Advanced VATS resections: radiation therapy and VATS

Mark F. Berry

Department of Cardiothoracic Surgery, Stanford University, Stanford, CA, USA

Correspondence to: Mark F. Berry, MD. Associate Professor, Department of Cardiothoracic Surgery, 300 Quarry Drive, Falk Cardiovascular Research Building, 2nd Floor, Stanford, CA 94305, USA. Email: berry037@stanford.edu.

Abstract: A history of radiation therapy can increase the technical complexity of a major lung resection. Outcomes when major lung resection is performed after radiation have improved over time, but previous radiation remains a risk factor for complications after surgery. Despite the increased risks, major lung resection may be indicated in specific oncologic situations after radiation. Experience with major lung resection after thoracotomy has been published in multiple studies, and the risks and difficulties in this situation are generally well understood. The literature regarding outcomes when video-assisted thoracic surgery (VATS) is used after radiation is much more sparse, but the studies that have been published suggest that approach is safe and feasible for select patients in surgeons with extensive VATS experience. This manuscript will review the role and risks of major lung resection after previous radiation via both thoracotomy and VATS, as well as specific considerations and techniques that may be appropriate when performing VATS after radiation therapy.

Keywords: Video-assisted thoracic surgery (VATS); lung resection; lung cancer; radiation

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Introduction

A history of both induction therapy in general as well as specifically previous radiation therapy is a risk factor for morbidity and mortality after major lung resection. However, both prospective and retrospective studies have shown that thoracotomy and major lung resection after induction treatment is feasible. Performing major lung resection with video-assisted thoracoscopic surgery (VATS) after induction therapy was initially felt to be contraindicated in the early period of VATS use, but small retrospective studies have shown the feasibility of using VATS for major lung resection even after induction treatment. Depending on the specific clinical scenario and, perhaps most importantly, a surgeon's experience with complex VATS lung resections, the use of VATS can be a safe and oncologically appropriate option for a patient after radiation. This manuscript will review the role and risks of major lung resection after previous radiation via both thoracotomy and VATS, as well as specific considerations and techniques that may be appropriate when performing VATS after radiation therapy.

Role of major lung resection after induction therapy

Clinical scenarios where surgery is indicated after radiation therapy

Performing major lung resection after radiation therapy is relatively uncommon. Induction chemotherapy or radiation therapy was used in only 1,801 (6.5%) of 27,844 patients who underwent lung resection in the Society of Thoracic Surgeons (STS) General Thoracic Surgery Database over the time period 2012–2014 (1). However pulmonary resection after radiation therapy may be appropriate in several scenarios (2). Induction therapy prior to surgical resection is typically planned for patients with stage IIIA NSCLC due to N2 nodal involvement who are considered resectable at the time of diagnosis (3). Prospective, randomized trials have demonstrated a benefit to induction chemotherapy over primary surgery for these patients (4-6).

Although the combination of induction chemotherapy with radiation therapy and then surgical resection for stage IIIA disease is feasible but has not been shown in randomized trials to improve survival, a survey of North American thoracic surgeons showed that most (70%) surgeons consider the most appropriate neoadjuvant therapy for stage III NSCLC to be chemotherapy combined with radiation (7-9). Most (80%) of these surgeons preferred a pre-surgery radiation dose of 45 Gy, while 19% reported using 66 Gy radiation and a very small minority utilized an even higher dose of radiation. Induction chemotherapy and radiation therapy prior to surgical resection is also typically pursued in patients with locally advanced superior sulcus tumors (T3 or T4) and N0 or N1 disease (10,11).

Other patients with locally advanced lung cancer may be treated with chemoradiotherapy when an initial resection is not technically feasible or does not appear likely to offer a survival benefit over non-operative therapy (2). These patients may have been initially deemed unsuitable for surgery for oncological or medical factors, such as initial clinical overstaging, patient refusal to consider surgery, poor lung function, or significant co-morbidities, only to have the patient or their oncologists reconsider that assessment after their initial course of therapy (12). Although uncommon, surgeons may consider resection after chemoradiation in these situations when patients have local or regional residual disease (3). Patients are also referred for major pulmonary resection to treat conditions such as necrotic lung or lung abscess refractory to medical therapy after definitive chemotherapy or radiation therapy (13). Finally, patients previously treated with definitive radiation therapy for a malignant process may develop a new metachronous primary malignancy for which surgery is deemed the optimal therapy.

