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The Ability of Surgery in T4 Lung Cancer

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ABSTRACT
According to the staging system, T4 cases have been identified as tumors larger than 7cm or invasive tumors on tissues, such as the diaphragm, mediastinum, heart, large vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or separate tumor nodule(s) on a different lobe on the same side. In this manuscript, the srugical treatment of T4 N0-1 lung cancer that made tracheal, carina, vertebra, thoracic inlet, vena cava superior, mediastinal structures and diyafragmatic invasion. Medical literature in the thoracic surgery and oncology network was reviewed, and studies, cases, and meta-analysis studies that included surgical treatment practices in oligometastatic small cell lung cancer treatment and their results were examined. A discussion was made by also analyzing the survival data in light of the literature studies and available guidelines. In recent years, indications of lung cancer surgery have also been expanded in parallel with the advancements in multidisciplinary surgery and in multidisciplinary oncological treatment protocols, and thus surgery has become applicable for more patients. T4 N 0-1 cases are approximately 30 % of all lung cancer cases and despite 5 year survival is about 10 %, there are survival advantages in patients who have complete resection. T4 tumor surgery should be applied in experienced centers and by multidisciplinary surgery teams. Treatment decisions should be individualized, and complete surgery should be considered for NO-1 cases whose activity rate could be high.
Keywords: T4, lung cancer, extended surgery.

INTRODUCTION

In recent years, indications of lung cancer surgery have also been expanded in parallel with the advancements in multidisciplinary surgery and in multidisciplinary oncological treatment protocols, and thus surgery has become applicable for more patients. The eighth revision of the tumor, node and metastasis (TNM) classification was analyzed by the Lung Cancer Society with the participation of more than 100,000 cases, 19 different countries and 46 centers. In this analysis, staging has been changed after careful consideration of the relationship between T, N, M factors and survival rates. The eighth TNM Classification entered into force on January 2017 with the participation of the Union for International Cancer Control and the American Joint Committee on Cancer.

According to the staging system, T4 cases have been identified as tumors larger than 7cm or invasive tumors on tissues, such as the diaphragm, mediastinum, heart, large vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or separate tumor nodule(s) on a different lobe on the same side. It should be noted that superior sulcus tumors turning into Pancoast tumors due to brachial plexus, subclavian artery vein invasions, and artery involvement intracardial intervention should be considered as T4 (1).

Stage III B cases correspond to approximately 30% of all cases. In this group, the 5-year survival rate was reported to be 10%, while there are apparent survival advantages in T4 - N 0-1 cases after complete resection (1).

The term extended resection was first defined by Chamberlain in 1959. This procedure consists of the resection of the tumor creating a local invasion together with the lung. The surgery should be conducted if complete resection is possible, and optimal conditions should be provided for this surgical procedure. Mediastinal lymph node involvement is very important in these cases undergoing major surgery. Even at the slightest doubt, invasive staging must be carried out. Surgery is contraindicated in the presence of N2. However, upper paratracheal lymph nodes for Pancoast tumors and sub-carinal lymph nodes for carinal tumors can be considered as local invasions and can be operated on.

Patients undergoing surgery should have the appropriate cardio-pulmonary reserve; advanced age is a relative contraindication. In order to speed up post-operative recovery in these patients undergoing major surgery, preoperative serum albumin level should be kept above 3 gr/dL, and if necessary, preoperative and postoperative enteral support therapy should be administered.

T4 NSCLC Cases and Surgical Treatment Forms

Trachea-carina invasion

Resection of lung tumor invasion on the lower end of the trachea, trachea bronchial angle, carina and main bronchus, and reconstruction of these areas using bronchoplastic methods (Figure 1-3). Isolated carina resection or carinal sleeve lobectomy can be administered as a tracheal sleeve pneumonectomy (TSP). Although this

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Figure 1. Carinal resection and reconstruction

Locus of the tumor (a); First the trachea, then the left main bronchus and right intermediary bronchus are cut (b); -/3 of back side of end to end anastomosis between the trachea and left bronchus are completed with individual suturing (c); Oval hole where the right bronchus can be anastomosed by removing one cartilage from "^" of the remaining sections is created (d); Finally, the right bronchus is anastomosed to this oval hole with end to end anastomosis, using the continuous suturing technique (e)

