

LIMITED RESECTION FOR LUNG CANCER: CURRENT ROLE

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Abstract

Sublobar resection for lung cancer—whether non-anatomic wedge resection or anatomic segmentectomy—has been performed for many decades. That it has never become a mainstream strategy for treating primary lung cancer is mainly due to evidence from the late 20th Century demonstrating that it offers inferior results compared to conventional lobectomy in terms of survival and loco-regional recurrence rates. In recent years, however, emerging clinical evidence has begun to suggest otherwise. In selected patients with small tumors up to 2 cm diameter located in the periphery of the lung, it has been shown that survival after sublobar resection may approach that of postlobectomy. More importantly, the latest revisions to the adenocarcinoma classification system has further helped to identify candidates for sublobar resection— with tumors showing radiological features of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) being associated with potentially good outcomes after this type of surgery. The refinement of criteria to select patients that may benefit from sublobar resection has helped fuel the current resurgence of interest. Recent evidence has been less successful at demonstrating that sublobar resection delivers less morbidity than lobectomy. However, such comparison with lobectomy may not be the point. Current evidence simply does not support sublobar resection as a competitor to lobectomy as routine management for lung cancer. Instead, sublobar resection has been proven to be safe and feasible in patients who may not be candidates at all for lobectomy. In that sense, the role of sublobar resection may be to offer the hope of resectional therapy to selected patients who would otherwise have been denied surgery.

Key words: Lung cancer, segmentectomy, sublobar resection, wedge resection

INTRODUCTION

In the mid-20th Century, pneumonectomy was established as the surgical procedure of choice for managing lung cancer. The operation pioneered by Dr Everts Graham was widely recognized as the best chance of curing a patient with this terrible disease (1). Fellow giants in the world of thoracic surgery Drs Ochsner and DeBakey further added that “The performance of simple lobectomy in carcinoma of the lung is just as illogical as partial removal of the breast in mammary carcinoma with no attempted extirpation of the regional lymph nodes. From a technical standpoint, total pneumonectomy is a much more surgical and anatomic procedure than is lobectomy. The latter at best consists more or less of a makeshift operation.” (2) Even though lobectomy had been successfully per-

formed in 1912, more than 20 years before Graham’s first pneumonectomy, so deeply entrenched was the belief that pneumonectomy was superior that it took decades of evidence to sway it.

Today, we now take for granted that lobectomy should be the default operation for lung cancer. It offers equally effective cancer treatment but significantly lower mortality and morbidity than pneumonectomy. Rather than the extent of surgical resection per se, surgeons now realize that it is the disease staging that is most important in determining the prognosis of the lung cancer patient. Lobectomy has indeed taken over the role of pneumonectomy as the paragon operation for this disease.

However, the philosopher would then argue: “If lobectomy is preferable to pneumonectomy because of less surgical trauma, why stop there? Why not

reduce the surgical footprint even more by performing a sublobar resection?" A sublobar resection would leave the patient with less respiratory compromise, and (at least with wedge resection) would be a technically simpler operation that ideally complements minimally invasive surgical approaches. However, the counter-argument would be that this may be perhaps a step too far. If too little is resected, the oncologic adequacy of the operation may be compromised, and no degree of morbidity reduction can justify the inability to treat the disease in the first place.

Over the years, clinical evidence has generally supported the latter argument. Most thoracic surgeons today would acknowledge that lobectomy still offers a better chance of curing lung cancer than any form of sublobar resection. As we gain a better appreciation of lung cancer pathology itself, we are also gradually realizing that not all tumors are the same. Some may be less 'virulent' and it could be hypothesized that they may be treatable with a more limited strategy. Also, as we extend the reach of surgery by developing ever less invasive surgical approaches, patients traditionally unfit for open thoracotomy are now falling under the bracket of candidacy for Video-Assisted Thoracic Surgery (VATS). Could these patients benefit further from having a sublobar resection instead of a lobectomy? There has therefore been an inexorable trend witnessed in recent years for increasing experimentation with sublobar resections. This is demonstrated by the booming numbers of publications and discussions on this topic. But has this interest and adventurism now been validated by clinical evidence supporting sublobar resection? Will sublobar resection supplant lobectomy as convincingly as lobectomy replaced pneumonectomy, or will sublobar resection forever remain a niche operation only?

