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Depth of chest wall invasion and lymph node metastasis in non-small cell lung cancer

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Abstract

Lymph node involvement is an important prognostic factor for non-small cell lung cancer. This study aims to investigate the relationship between lymph node involvement and the depth of chest wall invasion. Thirty-three patients who were operated on between 2015 and 2019 for radiologically and pathologically diagnosed chest wall invasion were retrospectively reviewed. Thirtytwo of the patients were male (97.3%) and 1 was female (2.7%) with an average age of 59.4 years. The tumor had a mean diameter of 5.81cm. The invasion was in the posterior part of the chest wall in 17 patients (51.5%), lateral in 11 (33.3%) and anterior chest wall in 5 patients (15.2%). Pleural, soft tissue and costal involvement was present in 32, 19 and 9 cases, respectively. A statistically negative correlation was observed between the depth of chest wall invasion and metastasis of lymph nodes no. 2, 4, 7, 10 and 11 (p:0.041, p:0.006, p:0.011, p:0.025, and p:0.009, respectively). As the invasion progresses towards the periphery, the result of the histopathological evaluation of the lymph nodes number 2, 4, 7, 10 and 11 was found to be benign in 73.1%, 64.6%, 91.4%, 87.5% and 64.9%, respectively. The correlation between the depth of invasion and lymph node metastasis, a subject of negligence up to now was evaluated. The findings presented herein have shown that in chest wall resections, the possibility of complete resection and the presence of lymphatic involvement which is an important prognostic marker are more important in terms of survival compared to the depth of invasion.

Keywords: Lung cancer, surgery, chest wall invasion, lymph node metastasis

Introduction

Lung cancer remains to be the leading cause of cancer-related deaths throughout the world. Resection is the primary treatment modality for lung cancers [1]. The five-year survival rate ranges from 70% to 80% in cases with stage I lung cancer whereas it is less than 10% in N2 and N3. Chest wall, vertebra, mediastinum, or diaphragm invasion (T3 and T4 tumors) are present in 3–8% of non-small cell lung cancers (NSCLCs). The prognosis of T3 tumors is controversial; however, this is typically not a criterion for unresectability. Early studies on this subject reported low long-term survival rates whereas better results have begun to be obtained with the implementation of extended resections in later studies [2-4].

Chest wall invasion is present in 5–8% of all patients with lung cancer [5,6]. Before the 1950s, chest wall invasion was accepted as a criterion of inoperability, however, Coleman [7] reported an increase in survival rates among patients who underwent lung resection plus chest wall resection. Chest wall invasion, generally, does not prevent resection in patients with lung cancer [2]. Surgery is often an important part of multimodal therapy. En-bloc resection of the chest wall combined with lung resection within the limits of operability is the best treatment method. The point to be considered here is N2 disease. Studies have shown that distant metastasis and N2 disease are the most important determinants of prognosis in NSCLC cases [8-10]. Surgery can be performed in T3 and T4 tumors which are proven to have no mediastinal lymph node involvement. Compared to traditional lung resections, morbidity and mortality can be higher in this surgery and these patients may require thoracic wall reconstruction. In addition to lung resection, impairment of thoracic wall integrity can lead to further loss of respiratory reserve. Therefore, conditions contributing to morbidity and mortality, including the risk of complications, prolonged stay in the hospital, and risk of infection, are more common in patients

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undergoing this surgical procedure. This may also influence the survival rates following locally advanced lung cancer surgery.

This study aimed to examine the cases with chest wall invasion in terms of lymphatic metastasis and to investigate the effect of the tumor growing towards the thoracic wall rather than towards the hilum of the lung on lymphatic metastasis. Although this problem is known by thoracic surgeons, it is not known by other clinical specialists. Another aim is to contribute to the knowledge of all specialists in this field.

Materials and Methods

After obtaining approval from Ankara City Hospital Ethics Committee of the Ministry of Health Provincial Health Directorate on 25/06/2020 (No: E1-20-817). Thirty-three patients who were diagnosed radiologically and/or pathologically to have chest wall invasion and were operated on between January 2015 and May 2019 were evaluated retrospectively. In our study, patient files were analyzed retrospectively. Patient consent form was not required for our study, which was completely file review. The ethics committee approved that the patient consent form was not required. The following data were evaluated within the scope of the study: gender, age, preoperative diagnosis method, thorax computed tomography (CT) findings, positron emission tomography-CT (PET-CT) findings, anatomical location of the mass, depth of invasion, operation performed, pathology results, tumor size, tumor cell type, metastatic lymph nodes, number of ribs removed, and criteria for invasion localization in the thoracic wall.

