REVIEW SERIES

Lung cancer • 6: The case for limited surgical resection in non-small cell lung cancer

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The choice between conservative resection or standard anatomical resection for stage I NSCLC depends on the size and biology of the tumour and the age and state of health of the patient.

The debate as to the extent of surgical resection required in the treatment of patients with operable stage I lung cancer has been around for many years. Surgeons have been focused on the degree to which surgical resection will affect long term survival in their patients. Traditional surgical dogma would suggest that extended resections, or so called anatomical resections such as lobectomy or pneumonectomy, will be superior in most instances to the more limited resections such as open or video assisted wedge excisions or formal segmental resections. However, it is important to understand that multiple factors contribute to overall survival following resection for stage I lung cancer.

A subgroup of patients with stage I lung cancer will have undetected tumour dissemination before resection, the risk of which is a function of tumour size and biology. The contribution of this factor to survival depends on the degree of local versus distant dissemination. Surgeons can only expect to affect local recurrence via regional resection of tumour residing in the primary lesion—that is, complete resection—or immediately adjacent lymph nodes. For patients destined to succumb to distant recurrence, the choice of surgical procedure may be moot.

There is also morbidity associated with the surgical procedure itself. The incision—whether it is a thoracotomy with division of the major thoracic musculature or a thoracoscopy with small trocar sites transgressing only the intercostal musculature—will impart a separate and real operative morbidity and possible mortality. Additional morbidity is related to the amount of functional lung lost at the time of the tumour resection. The larger the primary tumour, the less functioning lung will be lost with removal of the surgical specimen, even with anatomical resections. On the other hand, the presence of emphysematous blebs in the specimen may result in a paradoxical improvement in respiratory function following resection. The morbidity of the surgery itself will be most significant to survival in those patients with severe medical co-morbidities and in older patients. Understanding which surgical approach is appropriate in a given clinical setting requires a review of the factors affecting survival in patients treated operatively for stage I non-small cell lung cancer (NSCLC).

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FACTORS WHICH AFFECT SURVIVAL FOLLOWING RESECTION

It is clear that the size of the patient's tumour and its inherent biology will determine survival in the majority of patients resected by either conservative or more extended anatomical resection. The importance of tumour size to prognosis is reflected in the current staging system. Even among T1 tumours there is support for the idea that, with increasing size, tumours are more likely to be associated with disseminated distant disease. Koike *et al*[1] studied 496 patients with resected T1 NSCLC and compared ⩽2 cm tumours with those of 2.1–3 cm. They reported a statistically significant increase in both lymphatic and haematogenous metastases in the group of patients with larger tumours, and concluded that patients with small size T1 lung cancer have a better overall prognosis than patients with tumours approaching 3 cm. Swanson *et al*[2] reported on 40 patients with NSCLC <1 cm treated surgically at our institution. Nine patients underwent anatomical resection and 31 underwent wedge resection; 5 year survival was 88%, with no recurrence or late deaths among the patients who underwent anatomical resection.

Warren and Faber[3] published a comparison of segmental resection versus lobectomy in 173 patients with stage I NSCLC. Sixty eight patients underwent segmental resection and 105 underwent anatomical lobectomy. A survival advantage for lobectomy was noted for patients with T2 tumours but not for those with T1 lesions. Local recurrence rate was 4.9% after lobectomy compared with 22.7% following segmental resection. These data suggest that the most important factor in determining whether a local or anatomical resection should be performed is the size of the primary lesion.

Kodama *et al*[4] reported a head to head comparison between lobectomy and limited resection for T1N0M0 NSCLC. In this case series review 46 patients underwent intentional segmentectomy, although they were otherwise of excellent pulmonary function and could have been considered for an anatomical resection. The 5 year survival rate was more than 90% in the group undergoing intentional limited resection. This group was compared with 77 patients who underwent anatomical resection including lobectomy and mediastinal lymph node dissection. Limited resection was not associated with a difference in survival. The authors concluded that limited segmental resection should be considered an equivalent alternative for patients with T1N0M0 disease. This study further supports the concept that the primary determining factor as to

whether patients should undergo limited or more extended resection is primary tumour size.

The Lung Cancer Study Group looked at a large group of T1 patients prospectively randomised to undergo either a limited resection (wedge resection or segmentectomy) or standard lobectomy.[5] There was no statistical difference in overall survival. As noted by Warren and Faber,[3] the local recurrence rate was higher in patients undergoing limited resection. For this reason, this report has been used as a strong argument for the performance of lobectomy in most patients who are seen as fit surgical candidates. However, the failure of increased local recurrence to translate into reduced survival warrants consideration of additional prognostic factors in selecting the appropriate surgical approach.

