Introduction

According to the International Agency for Research on Cancer (IARC) GLOBOCAN World Cancer Report (1), lung cancer affects more than 1 million people a year worldwide, holding, by far, the first place among other forms of cancer incidence and mortality in the global male population in women, it is the fourth most frequently occurring malignant tumour—after breast cancer, cervical and colorectal cancer—but it’s the first in mortality rates (1).

In Greece according to the 2008 GLOBOCAN report, there were 6,667 cases recorded, 18% of the total incidence of all cancers in the population. Furthermore, there were 6,402 deaths due to lung cancer, 23.5% of all deaths due to cancer. Therefore, in our country, lung cancer is the most common and deadly form of cancer for the male population. The most important prognostic indicator in lung cancer is the extent of disease. The Union Internationale Contre le Cancer (UICC) and the American Joint Committee for Cancer Staging (AJCC) developed the tumour, node, and metastases (TNM) staging system which attempts to define those patients who might be suitable for radical surgery or radical radiotherapy, from the majority, who will only be suitable for palliative measures. Surgery has an important part for the therapy of patients with lung cancer. ‘Lobectomy is the gold standard treatment’. This statement may be challenged in cases of stage Ia cancer or in patients with limited pulmonary function. In these cases an anatomical segmentectomy with lymph node dissection is an acceptable alternative. Chest wall invasion is not a contraindication to resection. En-bloc rib resection and reconstruction is the treatment of choice. N2 disease represents both a spectrum of disease and the interface between surgical and non-surgical treatment of lung cancer. Evidence from trials suggests that multizone or unresectable N2 disease should be treated primarily by chemoradiotherapy. There may be a role for surgery if N2 is downstaged to N0 and lobectomy is possible, but pneumonectomy is avoidable. Small cell lung cancer (SCLC) is considered a systemic disease at diagnosis, because the potential for hematogenous and lymphogenic metastases is very high. The efficacy of surgical intervention for SCLC is not clear. Lung cancer resection can be performed using several surgical techniques. Video-assisted thoracoscopic surgery (VATS) lobectomy is a safe, efficient, well accepted and widespread technique among thoracic surgeons. The 5-year survival rate following complete resection of lung cancer is stage dependent. Incomplete resection rarely is useful and cures the patient.

Keywords: Lung cancer; non-small cell lung cancer (NSCLC); small cell lung cancer (SCLC); surgery; staging; video-assisted thoracoscopic surgery (VATS); lobectomy
were 6,667 recorded cases, 18% of the total incidence of all cancers in the population. Furthermore, there were 6,402 deaths due to lung cancer, 23.5% of all deaths due to cancer. In men the rates are important. Lung cancer occupies by far the leading position both in incidence rates—5,540 new cases, 26.3% of the total of all cancers in Greece—and in mortality rates—5,321 deaths, a figure that exceeds 32% of all cancer deaths in 2008. Therefore lung cancer is the most common and deadly form of cancer in our country for the male population.

In women, incidence rates are alarming. Lung cancer ranks third after breast cancer and colorectal cancer, but found extremely high mortality. Specifically, there were 1,127 new cases of lung cancer, 7% of all cases of cancer among Greek women in 2008 and 1,081 deaths, a figure that exceeds 10.2% of all deaths due to cancer in that same year.

The treatment for lung cancer depends upon tumour histology (small cell versus non-small cell), extent (stage) and patient specific factors (e.g., age, pulmonary function, comorbidity). The major subtypes of non-small cell lung cancer (NSCLC) include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, in decreasing order of frequency of occurrence.

In recent years there has been great progress in surgical technique and in the art of anaesthesia for lung surgery. Surgical therapy remains the cornerstone in the treatment of lung cancer and is the only way to address that offers long-term survival, at least in terms of patients with early-stage cancer and others who are at more advanced stages, after a very rigorous selection.

The surgical treatment of patients with stage I and II NSCLC

Staging of malignant tumours was a European initiative. Pierre Denoit [1912-1990], a surgical oncologist at Gustave-Roussy Institute in Paris, first started using the tumour, node, metastasis (TNM) classification system to describe the anatomic extent of disease (2). Later on, the International Union against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) adopted this system. For lung cancer, however, the big push came from the United States of America with Clifton Mountain, whose database served several editions and revisions of the TNM classification till the 6th edition (3).

In 1996, another European, Mr. Peter Goldstraw, a thoracic surgeon from the Royal Brompton Hospital, London, UK, lead the initiative to collect a large, international database, within the International Association for the Study of Lung Cancer (IASLC). He was the first Chairman of the IASLC International Staging Committee, and lead all the work of the committee resulting in several data-based recommendations to modify the 6th edition of the TNM classification, that were fully accepted by the UICC and the AJCC. The result was the revised 7th edition, the text of which is identical to the staging manuals of the IASLC, the UICC and the AJCC (4,5). Nearly 60% of the more than 100,000 cases registered in the IASLC database, were from European institutions, which gives evidence of the interest of the continent in lung cancer staging (6).

Surgery is the standard treatment for patients with clinical stage I and II NSCLC (Tables 1,2) in whom there is no evidence of mediastinal involvement prior to surgical resection. Although the role of surgery has not been validated through randomized trials, the favourable results reported in surgical series and the relative infrequency of long-term survival in patients treated without surgery established surgery as the treatment of choice.

The complete removal of the Stage I and II disease ensures a 5-year survival of about 60-80%.

By whom and where will stage I and II SCLC be coped with?