This article will review some of the historical evidence for and against sublobar resection for lung cancer, and focus on more recent clinical evidence to demonstrate what the current role of this surgical approach should be. Technical aspects of how wedge resections and segmentectomies are performed are beyond the scope of this article, but can be easily reviewed elsewhere (3).

HISTORICAL PERSPECTIVE

Until the mid-1990s, virtually all of the clinical evidence on sublobar resections was from retrospective case series. As early as 1973, a series of 69 patients undergoing segmentectomy for bronchogenic carcinoma demonstrated an actuarial 5-year survival rate of

56% (4). In 1990, Read et al. compared 131 patients who received lobectomy with 113 who received sublobar resection (including 107 segmentectomies) for T1N0 non-small cell lung cancer (NSCLC) (5). They found no difference in cancer-specific survival between the study arms, with 5-year survival in the sublobar group estimated to be as high as 92%. In 1997, Kodama et al. (6) compared 77 patients who received lobectomy with 46 patients receiving segmentectomy plus lymph node dissection. Again, no difference in survival was noted, and actuarial 5-year survival in the segmentectomy group was 93% compared to 88% in the lobectomy group. These studies were typical of publications on sublobar resection at the time. Despite the promising results, it was difficult to conclude confidently that sublobar resections were superior or even equivalent to lobectomy because of a number of study flaws. For example, some early studies did not limit resections to stage I disease; different studies had varying inclusion and exclusion criteria for sublobar resections; and not all studies considered cancer-specific survival only. As a result, the clinical evidence was insufficient to propel the role of sublobar resections.

In 1995, the only randomized trial of sublobar resection versus lobectomy for T1N0 NSCLC was published by the Lung Cancer Study Group (7). In this much quoted study, 122 patients with sublobar resection (including 82 segmentectomies) were compared with 125 lobectomies. The results showed that the death rate per year was 30% higher in the sublobar group with borderline statistical significance ($p=0.08$). However, the locoregional recurrence rate in the sublobar group was a staggering 300% higher than in the lobectomy group ($p=0.008$), with relatively worse results after wedge resection than after segmentectomy. This result confirmed fears at the time that sublobar resection was inadequate in terms of oncologic treatment. The paper was much used to criticize the use of sublobar resections, and for years afterwards surgeons were very wary of using this approach for lung cancer. However, closer scrutiny reveals that there was no consistent protocol for lymph node sampling in this study, and hence it is difficult to tell to what degree the worse recurrence rate in the sublobar group could have been due to occult nodal spread rather than insufficient pulmonary resection. It is telling that about a quarter of the patients supposedly clinically staged as T1N0 in this study were found to have positive mediastinal nodal metastasis. Not surprisingly, interest in sublobar resection has progressively increased again in recent years with further studies increasingly being published.

In 2005, Nakamura et al. (8) published the only major meta-analysis of the results of sublobar resection to date. A total of 14 studies were selected for meta-analysis, including 12 retrospective case series, one matched-pair study, and the above Lung Cancer Study Group randomized trial. Sublobar resection was performed in a total of 903 patients, while conventional lobectomy was performed in 1887 patients. Overall, 3 studies concluded that lobectomy offered superior survival, whilst the other 13 found no difference. It was found that the combined survival differences between the sublobar resection patients and the lobectomy patients at 1, 3, and 5 years after resection were 0.7, 1.9, and 3.6%, respectively. Although these differences were all in favour of lobectomy, none of these combined survival differences were statistically significant. In conclusion, therefore, the published data demonstrated that survival after sublobar resection for stage I lung cancer was comparable to lobectomy.