It is clear that genetic characteristics differ among tumours and contribute to survival duration. Bhattacharjee *et al*[6] recently published an expression profile analysis of a large group of surgically resected lung adenocarcinomas. These tumours were clustered into four subgroups not defined by clinical or pathological characteristics. One of these subgroups was associated with poor survival. In a report by Kwiatkowski *et al*[7] demographic, pathological, and molecular factors were examined for prognostic significance in 244 patients with stage I lung cancer. Nine independent negative prognostic factors were identified: solid tumour with mucin, wedge resection, tumour diameter >4 cm, the presence of lymphatic invasion, age >60 years, male sex, P53 expression, K-*ras* codon 12 mutations, and the absence of H-*ras* P21 expression. Even in the subset of patients undergoing lobectomy or pneumonectomy, tumour size and the five pathological and molecular factors remained independent predictors of survival.

In elderly and high risk patients there is no evidence that the extent of surgical resection will determine long term survival as long as the tumour is resected with clean surgical margins. In an analysis of 14 550 patients registered in the SEER database with documented stage I or stage II disease, Mery *et al*[8] showed that, in the elderly subgroup, limited resection may provide patients with a safe and effective surgical alternative. They found that the survival benefit of lobectomy over limited resection was not significant for patients older than 71 years.

Jaklitsch *et al*[9] found no difference in long term survival between elderly patients treated with a thoracoscopic wedge excision and those undergoing open lobectomy. It appears that the reduction in perioperative morbidity and mortality coupled with the overall shortened natural longevity of this group of patients equalised the two approaches in terms of survival. Indeed, it is possible that the morbidity of more extended resections may actually decrease the long term survival in this elderly group of patients. It would seem intuitive that minimally invasive approaches to surgical resection in these patients will lead to a lowered operative morbidity and mortality that may translate into overall improvement in survival.

In a multicentre study Landreneau *et al*[10] compared operative morbidity, recurrence, and survival in 219 consecutive patients with pathological T1N0 disease, of whom 42 had undergone open wedge excision, 60 video-assisted wedge resection, and 117 standard anatomical lobectomy. The group undergoing wedge excision consisted of older patients with reduced pulmonary reserve and a higher incidence of other medical co-morbidities than those who underwent anatomical lobectomy. Hospital stay was significantly less in the wedge resection groups and there were no operative deaths. There was no difference in 1 year survival between patients undergoing wedge excision by either approach and those who had a lobectomy. The overall 5 year survival was 58% for patients who underwent open wedge resection, 65% for those who had video-assisted resection, and 70% for patients undergoing lobectomy. There was a significantly greater non-cancer related death rate by 5 years in patients who had wedge resection (38%) compared with those who underwent lobectomy (18%), which suggests that they were preselected by the surgeon because of the presence of medical co-morbidities. The authors concluded that wedge resection done by thoracotomy or video-assisted techniques is a good alternative to standard anatomical resection for patients with T1N0 NSCLC with compromised cardiopulmonary reserve. They added, however, that in patients who remain a good surgical risk or in patients who have large tumours, anatomical lobectomy remains the treatment of choice.

The need for clean operative margins will dictate the use of lobectomy in a large number of patients with T2 lesions. In many patients—particularly female patients with smaller lungs—complete T2 tumour resection with negative microscopic margins can only be achieved with anatomical lobectomy. In T1 tumours it appears from previous studies of clinical outcome that other risk factors related primarily to the patient's age, state of health and tumour biology will determine survival, making the choice of surgical approach somewhat moot.

CONCLUSIONS

We would therefore recommend that patients be evaluated primarily by tumour size and that, for patients with tumours of <3 cm who have significant medical co-morbidities or who are elderly, conservative surgical resection is the method of choice for the majority. On the other hand, in patients with tumours of >3 cm, anatomical surgical resection remains the gold standard because of the need for complete surgical extirpation with negative microscopic margins.

The appropriate surgical approach to nodules of <1 cm remains an open question. As screening with CT gains popularity, the number of patients presenting with small lesions will continue to increase. While it is intuitively appealing for surgeons to apply wedge resection in this group of patients, the issue needs to be addressed in multicentre trials.

In conclusion, it appears that surgeons should be concerned with several factors in trying to determine whether conservative resection for NSCLC or standard anatomical resection should be employed. The first set of factors revolves around the clinical setting. The age of the patient and presence or absence of co-morbidities will determine the relative need for a more conservative incision, operative approach and standard surgical resection. In patients with large tumours, an anatomical resection appears to be required for complete surgical extirpation. However, in the elderly or high-risk patient a wedge excision or segmental resection will not compromise survival duration, and can usually be achieved with less operative time, blood loss, and a shorter postoperative recovery. In the future, preoperative molecular analysis of tumour biopsies may aid in more accurate prediction of distant recurrence in patients with stage I disease.

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