V, et al. Thoracic Wall reconstruction with acellular porcine dermal collagen matrix. Thorac Cardiovasc Surg. 2016;64(3):245–51.
20. Khalil HH, Kalkat M, Malahias MN, et al. Chest wall reconstruction with porcine acellular dermal matrix (Strattice) and autologous tissue transfer for high risk patients with chest wall tumors. Plast Reconstr Surg Glob Open. 2018;6(5):e1703.
21. D'Amico G, Manfredi R, Nita G, et al. Reconstruction of the thoracic wall with biologic mesh after resection for chest wall tumors: a presentation of a case series and original technique. Surg Innov. 2018;25(1):28–36.
22. Rocco G, Martucci N, La Rocca A, et al. Postoperative local morbidity and the use of vacuum-assisted closure after complex chest wall reconstructions with new and conventional materials. Ann Thorac Surg. 2014;98(1):291–6.
23. George RS, Kostopanagiotou K, Papagiannopoulos K. The expanded role of extracellular matrix patch in malignant and non-malignant chest wall reconstruction in thoracic surgery. Interact Cardiovasc Thorac Surg. 2014;18(3):335–9.

24. Spicer JD, Shewale JB, Antonoff MB, et al. The influence of reconstructive technique on perioperative pulmonary and infectious outcomes following chest wall resection. Ann Thorac Surg. 2016;102(5):1653–9.
25. Azoury SC, Grimm JC, Tuffaha SH, et al. Chest wall reconstruction: evolution over a decade and experience with a novel technique for complex defects. Ann Plast Surg. 2016;76(2):231–7.
26. Liu M, Wampfler JA, Dai J, et al. Chest wall resection for non-small cell lung cancer: a case-matched study of postoperative pulmonary function and quality of life. Lung Cancer. 2017;106:37–41.
27. Tacconi F, Ambrogi V, Mineo D, Mineo TC. The impact on quality of life after en-bloc resection for non-small-cell lung cancer involving the chest wall. Thorac Cancer. 2012;3(4):326–33.
28. Salo JTK, Repo JP, Roine RP, Sintonen H, Tukiainen EJ. Health-related quality of life after oncological resection and reconstruction of the chest wall. J Plast Reconstr Aesthet Surg. 2019;72(11):1776–84.

Traumatic Rib Fracture in the Absence of Flail Chest: Conservative Therapy or Surgical Fixation?

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Alex W. Helkin and Niels D. Martin

Introduction

Rib fractures are sustained in approximately of 10% of trauma patients and contribute significantly to morbidity and mortality [1]. Severe complications may arise in the setting of multiple rib fractures, with or without flail segment physiology, including an increased incidence of pneumonia, difficulty liberating from the ventilator, loss of thoracic volume, respiratory insufficiency, and chest wall deformities. Chronic pain beyond the hospital admission can occur even with single rib fractures, associated with decreased functional state, prolonged disability, and decreased quality of life [2].

Surgical stabilization of rib fractures (SSRF) can eliminate painful movement at fracture sites, fixate flail chest segments, repair severe chest wall deformities, and reestablish normal chest wall mechanics [3]. However, SSRF has been slow to gain momentum as a standard of care despite the belief that patients return to a functional physical state sooner as compared to non-operative management. Patients with rib fractures are admitted daily to hospitals around the country, however fewer than 1% of patients will undergo SSRF [4]. Reasons contributing to the low frequency of adaptation have been speculated to include lack of experience with the operation, lack of consensus for the indications, and lack of high-level supportive evidence [3].

While some meta-analyses [5–7] and professional society consensus statements [8] exist, the current data is inconsistent and represents a variety of patient populations, indications, techniques, study methodology, and outcomes. Patients with flail chest segments have been better studied than those without flail segments, and there

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exists some convincing data that SSRF is beneficial in these patients. However, even without flail segments, patients with multiple rib fractures experience significant morbidity and mortality, increasing with age and the number of rib fractures [9, 10]. The threshold of when to operate on patients without a flail segment is unclear. Here we will review and assimilate the data regarding the decision to perform rib fixation in non-flail segment injuries and identify populations that may benefit from this surgery.

Search Strategy

A Medline search was performed with the following keywords, "Blunt thoracic trauma, rib fixation, non-flail, rib fracture, chest wall stabilization, and surgical stabilization of rib fractures" (Table 61.1). Articles only in English, published between 2000 and 2019 (to represent the most current data), and for which the full text was available were reviewed. We focused on whether SSRF decreases ventilator days, ICU days, total hospital length of stay, and pneumonia during the index hospitalization for patients with multiple rib fractures, and whether SSRF decreases longer-term post-traumatic morbidities such as: pain, narcotics use, time to return to normal work/activities.

Results

Acute Outcomes

There are no randomized-control trials that compare SSRF to non-operative management (multimodal pain control and pulmonary toilet) in patients with multiple rib fractures without flail segments. The data supporting the practice of SSRF looking solely at non-flail chest injuries is sparse, with the available studies including a heterogeneous group of patients (which frequently include flail patients) and are largely retrospective and prospective non-randomized studies with significant limitations (Table 61.2) [11–15].

Nirula et al. in 2006, published a case-control study of 30 patients undergoing SSRF compared to control patients matched by age, Injury Severity Score, and chest Abbreviated Injury Score [11]. Fifty percent of the fixation group patients had non-flail significant rib fractures. The study found that SSRF patients had a similar

Table 61.1 PICO formatted terms for literature search

Patients	Intervention	Comparator	Outcomes
Patients with multiple rib fractures secondary to blunt thoracic trauma, with non-flail segments	Surgical stabilization of rib fractures	Non-operative (conservative) management	Ventilator days, pneumonia, ICU length of stay, hospital length of stay, mortality, quality of life, return to work

Table 61.2 Surgical stabilization of rib fracture studies with non-flail segment patients

Author (year)	Patients	Outcomes	Results	Quality of evidence	Comments
Nirula et al. (2006) [11]	Case-control study of 30 patients undergoing SSRF	– ICU LOS – Hospital LOS – Ventilator time	– Similar ICU and hospital LOS – Fewer ventilator days (2.9 vs. 9.4 days)	Moderate	50% of patients with non-flail segments
Richardson et al. (2007) [12]	Retrospective review of 3844 rib fracture patients, 7 SSRF	– Post-op pain – Ventilator weaning – Long-term disability – Chronic pain	– Good pain relief – Quick ventilator weaning – No disability	Low	No statistical analysis performed
Campbell et al. (2009) [13]	32 patients consecutive patients undergoing SSRF	– Survey responses for pain, pain with coughing, shortness of breath, chest stiffness, quality of life, return to work	– Low pain at rest (1.0/10) and with cough (1.3/10) – 60% with some chest stiffness – 20% with residual shortness of breath – Good quality of life – All back to work	Low	– Survey given between 1 month and 4 years from surgery – Low response rate (63%)
Kane et al. (2017) [14]	Retrospective review of 116 SSRF patient, collected prospectively, matches to trauma database patients	– Mortality – ICU LOS – Total LOS – Pneumonia – Tracheostomy	– Lower mortality (0.9% vs. 5.3%) – Lower pneumonia rate (13% decrease) – Longer ICU LOS (3 days vs. 0 days) – Longer hospital LOS (12 vs. 5 days) – Higher tracheostomy rate (8.6% vs. 4.5%)	Moderate	No non-flail sub group analysis
Pieracci et al. (2016) [15]	35 prospectively collected SSRF patients, crossover method (prior year with 35 non-operative patients)	– Respiratory failure – Tracheostomy – Pneumonia – Ventilator days – total LOS – mortality	– Lower respiratory failure (48.6% vs. 71.4%) – Lower tracheostomy rate (14.3% vs. 45.7%) – Fewer ventilator days (0 vs. 5.0 days) – Other measures not significant	Moderate	No non-flail sub group analysis

ICU intensive care unit, *LOS* length of stay, *SSRF* surgical stabilization of rib fractures

ICU and total hospital length of stay (LOS), however significantly less time on mechanical ventilation following surgery (2.9 ± 0.6 days vs. 9.4 ± .2.7 days in controls). As the control patients did not have surgery, the matched control patients used stabilization day as day zero for comparison.

Richardson et al. in 2007 performed a retrospective review of 3844 rib fracture patients over 9 years (1996–2005), seven of whom underwent SSRF [12]. On average, these patients had 8 rib fractures, with 3.5 ribs plated. Their outcome measures included relief of acute pain, weaning from mechanical ventilation, long-term disability, and chronic pain. The authors claimed SSRF was a useful solution as the seven patients were quickly weaned from the ventilator, experienced good long-term pain relief, and had no lasting disabilities, however, no objective data (survey results etc.) was reported or statistical analysis performed.

Campbell et al. in 2009 performed a retrospective review of 32 consecutive patients who underwent SSRF over a span of 4 years at their institution [13]. The patients all sustained blunt injury patterns and hemopneumothorax, indicating severe displacement. The outcomes measured were survey based, and included pain at rest and when coughing (0–10 numeric scale), chest wall stiffness, dyspnea, rehabilitation, and patient satisfaction (subjective reporting). Overall, the group reported positive outcomes (pain 1.0/10 at rest, 1.3/10 with coughing on average), however the survey results were diluted with significant biases. For example, the survey was administered between January and December 2008, while the operations were performed between February 2004 and November 2008. Only 63% responded to the survey.

Kane et al. in 2017 performed a retrospective review of a prospectively collected database of 116 patients undergoing SSRF, and compared their outcomes to a sample of 1000 non-operative rib fracture patients from the National Trauma Database [14]. In their study, patients undergoing SSRF had significantly lower mortality (0.9% vs. 5.3%) and pneumonia (13% lower) when compared with non-operative patients, at the expense of longer ICU (3 days vs. 0 days) and total lengths of stay (12 days vs. 5 days) and a higher tracheostomy rate (8.6% vs. 4.5%). This study also provided a subgroup analysis of patients aged 65 or greater with results that trended to decreased mortality, but did not achieve statistical significance. While the data separately analyzed age >65 years, ≥3 rib fractures, and ≥5 rib fractures, the 41/116 patients with non-flail chest injuries unfortunately did not undergo a separate subgroup analysis.