There is a worldwide scientific unanimity, saying that patients with Stage I and II NSCLC should be coped with, by specialized thoracic surgeons in specialized centers.

The specialization ensures a better outcome. It is emphatically considered that thoracic surgeons that exclusively perform thoracic surgeries at a 75% live better.

According to a study by Goodney et al. in 2005, out of 25,545 patients that were submitted to lobectomy or pneumonectomy for lung cancer, patients that were operated in hospitals that applied more than >20 thoracic surgeries a year had a mortality rate of 5.1% if the operation was made by a thoracic surgeon and 6.1% if the operation was made by a general surgeon. Also, in hospitals that had more than >45 thoracic surgeries a year, there was a 5% mortality rate if the operation was made by a thoracic surgeon and 6.1% if the operation was made by a general surgeon (P<0.01) (7).

Besides, a 2009 Farjah et al. study, that included 19,745 patients, showed that patients with lung cancer that were operated by general thoracic surgeons had an 11% lower death risk, as opposed to patients that were operated on by general surgeons (8).

In 2011, Ellis et al. reviewed 222,233 patients that were submitted to thoracic surgeries for lung cancer. The general thoracic surgeons (realized thoracic surgeries in more than 75%) performed better in lymphatic cleansing, morbidity and mortality than general surgeons (realized thoracic surgeries in less than 75%). Ellis et al. concluded that surgeon specialty impacts the adequacy of oncologic staging, in patients undergoing resection for primary lung cancer. Specifically, general thoracic surgeons performed intraoperative oncologic staging significantly more often than their general surgeon and cardiac surgeon counterparts, while achieving significantly lower in-hospital mortality and complication rates (9).

During a systematic study-analysis of articles published
Table 1. TNM classification for non-small cell lung cancer.

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
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<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed, or the tumor is proven by the presence of malignant cells in sputum or bronchial washing but is not visualized by imaging or bronchoscopy</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
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<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
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<tr>
<td>T1</td>
<td>Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, no bronchoscopic evidence of invasion more proximal than the lobar bronchus (not in the main bronchus); Superficial spreading of tumor in the central airways (confined to the bronchial wall)</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≤2 cm in the greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt;2 cm but ≤3 cm in the greatest dimension</td>
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| T                        | Tumor >3 cm but ≤7 cm or tumor with any of the following:  
| T2a                        | Tumor >3 cm but ≤5 cm in the greatest dimension |
| T2b                        | Tumor >5 cm but ≤7 cm in the greatest dimension |
| T3                         | Tumor >7 cm or one that directly invades any of the following:  
| T4                         | Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; or separate tumor nodule(s) in a different ipsilateral lobe |

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<th>Regional lymph nodes (N)</th>
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<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in the ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in the contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes</td>
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<th>Distant metastasis (M)</th>
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<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis</td>
</tr>
</tbody>
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from January 1st 1990 until January 20th 2011, concerning the significance of the amount of incidence and the specialization of surgeons that applied surgical treatment to patients with lung cancer, Von Meyenfeldt discovered that the hospital volume and surgeon specialty are important determinants of the outcome in lung cancer resections (10).

Besides, the Ferraris et al. 2012 study concluded that patients operated on by thoracic surgeons have higher acuity compared to patients operated on by general surgeons. When patients are matched for comorbidities and serious preoperative risk factors, thoracic surgeons have improved outcomes, especially with regard to infectious complications and composite morbidity (11).

Studies have found that in cases involving thoracic surgeons, there is a lower operative mortality and morbidity, improved long-term survival, better adherence to established practice standards, and a lower cost compared with cases involving general surgeons. Some specific processes of care that account for these improved economic, operative, and oncological outcomes have been identified. Others are not yet specifically known and associated with specialization in thoracic surgery (12).
concluded that patients who undergo resection for lung cancer at hospitals that perform large numbers of such procedures are likely to have got complication rates that were twice as high at hospitals with the lowest volume and to survive longer than patients who have such surgery at hospitals with a low volume of lung-resection procedures (13).

Meguid et al. studied 46,951 operations on lung cancer patients and proved that in-hospital mortality is reduced for patients undergoing lung cancer resections at teaching hospitals versus non-teaching hospitals (3.2% vs. 4.0%; P<0.001), with results prominent at all but the highest volume institutions (14).

However Kozower BD and Stukenborg GJ that in 2011, studied 4,460 patients from 436 hospitals, claim that hospital lung cancer resection volume is not a predictor of mortality and should not be used as a proxy measure for surgical quality (15).

Furthermore, in an interesting study by Dimick JB and Welch HG, it is proven that paradoxically, hospitals with a history of zero mortality subsequently experience mortality rates that are the same or higher than those of other hospitals. And in conclusion, the patients considering surgery should not consider a reported mortality of zero as being a reliable indicator of future performance but to take suspicion of the overall performance of the centre (16).

It therefore qualifies as a general view, that patients with operable lung cancer should undergo surgical resection in organized centers with suitable care system and increased volume of cases by qualified and trained thoracic surgeons.

What is the ideal surgery for stage I and II NSCLC?

Surgery is the standard treatment for patients with clinical stage I and II NSCLC, in which there is no evidence of mediastinal involvement prior to surgical resection. Lobectomy, the surgical resection of a single lobe, is generally accepted as the optimal procedure for early stage NSCLC, because of its ability to preserve pulmonary function (17). In patients with early stage NSCLC, video-assisted thoracoscopic surgery (VATS) may be an alternative to open thoracotomy for patients undergoing lobectomy (18).

