Survival following lobectomy vs limited resection for stage I lung cancer: a meta-analysis

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Extent of resection needed to treat lung cancer has long been an issue. The sole randomised controlled trial, reported by the Lung Cancer Study Group, advised against limited resection as standard surgery even for small peripheral non-small-cell lung cancers (<3 cm), because of frequent local recurrences. Elsewhere, conflicting results have been reported from different institutions. We therefore conducted a meta-analysis of reported studies to compare survival of stage I patients between limited resection and standard lobectomy. A MEDLINE web search for computer-archived bibliographic data yielded 14 articles suitable for analysis. Combined survival differences (survival rate with lobectomy minus that with limited resection) at 1, 3, and 5 years after resection according to the DerSimonian–Laird random effects model were 0.7% (95% CI, –0.8 to 2.1; P = 0.3659), 1.9% (95% CI, –3.7 to 7.4; P = 0.5088), and 3.6% (95% CI, –0.4 to 10.5; P = 0.3603), respectively. None of these survival differences were significant, indicating that survival after limited resection for stage I lung cancer was comparable to that after lobectomy. However, since interstudy heterogeneity was detected, caution is required in interpretation of the results.

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Limited resection for lung cancer was proposed in the early 1970s (Le Roux, 1972). Acceptable results of segmentectomy in a large number of patients were reported by Jensik et al. (1973). Since then, several retrospective studies (Breyer and Jensik, 1985; Stair et al., 1985; Jensik, 1987; Temeck et al., 1992) considering efficacy of limited resection have been reported. In 1995, the Lung Cancer Study Group (LCSG) published final results of a randomised controlled trial (RCT) (Ginsberg and Rubinstein, 1995; Lederle, 1996) comparing local recurrence and survival after limited resection with those after standard lobectomy for stage I non-small-cell lung cancer (NSCLC). Representing the only randomised trial worldwide to address the question of whether limited resection truly is comparable to standard lobectomy, that trial showed frequent locoregional recurrences and a tendency toward poorer survival in the limited resection group.

Although the randomised trial (Ginsberg and Rubinstein, 1995) concluded that limited resection should not be standard surgery even for small peripheral NSCLC, several surgeons (Kodama et al., 1997; Tsubota et al., 1998; Koike et al., 2003) have continued to perform some intentional limited resections. Indeed, results reported from various institutions up to now have been conflicting. Considering recent implementation of minimally invasive surgical techniques such as video-assisted thoracoscopic surgery (VATS), efficacy of limited resection in small, node-negative NSCLC needs to be re-evaluated (Sugarbaker and Strauss, 2000).

We therefore conducted a meta-analysis of published studies to quantitatively review survival data for limited resection of lung cancer in comparison with data for standard lobectomy.

MATERIALS AND METHODS

Eligibility criteria for meta-analysis

This meta-analysis was limited to studies comparing survival data of limited resection with those of standard lobectomy. The following eligibility criteria were established before collecting articles: (1) 'Limited resection' was defined as sublobular resection, including wedge resection and segmentectomy. (2) Operative approaches could include either thoracotomy or VATS. (3) Survival rates for a specific time interval after operation were stated in the article. (4) Study subjects had to be limited to clinical stage I patients. (5) Median follow-up time was to exceed 2 years. (6) Articles were published in English in the periodical medical literature from 1970 to August 2004. (7) When multiple articles by the same author or study group analysed the same series of patients, a single most informative article was chosen for the meta-analysis.

Collection of published studies

The MEDLINE web search for computer-archived bibliographic data concerning limited resection and postoperative survival in lung cancer was primarily performed in August 2004. Keywords 'lung cancer + limited resection', 'lung cancer + wedge resection',
'lung cancer + segmentectomy', and 'limited resection + lobectomy' hit 627, 344, 193, and 117 citations, respectively. Manual selection of relevant studies was carried out based on the summary analysis. Overlapping or unrelated articles were excluded, and items from hand-searched bibliographies were added. Of 18 articles initially found by the methods above, two were excluded for being reported by the same author or study group analysing a series of patients more informatively considered in another article. In three articles, advanced disease stages were included. One report of these three also was among the two representing overlap. Thus, four articles (Errett et al., 1985; Pastirino et al., 1991; Sugarbaker and Strauss, 2000; Miller et al., 2002) were excluded (Table 1), while 14 articles fulfilled eligibility criteria.