More recently, De Zoysa et al. (9) conducted a systematic literature review on the topic. The authors examined 16 studies on sublobar resection, including 8 that were published after the 2005 meta-analysis. The authors noted that three studies showed a decreased survival in the sublobar resection patients. However, further analysis showed that the sublobar resection patients tended to be older and have limited node sampling. After adjusting for those variables, the authors found no significant difference in survival. The authors also noted that six studies showed tumor size to be an important consideration. In those studies, sublobar resection offered comparable survival to lobectomy only for tumors up to 2 cm in diameter. Lobectomy appeared to be superior for tumors larger than this. Three studies showed increased loco-regional recurrence with sublobar resection. On the other hand, three studies found that sublobar resection did indeed reduce morbidity after lung cancer surgery - with a lower complication rate, shorter hospital stays and better preservation of pulmonary function being reported.

However, with both the above meta-analysis and the systematic review, the authors advised caution in interpretation of the results. Some studies noted only cancer-specific survival and hence meta-analysis focusing on overall survival may be biased in favour of the sublobar group. As most of the studies were non-randomized, there may also have been selection bias in terms of pre-operative patient risk factors, tumors of different histological types or different sized tumors in the study arms. Also, as previously mentioned, most studies did not define a consistent lymph node sam-

pling protocol. Therefore despite the thoroughness of the meta-analysis and the systematic review, questions still remain about the current role of sublobar resection.

RECENT EVIDENCE FOR SUBLOBAR RESECTION

Since the 1995 Lung Cancer Study Group randomized trial above, it is fair to say that a large proportion of published papers on sublobar resection have tended to highlight the benefits of this strategy. The fact that there is inevitably some degree of publication bias when assessing such papers should not detract from their clinical significance. There is a genuine appreciation today that sublobar resections may be beneficial for selected patients with lung cancer. The evidence in favour of sublobar resection may be broadly divided into two categories: (i) evidence that sublobar resections reduce post-operative morbidity; and (ii) evidence that sublobar resections offer equivalent survival as lobectomy for lung cancer.

1. Evidence for reduced morbidity

In the Lung Cancer Study Group randomized trial, it was found that the mean drop in Forced Expiratory Volume in one second (FEV_1) at 12-18 months after a sublobar resection was 5.18% (7). After lobectomy, the mean drop was 11.09% and this difference was significant ($p=0.041$). Since that time, further studies have confirmed that sublobar resection preserves lung function better. Keenan et al. (10) compared 147 patients undergoing lobectomy with 54 undergoing segmentectomy. Lobectomy was associated with significant impairment in FEV_1 , Forced Vital Capacity (FVC), maximum voluntary ventilation, and diffusing capacity at one year after surgery. In contrast, patients receiving segmentectomy only experienced a reduction in diffusing capacity. In another study, Harada et al. (11) have shown that the ratios of postoperative to preoperative FEV_1 and FVC were both significantly better at 2 and 6 months after surgery when segmentectomy was performed as compared to lobectomy in similar patients ($p=0.0006$ and $p=0.0007$ respectively). This translated into a marginal difference in the ratio of postoperative to preoperative anaerobic threshold in favor of sublobar resection ($p=0.0616$).

In addition to lung function preservation, overall morbidity may also be reduced by sublobar resection. This may have particular implications for elderly patients that may not tolerate a conventional lobectomy. Kilic et al. (12) reported that, in patients above 75 years, segmentectomy could reduce the post-

operative major complication rate from 25.5% (with lobectomy) to just 11.5% ($p=0.02$). The operative mortality was 1.3% for segmentectomy and 4.7% for lobectomy, although the difference did not reach statistical significance. More recently, Okami et al. (13) compared the outcomes of 79 standard lobectomies and 54 sublobar resections for stage IA NSCLC in elderly patients aged 75 years or more. Patients were selected for sublobar resection in most cases because of poor cardio-pulmonary function. Despite this, patients in the sublobar resection group had similar mortality and morbidity rates as the lobectomy group, and had similar overall survival rates on follow-up. Such studies suggest that sublobar resection may offer a chance at curative resection to patients who would traditionally not have been offered any surgery at all, and would have received mainly palliative or conservative management.