Indeed, according to Paul et al., which studied 6,323 patients that underwent surgical removal for early stage NSCLC from 2002 until 2007, 5,042 of which open thoracotomy and 1,281 VATS, patients that underwent VATS had less complications, fewer blood losses and consequently needed less transfusions, lower arrhythmia percentage and reintubation, the drainage tube was removed earlier and the hospitalization was shorter, while mortality was the same. The writers conclude that with correctly chosen patients, thoracoscopic lobectomy is preferred to the open (19). However, the study pointed out the smaller duration of the VATS lobectomy, with an average of 173 min as opposed to 143 min.

Also, in 2012 while Park et al. were studying 6,292 patients, out of which 1,523 had VATS lobectomy and 4,769 standard lobectomy, they found out that VATS had fewer complications (38% vs. 44%, P<0.001) and median LOS (5 vs. 7 days; P<0.001). Additionally, the patients undergoing VATS at high-volume VATS hospitals had shorter median LOS (4 vs. 6 days, P=0.001) compared with low-volume VATS hospitals (20).

In 2000 Sugi et al. studied the prognosis of 100 patients with NSCLC stage T1N0M0 out of which 52 were submitted to standard lobectomy and 48 to VATS. The writers concluded that VATS lobectomy with lymph node dissection achieved an excellent 5-year survival, similar to that achieved by the conventional approach. (The overall survival rates 5 years after surgery were 85% and 90% in the open and VATS groups, respectively) (21).

In 2007 De L Stanbridge et al. described an anterior minimally invasive thoracotomy with video assistance and found that this technique of using small anterior minithoracotomy for direct visualization or endoscopic visualization allowed the majority (82%) of patients with a potentially resectable lung cancer at any stage to have a surgically safe lung resection and showed no difference in survival when compared with open approaches (22).

Although it is admitted that nodal staging of NSCLC should be as accurate as possible, the extent of mediastinal lymph
node assessment during surgery is controversial and there is no consensus.

There are different techniques used, ranging from simple visual inspection of the unopened mediastinum to an extended bilateral lymph node dissection. Furthermore, there are different terms used to define these techniques.

There are data which clearly show that systematic sampling or nodal dissection improves intraoperative staging.

The interesting article by Didier Lardinois et al. underlined that in the procedure of selected lymph node biopsy one or multiple suspicious lymph node(s) are biopsied. This is only justified to prove N1 or N2 disease in patients in whom resection is not possible (exploratory thoracotomy) (23).

Sampling is the removal of one or more lymph nodes guided by preoperative or intraoperative findings which are thought to be representative. Systematic sampling means a predetermined selection of the lymph node stations specified by the surgeon.

In systematic nodal dissection all the mediastinal tissue containing the lymph nodes is dissected and removed systematically within anatomical landmarks. For left-sided tumors, in order to get access to the high and low paratracheal nodes, the division of the ligamentum arteriosus can be added, resulting in the mobilization of the aortic arch. It was recommended that at least three mediastinal nodal stations (but always subcarinal) should be excised as a minimum requirement. The nodes are separately labeled and examined histologically. Beside the mediastinal nodes, the hilar and the intrapulmonary lymph nodes are dissected as well (24).

In lobe-specific systematic node dissection the mediastinal tissue containing specific lymph node stations is excised, depending on the lobar location of the primary tumor.

And finally in extended lymph node dissection bilateral mediastinal and cervical lymph node dissection is performed through median sternotomy and cervicotomy.

According to the findings of two randomized studies by Izbicki [2008] and Darling [2011], the mediastinal lymph node dissection (MLND) does not offer a survival advantage for resected stage I NSCLC (25,26).

Additionally a third randomized trial by Takizawa and al. comparing MLND and selective sampling did show that mediastinal lymph node sampling has got the similar effect to systematic nodal dissection in patients with clinical stage I NSCLC (27).

In the American College of Surgeons Oncology Group (ACOSOG) Z0030 trial by Allen et al. demonstrated that complete mediastinal lymphadenectomy adds little morbidity to a pulmonary resection for lung cancer (28).

As noted in the work of Didier Lardinois et al., the extended lymph node dissection of the mediastinum may be associated with excessive morbidity but according to the study of Naruke et al. in patients who had undergone radical operations—pulmonary resection combined with complete or extended MLND there was a significant difference between the prognosis for patients who had metastases to the subcarinal lymph nodes as compared to the prognosis for those who did not. The 5 years survival rates were 9.1% and 29.0%, respectively. In conclusion the procedure can be justified because of a survival benefit (29).

Smaller operations in surgical treatment of stage I and II NSCLC

The standard operation in surgical treatment for lung cancer has been lobectomy with systematic lymph node sampling or mediastinal node dissection. After lobectomy, patients with T1 N0 NSCLC experience up to an 80% 5-year cancer-free survival (30). In an attempt to preserve pulmonary function, in 1973 Jensik and colleagues were the first to suggest that a lesser resection—sublobar, might be an adequate operation for this stage of disease (31). However, the study of Robert J. Ginsburg and Lawrence V. Rubinstein in 1995 was catalytic. They designed a prospective, multiinstitutional randomized trial to compare limited resection with lobectomy for patients with peripheral T1 N0 NSCLC documented at operation. Analysis included locoregional and distant recurrence rates, 5-year survival rates, perioperative morbidity and mortality, and late pulmonary function assessment.

In patients undergoing limited resection locoregional recurrence rates was three times higher (5.4% vs. 1.9%, per patient per year). Overall survival was worse for sublobar resection (5-year survival 56% vs. 73%) but death from cancer was not statistically significant (26% vs. 19% for sublobar resection and lobectomy respectively).