Statistical analyses

DerSimonian–Laird random effects analysis (DerSimonian and Laird, 1986) was used to estimate the survival difference (i.e., survival rate after standard lobectomy minus that of limited resection) at the end points of 1, 3, and 5 years after operation. Generally used to combine heterogeneous studies, this method produces a combined survival difference and a 95% confidence interval with a heterogeneity test at each end point. Survival rates were derived from published survival curves when not provided explicitly in the text or tables. Subjects censored prior to each end point were subtracted from the denominators (number of patients for follow-up), giving a conservative confidence interval for the summary statistic. Censored cases were counted by placing tick marks on survival curves when provided, as described by Mitsudomi et al. (2000). The correlation coefficient ($r$) was calculated to examine the relationship between two variables. Significance was tested by the Bartlett test. For these tests, a $P$-value < 0.05 was considered significant. Publication bias was tested by the method of Egger et al. (1997); for this, a $P$-value < 0.1 was considered significant.

RESULTS

A total of 14 studies (Hoffmann and Randsell, 1980; Read et al., 1990; Date et al., 1994; Warren and Faber, 1994; Ginsberg and Rubinstein, 1995; Harpole et al., 1995; Lederle, 1996; Kodama et al., 1997; Landreneau et al., 1997; Pastirino et al., 1997; Kwikatkowski et al., 1998; Okada et al., 2001; Koike et al., 2003; Campione et al., 2004; Keenan et al., 2004) served as data sources for the present meta-analysis (Table 2). Their designs were retrospective in 12, matched-pair in one, and RCT in one. Limited resection was performed for a total of 903 patients, while comparable standard lobectomy was performed for 1887 patients. Overall classification of histologic types including additional 125 pneumonectomies in three studies (Harpole et al., 1995; Pastirino et al., 1997; Kwikatkowski et al., 1998) were 878 squamous cell carcinomas and 1617 nonsquamous cell carcinomas. Histologic types were not mentioned in two studies (Landreneau et al., 1997; Keenan et al., 2004) including 420 patients. Stages and tumour–nodes–metastasis (TNM) profiles of patients who underwent limited resection were IA (T1N0M0) and IB (T2N0M0).

Table 1  Studies excluded from the present meta-analysis

| Authors             | Study design | Stage | No. of limited resection | No. of lobectomy | Reasons for exclusion | Survival difference |
|---------------------|--------------|-------|--------------------------|------------------|-----------------------|---------------------|
| Errett et al. (1985)| RS           | IA+B  | 100 (W)                  | 97               | Included advanced and unknown stages | NS                  |
| Pastirino et al. (1991)| RS        | IA+B  | 61 (S+W)                 | 411              | Up dated by Pastirino et al. (1997) | NS                  |
| Sugarbaker and Strauss (2000) | Review | IA+B  | 58 (S+W)                 | 172              | Same series of patients was reported by Kwikatkowski et al. (1998) | Lobectomy better |
| Miller et al. (2002) | RS           | IA+B  | 25 (S+W)                 | 75               | Included advanced stages | Lobectomy better    |

RS = retrospective study; S = segmentectomy; W = wedge resection; ND = not described; NS = not significant.

Table 2  Studies included in the present meta-analysis

| Authors             | Study design | Stage | No. of limited resection | No. of lobectomy | Reasons for limited resection | Survival difference |
|---------------------|--------------|-------|--------------------------|------------------|-------------------------------|---------------------|
| Hoffmann and Randsell (1980) | RS           | IA    | 33 (W)                   | 40               | Poor cardiopulmonary function and smaller lesions | NS                  |
| Read et al. (1990)  | RS           | IA    | 113 (107S+6W)            | 131              | Poor pulmonary function       | NS (CSS)            |
| Date et al. (1994)  | MPS          | IA    | 16 (65+10W)              | 16               | Poor cardiopulmonary function and smaller lesions | Lobectomy better    |
| Warren and Faber (1994) | RS           | IA+B  | 66 (S)                   | 103              | Poor cardiopulmonary function and smaller lesions | NS                  |
| Harpole et al. (1995) | RS           | IA+B  | 75 (W)                   | 193              | Poor cardiopulmonary function and smaller lesions | NS (CSS)            |
| LCGS (1996)         | RCT          | IA    | 122 (82S+40W)            | 125              | Randomisation                  | NS                  |
| Kodama et al. (1997) | RS           | IA    | 46 (W)                   | 77               | Intentional resection for small lesions | NS                  |
| Landreneau et al. (1997) | RS        | IA    | 102 (W)                  | 117              | Poor cardiopulmonary function | NS                  |
| Pastirino et al. (1997) | RS           | IA+B  | 53 (S+W)                 | 367              | Poor cardiopulmonary function | NS                  |
| Kwikatkowski et al. (1998) | RS           | IA+B  | 58 (S+W)                 | 186              | Poor pulmonary function       | NS                  |
| Okada et al. (2001)  | RS           | IA    | 70 (S)                   | 139              | Intentional resection for small lesions $\leq$ 2 cm | NS                  |
| Koike et al. (2003)  | RS           | IA    | 14 (S)                   | 159              | Intentional resection for small lesions $\leq$ 2 cm | NS                  |
| Campione et al. (2004) | RS           | IA    | 21 (S)                   | 100              | Poor cardiopulmonary function | NS                  |
| Keenan et al. (2004) | RS           | IA+B  | 54 (B)                   | 147              | Poor pulmonary function       | NS                  |

