

Is limited pulmonary resection equivalent to lobectomy for surgical management of stage I non-small-cell lung cancer?

Maya K. De Zoysa^{a,*}, Dima Hamed^b, Tom Routledge^b and Marco Scarci^a

^a Department of Thoracic Surgery, St Joseph's Healthcare, McMaster University, Hamilton, Canada

^b Department of Thoracic Surgery, Guy's Hospital, London, UK

* Corresponding author. DeGroote School of Medicine, 1280 Main Street West, Hamilton, Ontario L8S4L8, Canada. Tel: +1-289-8080835; e-mail: maya.dezoysa@medportal.ca (M.K. De Zoysa).

Received 24 August 2011; received in revised form 10 January 2012; accepted 12 January 2012

Abstract

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was: is limited pulmonary resection equivalent to lobectomy in terms of morbidity, long-term survival and locoregional recurrence in patients with stage I non-small-cell lung cancer (NSCLC)? A total of 166 papers were found using the reported search; of which, 16 papers, including one meta-analysis and one randomized control trial (RCT), represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. With regards to 5-year survival rates, the evidence is conflicting: a 2005 meta-analysis and six other retrospective or prospective non-randomized analyses did not find any statistically significant difference when comparing lobectomy with limited resection. However, three studies found evidence of a decreased overall survival with limited resection, including the only randomized control trial, which showed a 50% increase in the cancer-related death rate ($P = 0.09$), and a 30% increase in the overall death rate in patients undergoing limited resection ($P = 0.08$). Age, tumour size and specific type of limited resection were also factors influencing the survival rates. Four studies, including the RCT, found increased locoregional recurrence rates with limited resection. There is also evidence that wedge resections, compared with segmentectomies, lead to lower survival and higher recurrence rates. In conclusion, lobectomy is still recommended for younger patients with adequate cardiopulmonary function. Although limited resection carries a decreased rate of complications and shorter hospital stays, it may also carry a higher rate of loco-regional recurrences. However, limited resection may be comparable for patients >71 years of age, and those with small peripheral tumours.

Keywords: Non-small cell lung cancer • Limited resection • Lobectomy • Segmentectomy • Wedge resection

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the *ICVTS* [1].

THREE-PART QUESTION

In [patients with stage I non-small-cell lung cancer] is [limited resection] equivalent to [lobectomy] in terms of [morbidity, long-term survival and locoregional recurrence].

CLINICAL SCENARIO

A 74-year old male patient presents to your thoracic clinic complaining of shortness of breath and weight loss. Preoperative staging confirm an early-stage NSCLC in the right upper lobe with no mediastinal nodal involvement. He is a lifelong smoker. The lung function test returns an FEV1 of 1.1 l and diffusing capacity of 40%. Although a lobectomy would represent the standard treatment, you are concerned about the fitness for surgery of the

patient and wonder if a limited pulmonary resection, as a less invasive surgery than lobectomy, would carry similar survival and cancer recurrence rates. You resolve to check the literature yourself.

SEARCH STRATEGY

MedLine 1950 to December 2011 using OVID interface [Non-small cell lung cancer.mp. OR Carcinoma, Non-Small-Cell Lung/] AND [lobectomy.mp] AND [limited pulmonary resection.mp OR wedge resection.mp OR segmentectomy.mp OR sublobar.mp]

The search was limited to English language articles and Human studies only.

In addition, the reference lists of each publication were searched.

SEARCH OUTCOME

A total of 166 papers were found using the reported search. From these, 16 papers provided the best evidence to answer the question. These are presented in Table 1.