2. Evidence for equivalent survival to lobectomy

In the Lung Cancer Study Group randomized trial, sublobar resection was associated with a loco-regional recurrence rate of over 17% (7). Studies since then have consistently shown loco-regional recurrence rates with segmentectomy to be only 2-8% (6, 14-16). These rates are already as good as or better than the rate seen in the lobectomy group in the Lung Cancer Study Group trial. In one of the most recent case series published at the time of writing, Donohue et al. (17) reported that for stage IA patients with T1a lesions receiving an anatomic segmentectomy, local recurrence was 5% and distant recurrence was 13%. Five-year recurrence-free survival of these patients was 69%. More important than the improved results alone is the fact that certain factors potentially associated with better survival after sublobar resection are now gradually being identified. These include: tumor size <2 cm; ensuring margin adequacy; performing segmentectomy rather than wedge resection where possible; and inclusion of nodal dissection during any sublobar resection.

Early studies suggesting better outcomes after sublobar resection for smaller tumors were mentioned above. More recently, Fernando et al. (18) compared outcomes of 124 patients after sublobar resection with those of 167 patients after lobar resection. For tumors smaller than 2 cm, there was no difference in survival between the sublobar resection and lobar resection groups. However, for the larger tumors (2-3 cm), median survival was significantly better in the lobar resection group (70 versus 44.7 months, $p=0.003$). Okada et al. (19) investigated 778 patients with stage I NSCLC. The 5-year cancer-specific survivals of patients with

stage I disease with a tumor of 20 mm or less in diameter were no different if a lobectomy, segmentectomy or wedge resection was performed. For tumors of 21 to 30 mm in diameter, there was no difference in 5-year cancer-specific survival between patients receiving lobectomy and segmentectomy (87.4% versus 84.6%). However, for tumors larger than 30 mm in diameter, the 5-year cancer-specific survivals were 81.3% after lobectomy compared to only 62.9% after segmentectomy ($p=0.00492$).

More recently, a study by Kates et al. (20) used the Surveillance, Epidemiology, and End Results (SEER) registry in the United States to identify 688 patients who underwent sublobar resection and 1402 who underwent lobectomy for stage I NSCLC up to 1 cm in size. Using propensity score analysis to adjust for potential differences in the baseline characteristics of patients in the two treatment groups, it was found that overall and lung cancer-specific survival rates of patients in the study arms were statistically no different. This result seems to support sublobar resection for smaller tumors. However, another study using the same SEER database and published in the same year failed to corroborate this finding (21). Looking at an even larger cohort of 14473 patients with stage I adenocarcinoma or squamous cell carcinoma, the authors found that patients who underwent lobectomy had superior overall and cancer-specific survival rates, regardless of tumor size. Even when comparing patients with tumor sizes of less than 2 cm diameter, survival analysis confirmed that lobectomy offered better overall and cancer-specific survival than sublobar resection ($p=0.0002$ and $p=0.0047$ respectively). Evidently, the association between tumor size and outcomes of sublobar resection is not yet set in stone.

The best evidence for the importance of an adequate margin comes from the study of El-Sherif et al. (22) that looked at 55 wedge and 26 segmental resections performed for patients with NSCLC. In 6 of 41 patients (14.6%) with a resection margin of less than 1 cm local recurrence developed. This compared with local recurrence in 3 of 40 patients (7.5%) in the group with a resection margin of equal to or more than 1 cm ($p=0.04$).

The most widely appreciated prognostic factor for sublobar resection in recent years appears to be the performance of segmentectomy instead of wedge resection. In a study of 87 patients with stage IA NSCLC, wedge resection was performed in 31 patients and segmentectomy in 56 patients (23). There were significantly fewer loco-regional recurrences ($p=0.001$), and a better cancer-related survival ($p=0.016$) following segmentectomy compared

to wedge resection. Nakamura et al. (24) recently investigated a cohort of 411 patients with clinical stage I NSCLC who underwent VATS resections, including lobectomy in 289, segmentectomy in 38, and wedge resection in 84. Survival was poorer in the wedge resection patients. The 5-year survival rates for the lobectomy, segmentectomy, and wedge resection groups were 82.1%, 87.2%, and 55.4% respectively. The hazard ratio of wedge resection relative to lobectomy was 4.30. In the Okada study above (19), although no difference in survival was found between patients receiving lobectomy and segmentectomy when the tumor was no larger than 30mm, patients with this size of tumor had significantly worse 5-year cancer-specific survival (39.4%, $p < 0.0001$).

