

## Best evidence topic - Thoracic general

## Should lobectomy or pneumonectomy patients with microscopic involvement of the bronchial resection margin undergo re-operation to improve their long-term survival?

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**Abstract**

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was whether re-operative surgery or radiotherapy should be given to patients with residual microscopic tumour at the bronchial resection margin. Altogether 427 papers were identified using the reported search of which 13 represented the best evidence on this topic. The author, journal, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses were tabulated. We conclude that for patients with stage I-II tumours who could easily tolerate re-operation, further resection is an acceptable treatment option and may improve survival. However, only 4 of the 13 studies that we identified recommend this strategy. In addition, there is no convincing evidence that radiotherapy significantly improves survival for patients not selected for re-operation.

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**Keywords:** Thoracic surgery; Residual neoplasm; Bronchial carcinoma; Review; Evidence based medicine

**1. Introduction**

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

**2. Clinical scenario**

You performed a right lower lobectomy on a 67-year-old gentleman who had a 4-cm squamous cell carcinoma of the right lower lobe. He is a lifelong smoker but his lung function tests showed that he could tolerate a lobectomy or pneumonectomy, although a pneumonectomy would probably have left him with some shortness of breath. You are now due to see him in your clinic but you discover that the histologist found a tumour involving the bronchial resection margin. You wonder whether to offer this patient completion pneumonectomy or whether to send him to an oncologist for post-operative radiotherapy and spare him this additional operation. Thus, you resolve to search the literature before seeing him that afternoon.

**3. Three-part question**

In [patients post lung resection with microscopic bronchial residual tumour] is [re-operation] of any benefit for [long-term survival].

**4. Search strategy**

Medline 1966–May 2005 using the OVID interface [exp Pneumonectomy/OR Pneumonectomy.mp OR lung resection.mp] AND [exp Neoplasm, Residual/OR exp Neoplasm Recurrence, Local/OR incomplete resection.mp OR bronchial resection margin.mp] AND [exp Survival/OR Survival.mp OR exp Mortality/OR mortality.mp] limit to humans.

**5. Search outcome**

A total of 427 papers were found of which 14 papers were relevant (Table 1).

**6. Results**

Thirteen studies were found, all of which were cohort studies reporting the survival of patients with histologically identified residual tumour at the bronchial resection margin.

Law et al. [2] in 1982 reported 64 patients who had microscopic involvement of the bronchial resection margin. They found the patients with mucosal bronchial involvement had better survival than other forms of residual tumour and almost as good as when no spread had been apparent at surgery. Of the 26 patients with mucosal bronchial margin involvement, only seven subsequently developed a macroscopic recurrence of tumour. The 5-year survival for patients with full resection was 40%, and for

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Table 1  
Best evidence papers

Author	Patient group	Study type	Outcomes	Key results	Comments
Law et al. (1982), Thorax UK, [2]	64 patients with positive resection margins from a total of 1000 pts undergoing lobectomy or pneumectomy from 1966–1975	Retrospective Cohort study (level 3b)	5-year survival	No evidence of recurrence or residual tumour survival 40% 9/29 (27%) with mucosal spread 0/18 survivors with peribronchial spread (no 3 year survivors) 1/8 (13%) Lymphatic permeation	It was found that residual tumour did not adversely affect survival Only 7/26 with residual tumour suffered macroscopic bronchial stump recurrence
Liewald et al. (1992), JTCVS, Germany, [3]	21 patients with positive resection margins from 805 pts undergoing lung resection from 1978–1988  Mediastinal lymphadenectomy performed in 15 and Intraoperative frozen section performed in 8 of these 21 patients	Retrospective cohort study (level 3b)	Survival  Incidence of residual tumour  Intraoperative frozen section	Extramucosal microscopic residual disease median 10.3 months survival Mucosal microscopic residual disease median 26 months survival Eighteen of 21 pts received radiation therapy Two pts had completion pneumonectomy 21/805 patients (2.6%) 4 of 8 patients with frozen section had residual tumour overlooked on first assessment	Re-operation for patients with Stage I and II with N0 and N1 recommended, together with intraoperative frozen section of bronchial resection margin for all patients
Gebitekin et al. (1994), Eur J Cardiothorac Surg, UK, [4]	40 patients with positive resection margins from 735 patients undergoing lung resection between 1980–1989  37.5% of patients received radiotherapy	Retrospective cohort study (level 3b)	5-year survival	Positive bronchial resection margin 21.6%, median survival 15 months. This was not improved with radiotherapy (18% RT vs. 23% no RT)  Negative resection margin 32% (52% stage I, 37% stage II)	No statistically significant impact on survival with microscopic residual disease. No benefit with Radiotherapy