Finally, Pierraci et al. in 2016 examined the efficacy of SSRF in patients with severe rib fractures (including flail chest, non-flail with severely displaced fractures in >3 ribs, and loss of 30% or greater hemi-thoracic volume) [15]. The patient recruitment involved a prospectively collected crossover method, with the first year of data including all patients meeting the above criteria treated non-operatively, while the following year was the operative year. In the unadjusted outcomes, the operative group had a lower incidence of respiratory failure (48.6% vs. 71.4%) and tracheostomy (14.3% vs. 45.7%), and fewer ventilator days (0 vs. 5.0 days). The other outcomes measures, including pneumonia, hospital length of stay, and ICU length of stay, were not significantly different. Unfortunately, a subgroup analysis for the non-flail patients was not specifically reported.

Of note, the studies above reported a variety of operative techniques including wires, orthopedic plates and an orthopedic wrap system. There is no data comparing the various contemporary plating systems that exist via several different industry vendors. The decision and selection of SSRF systems are generally based on surgeon experience, preference, and corporate contracts.

Frequency of Use

Despite some guidance and support from the literature, surgical rib fixation, with or without diagnosed flail segments, remains an emerging practice, even within institutions. One recent study of the practice patterns of SSRF statewide determined that from 2016 to 2017 only 57 of 12,910 patients with multiple rib fractures underwent SSRF [16]. The operation was performed in only half of the trauma centers statewide. Interestingly, only 10/57 of the patients undergoing SSRF had flail segments.

Long-Term Outcomes

Two studies in particular, by Kerr-Valentic et al. and Mayberry et al., assessed longer term pain levels and disability with rib fractures rather than the standard hospital-centered metrics, such as mortality and length of stay [17, 18]. These trials found rib fracture patients, regardless of age, report significant disability at 30 days post injury, and that on average, they miss from 70 to over 100 days of work. Additionally, they found retrospectively 46 patients undergoing SSRF (15 for severely displaced non-flail fractures, and 13 for chest wall deformity and other indications) had acceptable long-term pain and equivalent health status post-operatively compared to the uninjured general population.

Conclusions and Recommendations

We recommend consideration for rib fixation in non-flail chest fractures for chest wall instability associated with acute worsening of pulmonary function, uncontrolled pain, severe chest wall deformity, pulmonary herniation or impalement, or in patients requiring thoracotomy for another procedure. We believe this will not only reduce pain, but improve pulmonary toileting and ventilator liberation in the acute setting, reduce chronic pain, improve quality of life and allow for return to work earlier.

Contemporary practices in SSRF are starting to include the outcomes listed above despite adequate trials. Further research involving SSRF is needed. One more reasonable study would be to match patients who underwent SSRF with patients identified via registry with similar demographics and rib fracture patterns, and survey their recovery, including chronic pain, use of narcotics, return to work or normal activities, and overall quality of life. This would provide a better comparison of patients based on rib fracture pattern and whether or not they underwent surgery.

Additionally, a randomized control trial comparing SSRF with non-operative management in patients with multiple rib fractures, using pre-determined criteria and identical multimodal pain control algorithms, would provide the level of evidence needed to expand the use of this procedure. Two such studies are currently being conducted, FixCon in the Netherlands and CWISNONFLAIL in the United States [19, 20]. The patient populations studied in both trials will include patients from multiple centers with severe, non-flail rib fracture patterns (≥3 severe displaced ribs), or pre-determined pulmonary specific physiologic derangements, such as respiratory rate, incentive spirometer performance, and pain scores. Flail chest patients will be specifically excluded. Experimental groups will undergo open reduction and internal fixation while both the operative and control groups will have either protocolized pain control (CWISNONFLAIL) or be left to provider judgment (FixCon). The primary outcome for the FixCon trial will be incidence of pneumonia with ventilator days, pain, pulmonary function, etc. as secondary outcomes. The CWISNONFLAIL trial will primarily look at quality of life metrics surveyed on post-operative visits, with similar secondary outcomes as the FixCon trial.

Recommendations

- Surgical rib fixation is recommended for patients with multiple severe rib fractures who have severe pain or chest wall instability that substantially inhibits pulmonary toileting or pulmonary mechanics (evidence quality moderate, weak recommendation).
- Surgical rib fixation is recommended for patients with multiple severe rib fractures with fracture patterns likely to lead to chronic pain (evidence quality low, weak recommendation).

A Personal View of the Data

Our approach to this data is that, while rib fracture patients can be treated non-operatively and get discharged from the hospital, many are left debilitated with chronic pain and/or never return to their pre-trauma functional state. We believe SSRF restores function, improves quality of life and return to work, and eventually the data will reflect such. When approaching the decision to perform SSRF, we consider a patient's clinical outcome as much as the standard metrics. Specifically, we try to answer the following questions: Is the fracture pattern detrimental and responsible for the clinical picture? Is SSRF technically feasible to reestablish a rigid chest wall? Are we early enough in the course to meaningfully mitigate potential morbidities? Is the fracture such that, without fixation, the patient is likely to experience debilitating chronic pain? We believe answering these questions is crucial to proceeding to SSRF.

As SSRF utilization increases, data will become available to answer more refined questions in the future. Surgeons will be able to better predict which patients or

fracture patterns will benefit from fixation the most, what the optimal timing is for surgery in relation to the acute injury, and the ideal number of fixed ribs versus unfixed ribs to balance the risks and benefits of surgery.

Conflict of Interest No author has a conflict of interest or financial disclosure necessary.

References

1. Lafferty PM, Anavian J, Will RE, Cole PA. Operative treatment of chest wall injuries: indications, technique, and outcomes. JBJS. 2011;93(1):97–110.
2. Gordy S, Fabricant L, Ham B, Mullins R, Mayberry J. The contribution of rib fractures to chronic pain and disability. Am J Surg. 2014;207(5):659–63.
3. Pieracci FM, Majercik S, Ali-Osman F, et al. Consensus statement: surgical stabilization of rib fractures rib fracture colloquium clinical practice guidelines. Injury. 2017;48(2):307.
4. Dehghan N, De Mestral C, McKee MD, Schemitsch EH, Nathens A. Flail chest injuries: a review of outcomes and treatment practices from the National Trauma Data Bank. J Trauma Acute Care Surg. 2014;76(2):462–8.
5. Leinicke JA, Elmore L, Freeman BD, Colditz GA. Operative management of rib fractures in the setting of flail chest: a systematic review and meta-analysis. Ann Surg. 2013;258(6):914–21.
6. Slobogean GP, MacPherson CA, Sun T, Pelletier M-E, Hameed SM. Surgical fixation vs nonoperative management of flail chest: a meta-analysis. J Am Coll Surg. 2013;216(2):302–311.e301.
7. Coughlin TA, Ng JW, Rollins KE, Forward DP, Ollivere BJ. Management of rib fractures in traumatic flail chest: a meta-analysis of randomised controlled trials. Bone Joint J. 2016;98-B(8):1119–25.
8. Kasotakis G, Hasenboehler EA, Streib EW, et al. Operative fixation of rib fractures after blunt trauma: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2017;82(3):618–26.
9. Bulger EM, Arneson MA, Mock CN, Jurkovich GJ. Rib fractures in the elderly. J Trauma. 2000;48:1040–6.
10. Stawicki SP, Grossman MD, Hoey BA, et al. Rib fractures in the elderly: a marker of injury severity. J Am Geriatr Soc. 2004;52:805–8.
11. Nirula R, Allen B, Layman R, Falimirski ME, Somberg LB. Rib fracture stabilization in patients sustaining blunt chest injury. Am Surg. 2006;72(4):307–9.
12. Richardson JD, Franklin GA, Heffley S, Seligson D. Operative fixation of chest wall fractures: an underused procedure. Am Surg. 2007;73:591–6.
13. Campbell N, Conaglen P, Martin K, Antippa P. Surgical stabilization of rib fractures using inion OTPS wraps. Techniques and quality of life follow up. J Trauma. 2009;67:596–601.
14. Kane ED, Jeremitsky E, Bittner KR, Kartiko S, Doben AR. Surgical stabilization of rib fractures: a single institution experience. J Am Coll Surg. 2018;226(6):961–6.
15. Pieracci FM, Lin Y, Rodil M, Synder M, Herbert B, Tran DK, Stoval RT, Johnson JL, Biffl WL, Barnett CC, et al. A prospective, controlled clinical evaluation of surgical stabilization of severe rib fractures. J Trauma Acute Care Surg. 2016;80(2):187–94.
16. Mullens CL, et al. A statewide assessment of rib fixation patterns reveals missed opportunities. J Surg Res. 2019;244:205–11.
17. Kerr-Valentic MA, Arthur M, Mullins RJ, Pearson TE, Mayberry JC. Rib fracture pain and disability: can we do better? J Trauma Acute Care Surg. 2003;54(6):1058–64.
18. Mayberry JC, Ham LB, Schipper PH, Ellis TJ, Mullins RJ. Surveyed opinion of American trauma, orthopedic, and thoracic surgeons on rib and sternal fracture repair. J Trauma Acute Care Surg. 2009;66(3):875–9.
19. Wijffels M, Prins JT, Polinder S, Blokhuis T, et al. Early fixation versus conservative therapy of multiple, simple rib fractures (FixCon): protocol for a multicenter randomized controlled

trial. World J Emerg Surg. 2019;14:38. https://doi.org/10.1186/s13017-019-0258-x. eCollection 2019.
20. Pieracci FM, et al. A multicenter randomized controlled trial of surgical stabilization of rib fractures in patients with severe non-flail fracture patterns (CWISNONFLAIL). https://cwisociety.org/research/nonflailrct/. Accessed 04 Jan 2020.

Is Surgical Management of Flail Chest Effective?

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Marcus Eby and Christopher W. Seder

Introduction

Flail chest is defined as fractures of at least three or more adjacent ribs in at least two places and is most commonly observed following blunt chest trauma [1]. Flail chest presents with a segment of the chest wall demonstrating paradoxical motion during respiration [2]. Although the force required to cause flail chest is often associated with additional thoracic injury, such as pulmonary contusion, flail chest alone has been shown to negatively affect respiratory mechanics due to the associated paradoxical movement [3]. Therefore, flail chest in itself can carry significant intrinsic morbidity. Current recommendations for surgical management of flail chest remain controversial, as available studies on the topic are mostly underpowered or retrospective in nature. Regardless, these studies do suggest that boney stabilization should be considered in specific situations of severe flail chest for individuals who fail to improve with non-operative care alone [4]. Surgeons who aim to improve the respiratory mechanics of patients with flail chest using rib fixation must be familiar with the indications for surgery to maximize the efficacy of the intervention.

