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Does surgical margin affect recurrence and survival after sublobar pulmonary resection for lung cancer?

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Abstract

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was: How does surgical margin distance affect recurrence and survival after sublobar pulmonary resection for lung cancer? Altogether, 172 papers were found using the search strategy, of which 12 studies with 1946 stage I non-small-cell lung cancer (NSCLC) patients using sublobar resection (wedge resection or segmentectomy) represented to be 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. Overall, 11 cohort studies and 1 prospective study were included. Four cohort studies demonstrated positive prognostic significance of surgical margin with specific cut-off points in each paper (ranged from 9 to 15 mm). Two retrospective studies and 1 prospective study found that a margin-to-tumour ratio of ≥1 was associated with better cytology and prognosis results. Other 5 studies showed that larger margin distance provided a favourable prognosis for NSCLC patients with poor-prognostic factors, including solid-dominant type, high invasive component size and Spread through Air Spaces-positive subtype. After reviewing all the included articles, we conclude that the standard of margin distance of >10 mm or margin-to-tumour ratio ≥1 should be recommended for stage I NSCLC patients undergoing sublobar resection, especially in wedge resection. Patients with poor-prognostic factors like solid-predominant tumour or non-lepidic adenocarcinoma may benefit from larger margin distance and the proper margin distance for them still needs to be determined. For Spread through Air Spaces-positive patients, sublobar resection may not be the alternative to lobectomy.

Keywords: Lung cancer • Margin distance

INTRODUCTION

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

THREE-PART QUESTION

In [patients with stage I lung cancer undergoing sublobar resection], does [surgical margin distance] affect [recurrence and survival]?

CLINICAL SCENARIO

Your clinical team is reviewing a 70-year-old man with a 15-mm lung nodule, which was diagnosed as stage I NSCLC. He had no history of pulmonary surgeries or other comorbidities. Based on radiographic and pathological findings, your trainee asks how to determine the resection range to achieve a better prognosis with proper pulmonary function preserved.

SEARCH STRATEGY

A literature search was performed on the Medline database (1950–April 2021) through the PubMed interface using the terms ((margin[Title/Abstract]) AND (lung neoplasms[MeSH Terms])) AND ((((sublobectomy[Title/Abstract]) OR (Segmentectomy[Title/Abstract])) OR (Wedge resection[Title/Abstract])) OR (sublobar resection[Title/Abstract])).

SEARCH OUTCOME

A total of 172 publications were found. After screening all the abstracts, we excluded 160 papers due to irrelevance. The 12 papers remained provided the best available evidence to answer the clinical question, which are presented in Table 1.

[†]The first two authors contributed equally to this article.