Table 1: Best evidence papers

Author, date, country, level of evidence	Patient group	Outcomes		Key results	Comments
		5-year (or specified) survival rate	Locoregional recurrence		
Nakamura <i>et al.</i> (2005), Japan Meta-analysis (level 1a)	Lobectomy: 1887 (Wedge resection + Segmentectomy): 903	Survival difference (5 years) = 3.6%	N/A	No significant difference in survival	Considerable heterogeneity, particularly after 5 years (Q = 33.6 P = 0.0004)
Ginsberg <i>et al.</i> (1995), USA Randomized control trial (level 1b)	Lobectomy: 125 (Wedge resection + Segmentectomy): 122	Overall death rate (persons/year): Lobectomy: 0.089 Limited resection: 0.117	(persons/year) Lobectomy: 0.020 Limited resection: 0.060	30% increase in the death rate with limited resection (P = 0.08) 300% increase in locoregional recurrence (P = 0.008)	Inconsistent mediastinal lymph node sampling
Kraev <i>et al.</i> (2007) USA Retrospective cohort study (level 2b)	Lobectomy: 215 Wedge resection: 74	Survival times: Lobectomy: 5.8 ± 0.3 years Wedge resection: 4.1 ± 0.3 years	N/A	No significant difference in the overall survival. Increased survival with lobectomy for tumours <3 cm in size (P = 0.029)	Small-cell lung cancers were also included
Landreneau <i>et al.</i> (1997), USA Retrospective cohort study (level 2b)	Lobectomy: 117 Wedge resection (open): 42 Wedge resection (VATS): 60	Lobectomy: 70% Wedge resection (Open): 58% Wedge resection (VATS): 65%	Wedge resection (Open): 30% Wedge resection (VATS): 26% Lobectomy-19%	Significant increase in survival with lobectomy (P = 0.02) No significant difference in locoregional recurrence	The 5-year survival differences were mainly due to non-cancer-related deaths
El-Sherif <i>et al.</i> (2006) USA Retrospective cohort study (level 2b)	Lobectomy: 577 Segmentectomy: 85 Wedge resection: 122	Lobectomy: 54% (Wedge resection + Segmentectomy)-40%	Lobectomy: 28% (Wedge resection + Segmentectomy): 29%	Significant increase in survival with lobectomy (P = 0.0038) No difference in locoregional recurrence Decrease in 5-year disease-free survival from 58% (lobectomy) to 50% (sublobar) in stage 1B patients (P = 0.0093)	Surgical approach unknown
Koike <i>et al.</i> (2002), Japan Prospective non-randomized analysis (level 2b)	Lobectomy: 159 Segmentectomy: 60 Wedge resection: 14	Lobectomy: 90% (Wedge resection + Segmentectomy)-89%	Lobectomy: 1.3% (Wedge resection + Segmentectomy): 2.7%	No significant difference in survival No significant difference in locoregional recurrence	Inconsistent mediastinal lymph node sampling
Keenan <i>et al.</i> (2004), USA Retrospective analysis (level 2b)	Lobectomy: 146 Segmentectomy: 54	(Kaplan-Meier 4-year survival) Lobectomy: 67% Segmentectomy: 62%	Lobectomy: 7.5% Segmentectomy: 11.1%	No significant difference in survival No significant difference in locoregional recurrence	Inconsistent mediastinal lymph node sampling
Read <i>et al.</i> (1990), USA Retrospective study (level 2b)	Lobectomy: 113 Segmentectomy: 107 Wedge resection: 6	Lobectomy: 74% Segmentectomy: 84%	Lobectomy: 11.5% Segmentectomy: 4.4%	No significant difference in survival	