This chapter addresses the potential benefits of operative chest stabilization, which patients are ideal candidates for rib fixation, and its efficacy over non-operative care in an attempt to reduce morbidity and length of stay and improve the overall quality of life for patients with severe flail chest.

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Search Strategy

A PubMed literature search of English language publications from 2000 to 2019 was used to identify studies on the effects of surgical chest stabilization in patients with traumatic acute flail chest (Table 62.1). Terms used in the search were "flail chest," "rib fractures," "surgical management," "rib fixation," and "thoracic surgery." Studies were excluded if they only addressed the possible benefits of "novel" rib fixation techniques rather than focus on the overall benefits of boney stabilization vs. supportive care alone for patients with flail chest and its associated morbidities. The data obtained from the search was classified using the GRADE system.

Results

Selecting Appropriate Patients for Rib Fixation

The general management of patients with acute flail chest should begin with nonsurgical treatment modalities and advance to surgical intervention, as needed. Since choosing to perform operative management for severe flail chest via boney stabilization carries an inherent cost and morbidity in itself, care should be taken in selecting patients that would benefit most from this intervention. To date, multiple studies and review articles have examined when it is most advantageous to perform surgical intervention for flail chest [5]. Even so, patients deemed to be appropriate candidates for rib fixation often vary from surgeon to surgeon. To make the patient selection process more ubiquitous and maximize rib fixation efficacy, the most currently accepted indications for boney chest wall stabilization as defined by previously completed studies are summarized in Table 62.2 [6–8].

Table 62.1 PICO formatted terms for literature search

P: Patients	I: Intervention	C: Comparator	O: Outcomes
Patients with acute flail chest and respiratory compromise	Boney stabilization	Optimal non-operative care	Complications, hospital length of stay (LOS), quality of life (QOL)

Table 62.2 Indications for surgical rib fixation in patients with acute flail chest

• Deteriorating pulmonary function despite optimal respiratory therapy and escalating analgesia requirements
• Flail chest with extensive chest wall deformity to prevent the development of future restrictive respiratory disorders
• Patient who require a thoracotomy for other thoracic injuries
• Intubated patients without severe pulmonary contusions who fail to wean from the ventilator in the presence of flail chest

The Efficacy of Rib Fixation vs. Non-Operative Care for Severe Flail Chest

The indications for surgical rib fixation listed in Table 62.2 can be used to help guide a treatment algorithm for individuals who will benefit most from surgical intervention when flail chest is present. Using these selection criteria, multiple studies have demonstrated potential benefits to rib fixation over supportive care alone in the setting of flail chest [9]. Available studies reviewing the possible benefits of surgical fixation for flail chest compared to supportive care alone are listed in Table 62.3 [6, 10, 11, 15–22]. One of the few randomized, prospective trials examining this topic revealed surgical stabilization versus ongoing pneumatic stabilization (intubation) was associated with decreases in the risk of pneumonia

Table 62.3 Studies examining efficacy of surgical fixation for flail chest

References	Patients	Design	Outcomes	Key results	
				Fixation	No fixation
Ahmed et al. (1995) [15]	$n = 64$	Retrospective cohort study	DMV (days)	3.9	15
			ICULOS (days)	9	21
			Pneumonia (%)	15	50
			Mortality (%)	8	29
Karev (1997) [16]	$n = 40$	Retrospective cohort study	DMV (days)	2.3	6.3*
			Pneumonia (%)	15	34*
			Mortality (%)	22.5	46*
Voggenreiter et al. (1998) [6]	$n = 20$	Retrospective cohort study	DMV (days)	6.5	27*
			Pneumonia (%)	15	39*
Tanaka et al. (2002) [10]	$n = 37$	RCT	DMV (days)	10.8	18*
			ICULOS (days)	16.5	27*
			Pneumonia (%)	24	77*
Balci et al. (2004) [17]	$n = 64$	Retrospective cohort study	DMV (days)	3.1	7.2
			Mortality (%)	11	27
Granetzny et al. (2005) [18]	$n = 40$	RCT	DMV (days)	2	12
			ICULOS (days)	9	14
			Pneumonia (%)	10	50
			Mortality (%)	10	15
Nirula et al. (2006) [19]	$n = 60$	Prospective controlled study	DMV (days)	6.5	11.2*
			ICULOS (days)	12.1	14.1

(continued)

Table 62.3 (continued)

References	Patients	Design	Outcomes	Key results	
				Fixation	No fixation
Althausen et al. (2011) [20]	$n = 50$	Retrospective controlled study	DMV (days)	4.1	9.7*
			ICULOS (days)	7.59	9.68
			Pneumonia	4.6	25*
			Mortality	0	0
Marasco et al. (2013) [21]	$n = 46$	RCT	DMV (days)	6.3	7.5
			ICULOS (days)	13.5	18.7*
			Pneumonia (%)	48	74
			Mortality (%)	0	4
Slobogean et al. (2013) [11]	$n = 732$; 11 studies	Meta-analysis	DMV (days)	−7.5; 95% CI: −9.9 to −5	
			ICULOS (days)	−4.8; 95% CI: −1.6 to −7.9	
			Pneumonia	OR: 0.18; (0.11–0.32)	
			Mortality	OR: 0.31; (0.20–0.48)	
Leinicke et al. (2013) [22]	$n = 538$; 9 studies	Meta-analysis	DMV (days)	−4.52; (−5.54 to −3.5)	
			ICULOS (days)	−3.40; (−6.0 to −0.80)	
			Pneumonia	RR: 0.45; (0.29–0.67)	
			Mortality	RR: 0.43; (0.28–0.69)	

DMV duration of mechanical ventilation (days), *ICULOS* intensive care unit length of stay (days), *RR* relative risk, *RCT* randomized controlled trial
*$p < 0.05$

(24% vs. 77%, $p < 0.05$), length of ventilator support (10.3 vs. 18.3 days, $p < 0.05$), and days spent in the intensive care unit (16.5 vs. 26.8 days, $p < 0.05$). These results favored surgical stabilization as the preferred treatment modality for flail chest in intubated patients failing to wean from the ventilator [10]. The benefits of rib fixation over non-operative interventions are further validated by a meta-analysis performed by Slobogean et al. demonstrating a decrease in chest pain (odds ratio (OR) 0.4), dyspnea (OR 0.4), risk of pneumonia (OR 0.18), duration of ventilator support (decreased by 7.5 days), intensive care length of stay (decreased by 4.8 days), overall hospital stay (decreased by 4 days), and overall mortality (OR 0.31) [11]. From

these studies, it appears that early restoration of chest wall rigidity optimizes respiratory mechanics in the setting of flail chest and suggests that early rib fixation can directly reduce the rates of pneumonia, chest pain, duration of ventilation support, intensive care length of stay, hospital length of stay, and overall mortality when performed on the appropriately selected patients (patients with the characteristics seen in Table 62.2) [10–13].

Contraindications to Rib Fixation for Flail Chest

Surgical intervention for flail chest carries an intrinsic morbidity and should be performed only when the benefits are thought to outweigh the risks. Since severe flail chest is due to blunt chest trauma, these injuries may be associated with open rib fractures. As such, boney stabilization with metal plating is contraindicated when concomitant contaminated wounds are present at the site of planned fixation, as this has potential to increase both morbidity and mortality by introduction of foreign material into an infected field.

Severe pulmonary contusion has also often been considered a contraindication to surgical stabilization of flail chest [14]. The ventilation dysfunction associated with pulmonary contusion cannot be remedied via surgical intervention, and subjecting the patient to an invasive procedure may worsen the patient's already compromised respiratory function. When present, studies have suggested that severe pulmonary contusions are best treated conservatively with respiratory monitoring, mechanical ventilation, and chest physiotherapy to allow the lung contusion to heal [11, 14].

Conclusions and Recommendations

Patients with flail chest commonly suffer from significant pain and impaired respiratory mechanics. The presence of flail chest has been shown to be associated with multiple pulmonary complications including atelectasis, pneumonia, an increase in medications prescribed and interventions performed to alleviate pain, and subsequent development of ventilator dependent respiratory failure. In this regard, flail chest can contribute to an increase in overall hospital cost, ventilator time, intensive care length of stay, and mortality.

Current evidence suggests that surgical boney stabilization of flail chest, when performed on appropriately selected patients, has the potential to reduce these complications. Based upon the best available evidence, rib fixation is recommended for patients with flail chest who suffer from worsening respiratory failure, major chest wall deformity, or poor pain control despite escalation of non-operative methods. Surgical stabilization for flail chest via rib fixation is an effective therapy with the potential to provide benefit and should be performed in properly selected patients.

Recommendations

- For patients diagnosed with acute flail chest following blunt chest trauma who have escalating analgesic requirements or fail non-operative management, we recommend surgical intervention with boney stabilization using rib fixation (evidence quality high; strong recommendation).
- We do not recommend surgical fixation for flail chest if open fractured ribs, contaminated wounds, or underlying severe pulmonary contusions is present (evidence quality low; weak recommendation).

A Personal View of the Data

In our practice, we have seen severe flail chest result in impaired respiratory mechanics, escalating analgesic requirements, and prolonged ventilator support. We have adopted a policy of performing boney stabilization early for patients meeting the criteria in Table 62.2 with observed improvements in overall quality of life, pain control, ventilator time, hospital length of stay, and mortality. Thus, we feel operative rib fixation should be considered by surgeons in appropriately selected patients when faced with this challenging entity.