Risks of surgery after radiation

Several early reports identified increased morbidity and mortality after the use of induction chemotherapy and radiation therapy prior to major lung resection (14,15). In particular, mortality is significantly higher when patients undergo pneumonectomy compared to lobectomy after induction therapy (7,15-17). Advances in surgical and perioperative care have likely reduced the potential impact of induction chemotherapy alone, as subsequent reports have shown no significant difference in mortality or morbidity in patients receiving surgery alone versus pre-operative chemotherapy followed by surgery for non-small cell lung cancer (18-20). Despite the advances and recent studies, induction therapy likely does generally confer at least some increased surgical risk. A report from the STS General Thoracic Surgery Database that reviewed 4,979 lobectomies performed between 2002 and 2006 showed induction therapy was a risk for a prolonged length of hospital stay, considered a surrogate for morbidity (21). An even more recent study of 27,844 patients who underwent lung resection in the STS General Thoracic Surgery Database over the more recent time period 2012–2014 continued to show that induction therapy was an independent risk factor for both major morbidity [odds ratio (OR) 1.2] and mortality (OR 1.51) (1). Risks that may be higher after induction therapy include bleeding during dissection of hilar structures that have extensive inflammatory or fibrotic radiation changes, bronchopleural fistula due to reduced bronchial tissue viability, and respiratory failure (22,23).

Results after lung resection via thoracotomy after radiation

Multiple studies have reported results of performing thoracotomy and major lung resection after previous treatment with radiation, typically also with chemotherapy (7,14-17,24-31) (*Table 1*). Early experience generally involved significant morbidity and mortality. Fowler *et al.* reported that one patient among six who had lobectomy had adult respiratory distress syndrome (ARDS) and three of seven pneumonectomy patients had a perioperative death when surgery was performed after 60 Gy radiation and concomitant chemotherapy (15). Bonomi *et al.* reported that 6 of 16 patients who had received split-course thoracic radiation (total 40 Gy) and chemotherapy followed by a thoracotomy had serious postoperative complications, including one death form ARDS, two bronchopleural fistulas, and one pneumonia (14). Deutsch *et al.* reported 3 perioperative deaths among 16 patients (19% mortality) with clinically staged IIIA non-small cell lung cancer who received induction chemotherapy and radiation therapy (60 Gy) and then thoracotomy (6 pneumonectomies) (16).

Subsequent larger retrospective studies have expanded on the perioperative risks of induction therapy. One of the largest published experience with thoracotomy after induction chemotherapy is a retrospective review of 470 patients (297 lobectomy, 97 pneumonectomy, 18 segmentectomy or wedge resection, 58 exploration only) treated at Memorial Sloan Kettering between 1993

Table 1 Studies reporting on major lung resection via thoracotomy after induction therapy

Reference	Study design[a]	Study findings
Fowler (15)	Retrospective, 13 patients treated with chemoradiation (60 Gy)	43% pneumonectomy mortality
Bonomi (14)	Retrospective, 16 patients treated with chemoradiation (40 Gy)	38% significant morbidity
Deutsch (16)	Retrospective, 16 patients treated with chemoradiation (60 Gy)	19% overall mortality, 33% pneumonectomy mortality
Martin (17)	Retrospective, 470 patients treated with chemotherapy (all) and radiation (18%; 50 Gy)	2.4% lobectomy mortality; right pneumonectomy (23.9%) had significantly higher mortality than left (0%)
Stamatis (25)	Retrospective, 350 patients treated with chemoradiation (45 Gy)	4.9% mortality and 44% morbidity; not using bronchial stump was risk for morbidity
Albain (7)	Prospective, 202 patients treated with chemoradiation (45 Gy)	Treatment-related mortality of 1% for lobectomy, 26% for pneumonectomy
Fujita (26)	Retrospective, 124 patients treated with chemoradiation (40 Gy)	2.4% mortality; radiation >45 Gy was morbidity risk factor
Yokomise (27)	Retrospective, 41 patients treated with chemoradiation (50 Gy)	0% mortality
Cerfolio (28)	Retrospective, 216 patients treated with chemoradiation (60 Gy)	2.3% mortality; intercostal muscle flap used in all patients
Sonett (29)	Retrospective, 40 patients treated with chemoradiation (62 Gy)	0% mortality
Bauman (30)	Retrospective, 24 patients treated with chemotherapy (all but 2) and radiation (63.9 Gy)	58% morbidity; vascularized flap used to cover stump in 19 patients
Stupp (31)	Prospective, 46 patients treated with chemotherapy (all) and radiation [used in 76% (n=35), 44 Gy]	14/46 morbidity, 5.7% 30-day mortality (n=2)
Barnett (24)	Retrospective, 549 patients treated with induction chemotherapy (all) and radiation (17%)	Morbidity rate was 250 patients (46%) and in-hospital mortality was 1.8% (10/549), with only one death after right pneumonectomy (1/30, 3%).