Continued

Table 1: Continued

Author, date, country, level of evidence	Patient group	Outcomes		Key results	Comments
		5-year (or specified) survival rate	Locoregional recurrence		
Warren <i>et al.</i> (1994), USA Retrospective analysis (level 2b)	Lobectomy: 103 Segmentectomy: 66	Lobectomy: 65% Segmentectomy: 45% Calculated from survival graphs	Lobectomy: 4.9% Segmentectomy: 22.7%	Significant increase in overall survival with lobectomy. ($P = 0.035$) No significant survival difference for tumours <3 cm Significant increase in locoregional recurrence with segmentectomy	Surgical approach unknown
Okada <i>et al.</i> (2006), Japan Prospective nonrandomized study (level 2b)	Lobectomy: 305 (Wedge resection + Segmentectomy): 262	Lobectomy: 89.6% (Wedge resection + Segmentectomy): 89.1%	N/A	No significant difference in survival	Significant crossover between groups
Okada <i>et al.</i> (2001), Japan Prospective nonrandomized study (level 2b)	Lobectomy: 139 Segmentectomy: 70 Stage 1 NSCLC <2 cm	Lobectomy: 87.3% Segmentectomy: 77.7%	N/A	No significant difference in survival	Significant crossover between groups
Harpole <i>et al.</i> (1995), USA Retrospective analysis (level 2b)	Lobectomy: 193 Wedge resection: 75 Pneumonectomy: 21	Lobectomy: 62% Wedge resection: 61% Pneumonectomy: 270%	Lobectomy: 9.3% Wedge resection: 16% Pneumonectomy: 214.3%	No significant difference in survival No significant difference in locoregional recurrence	Trend towards decreased survival in wedge resection over lobectomy with tumours >3 cm ($P = 0.067$)
Mery <i>et al.</i> (2005), USA Retrospective cohort study (level 2b)	Lobectomy: 9875 (Wedge resection + Segmentectomy)- 1403 Pneumonectomy: 292	Median survival time: <65 years-71 months 65-74 years-47 months ≥75 years-28 months	N/A	Significant increase in survival with lobectomy in patients <75 years old	Considerable heterogeneity of data. Stage II NSCLC also included in study
Rami-Porta <i>et al.</i> Spain (2009) Evidence-based clinical practice guidelines		(1) Sublobar resections should be avoided in patients who can tolerate lobectomy (Grade of recommendation: A) (2) In patients unable to undergo lobectomy, sublobar resection is an alternative that will confer similar prognosis (Degree of recommendation: B) (3) Wedge resection should be reserved for patients aged >71 years (Degree of recommendation: B) (4) If the intra-operative diagnosis of bronchioloalveolar carcinoma is certain, because of its non-invasive nature and lack of nodal involvement, sublobar resection with no systematic nodal dissection may be sufficient treatment for this particular type of tumour (Degree of recommendation: B)			
Okumura <i>et al.</i> (2007), Japan Retrospective study (level 2b)	Lobectomy: 1241 Segmentectomy: 144	Tumours ≤2 cm: Lobectomy: 18% Segmentectomy: 83% Tumours >2 cm: Lobectomy: 78% Segmentectomy: 58%	N/A	Significant increase in survival with lobectomy in tumours >2 cm ($P = 0.057$)	
Nakamura <i>et al.</i> (2011), Japan Prospective non-randomized study (level 2b)	Lobectomy: 289 Segmentectomy: 38 Wedge resection: 84	Lobectomy: 82.1% Segmentectomy: 87.2% Wedge resection: 55.4%	Lobectomy: 18.0% Segmentectomy: 7.9% Wedge resection: 15.5%	Significant decrease in survival with wedge resection (vs. lobectomy and segmentectomy) ($P = 0.0003$)	

RESULTS

Is there a better survival with lobectomy or limited resection for stage I NSCLC? Out of the 16 papers included in this literature review, seven papers, including the only meta-analysis conducted on the topic, found no significant difference in the overall 5-year survival rate when comparing lobectomy and limited resection [2–8].

Three studies showed a decreased survival in the sublobar resection patient population. Ginsberg and Rubinstein [9] conducted the only published randomized control trial comparing lobectomy and limited resection, showing a 30% increase in the overall death rate, and a 50% increase in the cancer-related death rate ($P=0.08$ and 0.09 , respectively). Landreneau *et al.* [10] discovered a significant survival difference at 5 years—58% survival for open wedge resection and 70% for lobectomy ($P=0.02$). El-Sherif *et al.* [11] also reported a decreased survival with limited resection (lobectomy, 54%; limited resection, 40%; $P=0.0038$). However, further analysis of the data showed that limited resection patients tended to be older and have limited node sampling. After adjusting for those variables, there was no significant difference in the survival.