Finally, they demonstrated that limited pulmonary resection does not confer improved perioperative morbidity, mortality, or late postoperative pulmonary function. Because of the higher death rate and locoregional recurrence rate associated with limited resection, lobectomy still must be considered the surgical procedure of choice for patients with peripheral T1 N0 NSCLC (32).

Okada M et al. designed an interesting study to compare sublobar resection (segmentectomy or wedge resection) with lobar resection to test which one is the appropriate procedure for peripheral cT1N0M0 NSCLC of 2 cm or less. Median follow-up was more than 5 years. Disease-free and overall survivals were similar in both groups with 5-year survivals of 85.9% and 89.6% for the sublobar resection group and 83.4% and 89.1% for the lobar resection group, respectively. Multivariate analysis confirmed that the recurrence rate and prognosis associated with sublobar resection were not inferior to those obtained with lobar resection. Postoperative lung function was significantly better in patients who underwent sublobar resection.

The researchers concluded that sublobar resection should be considered as an alternative for stage Ia NSCLCs 2 cm or less,
even in low-risk patients (33).

Koike et al. demonstrated that in patients with peripheral T1N0MO NSCLC whose maximum tumor diameter was 2 cm or less, the outcome of limited pulmonary resection is comparable with that of pulmonary lobectomy. 5-year survival 89.1% vs. 90.1% (34).

El-Sherif et al. compared the outcomes of all stage I NSCLC patients undergoing resection from 1990 to 2003. Lobectomy (577 patients) was the standard of care for patients with adequate cardiopulmonary reserve. Sublobar resection (207 patients) was reserved for patients with cardiopulmonary impairment prohibiting lobectomy. Compared with lobectomy, sublobar resection had no significant impact on disease-free survival (35).

Kates et al. tried to compare survival after lobectomy and limited resection among patients with stage Ia tumors ≤1 cm by using a large, US-based cancer registry. They identified 2,090 patients with stage I NSCLC ≤1 cm in size who underwent lobectomy or limited resection. They ultimately concluded that limited resection and lobectomy may lead to equivalent survival rates among patients with stage I NSCLC tumors ≤1 cm in size (36).

Wisnivesky et al. using the Surveillance, Epidemiology, and End Results registry, linked to Medicare records, identified 1,165 cases of stage I lung cancer < or =2 cm in size that underwent lobectomy or limited resection. The researchers found that survival of patients >65 years of age undergoing limited resection or lobectomy for stage Ia tumors < or =2 cm appears to be similar and conclude that limited resection may be an effective therapeutic alternative for these patients (37).

Some studies have shown low rates of surgical treatment of elderly patients with lung cancer due to morbidity and mortality.

However, the reported perioperative mortality of patients undergoing lobectomy with thoracotomy are 2% for age <60 years, 5% for age 60 to 69 years, 6% for age 70 to 79 years and 8% for age >80 years.

Moreover, perioperative mortality of patients undergoing pneumonectomy with thoracotomy is 7% for age <70 years, 16% for age 70 to 79 years and 28% for age >80 years (38).

But in a Mery et al. study with 14,555 patients it was proved that the median survival times were 71, 47, and 28 months, respectively, for patients <65, 65 to 74, and > or =75 years of age (P<0.0001). For the young patients, lobectomies conferred better survival times than limited resections. However, the statistical difference in long-term survival between those patients undergoing lobectomies and those undergoing limited resections disappeared at 71 years (39).

Dominguez-Ventura et al. studied the predictors of morbidity and mortality after pulmonary resection for lung cancer in 379 patients 80 years of age or older. Lobectomy had a higher risk of preoperative complication versus sublobar operation (51% vs. 36%) but 30-day mortality was not statistically significant (5% vs. 8.4%) for lobectomy and sublobar resection respectively. The overall operative mortality was 6.3% and significant predictors were congestive heart failure and prior myocardial infarction. Factors not associated with mortality included previous myocardial revascularization, renal insufficiency (creatinine >1.5 mg/dL), and diabetes mellitus (40).

All these data showed that sublobar resection in appropriate selected patients, result in reasonable outcomes. But clearly notes that the general condition of the patient dictates decisions and affects the type of surgery that was finally progressing and not chronological age.

**Which of the smallest operations in surgical treatment of stage I and II NSCLC, surpasses, segmentectomy or wedge resection?**

Undoubtedly the segmentectomy has the advantage of complete ablation of the vascular and lymphatic drainage of the primary tumor but also appears to provide better parenchymal resection limits.

Sienel et al. decided to analyze the cancer-related survival of the wedge resection with systematic lymphadenectomy and the segmentectomy with systematic lymphadenectomy in patients with stage I lung cancer. There were significantly less locoregional recurrences and a better cancer-related survival following segmentectomies compared to wedge resections. Therefore if limited functional operability requires a sublobar resection for a patient of stage I NSCLC, the authors conclude that it is preferable segmental with systematic lymphadenectomy resection of the wedge (41).

Nakamura et al. compared the surgical outcomes of lobectomy, segmentectomy and wedge resection by VATS for clinical stage I NSCLC, retrospectively. The 5-year survival rates for the lobectomy, segmentectomy, and wedge resection groups were 82.1%, 87.2%, and 55.4%, respectively (42). These and other data suggest strongly that wedge resection for clinical stage I NSCLC should be carefully indicated and requires adequate patient selection.

