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Extended Resections of Non-Small Cell Lung Cancers Invading the Aorta, Pulmonary Artery, Left Atrium or Esophagus: Can They Be Justified?

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Non-small cell lung cancer; T4; aorta; pulmonary artery; left atrium; esophagus; extended resection

Introduction

Surgical resection remains a critical component of multidisciplinary therapy for locally advanced lung cancers. Non-small cell lung cancers (NSCLC) are highly lethal neoplasms, particularly when diagnosed in advanced stage. More than 50% of NSCLC patients present with metastatic disease or tumors that are unresectable¹. In stage I NSCLC, for which surgery provides the best chance for cure, overall 5-year survival rates following resection range from 65-75% for stage IA and IB tumors, respectively². This is in comparison to 5-year survival rates of 24% for stage IIIA and 9% for stage IIIB (T4N2M0) disease³. The therapeutic approach for advanced stage NSCLC is controversial, particularly in the surgical management of a subset of T4 tumors invading the heart, great vessels and other mediastinal structures. However, with modern advances in imaging, surgical techniques, and perioperative care, extended resections may improve survival for highly selected patients.

Historical Background

With the advent of cardiopulmonary bypass in the late 1950's, surgeons realized the potential for extracorporeal circulation to facilitate resection of pulmonary malignancies involving the great vessels or atria. In 1965, Neville and colleagues⁴ reported a series of six lung cancer patients in whom cardiopulmonary bypass was used during carinal resection or sleeve lobectomy. One more patient underwent left intrapericardial pneumonectomy with

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resection and interposition graft repair of the descending aorta. Disappointingly, six out of seven patients died in the immediate postoperative period from bleeding, heart failure or pulmonary edema. Several years later, Bailey et al.⁵ described two lung cancer patients in whom cardiopulmonary bypass was used to facilitate extended left pneumonectomy. The first patient required left intrapericardial pneumonectomy with en bloc resection and direct suture repair of the left atrium, as well as resection and interposition graft repair of the descending aorta. The second patient underwent left intrapericardial pneumonectomy, resection and repair of the left atrium, as well as resection and repair of the distal main pulmonary artery. Both patients were fully heparinized and cannulated for venous return via the main pulmonary artery, and arterial inflow by two sites in the aorta, proximal and distal to the lines of surgical resection. The first patient developed coagulopathy and died in the early postoperative period. The second patient, whose pathologic stage by description was T4N1, survived 14 months before succumbing to metastatic disease. Although sophisticated staging systems and prognostic indicators for lung cancer had not yet been developed, the aforementioned authors understood the principles of en bloc tumor resection with minimal manipulation, the significance of tumor histology and mediastinal lymph node metastases, and the consequences of coagulopathy complicating pneumonectomy.

More Recent Experience

The value of surgical resection for the treatment of T4 NSCLCs invading the aorta, pulmonary artery, left atrium and esophagus remains open to debate. Presently, most patients are not offered resection in part because of the potential for significant morbidity and mortality. However perioperative risk in this subset of patients has improved over time (Table 1). In 1987, Burt ME et al.⁶ published a retrospective review of 225 patients who underwent thoracotomy for primary NSCLC invading the mediastinum. Lesions were classified as T3 — “a tumor of any size with direct extension into an adjacent structure such as the mediastinum and its contents” — according to TNM descriptors used by the UICC in the early 1980s. This included tumors which invaded adjacent organs^{7,8}. Approximately 10% of patients with mediastinal invasion had aorta involvement, one-third of whom had simultaneous involvement of the pulmonary artery⁶. The majority of these patients also had mediastinal lymph node metastases. They observed a superior perioperative mortality rate of 2.7%, and a nonfatal complication rate of 13%. Complete (R0) resection was associated with a survival advantage, with a median survival of 17 months and 5-year survival of 9%. In 1989, Nakahara K et al.⁹ reported successful en bloc pulmonary and aortic resection in three lung cancer patients with the use of cardiopulmonary bypass, one of whom was alive 17 months following surgery.