[a], radiation dose shown is a median value.

and 1999, where 85 patients (18%) also received radiation (median dose 50 Gy, range 10 to 72 Gy) (17). Overall mortality was 3.8% (2.4% for lobectomy and 11.3% for pneumonectomy) and morbidity was 38.1%. All deaths after pneumonectomy occurred after a right-sided procedure, for which the mortality was 23.9%. A follow-up study from the same institution showed improved outcomes when they examined 549 patients who underwent surgery after induction chemotherapy in subsequent years [2000–2006], among whom 17% also had radiation (24). In this cohort, the morbidity rate was 46% and in-hospital mortality was 1.8%, with only one death after right pneumonectomy (3%).

Several other relatively large studies have reported results of patients who had been treated with both induction chemotherapy and radiation prior to lung resection. Stamatis *et al.* reported a hospital mortality of 4.9% and an overall morbidity of 44% for 350 patients treated with induction chemoradiation in a retrospective review of two phase II studies and one phase III study from 1991 to 2000 (25). Fujita *et al.* found that radiation dose greater than 45 Gy was a morbidity risk factor in another retrospective review of 124 patients who received chemoradiation between 1990 and 2003 (26). In this study, 90 patients had lobectomy and 25 patients had pneumonectomy with an overall 30 day mortality of 2.4%. Other relatively small retrospective studies have demonstrated similar surgical outcomes. Yokomise *et al.* reported on a single-surgeon series of 41 patients who were treated with platinum-based chemotherapy with concurrent radiation (50 Gy) followed by surgical resection (lobectomy or bilobectomy 28 patients, pneumonectomy 13 patients) with no mortalities (27).

Several studies have documented outcomes of patients who had received higher doses of radiation. Cerfolio *et al.* reported a mortality of 2.3% and overall morbidity of 37% (17% considered major) for 216 patients treated with induction chemotherapy and high dose radiation (median dose 60 Gy, range 60–72 Gy) followed by thoracotomy (lobectomy/bilobectomy 152, pneumonectomy 11, segmentectomy 14, wedge or no resection 35), where all patients had their bronchial stumps buttressed by intercostal muscle flaps (28). Sonett *et al.* reported 0% operative mortality for 40 patients (29 lobectomies and 11 pneumonectomies) with non-small cell lung cancer that had received neoadjuvant therapy that included thoracic radiation (mean 62 Gy, range 59.4 to 66.6 Gy) and concurrent platinum-based chemotherapy (29). Bauman *et al.* reported on 24 patients who were treated with definitive chemoradiation (median radiation dose 63.9 Gy with a range of 59.4 to 70.2 Gy, 2 of the patients received radiation alone) for locally advanced non-small cell lung cancer, and then subsequently underwent salvage lung resection for local recurrence (30). There was 1 perioperative death and an overall morbidity of 58%, with the most common complications being supraventricular tachycardia (29%), pneumonia (17%), vocal cord palsy (17%), tracheostomy (8%), and major vessel injury (8%). Yang *et al.* also reported on 31 patients that underwent lobectomy after curative-intent definitive radiotherapy (60 Gy), with or without chemotherapy with no perioperative deaths and 48% morbidity (12).