Figure 2. Barclay surgery: After carinal resection of the left tracheobronchial tumor, end to end anastomosis of the right main bronchus to the trachea and end to side anastomosis of the left main bronchus to intermediary bronchus

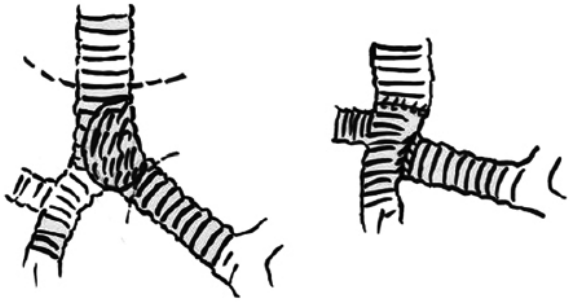
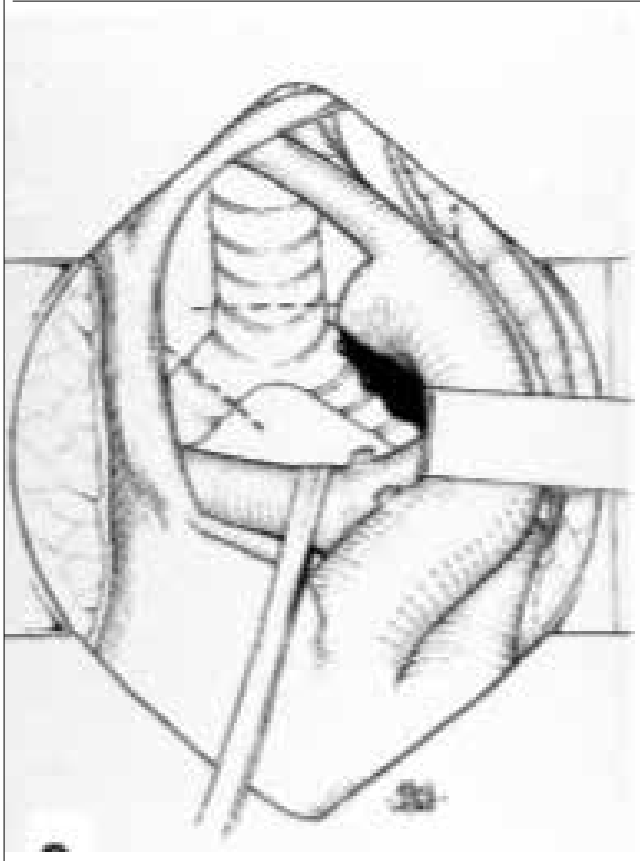


Figure 3. Transsternal approach for left TSP



method is used for NSCLC cases more frequently; it is also used for carcinoid tumor and adenoid cystic carcinoma. Positive surgical margin after standard pneumonectomy is another indication.

Through endotracheal tubes and jet ventilation application, this operation can now be applied without cardio-pulmonary bypass. Planning and staging should be extremely carefully before TSP application, which has a high morbidity rate.

As anastomosis of the trachea and main bronchus can increase the blood pressure, the length of the distal trachea must be limited to 3-4 rings or 2-3 cm, while the left main bronchus invasion must be limited to 1-1.5 cm. Pre-operative bronchoscopic examination, therefore, is highly important. The invasion margin should be measured with care, areas which can be surgical margins should be identified, and a biopsy should be carried out. Even if sleeve lobectomy is planned, it should be noted that TSP can be preferred (2-3).

It should be noted that the tumors localized here can be invasive to the superior vena cava, main pulmonary artery, left atrium and esophagus due to the anatomy of this area; therefore, these areas should be examined preoperatively, using angiography and transesophageal ultrasound.

The most important matter to be considered in the staging process is the presence of N2 disease. Therefore, mediastinoscopy is recommended in the beginning of the operation due to the possible negative effect of preoperative mediastinoscopy-induced inflammation on carinal resection. Furthermore, mediastinoscopy should provide insight for the evaluation of the external pressure on the trachea.

