

Original Article

Analyzing the surgical resection of lung cancer

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Abstract: *Background:* Lung cancer is the leading cause of cancer deaths worldwide, compounded by late diagnosis. Tumor resection by surgery has been performed for selected lung cancer patients in specialized centers over the last century. Despite encouraging results from case-series reports, there remains a lack of robust clinical analysis of prevalent surgical techniques, especially in cases of pre- and post-operative smokers. The present systematic review and meta-analysis aimed to assess the different surgical techniques, their success rate and the various compounding factors that dictate the success of the intervention. *Methods:* A systematic search was performed using Ovid; Medline & E mbase, EBSCO; CINHAL, PsychINFO & SocINDEX and Cochrane Library databases to identify relevant studies. *Results and conclusions:* The identified studies were too heterogeneous to be combined using a formal meta-analysis. Therefore, a narrative synthesis was performed. Advances in operative and postoperative care have led to a decline in complications; however, mortality rates during the last decades have increased due to incidence of associated co-morbidity. The optimal timing of smoking cessation before lung resection is not known; however, it is highly recommended that lung cancer patients completely quit smoking to enhance the effectiveness of both surgical and chemotherapeutic treatment. There is a need to conduct more methodologically sound studies.

Keywords: Lung cancer, surgical resection, smoking cessation

Introduction

The public health significance of lung cancer is reflected by the fact that this disease is one of the most common cancers in the world and it has a high case fatality rate. In the span of a few decades, lung cancer has gone from being a rare disease to the most common cancer worldwide and the greatest cause of cancer death globally [1, 2]. In 2008, lung cancer accounted for 13% (1.6 million) of the total cases and 18% (1.4 million) of the deaths, worldwide [2]. Non-small cell lung cancer (NSCLC) comprises 80% of all cases. Mortality from lung cancer basically occurs through the metastatic spread of malignant cells to distant organs.

It is estimated that only 10% of new cases of bronchogenic carcinoma are potentially cured by surgery [3]. Surgery is the treatment of

choice for patients with stage I-II disease and selected patients with stage IIIA disease. Compared with radiotherapy in early stage disease, surgical treatment is the best alternative [4]. In European countries the proportion of patients with diagnosed lung cancer who undergo surgery for lung cancer varies between 10 and 20% [5, 6]. In the UK the resection rates in some areas are around 10%, but with quick access investigations the rate can easily be increased to 25% [7]. In the United States it is estimated that approximately 25-30% of patients with NSCLC are offered surgery with curative intent [8].

Surgery for tuberculosis formed the basis for lung cancer surgery techniques, but after the introduction of potent drugs for tuberculosis in the 1950's, lung cancer surgery became the major focus in chest surgery [9]. The first successful pneumonectomy was performed in

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1933 by Drs. Graham and Singer in the USA [10]. The rate of complications was high during the first years, with a reported early mortality of 30% in 1944. The rate of explorative thoracotomy without resection was also high (50%) [11]. By 1940 lobectomy and pneumonectomy were performed regularly for NSCLC with remarkable progress in early surgical results [9]. During the next decades, radical pneumonectomy remained the golden standard, with a relatively low operative mortality, to be replaced in the 1960s by lobectomy as the standard in localized disease, resulting in a better surgical outcome and greater pulmonary reserve [12].

Despite encouraging results from case-series reports, there remains a lack of robust clinical analysis of prevalent surgical techniques, especially in cases of pre- and post-operative smokers. Therefore, the objective of the current study was to perform a systematic review and meta-analysis aimed to assess the different surgical techniques, their success rate and the various compounding factors that dictate the success of the intervention.

Materials and methods

Search strategy

The following electronic databases were used to identify suitable studies: Ovid; Medline & Embase, EBSCO; CINAHL, PsychINFO & SocINDEX and Cochrane Library. These were searched using the following search terms including the Boolean operator "AND": [lung cancer] AND [surgical resection] AND [outcome] AND [smoking] AND [therapy or intervention] AND [adult]. A multi database search was conducted using the above search terms.