References

1. Keel M, Meier C. Chest injuries—what is new? Curr Opin Crit Care. 2007;13:674–9.
2. Nirula R, Diaz JJ, Trunkey DD, et al. Rib fracture repair: indications, technical issues, and future directions. World J Surg. 2009;33:14–22.
3. Lodhia JV, Konstantinidis K, Papagiannopoulos K. Surgical management of multiple rib fractures/flail chest. J Thorac Dis. 2019;11(4):1668–75.
4. Majeed FA, Zafar U, Imtiaz T, Ali Shah SZ, Ali A, Mehmood U. Rib fixation versus conservative management of rib fractures in trauma patients. J Ayub Med Coll Abbottabad. 2018;30(4):576–84.
5. de Campos JRM, White TW. Chest wall stabilization in trauma patients: why, when, and how? J Thorac Dis. 2018;10(8):951–62.
6. Voggenreiter G, Neudeck F, Aufmkolk M, Obertacke U, Schmit-Neuerburg KP. Operative chest wall stabilization in flail chest: outcomes of patients with or without pulmonary contusion. J Am Coll Surg. 1998;187:130–8.
7. Richardson JD, Adams L, Flint LM. Selective management of flail chest and pulmonary contusion. Ann Surg. 1982;196:481–7.
8. Lardinois D, Krueger T, Dusmett M, Ghisletta M, Gugger N, Ris HP. Pulmonary function testing after operative stabilization of the chest wall for flail chest. Eur J Cardiothorac Surg. 2001;20:496–501.
9. de Lesquen H, Avaro JP, Gust L, Ford RM, Beranger F, Natale C, Bonnet PM, D'Journo XB. Surgical management for the first 48 h following blunt chest trauma: state of the art (excluding vascular injuries). Interact Cardiovasc Thorac Surg. 2015;20(3):399–408.
10. Tanaka H, Yukioka T, Yamaguti Y, et al. Surgical stabilization or internal pneumatic stabilization? A prospective randomised study of management of severe flail chest patients. J Trauma. 2002;52:727–32.

11. Slobogean GP, MacPherson CA, Sun T, et al. Surgical fixation vs nonoperative management of flail chest: a meta-analysis. J Am Coll Surg. 2013;11(216):302–11.
12. Michelitsch C, Acklin YP, Hässig G, Sommer C, Furrer M. Operative stabilization of chest wall trauma: single-center report of initial management and long-term outcome. World J Surg. 2018;42(12):3918–26.
13. Molnar TF. Surgical management of chest wall trauma. Thorac Surg Clin. 2010;20(4):475–85.
14. He Z, Zhang D, Xiao H, Zhu Q, Xuan Y, Su K, Liao M, Tang Y, Xu E. The ideal methods for the management of rib fractures. J Thorac Dis. 2019;11(8):1078–89.
15. Ahmed Z, Mohyuddin Z. Management of flail chest injury: internal fixation versus endotracheal intubation and ventilation. J Thorac Cardiovasc Surg. 1995;110(6):1676–80.
16. Karev DV. Operative management of the flail chest. Wiad Lek. 1997;50(1):205–8.
17. Balci AE, Eren S, Cakir O, Eren MN. Open fixation in flail chest: review of 64 patients. Asian Cardiovasc Thorac Ann. 2004;12:11–5.
18. Granetzny A, Abd El-Aal M, Emam E, Shalaby A, Boseila A. Surgical versus conservative treatment of flail chest. Evaluation of the pulmonary status. Interact Cardiovasc Thorac Surg. 2005;4:583–7.
19. Nirula R, Allen B, Layman R, Falimirski ME, Somberg LB. Rib fracture stabilization in patients sustaining blunt chest injury. Am Surg. 2006;72:307–9.
20. Althausen PL, Shannon S, Watts C, Thomas K, Bain MA, Coll D, et al. Early surgical stabilization of flail chest with locked plate fixation. J Orthop Trauma. 2011;25:641–7.
21. Marasco SF, Davies AR, Cooper J, Varma D, Bennett V, Nevill R, et al. Prospective randomized controlled trial of operative rib fixation in traumatic flail chest. J Am Coll Surg. 2013;216:924–32.
22. Leinicke JA, Elmore L, Freeman BD, Colditz GA. Operative management of rib fractures in the setting of flail chest: a systematic review and meta-analysis. Ann Surg. 2013;258:14–21.

Epidural vs Regional Blocks for VATS and Thoracotomy

63

Dinesh J. Kurian and Husam Alghanem

Introduction

It is the duty of every physician to alleviate suffering when possible. Thoracic surgery has a high rate of acute pain, which may be attributed to surgical instrumentation of the skin, muscle, ribs, intercostal nerves, and pleura. Thoracotomies are known to have a high rate of conversion to chronic pain, and although exact mechanisms for this conversion are unclear, uncontrolled acute postoperative pain has been found to be a strong predictor [1]. Acute postoperative pain may delay recovery by leading to complications from splinting and hypoventilation, and may even be an independent risk factor for delirium in susceptible patients [2].

For these reasons, the Enhanced Recovery after Surgery (ERAS) Society and the European Society of Thoracic Surgeons have made a strong recommendation to use regional anesthesia for patients to facilitate an accelerated recovery [3]. The aim of this chapter is to help readers gain a greater sense of what options exist for patients undergoing thoracic surgery, whether via VATS or thoracotomy approach, and what level of evidence is available to support the use of each regional technique.

Search Strategy

Databases searched included PubMed, Cochrane, and Articles Plus. Primary search terms included the names of the regional techniques as well as "regional," "block," "thoracic," "thoracotomy," "thoracoscopic," "VATS," or "video-assisted" (Table 63.1). Filters used included "clinical trial," "randomized controlled trial," "meta-analysis," and "case report." An emphasis was placed on studies from the last

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Table 63.1 PICO formatted terms for literature search

P—Patient	I—Intervention	C—Comparator	O—Outcomes
Patients undergoing thoracic surgery	Thoracic Epidural Anesthesia (TEA) Paravertebral Block (PVB) Erector Spinae Plane block (ESP) Retrolaminar block (RLB) Serratus Anterior Plane Block (SAP) Intercostal nerve block (ICNB)	Sham block Patient controlled Analgesia (PCA) IV opioid Systemic analgesia Local anesthetic	Pain Chronic pain Morbidity Mortality Complications Length of stay (LOS) Cancer recurrence

20 years, but no absolute date cutoffs were used. For techniques that had greater volumes of published literature (thoracic epidurals and paravertebral blocks) case reports were generally excluded. Also, an emphasis was placed on clinical trials comparing regional techniques to other regional techniques or to non-regional techniques, as opposed to trials that compared medication mixtures, concentrations, or infusion rates within a single regional technique. Initial search results were 237 for thoracic epidural, 87 for paravertebral, and 86 for intercostal studies. Including case reports and proof-of-concept articles, the number of initial search results were 33 for serratus anterior, 15 for erector spinae, and 7 for retrolaminar studies. The references of relevant articles were also used as a source of additional articles. Approximately 85 total articles were tabulated and included.

Results

Direct Blockade of Spinal Roots: Neuraxial and Paraneuraxial Blocks

Thoracic Epidural for Analgesia (TEA)

Complications of TEA are rare. The most feared complication of TEA is neurologic injury, which may be as rare as 0.4% for upper thoracic epidural placements [4]. Neurologic injury may be caused by formation of an epidural hematoma in patients with impaired coagulation. Guidelines suggest avoiding performance of interventional spine procedures (including TEA) for patients on anticoagulants other than subcutaneous heparin, or agents that may impair platelet function other than NSAIDs [5]. Rates of infection are comparably rare; some patients may have urinary retention [4]. Although TEA causes sympathetic blockade, prospective randomized data has revealed that it does not interfere with the hypoxia pulmonary vasoconstriction reflex sufficiently to cause hypoxia during one-lung ventilation [6, 7].

Because epidural catheters have the potential to offer continuous analgesia, reduce systemic opioids, and promote better chest excursion, many consider it to be the gold standard of analgesia for thoracic surgery [8]. Some centers have included routine use of TEA for enhanced recovery protocols for VATS lobectomies because prospective randomized studies have demonstrated that when compared to PCA, TEA facilitated faster recovery of bowel function without increasing LOS [9]. Although the analgesic benefit of TEA for thoracotomy has been well established, it was found that patients undergoing VATS also have improved analgesia when compared to those who received no block [10]. Epidural analgesia has also been thought to reduce pulmonary complications by avoiding the respiratory depressant effects of narcotics, and allowing more complete chest wall excursion during spontaneous breathing [4]. This benefit has also been observed for lung transplant recipients, who were found to have reduced LOS and reduced ventilator time [11].

Perhaps one of the most interesting questions on the use of epidural anesthesia is whether it can have an impact on the rate of cancer recurrence after oncologic surgery. Although cancer biology is extremely complex, two factors associated with increased risk of cancer recurrence appear to be modulated: a reduction in opioids [12–14], and a reduction in adrenergic stimulation [15–17]. While a wealth of retrospective evidence on non-thoracic surgery suggests epidurals are associated with decreased risk of cancer recurrence [18–20], less data is available for thoracic surgery. Retrospective data for non-small cell lung cancer did not observe any association between use of TEA and improved 2-year, 3-year, or 5-year cancer free survival [21, 22]. For esophagectomy patients, however, a retrospective review of the Surveillance, Epidemiology, and End Results (SEER) Medicare database did find an association of improved 90-day and 5-year survival in patients receiving an epidural, even after adjusting for propensity to receive an epidural [23].

Another purported benefit of sympathetic blockade is the possibility of reducing the burden of tachyarrythmias, which are a known complication of thoracic surgery [24]. One small single center randomized trial observed that when compared to using epidural opioids alone, use of epidural local anesthetic was found to reduce the burden of tachyarrythmias (Table 63.2) [25].

Paravertebral Block (PVB)

Paravertebral catheters, sometimes alternatively referenced as extrapleural, subpleural, or retropleural catheters [26], have proven to be effective during VATS [27]. When compared to TEA for thoracotomy operations, several randomized controlled trials have observed that PVB catheters may offer equivalent analgesia to TEA catheters delivering local anesthetic [28] with fewer complications such as hypotension [29–31]. One major difference between TEA and PVB catheters is that TEA catheters provide an alternative avenue for targeted opioid administration. One systematic review found that TEA using both opioid and local anesthetic offered superior analgesia to PVB, but at the expense of side effects such as hypotension and urinary retention [32]. The higher incidence of hypotension and urinary retention appears to be a common theme found in other meta analyses and systematic reviews [33–36].

Table 63.2 Evidence for TEA in thoracic surgery

Proposed claim	Quality of evidence	Summary
Improved analgesia for VATS compared to any alternative block	Moderate	For patients who have long anticipated length of stay or complex pain management issues, an epidural may be optimal
Improved analgesia for thoracotomy	High	Patients undergoing a planned thoracotomy will benefit from an epidural unless contraindications are present
Reduction in opioid use	High	Patients who receive an epidural are very likely to require fewer systemic opioids
Reduced SVT burden	Moderate	TEA or PVB may reduce tachyarrhythmia burden
Improved survival for lung cancer	Moderate	Epidurals are unlikely to improve cancer-free survival for non-small cell lung cancer operations
Improved survival for esophageal cancer	Moderate	Epidurals may improve cancer-free survival for esophageal cancer operations

A Cochrane review comparing TEA and PVB for thoracic surgery was unable to detect any difference in reducing conversion to chronic pain for either technique [36].