Some studies showed differences in the survival, but with certain limitations. Mery *et al.* [12] showed a decreased survival with limited resection with patients younger than 71 years of age, and Nakamura *et al.* [13] reported a decreased survival specifically with wedge resections, whereas segmentectomy was comparable to lobectomy. The tumour size was also a significant factor: Okada *et al.* [6, 7], Okumura *et al.* [14], Warren and Faber [15], El-Sherif *et al.* [11] and Koike *et al.* [3], all showed no significant difference in the survival for tumours ≤ 2 cm in size. Above this landmark, lobectomy has been associated with an improved survival compared with limited resection: Harpole *et al.* [8] reported a non-significant trend towards a decreased survival with wedge resection over lobectomy in patients with tumours >3 cm ($P=0.067$), and Okumura *et al.* [14] showed a decrease in the survival from 78% (lobectomy) to 58% (segmentectomy) for patients with tumours >2 cm ($P=0.057$). The one potential exception is the study by Kraev *et al.*, which demonstrated an improved survival with lobectomy for tumours <3 cm ($P=0.029$) [16].

On the question of increased local recurrence with limited resection compared with lobectomy, Ginsberg *et al.* [9] reported a 300% increase in the locoregional recurrence rate in the limited resection population ($P=0.008$), and similarly Warren *et al.* [15] also showed a significant increase in the recurrence rate (lobectomy, 4.9%; segmentectomy, 22.7%). Harpole *et al.* [8] determined a non-significant trend towards an increased locoregional recurrence in wedge resection patients. With regards to disease-free survival, El-Sharif *et al.* reported a decrease in the survival in sublobar resection patients, but this was only limited to stage 1B tumours (lobectomy, 58%; sublobar, 50%, $P=0.0093$) [11]. However, as described by Rami-Porta and Tsuboi, this is generally a reasonable trade for sparing lung parenchyma [17].

Does sublobar resection translate into a reduction in morbidity? Some studies did support this: Harpole *et al.* [8] indicated a lower complication rate, Landreneau *et al.* [10] reported shorter hospital stays and Keenan *et al.* [4] showed a preservation of pulmonary function in patients who underwent limited resection compared with lobectomy. However, Ginsberg *et al.* [9] showed

no significant difference in perioperative morbidity or post-operative pulmonary function between lobectomy and limited resection patients.

Some of the conflicting evidence provided by these studies may be attributed to various combinations of wedge resections and segmentectomies, which often create a single studied limited resection group [2, 7, 9, 11, 12]. Wedge resections and segmentectomies are not technically or oncologically equivalent, and there is increasing evidence that there are differences in terms of survival and recurrent rates [17, 18]. An example of this would be the recent study by Nakamura *et al.* [13], which showed a significantly lower survival rate wedge resection patients (55.4%) compared with segmentectomy or lobectomy (87.2 and 82.1%, respectively).

Evidence-based clinical guidelines published in 2009 state that sublobar resections should be avoided in patients who can tolerate lobectomy, with the possible exception of pure bronchioloalveolar carcinoma, where limited resection may be sufficient. However, in patients who unable to undergo lobectomy, sublobar resection is an alternative that will confer similar prognosis [17]. The 2011 NICE lung cancer guidelines also offer a similar recommendation [19].

CLINICAL BOTTOM LINE

Lobectomy remains the most reliable surgical treatment for early-stage NSCLC in young patients with adequate pulmonary reserve and cardiac function. Although limited resection carries a decreased rate of complications and shorter hospital stays, it may also carry a higher rate of loco-regional recurrences. As for older patients with cardio-pulmonary impairment or small peripheral tumours, limited resection may achieve similar survival rates when compared with lobectomy.

Conflict of interest: none declared.