In 1994, Tsuchiya et al.¹⁰ summarized the results of en bloc lung and aortic resection as a portion of a larger clinical series involving T4 tumors. Twenty-one patients with aortic involvement had dissection in a subadventitial plane. Resection was believed to be incomplete in 12 of these patients. Seven patients with aortic involvement (six with invasion near the ligamentum arteriosum, one with subclavian artery involvement) underwent complete resection. Two patients received graft replacement using subclavian artery to descending aorta bypass. An additional seven patients underwent resection of the main pulmonary artery using full cardiopulmonary bypass support. Not surprisingly, multivariate analysis revealed

that survival was dependent on perioperative bleeding, postoperative pneumonia, completeness of resection and nodal status. Pathologic staging and survival for these patients undergoing aortic resection was not documented clearly in the publication. However, it was noted that one of the patients was alive nine years following the operation. In that same year, Martini et al.¹¹ also described 102 patients with NSCLC invading the mediastinum, excluding those who had N2 disease. In this study, patients were divided into subgroups based on extent of mediastinal invasion and classified as T3 or T4. Forty-four of the patients had T4 tumors which invaded the aorta, superior vena cava, esophagus, trachea, spine or atrium. Overall, operative mortality was 6% and 5-year survival was 19%. With complete resection, 5-year survival was 30%.

In response to the emerging controversy surrounding extended resections of T4 NSCLC, multiple retrospective studies were published providing additional data to support the concept that properly selected patients could benefit from the procedure¹². These observational studies attempted to identify those patients who were more likely to benefit from extended resection within a heterogeneous population of T4 tumors. In 2001, Bernard et al.¹³ conducted a retrospective cohort study of 77 patients with T4 NSCLCs which invaded the mediastinum by direct extension or were comprised of multiple synchronous lesions within the same lobe of the lung, the latter of which are now classified as T3 lesions¹. One-year and 5-year survival rates were 33% and 0% for 8 patients with aortic invasion, 40% and 8% for 19 patients with left atrial invasion, and 20% and 12% for 8 patients with esophageal invasion. Nodal status (pN0 or pN1 vs. pN2) was associated with survival. Improved 5-year survival rates were also described in retrospective studies of extended resection of T4 NSCLCs with mediastinal involvement alone. Wu et al.¹⁴ and Yang et al.¹⁵ reported 5-year overall survival rates of 22% and 23%, respectively. In 2003, Pitz et al.¹⁶ noted an improved 5-year survival rate of 46% following R0 resection of T4 tumors with invasion of major mediastinal structures including the aorta, pulmonary artery, left atrium and esophagus. Yet, this was also associated with significant hospital mortality (19%). Similarly, in two retrospective reviews by Mu et al.¹⁷ and Wang et al.¹⁸, each involving more than 100 patients, overall 5-year survival rates of 37.5% and 41% were observed in T4 NSCLCs invading the left atrium and great vessels. Operative morbidity and mortality were not reported for these series.

In a retrospective cohort study using the SEER database, Farjah et al.¹⁹ examined trends in the operative management and outcomes of patients with T4 lung cancers treated between 1992 — 2002 in the United States. A total of 13,077 patients with stage IIIB disease defined by T4 tumors were identified, out of which only 9% underwent resection. The specific locations of the T4 tumors were not evaluated. Thirty-day mortality was 10% and this did not change significantly over time. Factors associated with higher odds of operative mortality included increasing age, CCI (Klabunde-modified Charlson Comorbidity Index)²⁰ higher than 0, tumor size three centimeters or larger, or pneumonectomy. Five-year overall survival and lung cancer cause-specific survival did increase over time from 15% to 35% and 33% to 50%, respectively. The authors concluded that the temporal changes observed in the operative management of T4 tumors coincided with improvements in long-term survival, and that these findings supported resection for select patients with these neoplasms.