For patients undergoing VATS operations, there are fewer randomized controlled studies to draw from. One systematic review of four small randomized controlled trials found that, similar to thoracotomy procedures, PVBs were found to have comparable analgesia to TEA with fewer adverse effects including hypotension and urinary retention [37].

Since PVB infusions do not contain opioid it is possible that they may reduce cancer recurrence. Most studies have not shown a difference between PVB and TEA in use of supplemental systemic opioid [36]. Although paravertebral blocks have not been observed to reduce cancer recurrence for lung surgery, one retrospective cohort study did observe that PVBs were associated with higher overall survival [38].

Although PVBs would only cause unilateral sympathetic blockade, one small randomized control trial found that patients receiving PVB had a lower incidence of SVTs (primarily atrial fibrillation) when compared to those randomized to receive intercostal nerve blocks (Table 63.3) [39].

Direct and Indirect Regional Block Techniques: Fascial Plane and Intercostal Nerve Blocks

Erector Spinae Plane (ESP) Block

Unlike the previously described blocks, the needle for ESP is placed remote to the nerves of interest, and spread of local anesthetic is by the effect of the volume within the fascial plane [40–42]. An ESP block can be performed using single shot or continuous catheter technique. Due to the relative novelty of this block, most

Table 63.3 Evidence for PVB in thoracic surgery

Proposed claim	Quality of evidence	Summary
Equivalent analgesia for VATS compared to TEA	High	For patients who have VATS operations with short expected LOS, PVB can offer equivalent analgesia to TEA
Equivalent analgesia for thoracotomy compared to TEA	High	Patients undergoing a planned thoracotomy will benefit from a PVB catheter in centers with sufficient technical expertise
Reduced hypotension compared to TEA	High	A PVB may be preferable to TEA to reduce hypotension
Reduced urinary retention compared to TEA	High	PVBs may be preferable to TEA to reduce urinary retention
Reduced LOS compared to TEA	Low	PVBs may reduce length of stay in patients who are not anticipated to have uncomplicated recovery

Table 63.4 Evidence for peripheral and fascial plane blocks

Proposed claim	Quality of evidence	Summary
Analgesia for VATS	Low	ESP and SAP blocks offer superior analgesia to no block
		Insufficient data currently exists to recommend ESP or SAP over PVB or TEA for VATS
	Moderate	ESP is likely superior to SAP or RLB for postoperative analgesia
Analgesia for thoracotomy	Low	ESP and SAP blocks offer superior analgesia to no block
		Insufficient data currently exists to recommend ESP or SAP over PVB or TEA for thoracotomy
Safety of performing in anticoagulated patient	Moderate	ESP, RLB, SAP, and ICNB blocks may be safe to perform in a patient who has impaired coagulation or platelet function
Liposomal vs standard bupivacaine for ICNB	Moderate	Liposomal bupivacaine may offer superior analgesia when compared to standard release bupivacaine for ICNB

available evidence consists of case reports, though some retrospective reviews and a few small single center prospective studies have been conducted (Table 63.4).

For VATS approaches for lung surgery, case reports describe analgesic benefit for the ESP block for indications varying from single port procedures for spontaneous pneumothorax ranging up to multi-port with utility window for lobectomy [43–46]. ESP blocks have also been used for rescue analgesia for VATS resection of extrapleural metastasis in a patient with a thymoma [47].

Only one prospective randomized trial of ESP blocks demonstrated lower Visual Analogue Scale (VAS) scores as well as significantly lower opioid consumption in the patients who received an ESP block compared to those who received no block, as well as additional benefits such as reduced pruritus and less

nausea, presumably resulting from the lower opioid consumption [48]. The limitations are that this was conducted as a single center trial consisting of 60 patients, and was limited to patients of American Society of Anesthesiology (ASA) physical status classification 1–2, ages 18–65, and no blinding (or sham block) was performed.

For thoracotomy approaches for lung surgery, ESP blocks have been reported to offer analgesic benefit to a pediatric patient using an ESP catheter [49], and lung transplant recipient [50]. ESP blocks have also been reportedly used for rescue analgesia for a failed epidural in a patient who underwent a lobectomy via thoracotomy incision [51]. One patient underwent an open esophagectomy for esophageal cancer with three ESP catheters, a strategy which reportedly offered good thoracic analgesia despite inadequate epigastric analgesia [52].

When pooling many of these case reports, ESP blocks (single shot or continuous catheter technique) seem to be effective in reducing opioids in 76% of patients who receive the block [53]. It appears to have a good safety profile, and has been performed in patients on dual antiplatelet therapy [54]. Only one published case report of pneumothorax has been published [55].

Some prospective randomized data exists for patients undergoing other procedures on the thorax. One study in 42 mastectomy patients compared ESP single-shot blocks using two different concentrations of bupivacaine (0.375% vs 0.25%) and found that the higher concentration provided superior analgesia with lower tramadol use [56]. Another study of 106 sternotomy cardiac surgery patients (indications including CAD, ASD, and mitral disease) found that patients receiving single shot ESP blocks had improved analgesia compared to only multimodal analgesia without regional technique, and that the requirement for rescue analgesia was lower within the first 8 h. Additionally, they noted reduced time on the ventilator, reduced time to ambulation, reduced time to first oral intake, and reduced ICU length of stay [57].

Retrolaminar Block (RLB)

The technique was first described to provide analgesia for breast surgery [58]. As with the ESP block, the proposed mechanism of analgesia is spread into the epidural and paravertebral space [59]. There is a severe paucity of high-quality evidence on the use of RLB for thoracic surgery. A case series described continuous RLB for analgesia after rib fractures, and this technique may lead to improvements in analgesia without complications [60]. One letter to the editor described use of an RLB for a lobectomy (incision type unspecified) for a patient with spontaneous hemopneumothorax [61]. One review article on the limited available data suggests that although RLB and ESP injections share a common fascial plane, RLB blocks may be better targeted to cover dorsal rami of the spinal roots, whereas ESP injections are more likely to offer lateral spread for a wider range of analgesia over the hemithorax [62].

Serratus Anterior Plane (SAP) Block

First described in 2013, the SAP block was originally used for breast surgery [63]. The SAP block is thought to achieve this effect via spread to the intercostal nerves (most commonly T2–T6 with some variability), the long thoracic, and thoracodorsal nerves. For this reason, the integrity of the facial plane is essential to the success of the block, and all included studies evaluated the effect of the block being performed pre-incision.

For patients undergoing VATS approaches to lung surgery, some single-center prospective randomized data exists. When compared to PCA with Tramadol, patients randomized to receive SAP blocks for VATS operations were found to have lower VAS scores and lower tramadol use within the first 24 h [64]. This finding was concordant with a later prospective randomized study evaluating patients who underwent SAP vs sham block who underwent VATS wedge resections, segmentectomies, or lobectomies—patients receiving the real block had lower pain scores and opioid use with better QoR-40 scores [65]. For patients undergoing VATS lobectomy, those randomized to receive the block were found to have lower requirements for intraoperative opioids, better hemodynamic stability, and faster emergence time [66] though the generalizability of these findings may be limited by the anesthetic plan used. Another prospective randomized study in patients who had thoracoscopic procedures found that patients receiving the SAP block had lower VAS scores and a lower probability of finding "dissatisfaction" with their analgesia [67].

One single center prospective randomized trial of 60 patients compared SAP to ESP blocks for patients undergoing VATS operations (including wedge resections, decortications, bullectomy, biopsy, pleurodesis, and diaphragmatic plication). Patients receiving the ESP block were found to have better analgesia and a longer interval before requiring their first supplemental analgesic compared to patients receiving SAP block [68].

Two prospective randomized studies describe use of the SAP for patients undergoing thoracotomy approaches to surgery. One single center study compared the SAP bolus plus catheter to patients receiving TEA for lobectomy, pneumonectomy, pleuropneumonectomy, or metastasectomy via thoracotomy and found that patients in the SAP cohort had comparable analgesia up to the 14 h mark postoperatively, comparable morphine consumption, and lower instances of hypotension [69]. The primary limitations of this study include enrollment limited to only 40 ASA physical status II and III patients, with exclusion criteria for patients with chronic pain and those requiring post-op ventilation. Another prospective study of 90 patients randomized subjects to one of three arms—single shot SAP, single shot PVB, or no block—prior to lobectomy via thoracotomy for lung cancer surgery. Within the first 12 h, patients receiving any block had superior analgesia to those who had not received any block, though after 12 h the PVB cohort had better analgesia compared to the other two cohorts [70].

Surgically Placed Intercostal Nerve Blocks (ICNB)

Intercostal nerve blocks are thought to provide direct blockade of intercostal nerves to blunt pain signaling along the ribs that are subjected to surgical trauma during any operation. Some of the initial publications of surgically placed ICNBs involved placement of the block in the posterior aspect of the thoracic cavity, which was thought to spread (intentionally) to the paravertebral space [71]. Other examples of ICNB in the era of VATS was to place hypodermic needles under thoracoscopic guidance to deposit local anesthetic into the intercostal space [72]. Differences in technique, as well as number of levels blocked, may contribute to the heterogeneity of data.

For patients undergoing VATS operations, some recent studies have focused on comparing effect of ICNB to alternative blocks, and several have focused on comparing liposomal bupivacaine (LB) with epinephrine compared to non-liposomal bupivacaine with epinephrine.

One recent retrospective study of 108 patients compared a 5-level posterior ICNB vs TEA for a mixed surgical population undergoing VATS, robotic-assisted thoracoscopic surgery (RATS), and thoracotomy approaches to lobectomy and sublobectomy operations. The investigators reportedly found no difference in analgesia between groups, but noted that patients in the ICNB group had, on average, a shorter LOS by 1 day [73]. It is possible that by performing a posterior ICNB, the investigators may have successfully achieved spread into the paravertebral space. One single-center prospective randomized trial of PVB vs 2-level ICNB for VATS lung surgery (pneumonectomy, bilobectomy, lobectomy, wedge resection) found that patients in both groups had comparable analgesia, although the ICNB cohort had a statistically significantly higher burden of SVT, primarily atrial fibrillation [39]. It is possible that although ICNBs achieve some spread to the paravertebral space, the degree of sympathetic blockade may be more complete when performing a PVB.