Inclusion/exclusion criteria

All papers retrieved by the database and journal searches were examined using the following inclusion criteria: published in peer reviewed journal; study examined data from original research; participants are adults, 18 years and over; study is written in English; study uses quantitative methods and analysis; participants have received surgical resection alone or in combination with adjuvant therapy; outcome measures include psychosocial or quality of life (e.g. depression, anxiety, quality of life dimensions); established or standardized assess-

ment measures are used. Those not meeting the criteria above were excluded from the review. No restrictions were made regarding group size and the use of a control group. This was done to maximize the number of eligible studies.

Data extraction and analyses

Results from all searches were combined and duplicates were removed. The outcomes of the collected manuscripts were synthesized and formed the basis for the meta-analysis, which was done following recommendations from The Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines.

Results

It was envisaged that the identified studies were too heterogeneous to be combined using a formal meta-analysis. Therefore, a narrative synthesis was performed. The results are summarized according to the type of intervention used and outcome measures assessed.

Surgical methods

The standard in lung cancer surgery is open anatomical lobectomy, pneumonectomy or lobectomy with mediastinal node sampling or dissection (systematic sampling or complete-dissection) either through a postero-lateral incision or by anterior muscle sparing thoracotomy. This is of importance both for complete removal of the tumor and for precise pathological staging for decision-making concerning adjuvant therapy, as well as for possible therapeutic benefit. As shown in **Table 1**, characteristics of the enrolled studies in lung cancer surgery were summarized in general. Limited surgical resections in the form of segment resection should be considered in cases of poor pulmonary reserve [13, 14]. Japanese studies of limited resection with hilar lymphadenectomy for lesions smaller than 2 cm in diameter have shown five-year survival rates comparable to those of lobectomies [13]. However, lobectomy still remains the treatment of choice for non-small cell lung cancer (NSCLC) because of the lower risk for local recurrence than has been shown for limited resection [15, 16], even among patients with T1 tumors (increased mortality) [17]. Also, the operative risk is lower with lobectomy than with pneumonectomy, but the

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Table 1. Characteristics of the enrolled studies in lung cancer surgery

Researcher	Country	Year	Study design	Disease and stage	Lob (n)	Sublob (n)	Reasons for limited resection
Ginsberg RJ, et al	America	1995	RCT	NSCLC T1N0 IA	125	122 (82 S, 40 W)	Intentional
Landreneau RJ, et al	America	1997	RS	NSCLC T1N0M0 IA	117	102 (102 W)	Compromised
Kodama K, et al	Japan	1997	RS	NSCLC T1N0M0 <2 cm	77	63 (60 S, 3 W)	Intentional and compromised
Wertz H, et al	Germany	1998	RS	NSCLC stage I	215	36 (S, W)	Compromised
Okada M, et al	Japan	2001	RS/PS	NSCLC T1N0M0 <2 cm	139	70 (70 S)	Intentional
Koike T, et al	Japan	2003	RS	NSCLC stage IA <2 cm	159	74 (60 S, 14 W)	Intentional
Campione A, et al	Italy	2004	RS	NSCLC stage IA	99	21 (21 S)	Compromised
Watanabe T, et al	Japan	2005	PS	NSCLC stage IA <2 cm	57	34 (20 S, 14 W)	Intentional
Kraev A, et al	America	2007	RS	NSCLC stage I	215	74 (74 W)	NR
Sienel W, et al	Germany	2007	RS	NSCLC stage IA	150	49 (49 S)	Compromised
De Giacomo T, et al	Italy	2009	RS	NSCLC stage I	116	36	Compromised
Zhang L, et al	China	2013	RS	NSCLC stage IA <2 cm	28	26 (26 S)	NR
Smith CB, et al	America	2013	RS	NSCLC stage IA	0	1946 (378 S, 1568 W)	NR
Koike T, et al	Japan	2013	RS	NSCLC stage IA	0	328 (216 S, 112 W)	Intentional and compromised
Altorki NK, et al	America	2014	RS	NSCLC stage IA	294	53	NR

RS, retrospective study; PS, prospective study; RCT, randomized controlled trial; Lob, lobectomy; Sublob, sublobectomy; S, segmentectomy; W, wedge resection; NR, not reported.