In addition, in the above mentioned study by El-Sherif et al. (22), segmentectomy was used in 19 (47.5%) of the 40 patients with a resection margin of equal to or more than 1 cm, but only in 7 (17%) of the 41 patients with margins < 1 cm. It can be hypothesized that the survival advantage offered by segmentectomy over wedge resection may be at least partially explained by the greater likelihood of attaining adequate resection margins when performing a segmentectomy, or vice-versa. Furthermore, it has been suggested that the better prognosis associated with a smaller tumor may again be related to the greater chance of attaining a wider resection margin.

Another factor that is increasingly recognized as possibly important to the success of a sublobar resection is the need for adequate lymph node sampling or dissection. In a recent study, Wolf et al. (25) looked at 154 patients who received sublobar resection and 84 who received lobectomy for NSCLC where the primary tumor was 2cm or less in diameter. Overall, the results did not favour sublobar resection. Lobectomy was associated with longer overall survival ($p = 0.0027$), longer recurrence-free survival ($p = 0.0496$), and a lower rate of local recurrence ($p = 0.1117$). However, if only those 45 sublobar resection patients who also had mediastinal lymph node sampling during surgery were compared with the lobectomy patients, these differences were found to be no longer present.

IMPACT OF THE NEW IASLC/ATS/ERS ADENOCARCINOMA CLASSIFICATION ON SUBLOBAR RESECTIONS

No discussion of the current role of sublobar resection can be complete without mention of the latest adenocarcinoma classification introduced by a joint working group of the International Association for the Study of Lung Cancer (IASLC), American Thoracic

Society (ATS) and European Respiratory Society (ERS) (26). This classification introduces the new categories of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) that represent small (≤ 3 cm), solitary adenocarcinomas consisting purely of lepidic growth without invasion or with ≤ 0.5 cm invasion, respectively. These two new categories have essentially replaced the term bronchioloalveolar carcinoma (BAC), and have been introduced because they should have 100% or near-100% 5-yr disease-free survival, respectively, if completely resected (27). The significance of the new classification is that the definitions of AIS and MIA overlap almost precisely with the kinds of small, less aggressive tumors identified by the clinical evidence above as being the most ideal for sublobar resection. An appreciation of how best to diagnose AIS and MIA will hence aid immensely in selecting patients for such limited resection.

Over the years, BAC has been well linked to an appearance of 'ground glass opacity' (GGO) on CT scanning. Clinical studies correlating imaging and histopathology have consistently linked many, though not all, GGOs with pre-invasive, noninvasive or early forms of neoplastic growth, especially those of adenocarcinoma lineage (28, 29). In other words, a GGO on CT can be corroborative of a diagnosis of AIS or MIA. In a recent prospective study, a CT finding of a tumor of ≤ 2 cm with ≤ 0.25 consolidated component by volume was even used to define a radiological diagnosis of noninvasive peripheral lung adenocarcinoma or AIS (30).

There is emerging evidence that a GGO on CT can be useful in guiding management towards sublobar resection or even expectant management (27). Lobectomy is still considered the standard surgical treatment for tumours that have a solid appearance on chest CT (even if smaller than 2 cm) because such tumours are likely to be invasive carcinomas. On the other hand, recent guidelines and evidence from a large, randomised trial suggest that small nodules of ≤ 10 mm or ≤ 500 mm³ that are clearly 100% pure GGO lesions on chest CT may be considered as AIS or MIA, and hence may be suitable for close follow-up or sublobar resection rather than immediate lobectomy (31, 32). In a recent review by Rami-Porta and Tsuboi, nine case series were identified in which lobectomy or sublobar resection was performed for small localised BACs detected by HRCT as pure GGO with no nodal involvement (33). These are the lesions which are now classified as AIS or MIA. For these lesions, 5-yr survival rates were 100% in all but one of the series and there was no recurrence at follow-up. Evidently, these cases were as adequately managed by sublobar

