

Is there a survival advantage of incomplete resection of non-small-cell lung cancer that is found to be unresectable at thoracotomy?

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Abstract

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was: in patients with non-small-cell lung cancer that is found to be unresectable at thoracotomy, is incomplete resection superior for achieving survival advantage? Altogether more than 400 papers were found using the reported search, of which nine 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 were tabulated. In total, data from an estimated 1083 patients were analysed. Three-year survival rates varied from 0 to 22% in incomplete resection and from 0 to 10% in exploratory thoracotomy. Median survival ranged from 6.5 to 19.1 months in incomplete resection and from 5.3 to 17 months in exploratory thoracotomy. The majority of studies (8/9) found survival in incomplete resection to be superior. However, only 3/9 studies presented statistical analysis of results. The largest of these found superior postoperative survival in incomplete resection (including residual nodal disease), one study showed a significant survival difference for R1 but not R2 resection and another with small patient numbers ($n = 29$) found no significant difference. We conclude that the best evidence suggests that there may be a survival advantage from incomplete resection of non-small-cell lung cancer when there is microscopic (R1) or nodal residual disease, but not when macroscopic residual (R2) disease remains.

Keywords: Review • Non-small-cell lung • Incomplete resection • Macroscopic residual • Microscopic residual • Debulking • Exploratory thoracotomy

INTRODUCTION

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

THREE-PART QUESTION

In [NSCLC that is found not to be completely resectable at thoracotomy], is [incomplete resection] superior [for achieving survival advantage]?

CLINICAL SCENARIO

You are beginning a left upper lobectomy on a patient with non-small-cell lung cancer (NSCLC). The patient is a previously healthy 58-year old, staging bronchoscopy and mediastinoscopy were negative and preoperative imaging revealed no evidence of metastatic spread. You expect the carcinoma to be resectable and the patient to have a good prognosis. Unfortunately, as you

inspect the carcinoma on the operating table, you realize that it is adherent to the aorta and complete resection will be impossible. You explain to your assisting SHO that this will be an 'open-and-close' case. The SHO asks whether it might be worthwhile to remove as much of the carcinoma as possible. You are not sure whether there would be a survival advantage to incomplete resection of an NSCLC in this situation, and resolve to check the literature yourself.

SEARCH STRATEGY

Medline 1950 to August 2012 using OVID interface. The search terms were ('non-small-cell-lung' or 'lung-cancer' or 'bronchogenic-carcinoma') and ('incomplete-resection' or 'exploratory-thoracotomy' or 'mediastinal invasion' or 'chest-wall-invasion').

SEARCH OUTCOME

Using the reported search, 419 papers were found. From these, nine publications with English-language abstracts were identified

Table 1: Best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Rami-Porta <i>et al.</i> (2005), <i>Eur J Cardiothorac Surg</i> , Spain [2]	580 NSCLC patients who underwent incomplete resection or exploratory/diagnostic thoracotomy only	Operative mortality 5-year survival and median survival of those that survived surgery	Incomplete resection ($n = 256$): operative survival 88%, 5-year survival 20%, median survival 19.10 months Exploratory thoracotomy ($n = 223$): operative survival 93%, 5-year survival 5%, median survival 10.82 months Diagnostic thoracotomy ($n = 12$): operative survival 94%, 5-year survival 11%, median survival 7.67 months	Improved survival in incomplete resection vs exploratory thoracotomy ($P < 0.0001$), and incomplete resection vs diagnostic thoracotomy ($P = 0.0023$) Did not distinguish between R1/R2 residual, and 'incomplete resection' included residual nodal disease No statistically significant difference in operative mortality
Retrospective cohort study (level 3)	From a multicentre study of 2754 NSCLC surgical patients from 1993–1997			
Ichinose <i>et al.</i> (1993), <i>Lung Cancer</i> , Japan [4]	29 patients from single centre with NSCLC, who underwent incomplete resection or exploratory thoracotomy between 1972 and 1988	Median survival, 3-year survival	Incomplete resection ($n = 9$): 3-year survival 11.1%, median survival 6.5 months Exploratory thoracotomy ($n = 20$): 3-year survival 10%, median survival 17 months	No statistically significant difference in survival between the two groups ($P = 0.27$) No distinction made between R1 and R2 disease
Retrospective cohort study (level 3)	From a series of 98 patients at National Kyushu Cancer Centre Patients all fit for pneumonectomy, complete resection not possible because of the extent of primary tumour All the patients had postop radiotherapy			Excluded patients with microscopic residual at bronchial stump Nodal status: incomplete resection N0 ($n = 5$), N2 ($n = 4$) Exploratory thoracotomy N0 ($n = 7$), N2 ($n = 11$), unknown ($n = 2$)
Yang <i>et al.</i> (2009), <i>Ann Thorac Surg</i> , China [6]	40 patients T4 NSCLC with mediastinal involvement	Median survival, 3-year survival	Incomplete (R2) resection ($n = 9$): 3-year survival 0%, median survival 12.0 months	No significant survival difference between R2 resection and exploratory thoracotomy ($P = 0.376$)
Retrospective cohort study (level 3)	From a study of 146 patients at Sun Yat-sen University Cancer Center from 1997 to 2008		Incomplete (R1) resection ($n = 16$): 3-year survival 0%, median survival 19.2 months Exploratory thoracotomy ($n = 15$): 3-year survival 0%, median survival 5.3 months	Significantly better survival with R1 resection than exploratory thoracotomy ($P = 0.010$) No data on nodal status
Duque <i>et al.</i> (2005), <i>Chest</i> , Spain [3]	From the same set of 2754 patients from multiple centres as Rami-Porta <i>et al.</i> (2005) [2]	5-year survival	Incomplete resection ($n = 51$): 5-year survival 19.6%	Data extracted from other statistics, no significance analysis
Retrospective cohort study (level 3)	Separate analysis of patients with stage IIIB NSCLC was done		Exploratory thoracotomy ($n = 186$): 5-year survival 4.8%	No data on R1/R2 resection or nodal status
Martini <i>et al.</i> (1994), <i>Ann Thorac Surg</i> , USA [8]	From a set of 102 NSCLC patients with N0 or N1, T3 or T4 disease involving the mediastinum	5-year survival	Incomplete resection ($n = 25$): 5-year survival 12%	No data on R1/R2 resection or nodal status
Retrospective cohort study (level 3)	From Memorial Sloan-Kettering Cancer Centre from 1974 to 1992		Exploratory thoracotomy ($n = 31$): 5-year survival 0%	No statistical significance analysis All patients having exploratory thoracotomy and then having incomplete resection had interstitial implantation of radioactive source