$^a$Tumours peripherally located. $^b$Only intentional resection. $^c$Including 13 pneumonectomies. LCGS = Lung Cancer Study Group; S = segmentectomy; W = wedge resection; ND = not described; NS = not significant; MPS = matched-pair study; RCT = randomised controlled trial; RS = retrospective study; CSS = cancer-specific survival.
Studies included were considered highly heterogeneous for the following reasons. The percentage of nonsquamous cell carcinoma in each study ranged from 39.7% (Hoffmann and Ransdell, 1980) to 100% (Koike et al, 2003). Further, the percentage of male patients in each study ranged from 50.6% (Koike et al, 2003) to 100% (Hoffmann and Ransdell, 1980). Percentages of squamous cell carcinoma in each study showed strong association with male gender (Figure 1, r = 0.931, P < 0.0001). The reason for limited resection differed from study to study, but the most frequent reason was poor cardiopulmonary function in seven studies; limited resection was intentional in four studies and was part of an RCT design in one. The reason was not clearly mentioned in 3 studies. All of these differences might affect the respective studies and contribute to interstudy heterogeneity in the present meta-analysis.

Combined survival differences at 1, 3, and 5 years after resection were 0.7, 1.9, and 3.6%, respectively (Figure 2A–C). None of these combined survival differences were significant (see legend to Figure 2). Heterogeneity testing indicated that studies were heterogeneous at 3- and 5-year time points (see legend to Figure 2). Publication bias was not detected at 1, 3, or 5 years; all P-values > 0.1; 0.5402, 0.1807, and 0.3633, respectively.

DISCUSSION

The extent of lung resection most appropriate for small cancers has been discussed for a number of decades. Although limited resection for patients with poor cardiopulmonary reserve is regarded reasonable, intentional limited resection for patients expected to withstand standard lobectomy has not been established. We therefore performed a meta-analysis to determine the extent of lung resection most appropriate for small cancers. In our study (Nakamura et al, 2004), analyzing 100 patients who underwent limited resection without systematic lymph node dissection, the overall 5-year survival rate for 73 patients with small adenocarcinomas (≤ 2 cm) was 93.7%, which was significantly better than for those with larger adenocarcinomas (24.8%). In addition, we found the overall 5-year survival rate for patients with well-differentiated adenocarcinoma (81.2%) to be significantly better than for a group combining moderately and poorly differentiated adenocarcinomas (30.7%). Thus, in addition to tumour size, biologic characteristics importantly affect survival after limited resection. Since the most reliable results are likely to be those of the RCT, we believe that limited resection truly is inferior to lobectomy in terms of locoregional recurrence and survival in a study where eligibility for randomisation depends solely on tumour size (≤ 3 cm). However, we also would maintain that a subset of NSCLC can be resected completely by limited resection. One example would be a small, slowly growing, localised bronchioloalveolar carcinoma showing only ground-glass opacity (GGO) on computed tomography (Kaneko et al, 1996; Sone et al, 1998). In our opinion, these lesions can be resected...
completely by VATS wedge resection (Watanabe et al., 2002; Nakamura et al., 2004), given their low invasiveness and absence of lymph node metastases (Nakata et al., 2002).

In conclusion, the present meta-analysis of published data disclosed that survival after limited resection for stage I lung cancer is comparable to lobectomy. However, considerable heterogeneity among studies suggests that clinicopathologic features of patients who underwent limited resection in the studies analysed were quite different. We believe that some lung cancers can be cured by limited resection, if we can identify tumours of minimally invasive nature, such as small bronchioloalveolar carcinomas diagnosed by CT (Nakamura et al., 2004). Further clinicopathologic studies of the biologic nature of various lung cancers should help to address this problem.

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