resection as lobectomy. Another systematic review by the Lung Cancer Study Group also concluded that “tumors less than 2 cm and with greater than 50% density of GGOs are unlikely to have N1 or N2 lymph node metastasis. Five-year survival after limited resection in these tumors is approximately 100% with no incidence of recurrence, and hence these patients may ultimately prove to be the most appropriate candidates for intentional limited resection.” (34)

One recent study from Japan shows the above recommendations put into practice (35). This study differentiated clinical T1N0M0 adenocarcinoma patients with tumors measuring 2 cm or less in diameter into “air-containing type” or “solid-density type” according to their appearance on high-resolution CT. An air-containing tumor here may correspond broadly to a GGO. In a cohort of 123 patients receiving sublobar resection for stage IA adenocarcinoma, overall and relapse-free survival rates at 5 years were 95% and 100% respectively in patients with air-containing type tumors, as compared with 69% and 57% respectively in those with solid-density type tumors. Both survival rates were significantly better in patients with air-containing type tumors than in those with solid-density type tumors ($p < 0.0001$).

PATIENT SELECTION FOR SUBLOBAR RESECTION

From the above evidence, it would appear that if sublobar resection is offered to selected patients, cancer treatment of equivalent efficacy with lobectomy may be achievable. The selection criteria would be a tumor smaller than 2 cm (possibly 3 cm), ability to achieve a resection margin of greater than 1cm, and the ability to perform a segmentectomy rather than a wedge resection. The information pertaining to these considerations can be readily obtained on a standard CT for lung cancer imaging. Predictors for successful sublobar resection on CT include: location within the outer third of the lung parenchyma; lesion smaller than 3 cm in diameter; and no evidence of endobronchial involvement (36). Attempting sublobar resections if these conditions are not fulfilled potentially increases the risk of inadequate resection margins, staple line dehiscence, and distortion of the remaining parenchyma of the lung resulting after stapling. The above discussion regarding the potential role of CT in distinguishing AIS is another emerging factor in identifying patients that may best benefit from sublobar resection.

In addition, it must be remembered that all clinical evidence supporting the use of sublobar resection

relates specifically to patients with stage I NSCLC only. There has never been any good evidence suggesting that sublobar resection confers any survival benefit to patients with more advanced disease. Therefore, every effort must be made to ensure accurate staging to rule out metastasis. Positron emission tomographic (PET) scanning is certainly advisable. However, paradoxically, many candidates for sublobar resection may have AIS which may often not be metabolically very active and may show up poorly on PET. Wherever possible, it is thus advisable to investigate patients with a multi-disciplinary team approach involving at least pulmonologists and radiologists. In many patients, mediastinoscopy and/or endobronchial ultrasonography (EBUS) may prove helpful for mediastinal staging prior to committing to a sublobar resection.

The other major concern in the workup of the candidate for sublobar resection is that he/she is often being considered for this operation precisely because he/she is deemed unfit or at high risk for a lobectomy. Complete lung function testing is mandatory, including spirometry, arterial blood gas analysis, and even assessment of the carbon monoxide diffusion capacity (DLCO). As with lobectomy, an estimation of the predicted post-operative FEV₁ taking into account the volume of the segment or wedge planned to be resected is a useful first step in assessing risk of post-operative morbidity (37). If doubts remain regarding the patient's lung function, split-lung ventilation/perfusion nuclear scintigraphic assessment (VQ scan) should be used to assess the relative contribution to the patient's respiration of the segment planned to be removed. Although a weak contribution from the target segment should encourage resection, if the entire lobe is already largely non-functional anyway, one may still contemplate whether it may be preferable to perform a lobectomy rather than a sublobar resection. Besides the pulmonary status, it also goes without saying that the patient's cardiac status should also be assessed pre-operatively.