Table 2. Characteristics of the enrolled studies in mediastinal node dissection

Researcher	Country	Year	Study design	Disease and stage	nSND (n)	SND (n)	nSND method
Sugi K, et al	Japan	1998	RCT	peripheral NSCLC <2 cm	56	56	S
Izbicki JR, et al	Germany	1998	RCT	resectable NSCLC	93	78	L
Nakanishi R, et al	Japan	1997	RS	NSCLC N2 stage IIIA	0	53	
Keller SM, et al	America	2000	RCT	NSCLC stage II and IIIA	187	186	S
Doddoli C, et al	France	2005	RS	NSCLC stage I	207	207	S
Ma W, et al	China	2013	RCT	NSCLC stage IA	45	45	L
Su X, et al	China	2008	RS	NSCLC stage I	180	180	S
Shapiro M, et al	America	2013	RS	NSCLC N0/N1	88	282	L
Wu Y, et al	China	2014	RS	NSCLC stage I	78	105	S
Okada M, et al	Japan	2006	RS	NSCLC stage I	377	377	L

nSND, lymph nodal sampling and lobe-specific nodal dissection; SND, systematic nodal dissection; S, lymph node sampling; L, lobe-specific nodal dissection.

proportion of patients undergoing pneumonectomy varies from 6-20%, even among those with stage I disease [18, 19]. The completeness of surgery is assessed by frozen sections of resection margins, and further resection is performed if necessary.

Mediastinal surgery

Nodal micro metastasis (N1 and N2) is found in up to 20% of patients with adenocarcinoma of <2 cm in diameter [20]. In the **Table 2**, we summarized the characteristics of the enrolled studies in mediastinal node dissection. In a study concerning patients with localized bronchoalveolar carcinoma smaller than 2 cm in diameter, no such metastases were found [21].

It is reported that 12% of patients with a tumor <1 cm and 16-19% of patients with a tumor size of <3 cm have positive N2 nodes [22, 23]. Some authors postulate that in the light of these findings, complete systematic dissection of mediastinal lymph nodes should be carried out in all patients with resectable lung cancer [23, 24] and with no exception also among patients with clinical stage I disease [25]. Resection of the sentinel node (of lymph node most likely to be positive with respect to the tumor location) seems to be reasonable [26] and if the sentinel node is positive for pathology a complete mediastinal dissection is required for curative resection [26]. Some authors have claimed that complete mediasti-

nal node dissection is associated with improved survival among patients with stage II and IIIA disease [27]. Furthermore, surgically discovered T1-2, N2 disease should be treated with complete systematic mediastinal nodal dissection to improve survival [28]. Other investigators did not find any effect of complete systematic mediastinal lymphadenectomy on survival, either 1) among patients with a tumor smaller than 2 cm in diameter [23, 29], 2) among patients with stage I disease [18], or 3) among all patients with resectable NSCLC, over and beyond the effects of lymph node sampling (resection of only suspicious lymph nodes) [30]. Despite data showing a high rate of N2 disease in small tumors, most surgeons prefer the technique of systematic node sampling, consisting of multiple predetermined levels of sampling (according to the tumor location). This method is safe and effective and may result in lower morbidity and mortality compared to complete systematic nodal dissection in the mediastinum [31]. PET scan plays an important role in mediastinal surgery, as it yields low false negative results and will therefore reduce the need for complete systematic lymph node dissection or sampling among PET negative patients [32].

Other surgical alternatives

Surgery for more advanced disease than stage I-II is controversial. Extended operations for lung cancer are defined as resection of adjacent organs such as the chest wall, diaphragm, pericardium, left atrium, superior vena cava and, in superior sulcus tumors, in the apex of the chest. In such surgery, en bloc resection is advised in order to avoid tumor spillage. The five-year survival after resection of T3 disease, with tumor invasion of the chest wall, is excellent (45%) [33], as long as the lymph nodes are free from tumor spread (N0). After complete resection of a superior sulcus tumor, five-year survival of around 40% can be expected [34]. Lung resection among patients with malignant pleural effusion is not beneficial for survival, even in the absence of other pleural dissemination and when the effusion is considered as minor [35].