Results after lung resection via VATS after radiation

The use of VATS to achieve anatomic lung resections such as lobectomy was first reported in the 1990s (32). Both single-institution and multi-institution studies subsequently demonstrated VATS lobectomy to be safe and feasible, and then benefits over thoracotomy were shown in controlled studies (33-37). Advantages of VATS pulmonary resections include a lower incidence of postoperative complications, shorter length of chest tube duration and hospital stay, decreased post-operative pain, and preserved pulmonary function (34-36,38-42). A minimally invasive approach was shown to be particularly beneficial for higher risk patients such as older patients and patients with impaired pulmonary function (43-45). The widespread adoption of VATS lobectomy was somewhat slow, but 62% of lobectomies reported to the STS General Thoracic Database in the years 2012–2014 were done via VATS (1,34,35,38,39).

Initially, only patients with small, peripheral, early stage tumors were felt to be appropriate candidates for resection via VATS. Prior thoracic radiation and the use of induction therapy were relative contraindications (46). However, the use of VATS has now been reported in more advanced situations such as large and central tumors with clinically positive nodal disease as well as for achieving sleeve resections, chest wall resections, and pneumonectomy (47-51). The safety and feasibility of thoracoscopic lobectomy after induction therapy that includes radiation therapy has also been demonstrated in relatively small studies from generally high volume VATS institutions (12,52-57) (*Table 2*).

Performing VATS after radiation therapy

Operative planning

Although the studies discussed above has demonstrated the safety and feasibility of performing VATS after radiation therapy, it is important to note that all individual surgeons must carefully evaluate every situation if VATS is considered after radiation therapy. Surgeons must consider not only patient characteristics, but their own VATS experience, skill, and comfort level, as well as their institutional experience in terms of operative and perioperative support. Surgeons should probably not consider a VATS resection after radiation until they have attained an appropriate comfort level with less complex VATS anatomic resection procedures in general.

The process of avoiding complications when attempting a resection after radiation via VATS is generally no different than the process for any lung resection, and is dependent on appropriate preoperative workup and patient selection as well as very meticulous and careful intra-operative dissection and attention to detail (58,59). As with all most surgical procedures, the optimal strategy of managing complications of VATS pulmonary resections is to prevent their occurrence. Consideration of the radiographic appearance of the area of lung to be removed and the anticipated technical aspects in terms of hilar dissection is especially important when doing VATS after radiation. In these cases, focusing on hilar calcifications and adenopathy at the origin of the lobar bronchus that is to be divided as well as the number and locations of pulmonary artery and vein branches can allow surgeons to anticipate areas where dissection may be most difficult. The surgeon must always

Table 2 Studies reporting on major lung resection via thoracoscopy after induction therapy

Reference	Study design	Study findings
Petersen (52)	Retrospective series of 12 patients treated with chemotherapy (n=11) and radiation (n=8)	No perioperative deaths for 12 VATS lobectomies (1 conversion to thoracotomy). One patient with postoperative bleeding and 1 patient with an unspecified major complication
Shaw (54)	Retrospective series of 10 patients treated with chemoradiation	No perioperative deaths for 10 VATS lobectomies. Two patients with atrial arrhythmias and 1 patient with vocal cord paralysis
Sahai (53)	Retrospective of 10 patients treated with chemotherapy (all) or radiation (n=2)	Specific results of patients with induction therapy not reported
Yang (12)	Retrospective single center study, 317 patients treated with induction chemotherapy and lobectomy (n=272) or pneumonectomy (n=45), n=192 also got radiation	VATS was used in 69 of the 272 lobectomy patients. The impact of VATS was not considered in this study, but the use of chemoradiation did not increase the morbidity risk over chemotherapy alone
Boffa (55)	Retrospective multicenter study, 1,535 patients treated with induction therapy [28 (1.8%) had radiation alone and 1,035 (67.4%) had chemoradiation] for clinical stage IIIA NSCLC	A VATS approach was used in 276 (18%) patients, and the extent of lung resection was lobectomy in 1,112 patients (72.4%). The perioperative mortality was 2.5% (n=38). This study does not provide details on which patients had VATS and radiation
Yang (56)	31 patients that underwent lobectomy after curative-intent definitive radiotherapy (60 Gy), with or without chemotherapy	Six patients underwent a VATS approach with no conversions and 25 patients underwent an open approach. There were no perioperative deaths, and morbidity occurred in 15 patients (48%)
Huang (57)	43 patients who underwent VATS lobectomy after induction therapy (16 had radiation)	16 patients converted to thoracotomy. Overall 9.5% morbidity and 2.4% mortality

be ready and have the instruments needed to convert to thoracotomy if necessary.

