

Determination of safe margin in the surgical pathologic specimens of non-small cell carcinoma of the lung

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Abstract

Background and Aim: Local recurrences of the tumor at the surgical margin are serious problems in pulmonary resections for lung cancer. The aim of this study is to determine the involved margins and safe distances of the resection sites from tumor for prevention of local recurrences. **Material and Methods:** In this prospective study, 66 patients operated for non-small cell lung carcinoma (NSCLC) from Jan 2006 to Sep 2008 were evaluated. After performing pulmonary resections, multiple biopsies were taken up from 5 mm (A), 10 mm (B), 15 mm (C), and 20 mm (D) distance from tumor. The specimens were studied histopathologically. **Results:** From a total of 66 patients with NSCLC admitted to our referral hospital, 25 (38%) had adenocarcinoma, 18 (27.3%) squamous cell carcinoma, 5 (7.5%) large cell carcinoma, 4 (6%) bronchoalveolar cell carcinoma, 4 (6%) adenoid cystic carcinoma, 3 (4.6%) malignant carcinoid tumor and 7 (10.6%) had metastasis. The most common symptoms were dyspnea and cough. Histopathologically tumor positive margins were found in 84.8% (A), 10.6% (B), 4.5% (C), and 0% (D). There was a significant statistically difference between tumor involvement at distances 5 mm (A) versus 10-20 mm (B-D) ($P < 0.001$). **Conclusion:** A 20 mm distance from the gross tumor is considered as a safe surgical margin in any type of malignant pulmonary resections for prevention of local surgical recurrences if there was no pathologic examination before surgery.

Keywords: lung, safe margin, surgery, tumor

Rezumat

Determinarea marginii chirurgicale histologic sigure în cancerul pulmonar non-microcelular

Obiectiv: Recidivele locale ale tumorilor la limita rezecției chirurgicale reprezintă o problemă serioasă în rezecțiile pulmonare pentru cancer pulmonar. **Obiectivul** acestui studiu este identificarea marginilor interesate și determinarea distanțelor sigure ale rezecției pentru prevenția recidivelor locale. **Materiale și metodă:** În acest studiu prospectiv au fost incluși 66 de pacienți operați pentru cancer pulmonar non-microcelular (NSCLC) între ianuarie 2006 și septembrie 2008 în spitalul nostru terțiar. După efectuarea rezecțiilor pulmonare chirurgicale, s-au prelevat biopsii multiple la distanțe de tumoră de 5 mm (A), 10 mm (B), 15 mm (C) și 20 mm (D). Specimenele au fost examinate histopatologic. **Rezultate:** Din totalul de 66 de pacienți cu NSCLC, 25 (38%) aveau adenocarcinom, 18 (27,3%) carcinom epidermoid, 5 (7,5%) carcinom cu celule mari, 4 (6%) carcinom bronhioloalveolar, 4 (6%) carcinom adenoid chistic, 3 (4,6%) carcinoid malign și 7 (10,6%) metastaze. Cele mai obișnuite simptome erau dispneea și tusea. Margini histopatologic pozitive au fost identificate la 84,8% din fragmente (A), 10,6% (B), 4,5% (C) și 0% (D). A existat o diferență statistic semnificativă a interesării tumorale între distanța de 5 mm (A) și 10-20 mm (B-D) ($p < 0.001$). **Concluzie:** O distanță de 20 de mm față de masa tumorală este considerată o margine chirurgicală sigură în orice tip de rezecție pulmonară pentru cancer pentru prevenirea recidivelor locale, în absența unui examen histopatologic anterior intervenției chirurgicale. **Cuvinte-cheie:** plămân, margini sigure, chirurgie, tumoră

Introduction

Pulmonary resections such as lobectomy and pneumonectomy are the gold standard treatment for pulmonary carcinomas in low stages. Segmentectomy and wedge resections are used only for patients with low residual pulmonary function¹. Local recurrence in the surgical margin can be a serious problem in the surgery of pulmonary carcinoma². Although safe surgical margins can be determined by frozen section sampling during surgery in the operating room, defining the safe margins from the tumor is necessary and important for surgeons in performing any type of pulmonary resections. Hence, there are still challenges in determining accurate safe surgical margin in the literature^{3, 4}. In this study, we evaluated the surgical pathology of pulmonary specimens for determining the safe surgical margins to prevent probable local surgical recurrences.