Table 1: Best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
El-sherif *et al.* (2007), Ann Surg Oncol, America [2]	**Patients** 81 patients with stage I lung cancer, sublobar resection	**Recurrence** Local recurrence	<10-mm group: 14.6% (6/41) ≥10-mm group: 7.5% (3/40) ($P = 0.041$)	Wedge resection appears more frequently in sub-lobar resection with <1-cm margins ($P = 0.003$)
Cohort study (level 3)	**Margin distance** <10-mm group: $n = 41$ ≥10-mm group: $n = 40$ **Study period** January 1997 to June 2004 **Median postoperative follow-up** 20 months	Regional recurrence Distant recurrence **Survival** Survival DFS	<10 mm: 9.8% (4/41) ≥10 mm: 5% (2/40) ($P = 0.104$) <10 mm: 14.6% (6/41) ≥10 mm: 12.5% (5/40) ($P = 0.580$) $P = 0.19$ $P = 0.198$	
Sienel *et al.* (2007), Eur J Cardiothorac Surg, Germany [3]	**Patients** 49 patients with stage I lung cancer Segmentectomy	**Recurrence** Local recurrence	≤10-mm group: 23% >10-mm group: 0 ($P = 0.06$)	The higher recurrence rate in segments 1–3 might due to the insufficiency of patient numbers in other segments
Cohort study (level 3)	**Margin distance** ≤10-mm group: $n = 35$ >10-mm group: $n = 10$ **Study period:** 1987–2002 **Median postoperative follow-up** 54 months			
Mohiuddin *et al.* (2014), J Thorac Cardiovasc Surg, USA [4]	**Patients** 479 patients with stage I lung cancer, wedge resection **Margin distance**	**Recurrence** Local recurrence	2 mm: HR, 1.54; 95% CI, 1.11–2.14 5 mm: Referent 10 mm: HR, 0.55; 95% CI, 0.35-0.86 15 mm: HR, 0.41; 95% CI, 0.21-0.81 20 mm: HR, 0.46; 95% CI, 0.20-1.04 ($P = 0.033$)	Spline specification is validated to assess the hazard ratio among different groups
Cohort study (level 3)	1–5-mm group: $n = 169$ 6–10-mm group: $n = 123$ 11–20-mm group: $n = 138$ >20-mm group: $n = 49$ **Study period** January 2011 to August 2011	Local recurrence or death	2 mm: HR, 1.29; 95% CI, 1.02-1.64 5 mm: Referent 10 mm: HR, 0.70; 95% CI, 0.51-0.95 15 mm: HR, 0.56; 95% CI, 0.34-0.90 20 mm: HR, 0.54; 95% CI, 0.29-1.02	
Wolf *et al.* (2017), Ann Thorac Surg, USA [5]	**Patients** 138 patients with stage I lung cancer, wedge resection	**Recurrence** Recurrence per millimetre increase in margin	OR: 0.9; 95% CI: 0.83-0.98	The sensitivity analysis indicated that a margin distance >9 mm was associated with longer recurrence-free survival
Cohort study (level 3)	**Margin distance** Mean distance 8 mm **Study period** January 2000 to December 2005 **Mean postoperative follow-up** 49.6 months	**Survival** Survival per millimetre increase in margin	HR: 0.94; 95% CI: 0.90-0.98	
Maurizi *et al.* (2015), Ann Thorac Surg, Italy [13]	**Patients** 182 patients with stage I lung cancer, wedge resection	**Recurrence** Local recurrence	≤10-mm group: HR, 1 10–20-mm group: HR, 1.04; 95% CI, 0.40-2.68 >20-mm group: HR , 0.91; 95% CI, 0.34-2.41 ($P = 0.9$)	The follow-up period is relatively insufficient and might not be enough to detect recurrence in stage I NSCLC patients
Cohort study (level 3)	**Margin distance** ≤10-mm group: $n = 30$ 10–20-mm group: $n = 80$ >20-mm group: $n = 72$ **Study period** 2003–2013 **Median postoperative follow-up** 31 months	Distant recurrence **Survival** 3- and 5-Year OS	≤10-mm group: HR, 1 10–20-mm group: HR, 1.62; 95% CI, 0.49-5.32 >20-mm group: HR, 0.81; 95% CI , 0.22-2.93 ($P = 0.3$) ≤10-mm group: 66.9% and 66.9% 10–20-mm group: 85.5% and 85.5% >20-mm group : 69.5% and 57% ($P = 0.07$)	