Three retrospective studies compared liposomal vs standard release bupivacaine. Two of the three found lower opioid requirements in the LB group [74, 75], while the remaining study found no difference [76]. The latter study did find an advantage in lower length of stay and faster time to ambulation in the LB cohort [76]. When compared to TEA, one retrospective single-center study noted that patients receiving LB had lower pain scores and lower cost of medical therapy [72].

For patients undergoing thoracotomy, two prospective randomized trials compared 5-level ICNB to TEA. The first found no major difference in analgesia [77]. The more recent and larger study found comparable analgesia at rest, but that TEA improved pain control when clearing airway secretions and resulted in better post-op spirometry [78].

One prospective-randomized trial assessed the potential for ICNB to provide preventative analgesia, given the high rate of postoperative thoracotomy pain to convert to chronic pain. The investigators randomized patients in 2 × 2 fashion to one of four arms—pre-op vs post-op ICNB, and dextromethorphan vs placebo. They noted a statistically (though perhaps not clinically) significant reduction in morphine consumption in the cohort receiving dextromethorphan and pre-op ICNB [8].

Conclusions and Recommendations

While neuraxial and paraneuraxial techniques have over a century of proven success, some of the newer fascial plane techniques offer promising alternatives for patients who have contraindications to epidurals or paravertebrals for postoperative analgesia. Epidurals and paravertebral catheters would be the preferred choice in any patient who could benefit from sustained analgesia over a multiple days of inpatient recovery. For operations with shorter anticipated recovery, single shot paravertebral blocks are supported with higher quality evidence. For patients in whom paravertebrals cannot safely be performed, ESP blocks are likely to be safe and may be more effective than SAP or RLB injections though further high quality studies are necessary.

Despite the very encouraging findings, enthusiasm should be tempered by the paucity of high quality data that offers head-to-head comparison of ESP or SAP blocks versus well established blocks such as PVBs or TEA. An ESP or SAP block may be well suited for any patient with contraindications to TEA or PVB such as neuraxial precautions. ESPs have safely been done in patients being anticoagulated for cardiopulmonary bypass. ESP blocks may be superior to SAP blocks and are very likely superior to RLB blocks for thoracic wall pain. ESPs may be a safer choice in patients with anatomic derangements that preclude safe performance of a TEA or PVB. It may also be an appropriate choice as a rescue block for patients in whom the first attempt has failed.

Recommendations

- We recommend use of thoracic epidural analgesia for patients undergoing thoracotomy who have a long anticipated length of stay or complex pain management issues (evidence quality moderate, strong recommendation).
- We recommend use of a paravertebral block in patients who are undergoing VATS procedures or thoracotomy with expected short length of stay (evidence quality high, strong recommendation).
- We recommend peripheral or fascial plane blocks in any patient undergoing thoracic surgery who is not receiving a thoracic epidural catheter or a paravertebral block (evidence quality moderate, strong recommendation).

A Personal View of the Data

For patients with favorable anatomy without contraindications undergoing common VATS lung resections, I offer single shot paravertebral blocks. I discuss potential benefit of epidural catheters in any patient I suspect may have a complex recovery plan or in which there is a heightened desire to reduce opioids. For patients in whom I do not feel I can safely perform a paravertebrals, I offer single shot erector spinae blocks.

References

1. Blichfeldt-Eckhardt MR, Andersen C, Ørding H, Licht PB, Toft P. From acute to chronic pain after thoracic surgery: the significance of different components of the acute pain response. J Pain Res. 2018;11:1541–8.
2. Feast AR, White N, Lord K, Kupeli N, Vickerstaff V, Sampson EL. Pain and delirium in people with dementia in the acute general hospital setting. Age Ageing. 2018;47(6):841–6.
3. Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg. 2019;55(1):91–115.
4. Manion SC, Brennan TJ. Thoracic epidural analgesia and acute pain management. Anesthesiology. 2011;115(1):181–8.
5. Narouze S, Benzon HT, Provenzano DA, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. Reg Anesth Pain Med. 2015;40(3):182–212.
6. Casati A, Mascotto G, Iemi K, Nzepa-Batonga J, De Luca M. Epidural block does not worsen oxygenation during one-lung ventilation for lung resections under isoflurane/nitrous oxide anaesthesia. Eur J Anaesthesiol. 2005;22(5):363–8.
7. Jung SM, Cho CK, Kim YJ, et al. The effect of thoracic epidural anesthesia on pulmonary shunt fraction and arterial oxygenation during one-lung ventilation. J Cardiothorac Vasc Anesth. 2010;24(3):456–62.
8. Nosotti M, Rosso L, Tosi D, et al. Preventive analgesia in thoracic surgery: controlled, randomized, double-blinded study. Eur J Cardiothorac Surg. 2014;48(3):428–34.
9. Zejun N, Wei F, Lin L, He D, Haichen C. Improvement of recovery parameters using patient-controlled epidural analgesia for video-assisted thoracoscopic surgery lobectomy in enhanced recovery after surgery: a prospective, randomized single center study. Thorac Cancer. 2018;9(9):1174–9.
10. Yoshioka M, Mori T, Kobayashi H, et al. The efficacy of epidural analgesia after video-assisted thoracoscopic surgery: a randomized control study. Ann Thorac Cardiovasc Surg. 2006;12(5):313–8.
11. McLean SR, von Homeyer P, Cheng A, et al. Assessing the benefits of preoperative thoracic epidural placement for lung transplantation. J Cardiothorac Vasc Anesth. 2018;32(6):2654–61.
12. Mathew B, Lennon FE, Siegler J, et al. The novel role of the mu opioid receptor in lung cancer progression: a laboratory investigation. Anesth Analg. 2011;112(3):558–67.
13. Singleton PA, Moss J, Karp DD, Atkins JT, Janku F. The mu opioid receptor: a new target for cancer therapy? Cancer. 2015;121(16):2681–8.
14. Gupta K, Kshirsagar S, Chang L, et al. Morphine stimulates angiogenesis by activating pro-angiogenic and survival-promoting signaling and promotes breast tumor growth. Cancer Res. 2002;62(15):4491–8.
15. Choi CH, Song T, Kim TH, et al. Meta-analysis of the effects of beta blocker on survival time in cancer patients. J Cancer Res Clin Oncol. 2014;140(7):1179–88.
16. Benish M, Bartal I, Goldfarb Y, et al. Perioperative use of beta-blockers and COX-2 inhibitors may improve immune competence and reduce the risk of tumor metastasis. Ann Surg Oncol. 2008;15(7):2042–52.
17. Braadland PR, Ramberg H, Grytli HH, Taskén KA. β-Adrenergic receptor signaling in prostate cancer. Front Oncol. 2014;4(24):375.
18. Chen W-K, Miao C-H. The effect of anesthetic technique on survival in human cancers: a meta-analysis of retrospective and prospective studies. PLoS One. 2013;8(2):e56540.

19. Sun Y, Li T, Gan TJ. The effects of perioperative regional anesthesia and analgesia on cancer recurrence and survival after oncology surgery: a systematic review and meta-analysis. Reg Anesth Pain Med. 2015;40(5):589–98.
20. Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth. 2010;105(2):106–15.
21. Cata JP, Gottumukkala V, Thakar D, Keerty D, Gebhardt R, Liu DD. Effects of postoperative epidural analgesia on recurrence-free and overall survival in patients with nonsmall cell lung cancer. J Clin Anesth. 2014;26(1):3–17.
22. Wu H-L, Tai Y-H, Chan M-Y, Tsou M-Y, Chen H-H, Chang K-Y. Effects of epidural analgesia on cancer recurrence and long-term mortality in patients after non-small-cell lung cancer resection: a propensity score-matched study. BMJ Open. 2019;9(5):e027618.
23. Cummings KC III, Kou TD, Chak A, et al. Surgical approach and the impact of epidural analgesia on survival after esophagectomy for cancer: a population-based retrospective cohort study. PLoS One. 2019;14(1):e0211125.
24. Muehlschlegel JD, Burrage PS, Ngai JY, et al. Society of Cardiovascular Anesthesiologists/ European Association of Cardiothoracic Anaesthetists Practice Advisory for the Management of Perioperative Atrial Fibrillation in patients undergoing cardiac surgery. Anesth Analg. 2019;128(1):33–42.
25. Oka T, Ozawa Y, Ohkubo Y. Thoracic epidural bupivacaine attenuates supraventricular tachyarrhythmias after pulmonary resection. Anesth Analg. 2001;93(2):253–9.
26. Piraccini E, Pretto EA, Corso RM, Gambale G. Analgesia for thoracic surgery: the role of paravertebral block. HSR Proc Intensive Care Cardiovasc Anesth. 2011;3(3):157–60.
27. Detterbeck FC. Efficacy of methods of intercostal nerve blockade for pain relief after thoracotomy. Ann Thorac Surg. 2005;80(4):1550–9.
28. Wojtyś ME, Wąsikowski J, Wójcik N, et al. Assessment of postoperative pain management and comparison of effectiveness of pain relief treatment involving paravertebral block and thoracic epidural analgesia in patients undergoing posterolateral thoracotomy. J Cardiothorac Surg. 2019;14(1):1–11.
29. Gulbahar G, Kocer B, Muratli SN, et al. A comparison of epidural and paravertebral catheterisation techniques in post-thoracotomy pain management. Eur J Cardiothorac Surg. 2010;37(2):467–72.
30. Casati A, Alessandrini P, Nuzzi M, et al. A prospective, randomized, blinded comparison between continuous thoracic paravertebral and epidural infusion of 0.2% ropivacaine after lung resection surgery. Eur J Anaesthesiol. 2006;23(12):999–1004.
31. Kaiser AM, Zollinger A, De Lorenzi D, Largiadèr F, Weder W. Prospective, randomized comparison of extrapleural versus epidural analgesia for postthoracotomy pain. Ann Thorac Surg. 1998;66(2):367–72.
32. Scarci M, Joshi A, Attia R. In patients undergoing thoracic surgery is paravertebral block as effective as epidural analgesia for pain management? Interact Cardiovasc Thorac Surg. 2010;10(1):92–6.
33. Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy—a systematic review and meta-analysis of randomized trials. Br J Anaesth. 2006;96(4):418–26.
34. Joshi GP, Bonnet F, Shah R, et al. A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. Anesth Analg. 2008;107(3):1026–40.
35. Baidya DK, Khanna P, Maitra S. Analgesic efficacy and safety of thoracic paravertebral and epidural analgesia for thoracic surgery: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg. 2014;18(5):626–35.
36. Yeung JHY, Gates S, Naidu BV, Wilson MJA, Gao Smith F. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. Cochrane Database Syst Rev. 2016;2:CD009121.
37. Harky A, Clarke CG, Kar A, Bashir M. Epidural analgesia versus paravertebral block in video-assisted thoracoscopic surgery. Interact Cardiovasc Thorac Surg. 2019;28(3):404–6.