Superior outcomes are particularly evident when extended resections are performed at high volume, specialized institutions where surgical techniques and perioperative care have been refined. In 2008, Yildizeli et al.²¹ published an institutional review representing 25 years of experience in radical surgery for clinically staged T4 N0/N1 NSCLC. Of 271 patients with tumors involving the carina, superior vena cava, mediastinum, heart and great vessels, overall 30-day mortality and morbidity rates were 4% and 35%, respectively. Patients were divided into four subgroups: superior sulcus tumors (n = 126); carinal invasion (n = 92); SVC invasion (n = 39); and mediastinal (n = 14) including tumors which invaded the aorta (n = 2), pulmonary artery (n = 3), left atrium (n = 7) and esophagus (n = 2). A total of 11 patients died postoperatively, out of which 6 had bronchopleural fistulas. Organ specific mortality rates were listed for invasion of the aorta (14%), right or left pulmonary artery (21%), left atrium (50%) and esophagus (14%). Notably, only nine operations were performed using cardiopulmonary bypass. The most common complications were pulmonary edema and atelectasis. Median length of hospitalization was 15 days. Overall 5- and 10-year survivals were 36.6% and 25.9%, respectively, with a median survival of 28 months. Five-year survival for the mediastinal group alone was 61%. Multivariate analysis demonstrated that three factors independently influenced survival: nodal status (N0/N1 versus N2/N3/M1), complete resection (R0 versus R1; 40.4% versus 15.9%) and non-invasion of the subclavian artery. Likewise, in 2013, Spaggiari et al.²² reported survival after extended resection for 167 cases of lung cancers invading mediastinal structures. They observed an overall morbidity rate of 45% and postoperative mortality rates of 5% at 30 days and 11% at 90 days. Overall 5-year survival data according to nearby organ invasion was also documented. This demonstrated a trend toward better long-term survival in patients with aorta invasion. Organ specific postoperative complications were not reported in this study. Five-year survival rates were: aorta (37%), left atrium (25%), carina (22%) and SVC (26%). Factors which positively influenced survival included R0 resection and pN0 disease.

Extended Resections

Aorta

If there is no evidence of intrapleural dissemination, mediastinal nodal involvement, and there is direct tumor invasion of the aorta, en bloc pulmonary and aortic resection can be considered. Of particular note is the fixation of the tumor to the distal arch and proximal descending aorta, which limits one's ability to manipulate the hilum. The extent of the tumor within the lung will dictate whether lobectomy or pneumonectomy is necessary. The arch of the aorta is mobilized and control of the left subclavian and distal arch obtained. Whereas historically, aortic resections have been performed using left heart bypass, some centers use clamp and sew techniques or passive shunts without bypass^{15, 21-22, 28}

Several studies have demonstrated that long term survival is possible with resection of the aorta en bloc with primary tumor (Table 1)^{9-11, 13, 15, 16, 21-28}. In general, when compared to other mediastinal structures, resection of the aorta has been associated with a higher operative morbidity and mortality, and this seems to correlate with the use of cardiopulmonary bypass (CPB). In 2005, Ohta et al.²⁴ published a series of 16 patients who underwent thoracic aorta resection along with left pneumonectomy (n = 6), left upper

lobectomy (n = 9) and partial lung resection (n = 1) with the use of CPB in 10 patients, and a passive shunt between the ascending and descending aorta in four patients. Postoperative mortality was 12.5% and morbidity was 31%, with six major complications occurring in five patients. Four patients suffered significant postoperative bleeding. Three patients had intrapleural bleeding and one died from this event. One patient died from severe hemorrhage following an aortic laceration just distal to the left subclavian artery. Twelve (75%) patients had complete resection. Median survival time for all patients was 26 months, with a 5-year survival rate of 48.2%, and median and 5-year survivals for patients with pathologic N0 disease were 31 months and 70%, respectively.

Other studies, which have included patients with resection of T4 NSCLCs invading the aorta, have also demonstrated improved long-term survival but have not reported their respective morbidity or mortality rates. In a retrospective review of 13 patients with T4 tumors requiring aorta resection without the use of CPB, Mithos et al.²⁸ reported a 5-year survival of 31%; associated postoperative complications and mortality were not documented. Similarly, in the recent review published by Spaggiari et al.²² no extracorporeal circulation was used for the 14 patients requiring aorta resection. These authors noted a 5-year overall survival for patients with aorta invasion of 37%. Overall morbidity and 30-day mortality were 45% and 5%, respectively. Organ specific complication rates were not recorded.