**What are the safest, ideal margins of excision? What are the safest, ideal margins of resection?**

There are few studies that determine safe margins of excision. In 2000 Kara et al. showed that a bronchial resection margin of 1.5 cm in length from the macroscopic tumor will provide tumor-free margins in 93% of NSCLC cases. The Authors found that Adenocarcinoma showed more peribronchial extension (80.0%) whereas squamous cell carcinoma (63.6%) showed more bronchial extension (43).

This rule overturned the findings of Tomaszek. Tomaszek et al. studied 3,936 consecutive pulmonary resections that were performed between 1992 and 2007 at Mayo Clinic and showed that when complete surgical resection is achieved, the extent of the
bronchial margin has no clinically relevant impact on disease-free and overall survival in early-stage non-small-cell lung cancer. Therefore, they demonstrated that R0 resection is the best treatment (44).

Sawabata et al. in 2004 showed that the rate of malignant negative margins was 100% when the margin distance was greater than 20 mm, and the rate of malignant negative margins was 100% when the resected tumors had a margin distance greater than the maximum tumor diameter (45).

According El-Sherif et al. margin is an important consideration after sublobar resection of NSCLC. Wedge resection is frequently associated with margins less than 1 cm and a high risk for locoregional recurrence (46). In conclusion sufficient and safe margin of sublobar resection is considered of 2 cm.

Therefore, the best treatment of patients with stage I or II lung cancer are lobectomy with systematic lymphadenectomy, which is preferable to apply VATS in specialized centers with experience and knowledge.

Sublobar resection (segmentectomy versus wedge resection) is recommended for patients with decreased pulmonary function who may tolerate operative intervention.

Necessary to achieve clear margins above the maximum tumor diameter for lesions less than 2 cm and limits at least 2 cm for tumors greater than 2 cm.

Surgical treatment of the tumors invading chest wall (tumor T3)

Stoelben and Ludwig demonstrate that lung cancer invasion of the chest wall is not a common challenge and represents only about 5% of all patients resected for lung cancer and that in T3N0M0 tumours long-term survival reaches 40-50% (47) (Figure 1).

Magdeleinat et al., found that the completeness of resection, nodal involvement, depth of invasion, and age affect the survival of patients with lung cancer invading the chest wall. The authors believe that N2 disease should not be considered a contraindication to surgery because it seems that the actuarial 5-year survival after complete resection was 21% in T3N2 disease (48).

Sanli et al. and Deslauriers et al., reported that the most important factors affecting the survival in both T3 and T4 tumors (vertebra) as well as Pancoast tumors are the complete resection application and the pathologic nodal status (49,50).

In their study on 107 patients who underwent surgical resection for chest wall invading NSCLC, Lee et al. agree that the completeness of resection, nodal status, depth of invasion, tumor size, and adjuvant chemotherapy were prognostic factors for long-term survival. Overall 5-year survival rate was 26.3% (51).

The best materials for the restoration of the chest wall are: methyl metacrylate, polytetrafluoroethylene (PTFE), metallic rods and plates (52,53) (Figure 2).

Miller et al., reconstructed the chest wall with biomaterials. Their early results are promising. Biomaterials may be the preferred method of reconstruction for infected chest wall sites (54).

Berry et al., describe a new hybrid technique where thoracoscopic techniques were utilized to accomplish the pulmonary resection and a limited counter incision was used to perform the en-bloc resection of the chest wall, avoiding scapular mobilization and rib spreading (55).

Cerfolio et al., within the last years, used a new technique that avoids cutting of the extravascular (trapezius, rhomboids, serratus anterior) muscles. Ribs with invading cancer are resected from inside of the chest instead of cutting the uninvolved muscles over them. The approach used, can be a thoracotomy, robotic, or video-assisted technique (56).

Burkhart et al., in their work on 95 patients with lung cancer

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**Figure 1.** Lung cancer invading the chest wall.

**Figure 2.** This material, Proplast IA, is used for reconstruction of the extended chest wall defect.
invading the chest wall who underwent en bloc lung and chest wall resection found that this operation was safe but associated with significant morbidity. The best survival is observed in women who have T3N0M0 disease (stage IIB) (57).

Surgical treatment of the tumors invading diaphragm (tumor T3)

Invasion of the diaphragm is classified T3 in the new 7th TNM classification.

Weksler et al. studied from January 31, 1974, to August 17, 1995, a total of 4,668 patients that underwent exploration for resection of NSCLC at Memorial Hospital. By analyzing the database they identified eight patients (0.17%) who had exploratory thoracotomy for resection of NSCLC invading the diaphragm. The authors believe that patients without involved mediastinal nodes and in good general condition, diaphragmatic invasion should be treated by resecting the tumor “en bloc” with the diaphragm (58). Rocco et al. reported that T3 lung cancer disease invading the diaphragm is best treated with en bloc resections with wide tumor-free margins and prosthetic replacement of the diaphragm. The actuarial 5-year survival was 20% (59).

However, Yokoi et al. in their study on 63 patients who underwent resection of T3 lung cancer invading the diaphragm concluded that in selected patients with lung carcinoma and diaphragmatic invasion, combined resection of the lung and diaphragm offers the prospect of cure with acceptable mortality. The authors believe that primary lung tumors with diaphragmatic invasion, especially invasion of the muscle layer or deeper tissue, are not considered to be T3 lesions, because these cancers are generally technically resectable but oncologically almost incurable (60).

Survival is better, in patients with T3N0M0 disease, as well as with lung cancer invading the chest wall. Wide margins should be achieved. Direct primary repair of the diaphragm is possible in patients with limited invasion. In those with extensive involvement, complete resection and reconstruction of the diaphragm with a mesh (PTFE) is recommended (61).