Table 1 (Continued)

Author	Patient group	Study type	Outcomes	Key results	Comments
				<i>P</i> = NS	
			Incidence of residual tumour	40/735 patients (5.4%)	
			Recurrence	29/40 (72.5%) recurrence after median 17 months.	
Snijder et al. (1998), Ann Thorac Surg, Netherlands, [5]	23 patients who had positive resection margins from a total of 834 pts with resected stage I non small cell carcinoma from 1977–1993	Retrospective Cohort study (level 3b)	5-year survival	Survival in resection group 54% invasive tumour group with residual disease 27%, CIS recurrence 58% ( <i>P</i> = 0.03)	Residual disease significantly affects survival and further resection is recommended. Radiotherapy did not improve survival.
	13 patients had intraoperative frozen section			In re-operation group survival was 40%	
	5 of 23 patients had re-resection		Intraoperative frozen section	Of 8 studies CIS was found in 4 and invasive carcinoma in 3	
			Radiotherapy	25 months median survival in radiotherapy group, 50 months in no RT group	
			Incidence of residual tumour	23/834 patients (2.8%)	
Lacasse et al. (1998), Ann Thorac Surg, USA, [6]	25 patients with positive resection margins from 399 patients who had lung resection for tumour included in a prospective CT vs. mediastinoscopy study from 1987–1990	Retrospective analysis from a Prospective Cohort Study (level 3b)	3 year survival	Positive resection margin 16/28 (57%) recurrence	Concluded that positive resection margin did not impact survival
	199 patients suffered any recurrence		Predictors of survival	Negative resection margin 184/374 (49%) recurrence <i>P</i> = NS Tumour size (OR 1.2) Nodal status (OR 1.6) but not positive resection margin	Patients with positive resection margins received higher levels of adjuvant therapy
			Incidence of residual tumour	25/399 patients (6.2%)	
Ghiribelli et al. (1999), Eur J Cardiothorac Surg, Italy, [7]	47 patients with positive resection margins from 1384 patients from 1983–1998	Retrospective Cohort Study (level 3b)	5 year survival	Stage I: no residual disease 68%, residual disease 50%	Authors suggest frozen section for all patients undergoing lung resection. Patients with stage I-II and positive margins should have re-operation.
	All patients underwent complete mediastinal			Stage II: No residual 42%, residual 39%	

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Table 1 (Continued)

Author	Patient group	Study type	Outcomes	Key results	Comments
	lymphadenectomy			Stage III; residual or no residual 16%.	Patients with N2 disease should not have reoperation
	2 completion pneumonectomy and 17 pts had radiotherapy			Median survival of 47 pts was 22 months	
			Incidence of residual tumour	47/1384 patients (3.4%)	
			Intra-operative frozen section	4/9 frozen sections showed a false negative result with extramucosal involvement overlooked	
Hofmann et al. (2002), Eur J Cardiothorac Surg, Germany, [8]	26 patients with microscopic residual disease after 596 underwent lung resection from 1992–1997	Retrospective Cohort study (Level 3b)	5-year survival	14% 5 year survival for patients with positive margins  Post RT, median survival 14 months, without RT, 6 months ( $P=NS$ )	Poor survival for patients with positive margins but no significant benefit for radiotherapy.
	Frozen section and extended lymph node excision carried out in all patients			Extrabronchial residual tumor better survival	
	15/26 had post-operative radiation.		Detection with frozen section	9/15 patients who had frozen section but subsequent positive margins had this missed by the frozen section.	
Lequaglie et al. (2003), Eur J Cardiothorac Surg, Italy, [9]	56 patients who had residual disease at the bronchial resection margin from 4530 patients from 1988–1998	Retrospective Cohort Study (Level 3b)	Survival in patients with residual tumour	Stage I untreated 1/8 had recurrence Stage I radiation 7/11 relapses	They recommend no additional resection or radiotherapy for patients with involved resection margins
	No patient with in situ carcinoma was included.		Survival compared to patients without incomplete resection	Stage I–II complete resection 64.5%–62.5%	
	18 patients received radiotherapy, 2 received chemotherapy			Stage I–II incomplete resection 66.1%–63.5%	
			Incidence of residual tumour	56/4530 patients (1.2%)	
Shields TW, (1974), Surg Gynaecol Obstet, USA, [10]	221 patients with microscopically incomplete resection from 2371 patients in the Veterans	Retrospective Cohort Study (Level 3b)	1-year survival	24 of 67 patients with incomplete bronchial resection margin survived 1 year	Very heterogeneous groups of patients reported