38. Lee EK, Ahn HJ, Zo JI, Kim K, Jung DM, Park JH. Paravertebral block does not reduce cancer recurrence, but is related to higher overall survival in lung cancer surgery: a retrospective cohort study. Anesth Analg. 2017;125(4):1322–8.
39. Wu C, Ma W, Cen Q, Cai Q, Wang J, Cao Y. A comparison of the incidence of supraventricular arrhythmias between thoracic paravertebral and intercostal nerve blocks in patients undergoing thoracoscopic surgery: a randomised trial. Eur J Anaesthesiol. 2018;35(10):792–8.
40. Forero M, Adhikary SD, Lopez H, Tsui C, Chin KJ. The erector spinae plane block: a novel analgesic technique in thoracic neuropathic pain. Reg Anesth Pain Med. 2016;41(5):621–7.
41. Sabouri AS, Crawford L, Bick SK, Nozari A, Anderson TA. Is a retrolaminar approach to the thoracic paravertebral space possible? A human cadaveric study. Reg Anesth Pain Med. 2018;43(8):864–8.
42. Adhikary SD, Bernard S, Lopez H, Chin KJ. Erector spinae plane block versus retrolaminar block: a magnetic resonance imaging and anatomical study. Reg Anesth Pain Med. 2018;43(7):756–62.
43. Luis-Navarro JC, Seda-Guzmán M, Luis-Moreno C, López-Romero JL. The erector spinae plane block in 4 cases of video-assisted thoracic surgery. Rev Esp Anestesiol Reanim. 2018;65(4):204–8.
44. Hu B, Zhou H, Zou X. The erector spinae plane block (ESPB) for non-intubated video-assisted thoracoscopic surgery. J Clin Anesth. 2019;54:50–1.
45. Adhikary SD, Pruett A, Forero M, Thiruvenkatarajan V. Erector spinae plane block as an alternative to epidural analgesia for post-operative analgesia following video-assisted thoracoscopic surgery: a case study and a literature review on the spread of local anaesthetic in the erector spinae plane. Indian J Anaesth. 2018;62(1):75–8.
46. Bang S, Chung K, Chung J, Yoo S, Baek S, Lee SM. The erector spinae plane block for effective analgesia after lung lobectomy. Medicine. 2019;98(29):e16262–4.
47. Wilson JM, Lohser J, Klaibert B. Erector spinae plane block for postoperative rescue analgesia in thoracoscopic surgery. J Cardiothorac Vasc Anesth. 2018;32(6):e5–7.
48. Ciftci B, Ekinci M, Çelik EC, Tukac IC, Bayrak Y, Atalay YO. Efficacy of an ultrasound-guided erector spinae plane block for postoperative analgesia management after video-assisted thoracic surgery: a prospective randomized study. J Cardiothorac Vasc Anesth. 2020;34(2):444–9.
49. Patel NV, Glover C, Adler AC. Erector spinae plane catheter for postoperative analgesia after thoracotomy in a pediatric patient: a case report. A A Pract. 2019;12(9):299–301.
50. Kelava M, Anthony D, Elsharkawy H. Continuous erector spinae block for postoperative analgesia after thoracotomy in a lung transplant recipient. J Cardiothorac Vasc Anesth. 2018;32(5):e9–e11.
51. Raft J, Chin KJ, Belanger M-E, Clairoux A, Richebé P, Brulotte V. Continuous erector spinae plane block for thoracotomy analgesia after epidural failure. J Clin Anesth. 2019;54:132–3.
52. De Cassai A, Tonetti T, Galligioni H, Ori C. Erector spinae plane block as a multiple catheter technique for open esophagectomy: a case report. Rev Bras Anestesiol. 2019;69(1):95–8.
53. Tsui BCH, Fonseca A, Munshey F, McFadyen G, Caruso TJ. The erector spinae plane (ESP) block. A pooled review of 242 cases. J Clin Anesth. 2019;53:29–34.
54. Smith CA, Martin KM. Dual antiplatelet therapy does not scare away the erector spinae plane block. Korean J Anesthesiol. 2019;72(3):277–8.
55. Ueshima H. Pneumothorax after the erector spinae plane block. J Clin Anesth. 2018;48:12.
56. Altıparmak B, Korkmaz Toker M, Uysal Aİ, Gümüş Demirbilek S. Comparison of the efficacy of erector spinae plane block performed with different concentrations of bupivacaine on postoperative analgesia after mastectomy surgery: ramdomized, prospective, double blinded trial. BMC Anesthesiol. 2019;19(1):31–9.
57. Krishna SN, Chauhan S, Bhoi D, et al. Bilateral erector spinae plane block for acute postsurgical pain in adult cardiac surgical patients: a randomized controlled trial. J Cardiothorac Vasc Anesth. 2019;33(2):368–75.

58. Jüttner T, Werdehausen R, Hermanns H, et al. The paravertebral lamina technique: a new regional anesthesia approach for breast surgery. J Clin Anesth. 2011;23(6):443–50.
59. Yang HM, Choi YJ, Kwon HJ, O J, Cho TH, Kim SH. Comparison of injectate spread and nerve involvement between retrolaminar and erector spinae plane blocks in the thoracic region: a cadaveric study. Anaesthesia. 2018;73(10):1244–50.
60. Voscopoulos C, Palaniappan D, Zeballos J, Ko H, Janfaza D, Vlassakov K. The ultrasound-guided retrolaminar block. Can J Anaesth. 2013;60(9):888–95.
61. Nagane D, Ueshima H, Otake H. Upper lobectomy of the left lung using a left retrolaminar block. J Clin Anesth. 2018;49:74.
62. Onishi E, Toda N, Kameyama Y, Yamauchi M. Comparison of clinical efficacy and anatomical investigation between retrolaminar block and erector spinae plane block. Biomed Res Int. 2019;2019(9):1–8.
63. Blanco R, Parras T, McDonnell JG, Prats-Galino A. Serratus plane block: a novel ultrasound-guided thoracic wall nerve block. Anaesthesia. 2013;68(11):1107–13.
64. Ökmen K, Metin Ökmen B. Evaluation of the effect of serratus anterior plane block for pain treatment after video-assisted thoracoscopic surgery. Anaesth Crit Care Pain Med. 2018;37(4):349–53.
65. Kim D-H, Oh YJ, Lee JG, Ha D, Chang YJ, Kwak HJ. Efficacy of ultrasound-guided serratus plane block on postoperative quality of recovery and analgesia after video-assisted thoracic surgery: a randomized, triple-blind, placebo-controlled study. Anesth Analg. 2018;126(4):1353–61.
66. Lee J, Kim S. The effects of ultrasound-guided serratus plane block, in combination with general anesthesia, on intraoperative opioid consumption, emergence time, and hemodynamic stability during video-assisted thoracoscopic lobectomy: a randomized prospective study. Medicine. 2019;98(18):e15385.
67. Park MH, Kim JA, Ahn HJ, Yang MK, Son HJ, Seong BG. A randomised trial of serratus anterior plane block for analgesia after thoracoscopic surgery. Anaesthesia. 2018;73(10):1260–4.
68. Gaballah KM, Soltan WA, Bahgat NM. Ultrasound-guided serratus plane block versus erector spinae block for postoperative analgesia after video-assisted thoracoscopy: a pilot randomized controlled trial. J Cardiothorac Vasc Anesth. 2019;33(7):1946–53.
69. Khalil AE, Abdallah NM, Bashandy GM, Kaddah TA-H. Ultrasound-guided serratus anterior plane block versus thoracic epidural analgesia for thoracotomy pain. J Cardiothorac Vasc Anesth. 2017;31(1):152–8.
70. Saad FS, El Baradie SY, Abdel Aliem MAW, Ali MM, Kotb TAM. Ultrasound-guided serratus anterior plane block versus thoracic paravertebral block for perioperative analgesia in thoracotomy. Saudi J Anaesth. 2018;12(4):565–70.
71. Sabanathan S, Richardson J, Shah R. 1988: Continuous intercostal nerve block for pain relief after thoracotomy. Updated in 1995. Ann Thorac Surg. 1995;59(5):1261–3.
72. Medina M, Foiles SR, Francois M, et al. Comparison of cost and outcomes in patients receiving thoracic epidural versus liposomal bupivacaine for video-assisted thoracoscopic pulmonary resection. Am J Surg. 2019;217(3):520–4.
73. Rice DC, Cata JP, Mena GE, Rodriguez-Restrepo A, Correa AM, Mehran RJ. Posterior intercostal nerve block with liposomal bupivacaine: an alternative to thoracic epidural analgesia. Ann Thorac Surg. 2015;99(6):1953–60.
74. Parascandola SA, Ibañez J, Keir G, et al. Liposomal bupivacaine versus bupivacaine/epinephrine after video-assisted thoracoscopic wedge resection. Interact Cardiovasc Thorac Surg. 2017;24(6):925–30.
75. Kelley TM, Bailey DW, Sparks P, et al. Intercostal nerve blockade with Exparel® results in lower opioid usage during the first 24 hours after video-assisted thorascopic surgery. Am Surg. 2018;84(9):1433–8.
76. Dominguez DA, Ely S, Bach C, Lee T, Velotta JB. Impact of intercostal nerve blocks using liposomal versus standard bupivacaine on length of stay in minimally invasive thoracic surgery patients. J Thorac Dis. 2018;10(12):6873–9.

77. Concha M, Dagnino J, Cariaga M, Aguilera J, Aparicio R, Guerrero M. Analgesia after thoracotomy: epidural fentanyl/bupivacaine compared with intercostal nerve block plus intravenous morphine. J Cardiothorac Vasc Anesth. 2004;18(3):322–6.
78. Meierhenrich R, Hock D, Kühn S, et al. Analgesia and pulmonary function after lung surgery: is a single intercostal nerve block plus patient-controlled intravenous morphine as effective as patient-controlled epidural anaesthesia? A randomized non-inferiority clinical trial. Br J Anaesth. 2011;106(4):580–9.