THE ROLE OF ADJUVANT THERAPY

Because of concern over the potential of loco-regional recurrence after sublobar resection, adjuvant therapy has always been a topic of interest in this field. As early as the 1980s, postoperative radiation therapy was already suggested to reduce loco-regional recurrence after a wide wedge or segmental resection for lung cancer in patients with poor lung function (38). However, more recent clinical evidence has shown that after sublobar resection for stage I NSCLC, the

use of external beam radiation therapy was associated with significantly worse median overall and disease-specific survival compared with no additional local-regional therapy: 31 and 45 months vs 51 and 98 months, respectively ($p < 0.001$) (39). Therefore, there is currently little enthusiasm for this form of adjuvant therapy.

Instead, the adjuvant therapy most discussed at this time is intra-operative brachytherapy. Even though it is performed by relatively few surgeons after sublobar resection, the emerging evidence looks promising for selected patients. In recent years, Fernando et al. applied brachytherapy to 60 (48%) out of 124 patients receiving sublobar resection for stage I NSCLC (18). The brachytherapy consisted of iodine 125 seeds embedded onto a piece of polyglyconate mesh and placed over the staple line to achieve a prescribed dose of 10,000 to 12,000 cGy to a 0.5 cm depth. After a mean follow-up of 34.5 months, the brachytherapy decreased local recurrence rate significantly from 17.2% to 3.3% ($p = 0.012$). Birdas et al. (40) investigated 167 stage Ib NSCLC patients, comparing those 126 who underwent lobectomy with the 41 who had sublobar resection with iodine 125 brachytherapy over the resection staple line. They found that use of sublobar resection plus brachytherapy conferred similar rates of loco-regional recurrence, disease-free survival and overall survival as lobectomy - despite sublobar group patients having significantly worse preoperative pulmonary function. In a recent multi-center randomized trial specifically concerning 224 patients with stage I NSCLC who had poor lung function pre-operatively, those who had sublobar resection with intra-operative brachytherapy were compared with those who had sublobar resection alone. After 90 days of follow-up, the brachytherapy was deemed to be safe, not having been associated with any increase in rates of severe respiratory adverse events, or any decline in FEV₁, DLCO or dyspnea scores (41, 42). Survival data from this randomized trial have not yet been published at the time of writing this article.

FUTURE DIRECTIONS

As can be seen from the above summary of the clinical evidence for sublobar resection, many questions remain. Much of the evidence is from retrospective case series only. These series may have different protocols for nodal dissection, different patient selection criteria, and different outcome measures (different definitions for survival). Therefore this heterogeneity in the results being published is at present one of the

key barriers to greater acceptance of sublobar resections. To address this issue, large-scale prospective randomized trials are desperately needed. Two such trials are currently underway. One is the Cancer and Lymphoma Group B trial (CALGB 140503) aimed at comparing lobectomy and sublobar resection for stage IA NSCLC with peripheral tumors that are no larger than 2 cm in diameter (43). This study aims to recruit over 1200 patients and is currently reaching the end of the recruitment phase at the time of writing. The other major randomized trial currently in progress is the Japan Clinical Oncology Group and the West Japan Oncology Group trial (JCOG0802/WJOG4607L) (44). This is broadly similar to the CALGB trial, and also aims to recruit over 1100 patients with small-sized (diameter no larger than 2 cm) peripheral NSCLC. One key difference between the trials is that the Japanese study specifies segmentectomy for the experimental study arm, whereas the CALGB includes both segmentectomy and wedge resections in the sublobar resection study arm. The results of these two important studies promise to help define the future clinical role of sublobar resection vis-à-vis lobectomy for lung cancer.