Continued

Table 1: (Continued)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Hara et al. (1984), J Surg Oncol, Japan [5]	282 patients with stage III bronchogenic carcinoma	3-year survival, 5-year survival, median survival	Exploratory thoracotomy (n = 52): 5-year survival 0%, median survival 11 months	No significant difference in survival between the three groups (P-values not given)
Retrospective cohort study (level 3)	From National Kyushu Cancer centre, 1972–1981 Nearly all patients received postop radiotherapy or chemotherapy		Incomplete resection (n = 64): 3-year survival 7%, 5-year survival 0%, median 15 months Inoperable (n = 113): median survival 13 months	Included residual nodal disease in definition of incomplete resection In incomplete resection, survival was significantly better in patients with T3N0 disease than in T3N1 and T3N2 disease (P < 0.01)
Downey et al. (1999), Ann Thorac Surg, USA [7]	From a set of 334 patients with NSCLC with chest wall involvement	Median survival, 5-year survival	Incomplete resection (n = 94): 5-year survival 4%, median survival 9 months (range 1–165)	No distinction between R1 and R2 disease in survival data No distinction between nodal status
Retrospective cohort study (level 3)	From Memorial Sloan-Kettering Cancer Centre between 1974 and 1993 No metastases but variable nodal status		Exploratory thoracotomy (n = 65): 5-year survival 0%, median survival 7 months (range 1–70)	21 patients had R1 resection, with no brachytherapy 73 had R2 resection (75% had brachytherapy implants) 65 had no resection (86% had brachytherapy implants)
Burt et al. (1987), Surg Clin North Am, USA [9]	176 patients with NSCLC invading the mediastinum	3-year survival, 5-year survival	Incomplete resection with implantation (n = 33): 3-year survival 22%, 5-year survival 22%	No distinction between R1 and R2 disease No statistical analysis
Retrospective cohort study (level 3)	From Memorial Sloan-Kettering Cancer Centre 1974–1984 Patients had resection and/or thoracotomy with iodine-125 or iridium 129 implantation		Incomplete resection without implantation (n = 42): 3-year survival 0% No resection, implantation only (n = 101): 3-year survival 9%, 5-year survival 0%	Full text article not available
Ratto et al. (1988), Ital J Surg Sci, Italy [10]	75 patients with stage III NSCLC	2-year survival	Incomplete resection (n = 25): 2-year survival 14%	No information about nodal status or R1/R2 status
Retrospective cohort study (level 3)			Exploratory thoracotomy (n = 25): 2-year survival 7% No surgery (n = 25): 2-year survival 9%	Control group with no surgery; the authors concluded that neither incomplete resection nor exploratory thoracotomy improved survival Postop chemo and radiotherapy given

that provided the best evidence to answer the question. These are presented in Table 1.