Material and Methods

In a prospective study, 86 patients admitted for pulmonary carcinoma surgery from January 2006 to September 2008 at

our referral hospital were evaluated. This study was approved by Medical Ethics of Tabriz University of Medical Sciences.

Inclusion criteria (66 patients):

- Patients with non-small cell lung carcinoma (NSCLC) in stages I, II and IIIA;

- Operable metastatic pulmonary lesions.

Exclusion criteria (20 patients):

- Patients with NSCLC in stages IIIB and IV;

- Cardiopulmonary co-morbidities.

Patients' medical records were reviewed for symptoms, signs, radiographic imaging, diagnostic bronchoscopy, pulmonary function tests, staging mediastinoscopy and surgical managements.

Based on the results of the pathologic examination, the samples were divided into four groups, as follows:

- Group A: Tumoral involvement 0-5 mm from the tumor;

- Group B: Tumoral involvement 5-10 mm from the tumor;

- Group C: Tumoral involvement 10-15 mm from the tumor;

- Group D: Tumoral involvement 15-20 mm from the tumor.

Samples reported to have tumoral cells in microscopic pathological examination were considered as positive results. The obtained data were collected and analyzed.

Statistical analysis

The endpoints of the present study were to determine the safe surgical margins pathologically for NSCLC specimens. Data were presented as Mean $\pm$ SD & N (%). Variables were analyzed with the independent sample T test for continuous variables and Chi-square or Fisher Exact test for nominal or ordinal variables. P-value less than 0.05 were considered statistically significant. The statistical package for social science (SPSS 16) was used for statistical analysis.

Results

There were a total of 66 patients with NSCLC, 40 (60.6%) males and 26 (39.4%) females with mean ages of 55 ± 4.0 and 64 ± 3.0 years. The types of tumors were adenocarcinoma in 25 cases (38%), squamous cell carcinoma (SCC): 18 (27.3%), large cell carcinoma: 5 (7.5%), bronchoalveolar cell carcinoma: 4 (6%), adenoid cystic carcinoma: 4 (6%), malignant carcinoid tumor: 3 (4.6%), and metastasis: 7 (10.6%).

The most common symptoms of the patients were pulmonary distress and dyspnea in 30 (45.5%) patients, cough in 20 (30.3%) patients, chest pain in 10 (15.15%) patients, hemoptysis in 4 (6%) patients, asymptomatic 2 (3%) patients.

Two to three centimeter distance away from the tumors was the usual distance where we performed pulmonary resections. In all 66 patients, 4 samples were examined at distances of 5, 10, 15 and 20 mm from gross tumor. From all samples ($66 \times 4 = 264$ samples), a number of 198 were found positive (75%). The positive samples were distributed in the following distance groups:

- A (5 mm): 56 positive samples (84.8% of 66);
- B (10 mm): 7 positive samples (10.7% of 66);
- C (15 mm): 3 positive samples (4.5% of 66);
- D (20 mm): 0 positive samples (0%).

Table I shows the types of lung carcinomas in relation to safe surgical margins.

Table I

Types of lung carcinomas in relation to safe surgical margins (n = 66)

Type of tumor	A = 5 mm N(%)	B = 10 mm N(%)	C = 15 mm N(%)
Adenocarcinoma	20 (80)	5 (20)	0 (0)
Squamous cell carcinoma	18 (100)	0 (0)	0 (0)
Large cell carcinoma	0 (0)	2 (40)	3 (60)
Bronchoalveolar carcinoma	4 (100)	0 (0)	0 (0)
Adenoid cystic carcinoma	4 (100)	0 (0)	0 (0)
Metastasis	7 (100)	0 (0)	0 (0)
Malignant carcinoid	3 (100)	0 (0)	0 (0)

*No patient had D= 20 mm

Differences in distribution of tumor involvement in distances up to 5 mm and 5-20 mm were statistically significant as distances until 5 mm were mostly affected by tumor (totally 84.8%), while margins in distances from 5 mm to <20 mm were affected rarely (15.2%) and margins in distances of 20 mm were not affected by tumor (0%) ($P < 0.001$).