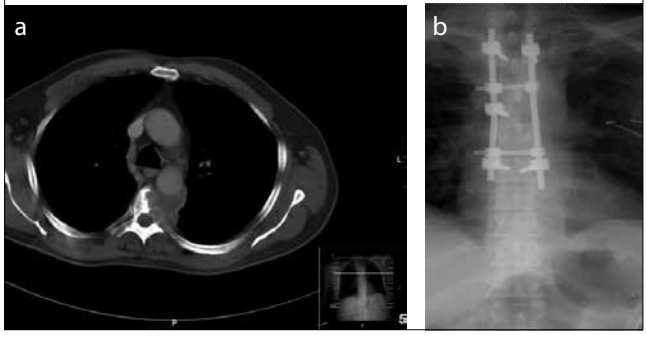
As SVC involvement and sub-carinal lymph node involvement can be totally resected, the first being technically, and the latter locally considered an invasion, they can be operable (2, 3, 4). Carinal sleeve resections can be applied in the right-side lesions more easily than the left ones. Besides this, left-side lesions are the tumors which are more likely to be inoperable because they are invasive to the aortopulmonary window; therefore, left TSP is applied less frequently. In the left-side tumors, first vascular structures are dissected at once trans pericardially with median sternotomy, then the operation is completed with left side thoracotomy. In the two-stage method, first, the carina and the main bronchus are dissected by right thoracotomy during the same session, the left main bronchus is cut, and the operation proceeds in the same way as right TSP. Left pneumonectomy is completed by left thoracotomy conducted in same session (2-4).

In order to prevent impairment in local feeding, excessive use of cautery should be avoided. After the trachea is cut, putting fixation sutures on the main bronchus through the cartilage makes the surgeon's work easier. The anastomosis technique and the materials to be used can change depending on the surgeon's

experience but supporting the anastomosis line with live tissues is important. To relieve the tension that can emerge on the anastomosis line, the inferior pulmonary ligament should be cut, the hilus should be dissected and a U-shaped incision should be made on the pericardium to relieve the tension on the area. In cases with increased tension, jaw wiring should be applied for one week.

It was reported in 1982 that the preoperative complication rate was 29.5% and survival rate was 15%. Dartevelle et al. (5), in his 138 patient series, reported that during the first 30 days, mortality was 9.4% and the average survival rate was 27 months, while 5-year and 10-year average survival rates were 41.3% and 27.7%, respectively. It was determined that the 5-year survival rate for N 0-1 cases and N2-3 cases were 47% and 24% respectively. Also induction treatment increased the intraoperative mortality rate from 6.7% to 13% in Turkey. Yaran et al. (4) applied 11 right and 2 left TSPs to 13 patients, and they reported that the average survival duration was 87 months and 5-year survival rate was 77% (4, 5).

Figure 4. a, b. Preoperative and postoperative images of our case on which total corpectomy with posterior instrumentation were applied



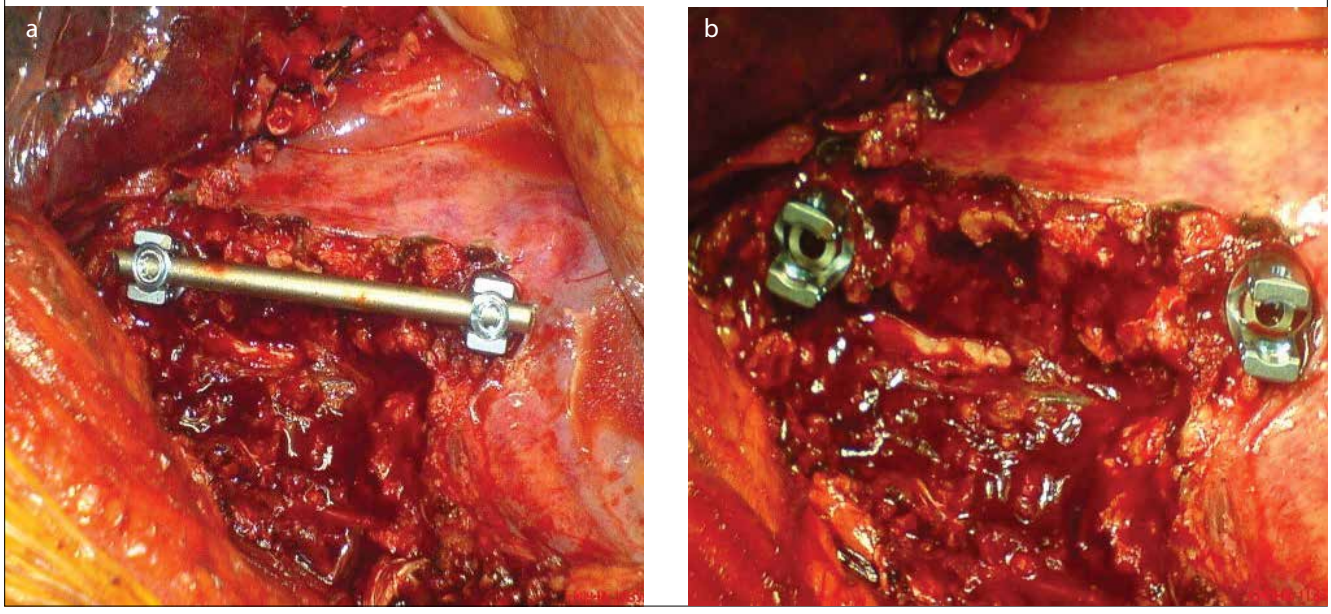
It was reported that the total complication rates in the post-operative period are approximately 30-50%, and the most important complications are anastomosis- induced fistula and empyema at a rate of 8-10%. Due to denervation related to the cutting of tracheobronchial system, mucociliary activity is lost and secretion stasis and pneumonia risk are increased (2-7).