The Nuss Procedure Versus the Modified Ravitch Repair for Pectus Excavatum in Adults

64

Daniel P. Raymond

Introduction

Although a relatively common congenital deformity affecting one in every 300–400 white male births [1], controversy surrounds many aspects of surgical management of pectus excavatum. Surgical correction was introduced by Ravitch in 1949 [2]. Although modified significantly, this was the procedure of choice until Nuss [3] introduced a minimally invasive alternative to the Ravitch procedure (RP) which offered smaller incisions, less dissection, and no cartilage removal or osteotomy: the Nuss procedure (NP). The NP has grown in popularity, yet questions remain regarding its relative efficacy in comparison to the RP. To date, no randomized trial has been performed to compare the two procedures. Moreover, there is little agreement in the literature regarding the actual goals of the operation. Is it to provide cosmesis or to improve cardiopulmonary function? In the pediatric population, repair for cosmetic purposes is widely practiced due to the potential benefit for psychosocial development [4]. In the adult population, this benefit is less profound and thus a physiologic improvement is desirable but a well-accepted objective measure remains elusive.

Search Strategy

Searches were performed utilizing Ovid MEDLINE™, PUBMED and the Cochrane Library with data abstracted from 2000 to 2019 in English language journals. Search terms utilized included pectus excavatum, Nuss, Ravitch, funnel chest and chest

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wall deformity (Table 64.1). Reference lists from all extracted articles were further reviewed to extract additional publications and obtain additional search terms.

Results

The current literature comparing the Nuss and Ravitch procedures is dominated by single center, retrospective series that often are relatively small. As a result, the most robust data comes from several meta-analyses that have been performed and are listed in Table 64.2. One must be careful in interpretating these reports as there is significant overlap in the studies and thus we must not over-inflate the conclusions. Nasr et al. [5] in 2010 evaluated nine studies, none of which was randomized, eight

Table 64.1 PICO formatted terms for literature search

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Adults with pectus excavatum	Nuss bar	Ravitch procedure	Functional benefits Cosmesis Costs Quality of life

Table 64.2 Metaanalyses of outcomes after surgical treatment for pectus excavatum

Author	Year	Population	Number of studies	Findings	Quality of evidence
Nasr et al. [5]	2010	Children and adults	9	Complication rates similar Reoperation rates higher for Nuss bar ($p = 0.001$) Postoperative pneumothorax ($p = 0.009$) and hemothorax more common after Nuss ($p = 0.05$) Duration of operation longer for Ravitch ($p = 0.05$) Postoperative length of stay similar Patient satisfaction similar	Low
Kangaratnam et al. [6]	2016	Adults	13	Higher complication rate after Nuss bar ($p = 0.05$) Higher rate of bar displacement after Nuss ($p = 0.02$) Higher rate of reoperations after Nuss ($p = 0.02$)	Low
Mao et al. [7]	2017	Children and adults	19	Shorter operating time with Nuss bar ($p < 0.001$) Less blood loss with Nuss bar ($p < 0.001$) Postoperative length of stay similar	Low

were retrospective, and no studies were excluded. Age was not reported. Ultimately, the study concluded that no significant differences could be identified between the two procedures with respect to overall complication rates or length of stay (LOS). They did note the Ravitch procedure was associated with a longer operating time (weighted mean difference [WMD] = 69.94 min ($p = 0.05$)). Furthermore, the rate of reoperation for bar migration or persistent deformity was higher in the Nuss group (OR 5.68 (2.51–12.85); $p = 0.0001$).

In 2016, Kangaratnam et al. [6] published a meta-analysis including the nine studies utilized by Nasr et al. [5], and added four additional studies: an older study by Nuss et al. [3] and three more contemporary studies. It included adult and pediatric patients and provided a clear description of the study selection process. Consistent with Nasr et al. [5], they demonstrated the Ravitch procedure took longer to perform but the length of stay and overall complication rates were not significantly different. Furthermore, subgroup analysis of complications was performed based on age. In the adult population, there was a significantly lower rate of early complications (occurring within 1 month of the procedure) in the Ravitch group (OR = 3.26; 95% CI: 1.01–10.46; $p = 0.05$). Likely a major contributor was the incidence of bar displacement in the Nuss patients (OR 7.1; 95% CI 1.37–36.52; $p = 0.02$). Not surprisingly, therefore, the adult Ravitch group had a lower rate of reoperation.

Mao et al. [7] produced an updated meta-analysis which included the majority of the manuscripts reviewed by Nasr et al. [5] and Kangaratnam et al. [6] with the addition of nine more contemporary studies, many from the Chinese literature. This included three labelled "randomized" trials, however at least one of them was not. Similar to their predecessors, they demonstrated that the operating time for the Nuss procedure was shorter by 77 min on average. They further demonstrated lower blood loss in the Nuss group by an average of 51 mL ($p < 0.001$) but found no difference in LOS. Notably, however, they found that, with the exclusion a the study by Fonkalsrud et al. [8], the LOS was shorter in the Nuss patients.

Malek and colleagues [1, 9] produced two additional meta-analyses evaluating pulmonary function and cardiovascular function following pectus excavatum repair in a mixed population. They noted no statistically significant differences in postoperative pulmonary function between the surgical groups. A similar analysis of surgical subgroups was not provided for the cardiovascular evaluation.

Looking specifically at perioperative pain, Papic and colleagues [10] performed a retrospective evaluation of 181 patients undergoing pectus excavatum repair at a single institution. The Ravitch patients were older (15.7 years vs. 14.6 years; $p = 0.004$) and had more severe Haller scores (5.2 vs. 4.1; $p < 0.001$). Nuss patients had higher average daily pain scores and received 25% more opioids ($p < 0.001$) than the Ravitch patients. In a multivariate analysis used to control for several variables including age, benzodiazepine use, and nonnarcotic pain medication use, the Nuss procedure remained a statistically significant predictor of greater narcotic use ($p = 0.002$). Further analysis suggested that narcotic consumption was especially high in the adult Nuss population.

Conclusions and Recommendations

Presently, satisfactory evidence does not exist to conclude that the Nuss or modified Ravitch procedure is superior in the adult population. There are certain themes in the literature that can be conveyed to patients when counseling regarding procedure choice. These include: the Ravitch procedure takes longer to perform; blood loss is higher with the Ravitch procedure although the relative loss for both procedures is low; complication rates in adults are higher after the Nuss procedure, primarily due to bar displacement; and the Nuss procedure is associated with greater postoperative pain.

Recommendation

- Both the Nuss procedure and the modified Ravitch procedure are recommended for correction of pectus excavatum deformities in appropriately selected adult patients (evidence quality low; weak recommendation).

A Personal View of the Data

Surgical repair of pectus excavatum in adults is a rare procedure. As a result, there is limited available data to evaluate the relative benefits of either the Nuss or Ravitch procedure. Although we may extrapolate from the pediatric population, there are fundamental differences which make this problematic. First, the indication in the pediatric population is psychosocial developmental reasons based on the presence of the defect. As a result, there has been lack of identification of objective physiologic measurements to determine efficacy, which would be of significant value in the adult population. Secondly, chest wall compliance declines with age [11]. It has been suggested that this difference in compliance and growth plate closure may explain some of the findings in the adult population such as an increased rate of bar displacement and pain associated with the Nuss procedure. An additional challenge in the adult population is the question of conditioning. It has been the author's impression that the patients who benefit most from correction are those who participate in a regular exercise program preoperatively and resume participation in that program postoperatively as quickly as possible. Deconditioning postoperatively could potentially be an effective means of negating any potential benefits of surgical correction of pectus excavatum.

Given the lack of clear superiority of one procedure, the ideal approach is to offer both and counsel the patient regarding the strengths and weaknesses of both approaches. This requires mastery of both procedures, which lends itself to a surgical team approach, especially given the relative rarity of the procedure.

References

1. Malek MH, Berger DE, Marelich WD, Coburn JW, Beck TW, Housh TJ. Pulmonary function following surgical repair of pectus excavatum: a meta-analysis. Eur J Cardiothorac Surg. 2006;30(4):637–43.
2. Ravitch MM. The operative treatment of pectus excavatum. Ann Surg. 1949;129(4):429–44.
3. Nuss D, Kelly RE Jr, Croitoru DP, Katz ME. A 10-year review of a minimally invasive technique for the correction of pectus excavatum. J Pediatr Surg. 1998;33(4):545–52.
4. Kelly RE Jr, Cash TF, Shamberger RC, Mitchell KK, Mellins RB, Lawson ML, Oldham K, Azizkhan RG, Hebra AV, Nuss D, Goretsky MJ, Sharp RJ, Holcomb GW 3rd, Shim WK, Megison SM, Moss RL, Fecteau AH, Colombani PM, Bagley T, Quinn A, Moskowitz AB. Surgical repair of pectus excavatum markedly improves body image and perceived ability for physical activity: multicenter study. Pediatrics. 2008;122(6):1218–22.
5. Nasr A, Fecteau A, Wales PW. Comparison of the Nuss and the Ravitch procedure for pectus excavatum repair: a meta-analysis. J Pediatr Surg. 2010;45(5):880–6.
6. Kanagaratnam A, Phan S, Tchantchaleishvili V, Phan K. Ravitch versus Nuss procedure for pectus excavatum: systematic review and meta-analysis. Ann Cardiothorac Surg. 2016;5(5):409–21.
7. Mao YZ, Tang S, Li S. Comparison of the Nuss versus Ravitch procedure for pectus excavatum repair: an updated meta-analysis. J Pediatr Surg. 2017;52(10):1545–52.
8. Fonkalsrud EW, Beanes S, Hebra A, Adamson W, Tagge E. Comparison of minimally invasive and modified Ravitch pectus excavatum repair. J Pediatr Surg. 2002;37(3):413–7.
9. Malek MH, Berger DE, Housh TJ, Marelich WD, Coburn JW, Beck TW. Cardiovascular function following surgical repair of pectus excavatum: a metaanalysis. Chest. 2006;130(2):506–16.
10. Papic JC, Finnell SM, Howenstein AM, Breckler F, Leys CM. Postoperative opioid analgesic use after Nuss versus Ravitch pectus excavatum repair. J Pediatr Surg. 2014;49(6):919–23.
11. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. Clin Interv Aging. 2006;1(3):253–60.

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