Pulmonary Artery

Resection and reconstruction of the pulmonary artery in patients with lung cancer is technically feasible. The procedure is usually indicated for tumors or satellite lymph nodes that involve the pulmonary artery at the hilum and preclude resection by simple lobectomy. The extent of involvement varies, from partial infiltration to more extensive and circumferential invasion²⁹. Early reports describing the technique were associated with significant mortality and poor overall survival, where all postoperative survivors died soon after resection from recurrent cancer^{10-11, 13, 26, 29-32}

To address the safety and long-term outcome for reconstruction of the pulmonary artery, Venuta et al.²⁹ recently reported their 20-year experience and demonstrated improved outcomes. Upon review of data gathered from 1989-2008, of 105 patients, overall morbidity was 28.5%. Two major complications were noted; one pulmonary artery thrombosis, requiring completion pneumonectomy on postoperative day two, and one massive hemoptysis leading to death in a patient who had undergone combined bronchovascular reconstruction. Of note, not all the patients evaluated had T4 tumors with invasion of the pulmonary artery. Only 22% were classified as stage IIIB, and the extent of tumor involvement was not documented. Operative mortality was 0.95%, and overall 5- and 10-year survivals were 44% and 20%, respectively. As expected, nodal status had a significant effect on survival. Patients with N0 disease had 5- and 10-year survival rates of 67% and 33%, compared to 20% and 3%, respectively for patients with N2 disease. Reconstruction involved patch reconstruction (n = 55), end-to-end anastomosis (n = 47) or interposition with use of a prosthetic conduit (n = 3). In 65 patients (62%), pulmonary artery reconstruction was performed along with bronchial sleeve resection, and in all other cases, either standard lobectomy or bilobectomy was performed. More recently, Berthet et al.³³ published their

single institutional experience of 178 patients with centrally located NSCLC requiring resection of the pulmonary artery, and reconstruction or replacement, with or without concomitant sleeve bronchial resection. While safety and efficacy of the procedure can be fairly assessed, a limited number of patients in this study had T4 tumors ($n = 1$), and therefore, comparisons of overall survival cannot be made. Pulmonary artery reconstruction was performed in 32 (35%) patients (2 by autologous pericardium patch and 20 by end-to-end anastomosis). Pulmonary artery replacement was performed in the remaining cases primarily with the use of cryopreserved arterial allograft (aortic allograft was used in three patients). R0 resection was achieved in all patients. There were no hospital deaths. Four major and two minor postoperative complications were reported, including one allograft thrombosis.

Mu et al.¹⁷ and Wang et al.¹⁸, have each retrospectively analyzed their survival data following resection of T4 NSCLCs which invade the great vessels and left atrium. Neither study documents postoperative complications. In the study by Mu and colleagues¹⁷, 136 patients required resection of the pulmonary artery ($n = 83$), SVC ($n = 21$) or left atrium ($n = 32$). Five-year overall survival was 43% for all patients and 53% in the pulmonary artery group. Wang et al.¹⁸ evaluated 105 patients with tumors invading the pulmonary artery ($n = 57$), SVC ($n = 23$) and left atrium ($n = 25$). They demonstrated similar survival rates, in which 5-year survival for all patients was 41%. In those patients undergoing pulmonary artery resection, 5-year survival was 46% and median survival was approximately 50 months.

Left Atrium

Non-small cell lung cancers can involve the left atrium either via direct invasion or by tumor embolus into the pulmonary vein. Many of the original reports describing resection of tumors involving adjacent mediastinal structures included patients with left atrial involvement, but the extent of atrial wall invasion was unclear^{6, 10-13, 27, 32}. Macchiarini and Darteville³⁴ reported that in 31 patients, 17 with direct invasion and 13 with tumor embolization, resection was associated with a 22% 5-year survival. However, all patients with embolic left atrial disease died of distant hematogenous metastasis with a median disease free interval of only six months³⁰.

In 2004 and 2005, two retrospective reviews were published detailing single institution experiences in the surgical management of T4 lesions invading the left atrium. Ratto et al.³⁵ reported on 19 patients with T4 lesions invading the left atrial wall. Atrial resection was performed by applying a vascular clamp to the left atrium, at times dissecting the interatrial septum for adequate tumor resection and directly suturing the defect. Pneumonectomy was performed in 12 patients and lobectomy in 7 patients. Complete resection was achieved in 11 patients (58%), but a significant percentage (58%) had pathologic N2 disease. Morbidity and mortality were 37% and 0%, respectively. Six patients experienced postoperative arrhythmia, and one had a cerebrovascular accident. Median survival was 25 months and 5-year survival was 14%. Spaggiari et al.³⁶ reported 15 patients who underwent extended pneumonectomy with partial resection of the left atrium. The authors describe a more homogenous population and surgical approach involving intrapericardial pneumonectomy with resection of the left