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Table 1 (Continued)

Author	Patient group	Study type	Outcomes	Key results	Comments
	Administration adjuvant trials. 67 patients had incomplete resection from bronchial resection margin			50% survival if residual tumour was microscopic only (25% 4 year survival)	No recommendations for patients with microscopic residual tumour given
			Incidence of residual tumour at bronchial resection margin	67/2371 patients (2.8%)	
Kaiser et al. (1989), Ann Thorac Surg, USA, [11]	45 patients with microscopic extramucosal residual disease from 2890 patients undergoing lung resection from 1975–1985	Retrospective Cohort Study (Level 3b)	Survival	15 months median survival 20% 3 year survival 30% 3 year survival for patients with N2 disease with no residual tumour	Most patients had stage III disease when residual tumour was detected  Re-operation is recommended in patients with stage I–II tumours, but this is not supported by the evidence presented
	All patients underwent complete mediastinal lymphadenectomy		Recurrence	81% had recurrence, 32% were local recurrence	
				Median survival after recurrence detection was 5 months	
			Incidence of residual tumour	45/2890 patients (1.6%)	
Heikkila et al. (1986), Ann Chir Gynaecol, Finland, [12]	44 patients with microscopic residual tumour out of 1044 patients undergoing lung resection from 1961–1970	Retrospective Cohort Study (Level 3b)	5-year survival	34% for all patients, 48% for stage I tumour	Post-operative radiotherapy recommended for residual tumour
	Most patients received post-operative radiotherapy		Incidence of residual tumour	44/1044 patients (4%)	No comparison group with no residual tumour given or a group without post-operative radiotherapy
Jeffrey (1972), Ann Roy Coll Surg Eng, UK, [13]	18 patients with bronchial residual tumour from 663 patients undergoing lung resection from 1952–1963.	Retrospective Cohort Study (Level 3b)	5-year survival	6/18 (33%) patients with residual bronchial tumour	No difference in mortality demonstrated
				183/663 (27%) of all resections	
			Incidence of residual tumour	P=NS 18/663 patients (2.7%)	

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Table 1 (Continued)

Author	Patient group	Study type	Outcomes	Key results	Comments
Soorae et al. (1979), JTCVS, Northern Ireland, [14]	64 patients with microscopic residual tumour from 434 patients undergoing lung resection from 1968–1972	Retrospective Cohort Study (Level 3b)	Survival  Incidence of residual tumour	50% 1-year and 23% 5-year survival  64/434 patients (14.7%)	Non control group survival is reported. Survival was deemed to be similar to complete resection patients

patients with mucosal involvement was 27%. Survival analysis showed this difference to be non-significant.

Liewald et al. [3] described 21 patients with microscopic involvement. They found that the median survival was only 12.1 months, which was a poor survival rate. Of the 21 patients, 18 had radiotherapy and two had completion pneumonectomy. They suggested that re-operation should be performed for patients with Stage I and II disease with N0 and N1 spread and intraoperative frozen section should be performed in all patients undergoing lung resection to confirm full excision. They also found that patients with squamous cell carcinoma had better prognosis than adenocarcinoma.