Surgical treatment of pancoast tumors (superior sulcus tumors-T3 disease)

Non-small-cell lung carcinomas of the superior sulcus, frequently termed Pancoast tumours, are some of the most challenging thoracic malignant diseases to treat because of their proximity to vital structures at the thoracic inlet. Originally deemed universally fatal, Pancoast tumours are now amenable to curative treatment because of improvements in combined modality therapy and development of new techniques for resection.

Kappers et al. reported that the combination of radiotherapy and concurrent chemotherapy followed by surgery (trimodality treatment) is currently regarded as optimal treatment for NSCLC of the superior sulcus or Pancoast tumour. The 2- and 5-year survival after induction treatment and surgery was 75% and 39%, respectively. Local recurrence rates were 0% after induction treatment and surgical resection, 32% after concurrent chemoradiotherapy and 72% after (sequential) radiotherapy and/or chemotherapy (62).

Kunitoh et al., concluded that this trimodality therapy (chemotherapy, radiotherapy thoracotomy) is safe and effective for the treatment of patients with superior sulcus tumors (63).

Yildizeli et al. recorded a successful outcome on 126 patients with superior sulcus tumors who underwent surgical treatment. Overall 5-year survival rate was 36.6% (64).

In their study, Demir et al. investigated the treatment modalities and factors influencing survival in surgically treated superior sulcus tumors and concluded that the presence of N2 disease and incomplete resection are the two most important factors affecting survival while induction chemotherapy/radiotherapy may increase the ability to achieve complete surgical resection (65).

Vos et al., report their experience on 54 patients that were treated by chemotherapy (cisplatin/etoposide) and concurrent radiotherapy (46-66 Gy) followed by surgical resection. A complete (R0) resection was performed in 82% of 54 patients and 2-year survival was 50% (66).

In conclusion, pancoast tumors (superior sulcus tumors or apical lung tumors) typically invade structures at the thoracic outlet, including the inferior elements of the brachial plexus (C8, T1 nerve roots and lower trunk). Historically, these tumors are rapidly fatal, but newer treatment with induction chemotherapy and radiotherapy, followed by surgical resection of the tumor has resulted in improved patient survival (67).

Surgical treatment of the patients with stage III

Historically, stage III lung cancer was defined as locoregionally advanced disease attributed to primary tumor extension into extrapulmonary structures or mediastinal lymph node involvement without evidence of distant metastases. Stage IIIa disease [T1, T2N2M0, T3N1, N2M0, T4 (two nodules in the ipsilateral lung, extension to adjacent organs) N0, N1, M0]. We have accepted the division of this patient group into three main subgroups:

(I) Patients disclosed intraoperative N2 disease despite thorough preoperative staging;

(II) Patients with preoperative evidence of N2 disease based on the findings of CT or CT-PET;

(III) Patients with disease apparently invaded the lymph nodes of the mediastinum (N2 involvement), bulky disease.
Patients with occult N2 disease despite thorough preoperative tests

In this group of patients shows “unexpected” mediastinal nodal involvement intraoperative (Figures 3, 4).

Goldstraw et al., in an interesting study which included 876 patients operated with NSCLC concluded that despite rigorous preoperative investigations, routine mediastinal node dissection demonstrated mediastinal node metastasis for the first time at thoracotomy in 26% of their patients (68).

Cerfolio et al., observed that in over 137 patients staged as N0 using PET/CT and CT, only 4.7% had N2 disease after surgery (69).

Al-Sarraf et al., in their study in 2008, found that over 215 patients with NSCLC who are clinically staged as N2/N3 negative in the mediastinum by integrated PET-CT, 16% will have occult N2 disease following resection (70).

Therefore even the diligent preoperative staging with modern testing shows that the true “unexpected” positive N2 disease is about 16%.

Allen et al., in their study with 1,023 patients, concluded that there is no significant statistical difference on morbidity and mortality of patients undergoing lymph node sampling or lymph node dissection (71).

The role of primary surgery in the management of occult N2 disease, “unexpected” mediastinal nodal involvement showed intraoperative, is important.

The surgery should be continued, with a lobectomy performed and MLND. Many surgeons have serious reservations whether the radical resection of the disease requires pneumonectomy. The overall 5-year survival rate of the patients with N2 disease identified, “unexpectedly”, at thoracotomy who undergoing complete and effective surgical resection is 30%. This is the conclusion of Rusch in their work published in 1996 (72).

However, it is important to emphasize that the proportion of patients in whom complete resection (R0 resection) is not achieved is about 35% for N2 disease (73).

Some authors claim the cancellation of surgery if complete resection is impossible since the 5-year survival is <5% (74).

Patients with preoperative evidence or suspected N2 disease

First of all, patients in whom the possibility of N2 involvement is suspected must undergo a careful staging evaluation (75).

A 2007 Cochrane meta-analysis by Burdett et al. about the role of pre-operative chemotherapy in the treatment of patients with non-small cell lung staging I-III showed that pre-operative chemotherapy increased survival with a hazard ratio of 0.82 (95% CI: 0.69-0.97) P=0.022 (76).

Similarly in a previous study when this meta-analysis limited to only patients with stage III disease a 0.73 (95% CI: 0.51-1.07; P=0.1) hazard ratio was found.

Additionally, in their work Gilligan et al. researched whether patients with operable NSCLC of any stage, outcomes could be improved by giving platinum-based chemotherapy before surgery. Finally the authors concluded that there was no evidence of a difference in overall survival with neo-adjuvant chemotherapy (77).