atrium and dissection along the groove of Sondergaard in an effort to increase the margin of resection. All patients had R0 resections. Morbidity was 15.3% with no major postoperative complications, and mortality was 0%. Long term survival was not reported; median follow-up was 16.5 months. At the completion of the study, nine patients (60%) were still alive, of whom eight had no evidence of disease. In a subsequent publication pertaining to 167 patients with T4 tumors, including 35 patients who underwent left atrial resection between 1998 and 2010, Spaggiari et al.²² reported an overall 5-year survival rate of 27%. Mu et al.¹⁷ and Wang et al.¹⁸ published similar results; respective 5-year survival rates for patients requiring left atrial resection were 18% (n = 32) and 36% (n = 25).

More recently, Galvaing et al.³⁷ published their results of 19 patients who underwent left atrial resection for T4 lung cancer between the years 2004 — 2012. In all patients, left atrial invasion was suspected preoperatively. Cardiac MRI was obtained to assess for the extent of invasion; none had suspected invasion of both atria, the presence of an intraatrial thrombi, or polypoid tumor inside the atrium. Patients were classified according to the extent of dissection along the interatrial septum, with the majority of dissection involving sectioning of the interatrial muscle. The authors report a R0 resection in 17 patients and R1 resection in the remaining 3 patients. Similar to previous reports, a significant number of patients had pN2 disease (37%). Overall postoperative morbidity rate was 53% (n = 10) and operative mortality was 11% (n = 2). The five-year survival rate was 44%. The recurrence rate was 21%; two patients had distant disease and two patients had local disease at the time of recurrence. Interestingly, three patients were alive for greater than six years postoperatively.

Esophagus

Involvement of the esophagus by direct extension of primary lung cancer is rare. However, local invasion has been reported and is typically limited to excision of the muscular wall^{6, 11-19, 21-23, 26, 31, 38}. Associated morbidity, mortality and long-term survival is therefore difficult to quantify. In a univariate analysis of survival rates according to T4 sites of mediastinal involvement, out of eight patients with esophageal resection, one patient survived five years¹³.

Preoperative Workup

The principles of en bloc pulmonary and mediastinal excision for T4 lung cancer must follow a well-defined algorithm during which the patient is thoroughly staged preoperatively and intraoperatively prior to definitive resection. Criteria should include appropriate pulmonary reserve for pneumonectomy, if indicated, and no evidence of mediastinal nodal or distant metastatic disease. Although incapable of definitively documenting aortic invasion by tumor, cardiac MR scans have emerged as highly useful adjuncts for delineating extent of tumor involvement in the mediastinum. Transesophageal echocardiography can also be used to detect left atrial invasion as well as to assess the extent of atherosclerotic disease in the distal aortic arch and proximal descending aorta, which could complicate resection. Histologically normal mucosa must be documented at the site of intended resection, and comprehensive mediastinoscopy should be performed to evaluate subcarinal and contralateral paratracheal nodal stations. Any evidence of contralateral mediastinal nodal

disease is an absolute contraindication to extended resection as expected median survival in patients with N3 disease is only 12 months³⁹ and the benefits of extended resections for patients with ipsilateral N2 involvement are limited at best. If no evidence of nodal disease is detected by mediastinoscopy, one can then proceed directly to thoracotomy or sternotomy to assess resectability and biopsy additional nodal stations not accessible by this technique. Thoracoscopic staging is a possible alternative modality. However, an open procedure minimizes intraoperative time and provides maximal opportunity to thoroughly evaluate all nodal stations. In their analysis of trends in the management and outcomes of T4 lung cancers from 1998-2002, Farjah et al.¹⁹ reported a high proportion (22%) of pN2/N3 disease. The authors suggest that this may be correlated with infrequent use of both PET and mediastinoscopy (10% in the year 2002), advocating for the use of a more extensive preoperative work-up to better select patients with N0-1 disease.

Neoadjuvant Therapy

The use of neoadjuvant therapy to achieve the goals of downstaging locally advanced lung cancers — by reducing tumor size and lymph node involvement, and potentially eradicating micrometastatic disease — can be applied to T4 tumors with invasion of the aorta, pulmonary artery, left atrium or esophagus. Induction therapy used for this subset of T4 tumors is an extension of stage IIIA (N2) preoperative chemotherapy or chemoradiotherapy, which is still heavily debated⁴⁰⁻⁴³. To date, induction therapy followed by extended resection for this small subset of T4 tumors has been disparately employed, with very little data to provide meaningful recommendations.