Pre-operating staging and work-up for thoracoscopic resection should be the same in general as for thoracotomy, which includes checking pulmonary function tests (PFTs) with diffusion measurements (58-60). The only absolute contraindication to VATS resection from a patient's clinical standpoint is the inability to tolerate single-lung ventilation, which involves very careful consideration of the patient's contralateral lung status. Although VATS resections have been shown to be able to be accomplished in patients with lung function that have typically been thought to be too poor to undergo more conventional resection via thoracotomy, it's imperative to consider that conversion to thoracotomy is possible for all patients for whom VATS resection is planned (61,62). Absolute tumor size criteria that would preclude VATS resections have not been defined, though large specimens may not be amenable to removal without rib spreading (60). In general, chest wall involvement requires thoracotomy for resection, though VATS can be used to perform the hilar portion of the surgery and allow placement of the incision better situated for the area of chest wall to be removed.

Pre-operative planning must involve not only the work-up described above, but also consideration of any intra-operative complications. The surgeon must anticipate and plan for potential complications such as massive hemorrhage and bronchial complications, as well as how to deal with unexpected equipment malfunctions. Additionally, the surgeon must at all times be sure to perform the same cancer operation with VATS as would be done with an open approach, utilizing individual vessel dissection and ligation with complete mediastinal lymph node dissection.

Conversion to thoracotomy

A very important consideration is always keeping in mind that conversion to thoracotomy is possible or even likely. The instruments needed for thoracotomy also must always be immediately available during thoracoscopic surgeries. Conversion to thoracotomy is a tool available to manage unexpected or difficult situations, and is not a complication in and of itself. Conversions may be due to difficulties with the procedure, including a narrow view angle, complicating conditions such as pleural adhesions, obscured tissue planes, or dense hilar lymphadenopathy, oncologic considerations such as the discovery of more extensive local disease than expected, and the surgeon's discomfort with VATS visualization and instruments (60). Although unexpected conversion to thoracotomy during VATS does not necessarily compromise prognosis, the decision to convert must be made promptly to reduce operating time, blood loss, and other possible complications (63,64). In cases where dissection is particularly difficult, the surgeon should strongly consider conversion in an elective manner before something occurs that requires emergent conversion and possibly patient instability (65). Accordingly, when attempting a VATS procedure, access ports must be placed to facilitate immediate conversion to open thoracotomy and to support instrument manipulation and anatomic accessibility of the stapler to close vessels and the bronchus (60).

Conversion rates for thoracoscopic lobectomy to open thoracotomy have been reported to range from 2% to as high as 23%, with these higher rates generally observed in patients with more advanced NSCLC (35,39,47,66-71). Causes of conversion are generally classified into four categories: intraoperative complications, technical problems, anatomical problems, and oncological conditions (60). Reasons for conversions can include bleeding from hilar structures, failure to make progress, poor visualization, equipment malfunction, and oncological reasons such as centrally located tumors requiring vascular control or sleeve resection, unexpected T3–T4 tumors that invade the chest wall, diaphragm, or superior vena cava. Conversion may also be required due to abnormal/adherent hilar nodes secondary to a prior inflammatory process or metastatic disease, diffuse pleural adhesions, absent or thick fissure, tumor size precluding removal through the utility incision, invasion of hilar structures, or positive margins that require additional resection. Patients do not necessarily have higher morbidity or mortality directly as a result of conversion to open thoracotomy (60,63). However, patients who have a conversion have been shown to have higher blood loss and longer operative times (64,72). Therefore, with a focus on a safe and complete resection, conversion should be regarded as a means of completing resections in a traditional manner rather than as a surgical failure.