Video assisted thoracoscopic surgery (VATS) was introduced in the early 1990s with the aim of reducing surgical trauma compared with open surgery [36]. There is evidence that this technique when used during lobectomy reduc-

es postoperative pain compared with muscle-sparing thoracotomy (sparing both the anterior serratus muscle and the latissimusdorsi), but no effects are sustained beyond 3 weeks of surgery [37]. VATS lobectomy does not seem to be contraindicated (according to lymph node sampling) among patients with stage I NSCLC, with a low rate of missed positive lymph nodes compared with complete dissection of mediastinal lymph nodes in open surgery [38]. Preliminary five year survival rates after VATS lobectomy are comparable to results after open surgery [39]. However, some authors warn against the VATS technique on the grounds that a complete mediastinal lymph node dissection is not performed [22], and there is a need for long-term follow-up to determine the recurrence rate [40].

Bronchoplastic resection (bronchial sleeve resection aiming to spare the lung parenchyma) is an alternative to pneumonectomy, particularly among patients with limited pulmonary reserve. The mortality is somewhat higher than after classic lobectomy (0-9%), but it is a relatively safe method in experienced hands [41]. Tracheal sleeve pneumonectomy is a more aggressive procedure in resection of NSCLC. This approach is used in tumors involving the lower trachea, carina and lung, with surgical mortality of up to 30% and limited five-year survival (about 15%) [42].

Early mortality and morbidity after surgical resection

Advances in operative and postoperative care have led to a decline in complications and mortality rates during the last decades [43-46]. Compared to the high mortality (30%) after pulmonary resections during the 1950s [9], the mortality is now generally lower than 5% [43, 47, 48]. Early mortality (defined as death within the first 30 days postoperatively or within the same period of hospitalization), has ranged from 1.2-4% after lobectomy [43, 48, 49] to 3.2-12% after pneumonectomy [43, 48-51] (with the highest rates after right-sided pneumonectomy [8]).

Since the proportion of older patients (>70 years) has increased in recent years, the incidence of associated co-morbidity has also increased [52]. Furthermore, cardiovascular and chronic obstructive pulmonary disease, in particular, is twice as common among lung can-

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cer patients as in the normal population [53]. It is estimated that 10% of patients undergoing lung cancer surgery have severe concurrent disease [54]. The early mortality was higher in this group than in patients without co-morbidity [50, 54, 55].

There are four potential life-threatening complications of lung resections, namely injury to the major vessels, cardiac arrhythmia, myocardial infarction and contralateral pneumothorax [56]. Intraoperative complications, however, are relatively rare, and postoperative complications more often have serious consequences. These may be directly related to the intervention, such as technical, pulmonary, cardiac, hemorrhagic or septic events, or related to the major operative procedure, such as cardiovascular, gastrointestinal, genitourinary, peripheral vascular, neurological and thromboembolic complications [56]. Complications can be divided into two categories: non-life-threatening and life-threatening disorders, often with more than one etiological factor involved. Most of the morbidity after lung resection consists of pulmonary complications, such as a need for prolonged mechanical ventilation, pneumonia, atelectasis, adult respiratory distress syndrome (ARDS), emphysema and a need for oxygen on hospital discharge [56-58], which may lead to serious morbidity or mortality [57-59]. During the last decades, the rate of complications after lung surgery has been reduced by new anesthetic and surgical techniques and by consideration of the patient's risk factor profile prior to surgery.

Several factors have been identified as influencing the rate of major complications after lung cancer surgery, for example increasing age, gender (male), and pneumonectomy (or extent of resection) [47, 50, 55, 60-62]. Some authors agree that older age alone should not be a contraindication to pulmonary resection [46, 63, 64], although special care should be observed in selecting patients for such surgery at older ages, in a view of the possibility of comorbidity, especially if pneumonectomy is necessary [52, 65]. Furthermore, weight loss, low serum albumin, low preoperative hemoglobin, preoperative smoking, peripheral vascular disease and hemiplegia are all associated with postoperative mortality and morbidity [47, 49, 62, 66].

To identify patients with reduced lung reserve before lung resection, there are a number of parameters that are measured. Reduced % diffusing capacity of the lung for carbon monoxide (%DL_{co}) [61, 67], low preoperative FEV1% [50, 68], and low predicted postoperative FEV1 [47] have all been postulated to have negative influence on the early outcome. Summarized together as a risk quotient, these factors seem to predict the risk for pulmonary complications better than each individual parameter alone [69]. A poor outcome at preoperative exercise testing has also been shown to correlate with postoperative cardiopulmonary complications [70].