Therefore, thorough analysis of these data demonstrates that patients with N2 disease identified preoperatively (or suspected) to be treated more favorably with neo-adjuvant chemotherapy followed radical resection.

However, many authors have been talking about whether there are certain subsets of patients with N2 disease in whom primary surgery is the best treatment. It seems that there are no safe criteria for the selection of patients.
Patients with bulky (unresectable) disease

Patients with extensive disease (bulky) are treated with a combination of chemotherapy and radiotherapy. However, for this group of patients the optimal therapy has not been determined yet (78) (Figures 5, 6).

Treatment of patients with NSCLC stage IIB disease

Unfortunately, most patients with lung cancer are diagnosed when the cancer is already advanced (stage IIB or IV), and they are no longer candidates for surgical resection (79). At stage IIB, classified patients with tumors T4N2M0 and any TN3M0. N3 lung cancer disease means: Metastasis in the contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes. T4 lung cancer disease means: tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; or separate tumor nodule(s) in a different ipsilateral lobe. These patients are considered inoperable (80).

Lung cancer surgery with solitary brain metastasis

Brain metastases occur in 30% to 50% of patients with NSCLC and confer a worse prognosis and quality of life (81). Some patients with resectable NSCLC have simultaneously solitary brain metastasis. This specialized group of patients is treated with removal of solitary brain metastasis followed by surgical resection of the primary tumor of the lung. Read et al., found that the survival rate after curative lung and brain resection was 21% at 5 years (82).

It is known by the work of Patchell et al., who showed that patients with cancer and a single metastasis to the brain who receive treatment with surgical resection plus radiotherapy live longer, have fewer recurrences of cancer in the brain, and have a better quality of life than similar patients treated with radiotherapy alone (83).

Burt et al., on 185 patients undergoing resection of brain metastases from NSCLC recorded the overall survival rates were as follows: 1 year, 55%; 2 years, 27%; 3 years, 18%; 5 years, 13%; and 10 years, 7% (median 14 months) (84).

Trillet et al. note that patients treated with surgery have a better survival (median 10 vs. 4.5 months) than the others, and among surgically treated patients only those treated with bifocal resection are long-term survivors (85).

Billing et al., in their work with 220 patients that underwent surgical treatment for brain metastases from NSCLC, argues that although the overall survival for patients who have brain metastases from NSCLC is poor, surgical resection may prove beneficial in a select group of patients with synchronous brain metastases and lung cancer without lymph node metastases with survival at 5 years about 21% (86).

Hu et al., reached to an interesting conclusion according to which the thoracic stage I NSCLC patients with solitary brain metastases in their study had a more favourable outcome than would be expected and was comparable to stage I NSCLC without brain metastases (87).

Lo et al., reported their surgical experience on 17 patients with synchronous primary lung cancer and solitary brain metastasis treated by pulmonary resection and neurosurgical intervention with a 5-year survival of about 27% (88).

Villarreal-Garza et al., in their study reviewed published series of patients with NSCLC and with brain metastases treated with aggressive thoracic management, with either lung tumour resection or thoracic radiation with or without chemotherapy as a
definitive treatment. Patients treated with aggressive radiotherapy with or without chemotherapy, achieved a 2-year survival of 16-60%. Patients treated with surgical resection for the primary lung tumour, achieved a 5-year survival by 11-24% (89).

Today solitary brain metastases are treated with surgery. Craniotomy is performed first, followed by thoracotomy shortly (2-3 weeks) after. The overall 5-year survival for patients with NSCLC and solitary brain metastases may reach up to 25%.

### Lung cancer surgery with solitary adrenal metastasis

In the 1980s several cases of simultaneous resection of NSCLC and adrenal metastasis with long-term survival were reported. However, first Porte et al., suggested the resection of synchronous lesions, solitary adrenal gland metastases, in 11 patients with operable NSCLC without N2 involvement with no additional mortality or morbidity (90). In 2001 the same author and coauthors confirmed the possibility of long-term survival after resection of isolated adrenal metastasis from NSCLC on 11 patients. Median survival was 11 months and 3 patients survived more than 5 years (91).

Pfannschmidt et al., on 11 patients that underwent curative resection for metastatic NSCLC of the adrenal gland concluded that adrenalectomy for clinically solitary, resectable metastases can be safely performed (92).

Sebag et al., emphasized on the benefits of a laparoscopic approach of tumor resection (93).

Mordant et al. found that NSCLC patients with synchronous solitary adrenal may benefit from lung resection on a curative intend in the case of adenocarcinoma and N0 extension whose complete resection is achievable with a lobectomy (94).

Kozower et al., believed that highly selected patients with a solitary focus of metastatic disease in the brain or adrenal gland appear to benefit from resection or stereotactic radiosurgery. This is particularly true in patients with a long disease-free interval (95).

Griffioen et al., in a recent work argue strongly that radical treatment of selected NSCLC patients presenting with 1-3 synchronous metastases, can result in favorable 2-year survivals (96).

### Surgery in SCLC

SCLC is considered a systemic disease at diagnosis, because the potential for hematogenous and lymphogenic metastases is very high. For many years, the diagnosis of SCLC was considered a contraindication for surgery because radiotherapy was at least equivalent in terms of local control, and the rate of resectability in SCLC patients was poor. When chemotherapy became the mainstay of treatment for SCLC, radiotherapy was its logical complement, and surgery was progressively abandoned.