Continued

Table 1: Continued

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
		3- and 5-Year DFS	≤10-mm group: 59.3% and 59.3% 10–20-mm group : 63.3% and 47.6% >20-mm group: 59.5% and 54.1% (*P* = 0.5)	
Schuchert *et al.* (2007), Ann Thorac Surg, USA [6] Cohort study (level 3)	**Patients** 182 patients with stage I lung cancer Segmentectomy **Study period** 2002–2006 **Mean postoperative follow-up** 18.1 months	**Recurrence** Total recurrence rate	M/T > 1 group: 6.2% M/T < 1 group: 25.0% (*P* = 0.0014)	The study did not provide exact patient numbers in each group categorized by different M/T ratios According to the result, the margin/tumour diameter ratio might also be an effective indicator for loco-regional recurrence in patients undergoing segmentectomy
Sawabata *et al.* (2012), Surg Today, Japan [7] Cohort study (level 3)	**Patients** 37 patients with stage I lung cancer, wedge resection **M/T** M/T < 1 group: *n* = 24 M/T ≥ 1 group: *n* = 13 **Study period** September 1999–September 2002 **Follow-up time**: range 5.3–14 years	**Survival** 5-Year RFS 5-Year survival	M/T < 1: 52.3% M/T ≥ 1: 84.6% (*P* = 0.05) M/T < 1: 54.2% M/T ≥ 1: 84.6% (*P* = 0.05)	Patients with M/T < 1 had a higher rate of positive cytology examination
Moon *et al.* (2017), World J Surg, Korea [8] Cohort study (level 3)	**Patients** 91 patients with stage I lung cancer, sublobar resection **Histological subtype** GGO-predominant tumour: *n* = 52 ≤5-mm group A: *n* = 14 >5-mm group B: *n* = 38 Solid-predominant tumour: *n* = 39 ≤5-mm group C: *n* = 11 >5-mm group D: *n* = 28 **Study period** January 2004–December 2013 **Median postoperative follow-up** 974 days	**Recurrence** Total recurrence Locoregional **Survival** 5-Year RFS	**GGO-predominant tumour** ≤5 mm: 0 >5 mm: 0 **Solid-predominant tumour** HR 3.868; 95 % CI 1.177–12.714 (*P* = 0.026) **Solid-predominant tumour** ≤5 mm: 7/11 >5 mm: 4/28 **GGO-predominant tumour** ≤5 mm: 100% >5 mm: 100% **Solid-predominant tumour** ≤5 mm: 24.2% >5 mm: 79.6% (*P* < 0.001)	
Moon *et al.* (2018), World J Surg, Korea [9] Cohort study (level 3)	**Patients** 133 patients with stage I lung cancer, sublobar resection **Histological subtype** Lepidic tumour: M/T < 1 group A: *n* = 37 M/T ≥ 1 group B: *n* = 27 Non-lepidic tumour: M/T < 1 group C: *n* = 27 M/T ≥ 1 group D: *n* = 32 **Study period** January 2008–December 2015 **Median postoperative follow-up** 1090 days (patients with lepidic tumours) 970 days (patients with non-lepidic tumours)	**Recurrence** Total recurrence Locoregional **Survival** 5-Year RFS	**Lepidic tumour** M/T < 1: 0 M/T ≥ 1: 0 **Non-lepidic tumour** M/T < 1 group C: 8/32 M/T ≥ 1 group D: 1/37 HR, 0.157; 95% CI, 0.027-0.898; (*P* = 0.037) **Non-lepidic tumour** M/T < 1 group C: 6/8 (75%) M/T ≥ 1 group D: 1/1 (100%) **Lepidic tumour** M/T < 1: 100% M/T ≥ 1: 100% **Non-lepidic tumour** M/T < 1: 49.9% M/T ≥ 1: 97.1% (*P* = 0.009)	
Moon *et al.* (2020), World J Surg, Korea [10]	**Patients** 193 patients with stage I lung cancer, sublobar resection	**Recurrence** Total recurrence	**Resection margin distance** HR, 0.147; 95% CI, 0.023-0.954 (*P* = 0.044)	

Continued

Table 1: Continued

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Cohort study (level 3)	**Histological subtype** Lepidic-dominant ADC (invasive component size ≤2 cm): all **Study period** 2008–2017 **Median postoperative follow-up** 1080 days	**Survival** 5-Year RFS	**Margin/tumour ratio** HR, 0.081; 95% CI, 0.008-0.850 (P = 0.036) **Margin/invasive component ratio** HR, 0.068; 95% CI, 0.008-0.567 (P = 0.013) **Margin/invasive component ratio** <1: 77.4% **Margin/invasive component ratio** >1: 100% (P < 0.001)	
Eguchi *et al.* (2019), J Thorac Oncol, USA [11] Cohort study (level 3)	**Patients** 349 patients with stage I lung cancer, sublobar resection **Subtype** STAS (-): n = 225 (M/T ≥ 1) group: n = 105 (M/T < 1) group: n = 120 STAS (+): n = 170 (M/T ≥ 1) group: n = 85 (M/T < 1) group: n = 85 **Study period** January 1995–December 2014	**Recurrence** Total recurrence Locoregional recurrence	**STAS (−)** M/T ≥ 1: 5% (4/105) M/T < 1: 12% (14/120) (P = 0.038) **STAS (+)** M/T ≥ 1: 29% (22/85) M/T < 1: 36% (25/85) (P = 0.3) **STAS (−)** M/T ≥ 1: 0 M/T < 1: 7% (8/120) (P = 0.008) **STAS (+)** M/T ≥ 1: 16% (13/85) M/T < 1: 25% (17/85) (P = 0.3)	Sublobar resection itself was associated with increased recurrence rate In STAS-negative lung cancer patients, an M/T of >1 correlates with better prognosis
Takahashi *et al.* (2019), Gen Thorac Cardiovasc Surg, Japan [12] Prospective study (level 3)	**Patients** 32 patients with stage I lung cancer, segmentectomy and wedge resection **M/T** M/T > 1 group: n = 12 M/T ≤ 1 group: n = 20 **Median observation period** 39 months	**Survival** 3-Year RFS 3-Year OS	M/T > 1: 91.7% M/T ≤ 1: 66.2% (P = 0.05) M/T > 1: 100% M/T ≤ 1: 59.7% (P = 0.06)	