RESULTS

The best evidence available comes from small numbers of patients within large retrospective studies that were not designed to answer this question, so the evidence is not high quality. Nine studies were found that included survival data on both

incomplete resection and exploratory thoracotomy, of which two used the same data set [2, 3] and another two may have had some overlap [4, 5]. In total, data from an estimated 1083 patients were analysed. Three-year survival rates ranged from 0 to 22% in incomplete resection and from 0 to 10% in exploratory thoracotomy. Median survival was reported in five studies [2, 4–7] and ranged from 6.5 to 19.1 months in incomplete resection and from 5.3 to 17 months in exploratory thoracotomy.

The meaning of the term ‘incomplete resection’ of NSCLC has unfortunately been a matter of controversy. Five studies

[3, 4, 6–8] used it to mean residual disease at the resection margin, two [2, 5] included residual nodal disease and in two [9, 10], the definition used was not clear.

Ichinose *et al.* [4] studied 29 patients where complete resection was impossible because of the extent of the primary carcinoma, who underwent either incomplete resection ($n = 9$, median survival 6.5 months) or exploratory thoracotomy ($n = 20$, median survival 17 months). There was no significant difference in survival ($P = 0.27$). The authors did not differentiate between R1 and R2 residual disease, but excluded patients with microscopic residual at bronchial stump, and recommended that grossly incomplete resection should be abandoned in favour of radiotherapy.

Yang *et al.* [6] reported a series of 40 patients with T4 NSCLC with mediastinal invasion, following R1 resection ($n = 16$, median survival 19.2 months), R2 resection ($n = 9$, median survival 12.0 months) or exploratory thoracotomy ($n = 15$, median survival 5.3 months). Survival was superior to exploratory thoracotomy in R1 resection ($P = 0.001$), but not in R2 resection ($P = 0.376$). This is the only study found that separated R1 and R2 resection and provides the best evidence that R2 resection does not provide survival advantage over thoracotomy alone.

Rami-Porta *et al.* [2] reported a large set of 5-year survival data that included patients who underwent incomplete resection ($n = 287$) or exploratory thoracotomy ($n = 274$). Excluding operative mortality (12% in incomplete resection and 6% in exploratory thoracotomy), there was superior survival in incomplete resection ($P < 0.0001$). No distinction was made between R1 and R2 residual disease, and 36% of incomplete resections were due to residual nodal disease rather than primary carcinoma. This is the largest study found and provides the strongest evidence that incomplete resection (including residual nodal disease) may improve postoperative survival.

Hara *et al.* [5] reported survival data of 227 patients with stage III NSCLC who had incomplete resection ($n = 64$, median survival 15 months), exploratory thoracotomy ($n = 52$, median survival 11 months) or conservative management ($n = 113$, median survival 13 months). They found survival curves to be 'nearly identical' in the three groups, but did not present statistical analysis. The authors included residual nodal disease in incomplete resection and concluded that reduction of tumour volume by incomplete resection did not improve survival.

Taken together, only three papers reported statistical analysis of survival data. Of these, one reported superior survival in incomplete resection (including residual nodal disease) [2], one reported no difference in survival [4] and one reported increased survival in R1 but not R2 resection [6]. Seven studies reported 2-, 3- or 5-year survival rates, in 6/7 survival was better in incomplete resection [2, 4, 7–10] and in 1/7 it was equal at 0% [6]. Five studies reported median survival, in 4/5 it was better in incomplete resection [2, 5–7] and in 1/5 it was better in exploratory thoracotomy [4]. If the five studies that defined an incomplete resection as positive resection margins are taken separately, 1/5 found no significant difference in survival [4], 1/5 found significantly increased survival in R1 but not R2 resection [6] and 3/5 [3, 7, 8] found superior survival in incomplete resection, but did not present statistical analysis.

CLINICAL BOTTOM LINE

The research undertaken to investigate whether incomplete resection gives any survival benefit over exploratory thoracotomy in NSCLC is not high quality and does not provide a definite conclusion. Interpretation of results is restricted by lack of information about the clinical characteristics of patients undergoing different procedures, and varying definitions of incomplete resection. Overall, 8/9 studies found survival in incomplete resection to be better than in exploratory thoracotomy. One-ninth found mixed results, as median survival in incomplete resection was worse, but 3-year survival was better. However, only 3/9 studies reported statistical analysis. Of these, one showed a significantly better survival in R1 but not in R2 resection [6], one with small patient numbers showed no significant difference [4] and one showed superior postoperative survival in incomplete resection (including residual nodal disease) compared with exploratory thoracotomy [2]. In summary, the best evidence suggests that there may be a survival advantage from incomplete resection of NSCLC when there is microscopic (R1) or nodal residual disease, but not when macroscopic residual (R2) disease remains.

Conflict of interest: none declared

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