Looking to the future, one of the greatest challenges to the role of sublobar resection is in the contemporary emergence of alternative treatment modalities. Stereotactic body radiation therapy (SBRT) and ablative therapies - such as radiofrequency ablation (RFA) and microwave ablation (MWA)-have already been established for the treatment of NSCLC in selected patients (45, 46). These modalities promise even less morbidity than sublobar resection because they are essentially non-operative and non-resectional in nature. Nonetheless, comparisons of sublobar resection and these alternative treatment approaches have proven difficult, as morbidity outcome measures-and even post-therapy quality of life assessments-often differ greatly between surgical and medical oncological studies. It has similarly proven difficult to reliably compare survival between patients receiving sublobar resection versus RFA/MWA versus SBRT. Published studies currently offer a great spread of disparate conclusions. Some suggest that survival is often similar in all three modalities at 1 year, but others suggest that sublobar resection may be superior with longer follow-up (47). Conversely, a recent propensity score-matched study from the Netherlands even goes as far as to suggest that SBRT offers better loco-regional control and similar survival when compared to VATS lobectomy-let alone sublobar resection (48). Nonetheless, such crude comparison is

probably unreliable given the inherent selection bias in the SBRT and RFA/MWA studies, with relatively sicker patients being treated with the non-resectional modalities.

To address some of the above issues in comparing sublobar resection with SBRT, a new prospective, multi-center, randomized trial has recently been started in the United States (49). The ACOSOG Z4099 trial aims to enrol 420 patients with clinical stage IA or selected IB NSCLC who are considered to be high risk for major pulmonary surgery. Patients are randomized to receive either sublobar resection (wedge resection or anatomical segmentectomy) with or without intra-operative iodine 125 brachytherapy, or 3 fractions of stereotactic body radiation therapy at 2-8 days intervals. The scale and methodology promise a better understanding of the relative survival benefits and consequent morbidity of sublobar resection versus SBRT, but with a trial completion date estimated to be in 2014 and a wait for post-treatment survival data it may be a while yet before conclusive results will be yielded.

Regardless of any published survival data, however, RFA/MWA and SBRT will perhaps inevitably be fundamentally limited by two issues. Firstly, with the non-resectional modalities, there is never any reliable method of ensuring that 100% of the tumor has been destroyed, whereas with sublobar resection the lesion is removed and an assessment of the margins can be made. Secondly, with the non-resectional modalities, there is no opportunity for histopathological assessment of the lymph nodes to exclude occult nodal metastasis. The clinical importance of these two issues needs to be resolved with future clinical studies. Only then can the relative roles of sublobar resection versus the non-resectional treatments in the treatment of high risk lung cancer patients be established.

CONCLUSION

Lobectomy remains firmly entrenched as the treatment of choice for early stage NSCLC. The quantity and quality of available evidence regarding sublobar resection simply cannot support any paradigm shift in clinical practice for managing lung cancer patients at this time. It currently consists of relatively small numbers of patients in retrospective case series. Perhaps the upcoming CALGB and Japanese randomized trials may help clarify the role for sublobar resection in future. However, with the clinical data on hand today, sublobar resection remains a useful treatment alterna-

tive for a very select population of NSCLC patients. This population is defined by:

- I. Inability to tolerate lobectomy because of pulmonary or other co-morbidities;
- II. Small tumors up to 2 cm diameter;
- III. Peripheral location of tumor in the lung;
- IV. Confirmed stage IA disease only;
- V. Predominantly GGO appearance on CT imaging.

For patients fitting these criteria, sublobar resection offers the promise of potentially reasonable disease-free survival rates. Such rates appear to be ever improving through continual refinement of the selection criteria and growing recognition of the key elements of the surgery (wide margins, preference for segmentectomy). The potential advantage of adjuvant therapy such as brachytherapy remains to be proven at this time, though such adjuvant therapy so far shows little harm if given.

What is less certain is whether sublobar resections offer 'less morbidity' than lobectomy. However, on further reflection, this point is moot. Sublobar resection at present needs not be compared to lobectomy, because lung cancer patients eligible for lobectomy evidently should receive that and not sublobar resection. Instead, sublobar resection should be compared to what patients ineligible for lobectomy would otherwise receive - radiotherapy or palliative management alone. With alternatives such as RFA/MWA and SBRT still in their infancy in terms of development, the evidence at least clearly suggests that sublobar resection offers better prognosis than conventional non-surgical management. In that sense, the current role of sublobar resection is to offer hope to those patients who would otherwise have none.

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