Discussion

Local recurrences of postsurgical stumps are due to the presence of occult retained tumoral cells in surgical margins. Patients with positive margins have significantly worse local regional control than those with negative margins^{2,5}. Despite complete resection, up to 20% to 30% of patients will develop recurrence disease. Recurrence following lung resection predominantly is influenced by tumor size, invasion to lymphatic and capillaries, and tumor infiltration. Optimization of surgical margins is one of the factors that may improve outcome. Sublobar resection demonstrates high local recurrence in comparison with lobectomy patients^{6,7}. Yano and colleagues reported 40/471 (8.5%) local recurrences and they also mentioned that survival of the patients was improved by adding radiation protocol⁸.

Ginsberg's randomized trial study showed 8/247 local recurrences in lobectomy patients in comparison with 21/247 local recurrences in sublobar patients in the treatment of T1N0M0 stage. In the retrospective study of Sherif, it was shown that 7-year survival rate of the disease free patients was equal between lobectomy and sublobar resection patients in stage IA, NSCLC and if all stage I, NSCLC tumors were included in the analysis, lobar patients had significantly better results than sublobar patients^{9,10}.

Sienel and colleagues studied the frequency of local recurrence following segmentectomy (49 patients) in stage IA, NSCLC and reported 6% recurrence in segmentectomy patients which was more frequent than in lobectomy patients (5%). In their performed operations, segmentectomy in the region of S1-3 had more local recurrences (23%) than segmentectomy in the S7-8 regions (12%) and resection margin ≤ 1 cm tended to be associated with local recurrences¹¹. We did not compare the segmentectomy and lobectomy specimens; however, the specimens were compared totally with the surgical pathologic distances from the tumor.

Goldstein and Maygarden reported that a 30 mm distance from the gross tumor is the surgical safe margin. Goldstein also reported a 7 mm distance from the tumor for performing wedge resections of adenocarcinoma and a 24 mm distance was the safe margins in lobectomy patients^{4,12}. Kara and colleagues in Turkey, in a study on 70 patients reported that a 15 mm distance from the tumor was the safe margin in 93% patients of NSCLC¹³. Their study revealed a statistically significant difference in relation to loco regional recurrence between lobectomy and segmentectomy patients. In the Mahesh study, it was reported that distances more than 20 mm are the safe surgical margins which is similar to the results of our study³. Ketchedjian in a parallel study, reported the 10 mm distance as the safe surgical margin in the distances 10 mm emphasizing the fact that margins more than 10 mm had lower surgical stump recurrences¹⁴.

Masayesava in Canada reported a 4 mm distance as the safe surgical margin². Tanggitgarnel's experience in resection of pulmonary metastasis revealed that the safe margin is a prognostic factor, in our study the prognostic factor was 5 mm¹⁵.

Lee et al recommended limited resections to be accepted in peripheral lesions with tumor sizes less than 30 mm¹⁶. Wedge and segmental resections are recommended in old and stage IA patients with low pulmonary function tests^{6,17}.

To prevent loco regional recurrences, we proposed that 20 mm, 15 mm, and 10 mm distances were the safe surgical margins for large cell carcinoma, adenocarcinoma, and squamous cell carcinoma of the lung. Safe surgical margins for bronchoalveolar, adenoid cystic carcinomas, malignant carcinoid tumors, and metastasis of the lung must be at least 5 mm.

Totally, in the surgery of NSCLC, metastases had lowest safe surgical margins (5 mm), and large cell carcinoma of the lung had the maximum safe surgical margin (20 mm).

Recently video assisted thorascopic surgery (VATS) is being used in segmentectomy and wedge resections. In pa-

tients with limited pulmonary function tests we performed wedge or segmental resections especially in metastasis and none of them were performed through VATS. In one cohort study, 5-year survival of the patients having undergone open wedge resection was 58% less than VATS wedge resections and classic standard pulmonary resections had prolonged survival^{2,3,18}.

Conclusion

A 20 mm distance from the gross tumor is considered as a safe surgical margin in any type of malignant pulmonary resections for prevention of local surgical recurrences if there is no pathologic examination before surgery. However, in patients with bronchoalveolar, cystic adenomatoid carcinoma, malignant carcinoid tumors and metastasis greater than 5 cm distance from the gross tumor can be considered as a safe surgical margin.