Smoking and surgery

As early as in 1944 it was suggested that smoking prior to surgery, in general, was associated with postoperative pulmonary complications [71]. In recent years, some authors have again pointed out the beneficial effect of preoperative smoking cessation on the early outcome of surgery [47, 49, 72]. The optimal duration of smoking cessation before surgery remains unclear, but among patients undergoing coronary artery bypass grafting (CABG), about 2 months without smoking are needed to reduced morbidity after thoracotomy [73]. Little is known about the optimal timing of smoking cessation before lung resection. A recent study showed an association between smoking within one month of pneumonectomy and increased risk for pulmonary complications, compared with patients who stopped smoking more than one month prior to surgery [72]. Smoked pack years preoperatively also correlate to survival after surgery; heavy smokers having a poorer prognosis than those who are not defined as heavy smokers [74]. Of interest also is the finding that those who have stopped smoking before surgery are more likely to continue being non-smokers postoperatively [75, 76]. Between 13 and 50% of smokers are expected to continue to smoke after surgery [75-77]. It has also been suggested that persistent smoking during other types of lung cancer therapy (chemotherapy) might lead to a poorer outcome, indicating the importance of smoking cessation among all lung cancer patients [78, 79].

Discussion

Over 150 prognostic factors [80] that influence long-term survival among patients with NSCLC

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have been identified. Most of these factors are of limited importance, however, in clinical practice. The factors can be divided into three categories: those related to the tumor, to the patient, and to the treatment.

Tumor stage is the single most important prognostic factor, based on tumor size (T factor), lymph node invasion (N factor) and distant metastases (M factor; generally only M0 patients are considered for surgical treatment) [81, 82]. Both T and N factors have an important impact on the prognosis among surgically treated patients [83, 84]. Blood vessel invasion [85, 86], visceral pleura invasion [87] and high serum levels of carcino-embryonic antigen all adversely influence survival [88, 89]. Overall, there appear to be no clear differences in survival by histopathological type [81, 84, 86, 90, 91], but there is some evidence of reduced survival among patients with adenocarcinoma [18, 92]. At least two authors have reported poorer prognoses among patients with adenocarcinoma undergoing pneumonectomy compared with patients with squamous cell carcinoma undergoing this operation, while no differences in survival were found following less extensive resections [93, 94]. These findings are likely to reflect a more aggressive N factor among patients with adenocarcinoma, which underlines the importance of taking tumor cell-type and tumor stage under consideration when comparing the outcome in different histopathological types [84, 93]. There are other molecular biological and proliferation markers that are documented as being risk factors for outcome, many of which are still under investigation [80].

Female sex and younger age (<65 or <70 years) have been postulated to have a protective effect in early stage carcinoma [5, 18, 82, 89, 90, 95], while arteriosclerosis, preoperative anemia, low FEV1 (<35% of predicted) [96] and weight loss prior to surgery negatively influence the prognosis [82, 85, 97]. Severe, but not mild or moderate comorbidity (using the Kapla-Feinstein index for co-morbidity) also affects long-term survival [54].

Overall, pneumonectomized patients tend to have a poorer prognosis than patients undergoing lobectomy [85, 98], although the recurrence rate is similar in the two groups. On the other hand, it has been postulated that there is no significance difference in prognosis between these two surgical alternatives after adjust-

ment for other risk factors [99]. Surgical experience (higher volume clinics and specialists) seems to influence the outcome, and both the long-term survival and early outcome seem to be better with high quality experience [100, 101].

In the future, advanced screening programs might increase the number of patients with early stage disease and more patients could be available for surgery. During the last century, modern lung cancer surgery has evolved from general surgical practice into a thoracic specialty. An increase in the incidence of lung cancer from 1930 prompted pioneers to operate on lung cancers in the absence of other treatment alternatives. Since survival continues to be limited even after complete resection of carcinomas, establishment of more effective adjuvant therapy is needed to improve the prognosis. The role of chemotherapy and of radiation in early stage NSCLC remains unresolved.

Disclosure of conflict of interest

None.

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