DFS: disease-free survival; HR: hazard ratio; M/T: margin-to-tumour ratio; NSCLC: non-small-cell lung cancer; OR: odds ratio; OS: overall survival; RFS: recurrence-free survival; STAS: Spread Through Air Spaces.

RESULTS

All the 12 studies were divided into 3 categories: the first 5 researches [2–6] focused on different margin distance. Two researches [7, 8] discussed margin-to-tumour ratio (M/T). The other 5 researches [9–13] were about the relevance between margin distance and prognosis in patients among different tumour classifications.

El-Sherif *et al.* [2] reviewed 81 patients undergoing wedge resection or segmentectomy. They found that a lower local recurrence rate was related to adequate resection margins and patients with surgical margin <1 cm showed a significantly higher risk of locoregional recurrence (P = 0.04). Therefore, maximizing anatomic surgical margins appears to be an important consideration for reducing local recurrence. Achieving a margin of ≥1 cm to obtain an adequate margin for small peripheral nodule was recommended. Comparing to wedge resection, segmentectomy is the preferred choice in NSCLC patients undergoing sublobar resection, for its advantage in achieving sufficient surgical margin (P = 0.003).

Similarly, a single-center study performed by Sienel *et al.* [3] demonstrated that among patients who underwent segmentectomy, 8 out of 35 (23%) patients with margins ≤10 mm developed a local recurrence while none was observed in patients with margin >10 mm (P = 0.06). A surgical margin of over 10 mm was suggested as a criterion for preoperative patient selection prior to segmentectomy.

Mohiuddin *et al.* [4] focused on a more detailed classification of margin distance for 479 NSCLC patients with 2 cm or less nodules. This study demonstrated that an increased margin distance was significantly associated with lower local recurrence, while no additional benefit was found in margin distance beyond 15 mm. The risk of local recurrence in patients with a 5-mm margin was 45% higher than that of patients with a 10-mm margin. Patients who underwent wedge resection with a 15-mm margin distance had a 59% lower risk of recurrence than that of patients with a 5-mm margin distance and 113% lower than that of patients with a 2-mm margin distance. This study provided a more detailed margin cut-off for NSCLC patients undergoing wedge resection.

A multicentre study performed by Wolf *et al.* [5] investigated the optimal margin distance in 138 patients. The study demonstrated that an increased margin distance was an independent predictive factor for lower recurrence risk [odds ratio (OR), 0.90; 95% confidence interval (CI), 0.83–0.98] and longer overall survival (OS) [hazard ratio (HR), 0.94; 95% CI, 0.90–0.98] for each 1-mm increase. After applying sensitivity analysis, an optimal margin distance >9 mm was estimated to be associated with longer recurrence-free survival (RFS) ($P = 0.178$), while patients with a margin distance of >11 mm had longer OS ($P = 0.060$).