Vertebra invasion

Although vertebra transverse spurs are identified as a T3 tumor, the vertebra bridge is a T4 tumor. Extended lung cancer resections have long been rarely reported for the following reasons: the bone structure of the vertebra is prone to complications that can result in paraplegia due to medulla spinalis, it is difficult to identify complete resection intraoperatively, and spinal surgery is a very different discipline from thoracic surgery. The first serious publications were made first by De Meester in 1989 and then by Ginsberg, and it was emphasized that complete resection is a required to ensure survival (4, 8, 9).

In cases with vertebra invasions, the spread of the tumor, dural sac invasion and compression are evaluated with the thorax and spinal MRI and this evaluation is sufficient most of the time. Spinal cord arteriography, on the other hand, is applied to evaluate anterior spinal artery in tumors with high vascularity. Its involvement is the criterion of inoperability. Thoracic CT determines the spread over the parietal pleura, muscle tissue and chest wall. The degree of vertebra involvement is important for the form of the resection. According to spinal surgeons, while partial or hemi corpectomy are conducted for involvements between 30-50%, total corpectomy and instrumentation to maintain spinal stability are applied for involvements above 50%. For involvements below 30%, the decision to apply instrumentation depends on whether the posterior structures are healthy or not. The issue of which protocols will be applied–a supplementary surgery containing induction

Figure 5. a, b. Instrumentation stages of our case on which anterior hemi corpectomy was applied



chemoradiotherapy treatment or a postoperative adjuvant chemoradiotherapy protocol–is another controversial subject. Medical oncologist and radiation oncologists would rather recommend treatment protocol involving induction treatment, while operating surgeons prefer adjuvant treatment protocols as the stabilization of the used metal instrument in the area receiving radiotherapy is not strong.

Survival analyses change depending on clinics due to the absence of randomized studies. It has been reported that invasion depth does not affect survival in cases where complete resection is applied while incomplete resections do not contribute to survival (10). Koizumi and Haraguchi (10) reported that 1, 3, and 5-year survival rates are 68.6%, 22.9% and 22.9% respectively. At our clinic, we are working with orthopedist spinal surgeons. (Figure 4, 5)

The medulla spinalis damage that can emerge due to the application of intraoperative routine neuromonitorization is predetermined and the patient is protected from paraplegia. An effort is made to conduct the operation in the most unblocked condition possible. For this purpose, the cancerous area is separated from the lung with a stapler and en-bloc resection is performed. Adjuvant treatment is preferred to neoadjuvant treatment. In our series consisting of 12 cases, which is in the publication phase, the first 30-day mortality is not available, while the 1-year survival rate is 87.5 and the 5-year survival is 19.1%.