REFERENCES

- [1] Dunning J, Prendergast B, Mackway-Jones K. Towards evidence-based medicine in cardiothoracic surgery: best BETS. *Interact CardioVasc Thorac Surg* 2003;2:405–9.
- [2] Nakamura H, Kawasaki N, Taguchi M, Kabasawa K. Survival following lobectomy vs. limited resection for stage I lung cancer: a meta-analysis. *Br J Cancer* 2005;92:1033–7.
- [3] Koike T, Yamato Y, Yoshiya K, Shimoyama T, Suzuki R. Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer. *J Thorac Cardiovasc Surg* 2003;125:924–8.
- [4] Keenan RJ, Landreneau RJ, Maley RH, Singh D, Marcherey R, Bartley S *et al.* Segmental resection spares pulmonary function in patients with stage I lung cancer. *Ann Thorac Surg* 2004;78:228–33.
- [5] Read RC, Yoder G, Schaeffer RC. Survival after conservative resection for T1 N0 M0 non-small cell lung cancer. *Ann Thorac Surg* 1990;49:391–8.
- [6] Okada M, Yoshikawa K, Hatta T, Tsubota N. Is segmentectomy with lymph node assessment an alternative to lobectomy for non-small cell lung cancer of 2 cm or smaller? *Ann Thorac Surg* 2001;71:956–60.
- [7] Okada M, Koike T, Higashiyama M, Yamata Y, Kodama K, Tsubota N. Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study. *J Thorac Cardiovasc Surg* 2006;132:769–75.
- [8] Harpole D, Herndon J, Young W, Wolfe W, Sabiston D. Stage I nonsmall cell lung cancer. A multivariate analysis of treatment methods and patterns of recurrence. *Cancer* 1995;76:787–96.
- [9] Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg* 1995;60:615–22.

- [10] Landreneau RJ, Sugarbaker DJ, Mack MJ, Hazelrigg SR, Luketich JD, Fetterman L *et al.* Wedge resection versus lobectomy for stage I (T1 N0 M0) non-small-cell lung cancer. *J Thorac Cardiovasc Surg* 1997;113: 691-8.
- [11] El-Sherif A, Gooding WE, Santos R, Pettiford B, Ferson PF, Fernando HC *et al.* Outcomes of sublobar resection versus lobectomy for stage I non-small cell lung cancer: a 13-year analysis. *Ann Thorac Surg* 2006;82:408-16.
- [12] Mery CM, Pappas AN, Bueno R, Colson Y, Linden P, Sugarbaker D *et al.* Similar long-term survival of elderly patients with non-small cell lung cancer treated with lobectomy or wedge resection within the Surveillance, Epidemiology, and End Results database. *Chest* 2005;128: 237-45.
- [13] Nakamura H, Taniguchi Y, Miwa K, Adachi Y, Fujioka S, Haruki T *et al.* Comparison of the surgical outcomes of thoracoscopic lobectomy, segmentectomy, and wedge resection for clinical stage I non-small cell lung cancer. *Thorac Cardiovasc Surg* 2011;59:137-41.
- [14] Okumura M, Goto M, Ideguchi K, Tamura M, Sasaki H, Tanaka H *et al.* Factors associated with outcome of segmentectomy for non-small cell lung cancer: long-term follow-up study at a single institution in Japan. *Lung Cancer* 2007;58:231-7.
- [15] Warren WH, Faber LP. Segmentectomy versus lobectomy in patients with stage I pulmonary carcinoma. Five-year survival and patterns of intrathoracic recurrence. *J Thorac Cardiovasc Surg* 1994;107: 1087-93.
- [16] Kraev A, Rassias D, Vetto J, Torosoff M, Ravichandran P, Clement C *et al.* Wedge resection vs. lobectomy: 10-year survival in stage I primary lung cancer. *Chest* 2007;131:136-40.
- [17] Rami-Porta R, Tsuboi M. Sublobar resection for lung cancer. *Eur Respir J* 2009;33:426-35.
- [18] Sieneel W, Dango S, Kirschbaum A, Cucuruz B, Hörth W, Stremmel C *et al.* Sublobar resections in stage IA non-small cell lung cancer: segmentectomies result in significantly better cancer-related survival than wedge resections. *Eur J Cardiothorac Surg* 2008;33:728-34.
- [19] Baldwin DR, White B, Schmidt-Hansen M, Champion AR, Melder AM. Diagnosis and treatment of lung cancer: summary of updated NICE guidance. *BMJ* 2011;342:d2110.