Gebitekin et al. [4] studied 40 patients with microscopic involvement of bronchial margin of the 735 patients who underwent pulmonary resection. Of the 40 cases with positive bronchial stump, 29 developed recurrence at a median of 17 months. Median recurrence for stage I was 30.5 months and stage II was 15 months, stage IIIa was 8.5 months and stage IIIb was 10.5 months. Overall five-year survival rate with patients with positive margin was 21.6% in contrast to the negative margin of 32%. This was not a statistically significant difference. They found no significant survival advantage for patients with stage I and II disease. They also found no advantage for these patients with adjuvant radiotherapy.

Snijder et al. [5] reported 28 patients with residual bronchial margin out of 834 patients who underwent resections. Five of the group underwent second thoracotomy for residual tumour. Five-year survival for patients with complete resection was 54% and in patients with residual tumour group it was 27%. They found that adjuvant radiotherapy did not improve survival in the patients with residual tumour. The median survival for patients receiving radiotherapy was 25.5 months and for revision operation it was 38.4 months. Disease recurred in 48.5% of the patients in the complete resection group as compared to 72.7% of the patients in the residual tumour group. Thus, patients with positive resection margins had a significantly poorer outcome and further resection was recommended if possible.

Lacasse et al. [6] reported 25 patients with positive bronchial margin. Sixteen of the 25 patients had recurrence and 10 of the 25 received adjuvant radiotherapy. They compared their survival to the total study population of 399 patients. Fifty-seven percent of patients with positive margins had recurrence compared to a 49% recurrence rate in the overall resection group which was not a significant

difference. They concluded that positive resection margins did not significantly impact on survival.

Ghiribelli et al. [7] described 47 patients with positive bronchial resection margins. Thirty patients had extramucosal and 17 had mucosal involvement. Survival was lower for patients with positive resection margins. The authors reported four false negative intra-operative frozen sections as the extrabronchial tissue was not fully assessed. Bronchial stump recurrence was 55% but there were no stump recurrences in patients who underwent completion pneumonectomy. They recommend intraoperative frozen section for all patients. They recommend re-operation for Stage I and II patients.

Hofmann et al. [8] reported 26 patients with microscopic spread out of 596 patients who underwent pulmonary resection. Twenty patients of the microscopic residual tumour were Stage IIIa. They reported 11 patients with false negative frozen section, the majority of them involving the peribronchial group. Fifteen patients received radiotherapy. Five year survival was 14% for all recurrence patients. They found no significant difference in survival between patients who did and did not receive post-operative radiotherapy in the N2 group (14 vs. 6 months).

Lequaglie et al. [9] reported on 56 patients out of a cohort of 4530 patients with positive margins. 25/56 patients (44.6%) developed disease relapse. Sixteen patients had loco-regional and nine had distant metastases. Overall 5-year survival was 44%. They found a similar prognosis for patients with stage I and II patients with microscopic residual disease to that of completely resected tumour, with a 5-year survival around 65%. They concluded that neither re-operation nor radiation therapy impacted survival.

Five further studies are tabulated, reporting cohorts from 1955 to 1985 [10–14].

In summary in these 13 papers, the incidence of residual tumour ranged from 1.2% to 14% with most reporting incidences around 2–4%. Two studies recommend intra-operative frozen section for all patients to minimise the possibility of residual tumour being missed although 4 papers reported patients missed using this strategy. Only 4 studies recommend re-operation with the remaining papers reporting no significant difference in survival for patients with residual tumour. Of the 4 studies recommending re-operation, all recommend this only for stage I or II tumours. In addition there was no good evidence that radiotherapy improved survival for these patients and only one paper recommended radiotherapy as a treatment option.

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**7. Clinical bottom line**

181 For patients with stage I–II tumours who could easily  
 182 tolerate re-operation, further resection is an acceptable  
 183 treatment option and may improve survival. However, only  
 184 4 of the 13 studies that we identified recommend this  
 185 strategy. In addition, there is no convincing evidence that  
 186 radiotherapy significantly improves survival for patients not  
 187 selected for re-operation.

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