Thoracic inlet invasion

Thoracic inlet tumors can be investigated under two groups. These are the tumors invasive to subclavian vessels other than anterior type brachial plexus. Posterior type are tumors invasive to the brachial plexus, subclavian vessels, vertebral artery, sympathetic chain, paravertebral muscles and vertebra. Cervical trachea, esophagus, brachial plexus above C8 and vertebra constitute common involvement contraindications. Limited vertebral involvements that can be resected with subclavian vessels and vertebrectomy do not constitute contraindications. Although in the preoperative diagnosis, MRI provide sufficient insight, angiography may still be required to check the condition of the vertebral artery inside the subclavian artery. If the vertebral artery is not well-developed, the patient may have brain infraction (5, 11). Although there are publications suggesting induction radiotherapy, post-operative adjuvant treatments are frequently preferred in the appropriate cases (5).

Even if there is a tendency to apply trans-clavicular cervico-thoracic (Dartevelle incision) thoracotomy to anterior tumors and extended posterior thoracotomy to posterior tumors (Poulson-Shaw incision), Dartevelle et al. (5) as an author on this subject reported that he applied his incisions as trans-clavicular cervico-thoracic applications (Figure 6). This incision is an L-shaped incision extended from the anterior of the sternocleidomastoid muscle to the intercostal area, and clavicle and manubrium resection are required. Through this incision, all anatomic structures can be accessed and checked more easily. It is resected depending on the subclavian artery involvement; end to end graft is anastomosed and the internal jugular subclavian vein can be bonded. T1 is frequently cut from the intervertebral foramen; rib resections, sympathetic ganglions and all invasive tissues are resected in unblocked condition through upper lobectomy. In vertebra involvement, posterior hemi vertebrectomy is added by switching to the prone position; in this case, all the tissue is extracted from the posterior proximity and vertebra instrumentation is carried out.

Dartevelle et al. (5) reported that the complete resection rate is 90.5%, 30-day operative mortality is 0.8%, 5 and 10-year survival rates in N0-1 cases are 41.5% and 29.7%, and 5-year survival rate in N2-3 cases is 9.4%. Subclavian vessels and limited vertebral involvements that can be resected by hemi vertebrectomy are negative prognostic factors, although they do not constitute a contraindication (5).

Figure 6. a, b. Dartevelle (trans-clavicular cervico thoracic) and Poulson Shaw (posterior extended) incisions

a

b

Figure 7. a, b. Tangential primary suture and pericardial patch application

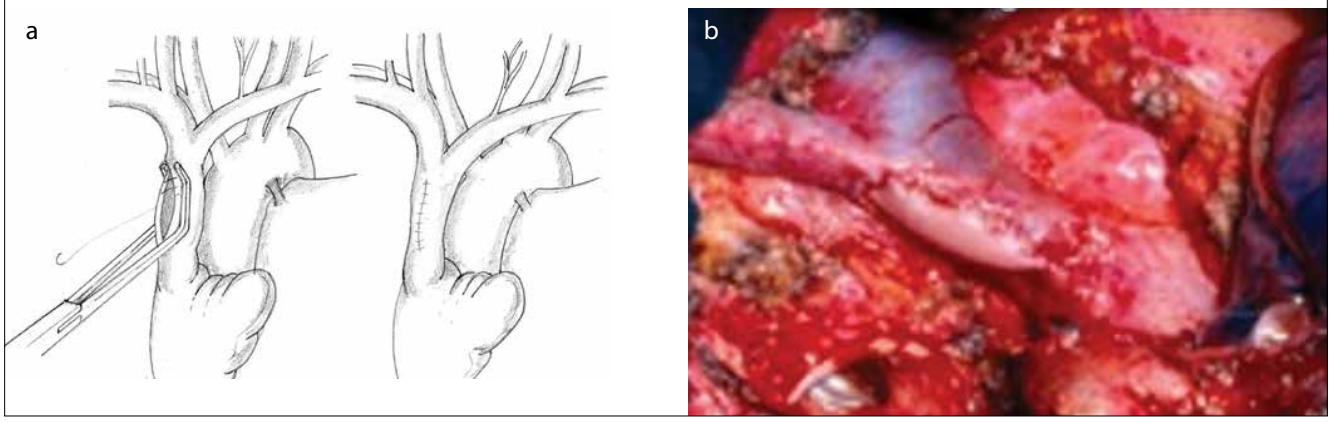


Figure 8. Our clinic's SVC graft application. Right innominate vein totally occluded, left innominate vein-right atrium PTFE graft application with median sternotomy

On the other hand, in tumors which are not completely invasive to the thoracic inlet, the Poulson -Shaw approach is applied and sometimes, both approaches should be used.