Conclusion

T4 tumors that invade the heart, great vessels or esophagus comprise a heterogenous group of locally invasive lung cancers. Prognosis is dependent upon nodal status; this relationship has been consistently demonstrated in many of the small series of extended resection. Current NCCN guidelines do not recommend surgery for T4 extension with N2-3 disease (stage IIIB). However, biopsy proven T4 N0-1 (stage IIIA) may be operable¹. Localized tumors with invasion of the aorta, pulmonary artery, left atrium or esophagus, represent a small subset of T4 disease. Acquiring sufficient randomized data to provide statistical proof of a survival advantage for patients undergoing extended resections for these neoplasms will likely never be possible. Therefore, we are left to critically analyze current documented experience to make clinical decisions on a case-by-case basis.

It is clear that the operative morbidity and mortality of extended resections for locally advanced T4 tumors have significantly improved over time, yet the risks are still high. The indications for such procedures and the anticipated outcomes should be clearly weighed in terms of potential perioperative complications and expertise of the surgical team. Patients with T4 N0-1 have the best prognosis and with complete resection may have the potential for cure. The use of induction therapy and surgery for advanced T4 tumors may improve survival. Current data suggest that for tumors which invade the aorta, pulmonary artery, left atrium or esophagus, resection should be considered in relation to multidisciplinary care. For

properly selected patients receiving treatment at high volume, experienced centers, extended resections may be warranted.

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Synopsis

Historically, extended resections for T4 non-small cell lung cancers which invade adjacent organs have been associated with significant morbidity and mortality, and poor long-term survival. However, notable improvements in imaging, surgical techniques and perioperative care during the past several decades have resulted in an increase in survival for highly selected patients. This manuscript provides a critical review of the existing statistical evidence regarding the utility of resections of T4 tumors invading the aorta, pulmonary artery, left atrium and esophagus.

KEY POINTS:

- T4 tumors that invade the heart, great vessels or esophagus comprise a heterogenous group of locally invasive lung cancers.
- Prognosis is dependent on nodal status.
- Resection should be considered in relation to multidisciplinary care.
- Notable improvements in imaging, surgical techniques and perioperative care during the past several decades have resulted in an increase in survival for highly selected patients.

Table 1:

Selected Summary of Extended Resections of T4 NSCLC

Reference	T4 sites of disease	Patients	Morbidity (%)	Mortality (%)	Overall Survival (% at 5 y)
Burt, 1987 ⁶	Aorta, pulmonary artery, esophagus	225	NR	2.7%	9%
Tsuchiya, 1994 ¹⁰	Aorta, left atrium, pulmonary artery, superior vena cava	101	NR	0.1%	13%
Martini, 1994 ¹¹	Aorta, left atrium, pulmonary artery, superior vena cava, esophagus, trachea, spine	102	NR	6%	19%
Bernard, 2001 ¹³	Aorta, left atrium, pulmonary artery, superior vena cava, esophagus, carina, spine	77	NR	NR	21% [*]
Pitz, 2003 ¹⁶	Aorta, left atrium, pulmonary artery, superior vena cava, esophagus, trachea, carina, spine	89	NR	19%	24%
Ratto, 2004 ³⁵	Left atrium	19	37%	0%	14%
Ohta, 2005 ²⁴	Aorta	16	31%	12.5%	48%
Yildizeli, 2008 ²¹	Aorta, left atrium, pulmonary artery, superior vena cava, esophagus, carina, spine, subclavian artery/vein, carotid artery, chest wall	271	35%	4%	61%
Wu, 2009 ¹⁴	Left atrium	46	52%	0%	22%
Yang, 2009 ¹⁵	Aorta, left atrium, pulmonary artery, superior vena cava, esophagus, trachea, carina, spine	146	53%	3.1%	23%
Spaggiari, 2013 ²²	Aorta, left atrium, superior vena cava, carina	167	45%	5%	23%
Galvaing, 2014 ³⁷	Left atrium	19	53%	11%	44%

NR, not recorded

^{*} Survival rate at 3 years