Anatomic considerations

Anatomic considerations that increase the difficulty of successfully performing VATS after radiation include obliteration of tissue planes, pleural adhesions, and the absence of fissures (60). Induction therapy, and radiation in particular, can distort normal anatomy due to perihilar fibrosis, leading to thicker and more adherent tissue planes around the hilar structures. Dissection in this situation may require sharp dissection, as blunt dissection or the use of cautery may not be feasible due to the obscured tissue planes. True pleural symphysis that requires conversion to thoracotomy may be unlikely for high volume VATS surgeons, but it may represent a contraindication to continuing via VATS in surgeons without extensive experience. Although creating space and entering the correct pleural plane can be difficult in the setting of dense adhesions, endoscopic adhesiolysis can often proceed quickly and safely using a combination of sharp and blunt dissection under videoscopic vision (60). VATS has the advantage over conventional thoracotomy in providing high resolution visualization of areas such as the apex and base of the hemithorax, which can be difficult to see even during thoracotomy when adhesions are present. In addition, successful VATS lobectomy can be accomplished in the setting of fused fissures, where the fused fissure is divided last, after dissection and division of the pulmonary vasculature and the bronchus (60).

One of the most dreaded complications for surgeons during anatomic lung resections is massive bleeding from pulmonary vessels (60). Dense adhesive disease that can occur after radiation often increases the risk of vascular injury during dissection, as described above. Dissection of vessels can generally be difficult in this situation, and risk of vessel injury and bleeding can be high even by thoracotomy. VATS pulmonary resections can be performed by capable VATS surgeons without an increased bleeding risk, probably at least partly facilitated by the visual magnification provided by the thoracoscope, but extreme care is required. As described above, sharp dissection may be necessary. Flexibility with the use of the thoracoscope can in some cases reduce the chance of vessel injury and significant bleeding. For example, movement of the thoracoscope from one port to another can improve or enhance visualization of the hilum (46). However, as described above, surgeons must carefully evaluate pre-operative imaging so they are aware of potentially dangerous or difficult areas, meticulously dissect planes in the hilum, and be ready to convert to thoracotomy at all times and preferably before a major vascular injury occurs when the dissection is difficult. In addition, surgeons may wish to obtain proximal control of the main pulmonary artery if the hilar dissection proves to be difficult.

Other methods to prevent complications

Bronchial stump reinforcement with muscle or a pleural flap may be considered after induction therapy to reduce the chance of fistula formation (73). Many surgeons routinely use flap coverage of the bronchial stump. Although a benefit has never been definitively proven, the routine use of bronchial stump flap coverage in several of the studies discussed above may have been at least partially responsible for the low observed morbidity and mortality rates with major lung resection after radiation therapy. Although harvest of flaps such as the intercostal muscle is typically done via thoracotomy, the harvesting of this muscle with a VATS approach has been described (74,75). Surgeons that plan for VATS lobectomy after radiation therapy, particularly if higher doses of radiation were used, should seek to develop the skill needed to harvest this flap. If harvesting the intercostal muscle is not feasible via VATS, other options include a pleural flap or a flap of pericardial fat to cover the bronchial stump.

Although reports disagree on the role of induction chemotherapy and radiation on the development of acute lung injury and adult respiratory distress syndrome after lung resection, there is some consensus on a strategy to reduce the risks of patients after preoperative therapy: minimization of intravenous fluids and both the fraction of inspired oxygen and airway pressures as much as possible after anesthesia induction (23,76-81). Although a surgeon may be too focused on the technical performance of the procedure to manage these things directly through the case, they should make a point of reviewing these perioperative management strategies with anesthesia prior to the case, as the anesthesiologists may not necessarily recognize the increased risks that accompany lung resection after induction therapy.

Conclusions

Almost all published studies that examine major lung resection after induction therapy that included radiation are retrospective in nature. These studies generally indicate that this treatment is associated with high potential risks, which can be reduced by careful patient selection, meticulous operative technique, and perioperative management (13). Bronchial stump coverage with a vascularized flap probably reduces perioperative morbidity, particularly when the dose of preoperative radiation is more than 45 Gy and when pneumonectomy has been performed. Although the use of thoracotomy and VATS after radiation therapy has never been prospectively directly compared in the literature, both approaches may be feasible depending on the specific circumstances. However, surgeons must carefully consider each individual clinical situation, including tumor location, as well as their own VATS experience before attempting a resection via VATS after radiation therapy.

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