Superior vena cava (SVC) invasion

Tumor with invasion into the SVC can happen directly or via the lymphatic gland. The lymphatic gland is surgically contraindicated in invasive cases. In cases where the SVC is fully occluded, the tumor, even if it is resectable, is surgically contraindicated due to both impaired hemodynamics and mediastinal invasion. MRI in preoperative diagnosis, echocardiography for atrial thrombus, and if needed, superior venocavography for the control of innominate vein patency, should be carried out.

In limited invasive cases where the SVC diameter is less than 50%, tangential primary suture or pericardial patch can be applied (Figure 7, 8). When these applications are impossible, clamping, resection and graft replacement must be applied. Posterolateral thoracotomy is usually sufficient; but in case of a difficulty in proximal anastomosis, cervical sternotomy can be added to thoracotomy. Graft replacement is a simple procedure as a vascular surgery in SVC involvement. Graft thrombosis is the main problem due to its structure containing high-rate blood flow at low pressure and since although the native vessel can provide the same response to the atrium pressure by becoming negative, the graft has no such characteristic. Therefore, long-term anticoagulation therapy is required.

The right ventricular preload is decreased as a result of SVC clamping and while systemic hypotension emerges, cerebral venous pressure increases. Therefore, vasoconstrictor agents, 50 IU/kg heparin and intravenous liquid are administered; if not, cerebral perfusion pressure will decrease, and fatal ischemia, intracranial thrombosis and edema will occur. For this purpose, keeping the systemic tension at 100 mmHg is sufficient.

Although internal shunting is recommended, clamping and graft replacement are the ideal methods. It was shown that clamping applied for 30 minutes does not cause any neurological damage. The graft is surrounded by the local tissues after the operation.

Dartevelle et al. (5) reported that the most suitable graft is polytetrafluoroethylene (PTFE), and that administering warfarin certainly provides a graft patency on the condition that the lifetime INR 2-3 level is kept after 2mg/kg/day intravenous hepa-

rin applied for 6 months post-operatively (5). Dartavelle et al.(5) reported the following: 30-day mortality is 8%, 6 months graft patency rate is 88%, average survival time is 23 months, and 5 and 10-year average survival rates are 36.7% and 32.1%. The 5 and 10-year survival rates were identified to be 46.6% and 37.7% respectively in the N0-1 group, and 21% in the N2-3 group (5).

Invasion of mediastinal structures

In tumors displaying central localization, intrapericardial pneumonectomy (IPP) is applied in the case of dissection difficulty and left atrium invasion due to invasion of the pulmonary artery and veins, lymphatic gland and retractions. For anatomic reasons, right central tumors can be invasive to the left atrium because of the right superior pulmonary vein being short. Left hilar tumors are more frequently invasive to the left atrium aorta and esophagus because of the aorta pulmonary window stratum. Therefore, left IPP is used less frequently. As invasion of the mediastinal structures leads to N2 disease, a detailed investigation should be carried out in these cases for neoadjuvant treatment response, persistent N2 presence, and cardiopulmonary capacity secondary to chemoradiotherapy.

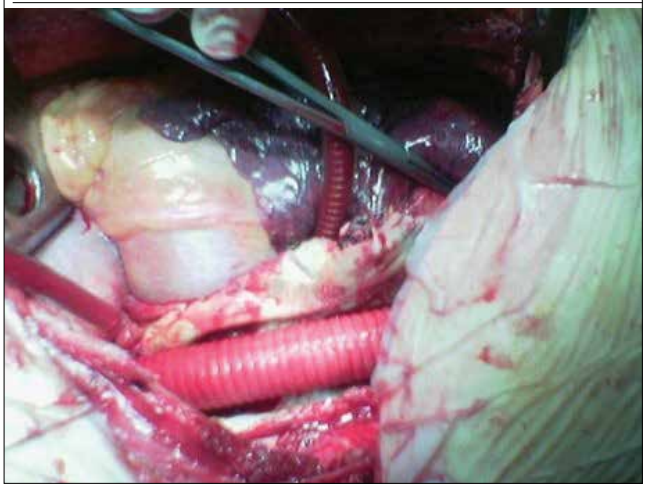
Up to this day, Mitsos et al. (12) have reviewed 14 substantial studies with high evidential value to investigate the application of pneumonectomy in the presence of persistent N2. As a result of this collected work, they reported that surgery can be applied safely and with acceptable mortality rates in cases diagnosed with Stage III-B persistent N2 and who have received neoadjuvant treatment (12). Atrium invasion, intrapericardial pulmonary artery vein invasion, and aorta invasion should be assessed from the viewpoint of cardiovascular surgery. Cardiopulmonary bypass technique can be used together with major aorta and pulmonary truncus surgeries for lung resections.