Maurizi *et al.* carried out a retrospective study. Totally, 182 pathological stage I NSCLC patients undergoing wedge resection were divided into 3 groups according to their surgical margin distance of 3 different ranges (<1 cm, from 1 to 2 cm, >2 cm). They found no statistical difference in the loco-regional ($P = 0.9$) and distant ($P = 0.3$) recurrence rates, OS ($P = 0.07$) and disease-free survival (DFS) ($P = 0.5$) among the 3 groups when R0 resection was achieved. Interestingly, the distant recurrence rate was halved in patients with a margin of >2 cm (6.9%) compared with patients whose margin distance was <1 cm (13.3%) or from 1 to 2 cm (13.8%). The follow-up period is relatively insufficient and might not be enough to detect recurrence in stage I NSCLC patients.

Schuchert *et al.* [6] focused on the M/T, a predictive factor of positive margin cytological findings in wedge resection for peripheral NSCLC. Among 182 cases, patients with an M/T of <1 showed a significantly higher recurrence rate than those with an M/T of >1 (25% vs 6.2%, $P = 0.0014$). There are 89% of recurrences (24/27) in patients with margins ≤2 cm.

Sawabata *et al.* [7] compared the prognosis in 37 patients according to margin/tumour ratio (M/T < 1 vs M/T ≥ 1). The 5-year RFS according to M/T was 52.3% vs 84.6% (M/T < 1 vs M/T ≥ 1; $P = 0.05$) and the 5-year survival was 54.2% vs 84.6% ($P = 0.05$). The authors concluded that a M/T ≥ 1 was significantly associated with negative margin cytology, longer RFS and OS, both the M/T and margin cytology findings were prognostic indicators in NSCLC. However, the number of included patients was relatively small in this study.

Three consecutive studies conducted by Moon *et al.* [8–10] evaluated the prognostic capability in patients according to their different tumour classifications. In all 91 cases, a margin width ≤5 mm was significantly related to poor 5-year RFS in patients with solid-predominant nodules (24.2% vs 79.6%, margin width ≤5 vs >5 mm, $P < 0.001$), while a margin distance of ≤5 mm did not affect the recurrence in patients with ground-glass opacity predominant nodules [8]. Similar results were also observed in histologically confirmed lepidic and non-lepidic lung cancer (totally 133 cases), where M/T was a significant risk factor for recurrence of non-lepidic tumour patients and did not affect lepidic tumour patients [9]. Moreover, in 193 adenocarcinoma patients, a margin distance/invasive component ratio >1 showed a significantly better prognosis when performing sublobar resection ($P < 0.001$) [10]. These studies provide further evidence of proper margin distance in poor-prognostic situations.

Eguchi *et al.* [11] investigated the impact of M/T ratio on recurrence in Spread Through Air Spaces (STAS)-positive and STAS-negative patients. Totally, 698 patients were involved (349 lobectomy vs 349 sublobar resection). Among patients with STAS-negative tumours, an M/T of ≥1 was associated with a significantly lower recurrence, and the 5-year cumulative incidence of recurrence for any recurrence was 5% vs 12% ($P = 0.038$). In contrast, the risk of recurrence in STAS-positive tumours was relatively high regardless of M/T ratio.

Takahashi *et al.* [12] performed a supplementary analysis on a multicentre prospective study of sublobar resection (KLSG-0801). They analysed the relationship between M/T ratio and prognosis among clinical stage I NSCLC patients with sublobar resection. There were 9 recurrent cases among all 32 cases. The 3-year RFS was 66.2% and 91.7% in patients with M/T ≤ 1 and M/T > 1, respectively ($P = 0.05$). As for the 3-year OS, though there was no statistical difference ($P = 0.6$), cases with M/T > 1 (100%) showed better prognosis than that of M/T ≤ 1 (59.7%). In addition, this study found that the margin cytology positive was significantly associated with worse prognosis.

CLINICAL BOTTOM LINE

Based on the available evidence, the standard of margin distance of >10 mm or M/T ≥ 1 should be recommended for stage I NSCLC patients undergoing sublobar resection, especially in wedge resection. Patients with poor-prognostic factors, like solid-predominant tumour or non-lepidic adenocarcinoma, may benefit from larger margin distance and the proper margin distance for them still need to be determined. For STAS-positive patients, sublobar resection may not be the alternative to lobectomy.

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