Conflict of interests

The authors had no conflict of interests in relation to this article. ■

References

1. Wagle DA, Keshwjee S, Ginsberg RJ. Lung Cancer: Surgical treatment. In: Sabiston and Spencer. Surgery of the chest, 7th ed. Philadelphia: Elsevier Saunders publisher; 2005. P.253-76.
2. Masaayesva BG, Tong BC, Brook MV, Pilkington T, Goldenberg D, Sidransky. Molecular margin analysis predicts local recurrence after sub lobar resection of lung cancer. *Int Thorac Cancer*. 2005; 113 (6):1022-5.
3. Mahesh B, Forrester-wood C, Yunus A, Ahsan R, Amer K, Morgan A, et al. Wedge resection distances and residual adenocarcinoma in lobectomy specimens. *Eur J Cardiothorac Surg* 2004; 26 (3): 474- 9.
4. Maygarden SJ, Detterbeck FC, Funkhouser WK. Bronchial margins in lung cancer resection specimens: Utility of frozen section and gross evaluation. *Mod Pathology* 2004;17 (9): 1080-86.
5. Lee JH, Machtay M, Kaiser LR, Friedberg JS, Hahn SM, Mc Kenna MG, et al. Non-Small Cell Cancer: Prognostic factors in patients treated with surgery and postoperative radiation therapy. *Radiology* 1999;213: 845-52.
6. Narsule CK, Ebright MI, Fernando HC. Sublobar versus lobar resection (Current status). *The Cancer Journal* 2011;17: 23-27.
7. Landreneau RJ, Abbas G, Awais O, Pennathur A, Siegfried J, Wilson DO, et al. Factors influencing recurrence following anatomic lung resection for non-small cell lung cancer. *J Clin Oncol* 2012; 30: 2012 (1-5 June) 12 th ASCO Annual Meeting.
8. Yano T, Hara N, Ichinose Y, Asoh H, Yokoyama H, Ohta M, et al. Local recurrence after complete resection for non- small cell carcinoma of the lung: Significance of local control by radiation treatment. *J Thorac Cardiovasc Surg* 1994;107:8-12.
9. Chamogeorgakis T, Leromonachos C, Georgiannakis E, Mallios D. Does lobectomy achieve better survival and recurrence rates than limited pulmonary resection for TINOMO non-small cell lung cancer patients? *Interactive Cardiovasc and Thoracic Surg* 2009; 364-72.
10. El-Sherif A, Fernando HC, Santos R, Pettiford B, Luketich JD, Close JM, et al. Margin and local recurrence after sublobar resection of non-small cell lung cancer. *Ann of Surgical Oncology* 2007; 14(8): 2400-8.
11. Sienel W, Stremmel C, Kirschbaum A, Hinterberger L, Stoelben E, Hasse J, et al. Frequency of local recurrence following segmentectomy of stage IA Non-small cell lung cancer is influenced by segment localization and width of resection margins- implications for patient selection for segmentectomy. *Eur J Cardiothorac Surg* 2007; 31: 522-28.
12. Goldenstein NS, Frekowitz M, Kestin L, Chmielewski GW, Welsh RJ. Sleeve pneumonectomy. *Thoracic Surg Clin* 2003; 14 (2): 183-90.
13. Kara M, Sak SD, Orhan D, Yavuzer S. Changing patterns of lung cancer 1.9 cm is still a safe length for bronchial resection margin? *Lung Cancer* 2000; 30 (3): 161-68.
14. Ketchedjian A, Daly B, Landreneau R, Fervnando H. Sublobar resection for the subcentimeter pulmonary nodule. *Thorac cardiovasc surg* 2005; 17: 128-133.
15. Tangitgamel S, Levenback CF, Beller U, Kavanagh JJ. Role of Surgical resection for lung, liver and central nervous system metastasis in patients with gynecological cancer. *Int J Gynecol Cancer* 2004; 14 (3): 399-422.
16. Lee Choing Jr TL, Ma RA. Lung cancer in the elderly patients. *Clin Chest Med Surg* 1993;14: 453-78.
17. Errett LE, Wilson J. Clin RCY, Munro DD. Wedge resection as an alternative procedure for peripheral bronchogenic carcinoma in poor risk patients. *J Thorac Cardiovasc Surg* 1985; 90 (5): 656-61.
18. Nicoles F C, Defranchi S. Diffuse lung disease. In: Shields TW. *General Thoracic Surgery*, 7th ed. Philadelphia: Wolters Klowre publisher; 2009.p.1213-1295.