Atrium resection is the extraction of the tumor involved atrium part together with the pulmonary veins. It is important for the remaining atrium to have the sufficient volume to be tolerated hemodynamically. Therefore, it should be clamped and held for a while before being resected. According to our experience, this takes 5 minutes. In the presence of invasion where a clamp cannot be placed, the atrium is constricted by contour sutures, then resected with scissors. 14 cases have had atrium resection at our clinic between 2002-2010. It was found that the first 30-day mortality is 2.4%, 1-year survival rate is 90.5% and 5-year survival rate is 27%.

The most frequently seen complication of intrapericardial pneumonectomy is arrhythmia and cardiac herniation. Hypotension, tachycardia and venous congestion can develop as a result of the VCI and pulmonary artery being bent in the presence of the right-side defect. Therefore, the pericardium should be closed every time. Strong contraction in the left side prevents herniation. Primarily closing the defects is sufficient. Although some cardiac surgeons recommend that a pericardial drain be placed constantly, we make a small puncture on the right pericardium and place stitches at intervals.

Eleven cases have had surgery due to lung cancer and aorta invasion in the joint study of İstanbul University Cerrahpaşa School of Medicine and Dokuz Eylül University Thoracic Surgery Clinics. Four cases underwent patch plasty and 7 cases underwent graft application. Three cases who underwent patch plasty were operated with a partial clamp, and other cases were operated through cardiopulmonary bypass. The average survival time is 16 months (Figure 9).

Figure 9. Intraoperative image of the patient on whom thoracic aorta partial resection, graft interposition and lower left lobectomy were applied following partial cardiopulmonary bypass on the heart functioning through venous cannulation to the left atrium and artery cannulation to the femoral artery in the case with lower left lobe tumor invasive to the aorta



Diaphragm invasion

Although the diaphragm is an easily resectable organ, the reason why it is classified as a T4 tumor is that it has a lymphatic network and drains directly to the mediastinum and the ductus thoracicus.

Complete resections including the lung and diaphragm are applied. Generally, it can be primarily closed. A reconstruction is applied with PTFE graft, if necessary.

CONCLUSION

It is debatable as to whether induction therapy is a requirement for T4 patients. The fact that published works and studies have been designed to support chemoradiotherapy, and the errors made when choosing patients, provide results favoring induction treatment. According to the results from the most extensive meta-analyses conducted on these publications, it was found that 151 publications were made between 1950-2010, and that all these publications are retrospective cohort studies, with no randomized phase III study and with 2-3 (medium) levels of evidence. Only 15 studies were found to be sufficient in terms of their levels of evidence. These studies recommended surgery as a first line treatment. Similarly, in a study conducted at MD Anderson Cancer Center, 143 cases were examined, and it was found that pre-operative and post-operative radiotherapy influences the survival rate at the same degree if the tumor can be resected at the beginning (14).

When reviewing the valuable studies regarding T4 NSCLC surgery, an average 5-year survival rate between 19.1-57% (6 studies) was determined in T4N0-N2 tumors. Pulmonary artery invasion has the best 5-year survival rate with 52.8%. It was also found that left atrium N0, N1 and N2 had 5-year survival rates of 28.94%, 27.92% and 17.95%, respectively. Meanwhile, the 3-year survival rate was detected to be 100%, 37.1% and 0% for aorta N0, N1 and N2, respectively, 11-29.4% for SVC (4 studies), 28-42.5% for carina (two studies), 16% for vertebral body, and 12% esophagus (13).

T4 tumor surgery should be applied in experienced centers and by multidisciplinary surgery teams. Treatment decisions should be individualized, and complete surgery should be considered for NO-1 cases whose activity rate could be high. For multidisciplinary surgery therapy of T4 NSCLC cases to be conducted with optimal accuracy, prospective randomized studies are needed. However, it is hard to reach a sufficient number of cases eligible for the surgery to be randomized.

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