However, the role of surgical intervention in the multimodality management of SCLC continues to be controversial. At most, only 5-8% of patients with this disease can be considered initially as potential surgical candidates. These are patients who can be clinically classified as having stage I, II or resectable stage IIIa disease, as defined by the International TNM. This small group of patients comprises 15-25% of patients with limited disease. Actually, this number is even smaller, if one excludes patients with N2 disease.

The efficacy of surgical intervention for SCLC there is not clear.

Yu et al., studied the clinical outcomes of patients undergoing surgical treatment for stage I SCLC from 1988 to 2004. They concluded that surgical intervention seems to offer reasonable overall survival results in a cohort of stage I patients who undergo lobectomy (97).

Koizumi T et al., between January 1991 and December 2010, thoracotomy was performed in a total of 3,776 cases of primary lung cancer. Among them, 69 cases of SCLC. In these lobectomy was performed in 53 patients, pneumonectomy was performed in 3 patients and segmentectomy or partial resection was performed in 13 patients.

According to the pathological stages in patients with resected SCLC, the 5-year survival rate was 43.1%, in stage I, 37.8% in stage II, and 17.7% in stage III, respectively.

Authors of the study showed that the clinical outcomes in patients initially underwent surgical resection for SCLC, are favourable and demonstrated a 5-year survival rate of 34.3% (98).

Chandra et al., reported an overall 5-year survival rate of 27% on 67 patients, who underwent thoracotomy for SCLC (99).

Lim et al. recently described good results at a 5-year survival rate of 52% for patients with limited disease SCLC stage I to III, who underwent lung resection (100).

In conclusion, many interesting studies agree that the indications for surgical interventions for SCLC are:

(I) Achieving local control of the disease;

(II) Treatment for tumours with mixed histology (SCLC and adenocarcinoma of the lung);

(III) In cases without lymph node metastasis after nodal evaluation using diagnostic imaging such as PET-CT, and mediastinoscopy or EBUS-TBNA (101-103).

### Advances in surgical treatment of lung cancer

Treatment of lung cancer is progressing rapidly, with significant advances in all modalities, including surgery, radiation, and chemotherapy. Although the best therapeutic approach for NSCLC is a multimodality therapy, surgical removal remains the cornerstone for early stage carcinomas (104). Lung cancer resection can be performed using several surgical techniques. Location, number and extension of surgical incisions, total or partial muscle sparring techniques, VATS and the use of robotic
devices for camera holding or fine vascular and lymphatic dissections are some of the variables considered when planning lung cancer resection (105). VATS lobectomy is a safe, efficient, well accepted and widespread technique among thoracic surgeons, but standard VATS forceps have rigid extremities and do not mimic wrist angulated movements. Furthermore, traditional VATS video-imaging is a simple two dimensional image (106). Robotic surgery is performed with telemanipulated flexible effector instruments; some of which can give surgeons tactile feedback; and under three-dimensional (3-D) video-imaging. Hilar pulmonary dissection for lung cancer can be performed by robotic devices in an efficient and safe way (107,108).

More indications for thoracoscopic treatment of lung cancer

Thoracoscopic lobectomy is well established for the treatment of early NSCLC. Its safety and efficacy for advanced-stage disease remain uncertain. Hennon and colleagues in 2011 found that thoracoscopic lobectomy for advanced-stage NSCLC can be performed safely, with results equivalent to open techniques. In their study on 125 patients there were no differences between the thoracoscopic and open groups in overall survival (43.7 vs. 22.9 months; P=0.59) and disease-free survival (34.7 vs. 16.7 months; P=0.84) (109). Although the effectiveness of surgical assisted thoracoscopy regarding disputed radicalness of lymphadenectomy but newer techniques arise which facilitate the treatment of patients with lung cancer. (Fluoroscopy assisted thoracoscopic resection, Video-assisted radiofrequency ablation, Single-Excision Thoracoscopy etc.) (110-113). The limits of thoracoscopic resections are expanding, with improved instruments for manipulating and dividing tissues as the bone. So the removal of the chest wall can be applied with thoracoscopy (114).

Wu applied thoracoscopic lobectomy in 36 patients using anaesthesia without tracheal intubation (using epidural anaesthesia, intrathoracic vagal blockade, and sedation) and showed that non intubated thoracoscopic lobectomy is technically feasible and was as safe as thoracoscopic lobectomy performed with tracheal intubation in the geriatric lung cancer patients (115). To minimize this damage, Oda et al., used total port-access, video-assisted thoracoscopic lobectomy via the subcostal trans-diaphragmatic approach by using three 5-mm intercostal ports and one 15-mm subcostal trans-diaphragmatic port for endostaplers and instruments >5 mm in diameter. The researchers believe that this approach is feasible and safe, easy for experienced VATS surgeons to learn, and has the potential advantage of minimizing postoperative pain (116). Akiba et al., demonstrate the utility of SECUREA, a polyurethane sponge with a radiopaque marker, for complete thoracoscopic MLND in patients with NSCLC (117).

In conclusion, VATS is emerging as a therapeutic option for a variety of thoracic applications. When applied to the patient with lung cancer, the therapeutic benefit of VATS lobectomy appears to be confined to node-negative, relatively small tumours. Operable patients with larger tumours are currently best served by thoracotomy and MLND. As an alternative to thoracotomy for stage I lung cancer, VATS lobectomy is associated with less postoperative pain, less surgical morbidity, fewer complications, and shorter hospitalization. Additionally, improved technology and instrumentation now allow for equivalent and sometimes superior surgical retraction and exposure that can mimic that of an open operation.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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