All patients preoperatively underwent physical examination, routine blood tests, chest radiography, bronchoscopy, respiratory function test, thorax-CT, cranial magnetic resonance imaging (MRI), and PET-CT. Thorax MRI was performed for patients with suspected large vessel or nerve invasion. Mediastinal lymph node evaluation were performed via CT and PET-CT, mediastinoscopy, lymph node biopsy guidance under endobronchial ultrasonography (EBUS). Resection was performed for T3 and T4 tumors without distant metastasis or lymph node metastasis, which had chest wall invasion. Chest wall resection was performed in the presence of chest pain, chest wall invasion on CT or MRI, and intraoperative detection of parietal pleural involvement of the tumor. The eighth edition of the TNM staging system was used to evaluate the cases. In T3 or T4 cases, extended resection was performed in the presence of invasion, which was accompanied by the involvement of pleura, soft tissue, and rib and was not easily separated with blunt dissection. Frozen section of the suspected involvement of the chest wall was performed in suspicious cases of involvement. En-bloc resection was performed in all patients who underwent operation, except only those who underwent mediastinoscopy. Mediastinal lymph node dissection was routinely performed in all patients. Correlation analysis was performed for the depth of chest wall invasion of the tumor and histopathological status of intrathoracic lymph nodes.

The data obtained was analyzed using SPSS software. Descriptive statistics were expressed as mean±standard deviation or median (smallest-largest) for continuous variables, and categorical variables as number of observation and percentages (%).

The Binary Logistic Regression Analysis was used to investigate whether thorax-CT and PET-CT findings were determinative in distinguishing the histopathologically metastatic and non-metastatic lymph node groups in each lymph node station instead of Pearson Chi-Square Test since more than 20 % of the cells had an expected count less than or equal to 5, which makes the p value for the test become invalid. Also, the correlation coefficients of metastatic and non-metastatic lymph node groups with the depth of invasion were calculated. P value of <0.05 was considered statistically significant.

Results

Chest wall invasion was detected in 33 (7.6%) out of 431 patients operated on for NSCLC. Among the patients, 32 were males and 1 was female. The age range of the patients was 40 to 75 years with a mean age of 59.4 years. All of the patients were active smokers. Chest pain was the first symptom of presentation in 32 patients. One patient presented with the complaint of weight loss. Preoperatively, NSCLC was diagnosed in 30 (90.9%) patients by transthoracic biopsy, 2 (6.1%) patients by bronchoscopic biopsy, while 1 (3%) patient was diagnosed by frozen section examination intraoperatively. Primary lesion was found to be located in the right lung in 24 (72.7%) patients and in the left lung in 9 (27.3%) patients. Involvement was located in the posterior chest wall in 17 (51.5%), lateral wall in 11 (33.3%) and anterior wall in 5 (15.2%) patients.

All of the preoperative and postoperative histopathological diagnoses were compatible. Postoperative histopathological evaluation revealed squamous cell carcinoma in 15 (45.5%), adenocarcinoma in 12 (36.4%), adenosquamous carcinoma in 4 (12.1%) and large cell carcinoma in 2 (6.1%) patients.

Tumor diameter varied between 3 and 12 cm (mean 6.21) in thorax-CT. A prominent CT finding extending the parietal pleura was identified in 16 patients. Neoadjuvant chemotherapy/radiotherapy was administered to eight patients based on council decision for chest wall invasion. Tumor sizes of these patients ranged from 8 to 10cm. The primary tumor size was 2–10 cm in the pieces removed during operation. The mean tumor diameter was measured to be 5.81cm. The results were observed to be compatible with the thorax-CT findings. The diameter of the tumor was found to be 3 cm and less in 4, between 3-5 cm in 15 and above 5 cm in 14 patients. The SUVmax of the masses ranged from 8.65 to 42.76 with an average of 18.9 in PET-CT.

The association of the size of the lymph nodes determined by preoperative thorax-CT and the results of the postoperative histopathological evaluation was analysed separately in each lymph node station. When reporting the thorax-CT, the lymph nodes with a short diameter of 1 cm and above and with an increase in size were deemed to be metastatic, while the ones under 1 cm were considered benign. The same evaluation was made for PET-CT. Lymph nodes with a SUVmax higher than 2.5 in PET-CT were considered to be metastatic whereas those lower than 2.5 were deemed as benign. They were compared with the histopathological examination results (Table 1).

Table 1. Intrathoracic lymph node stations; Thorax-CT, PET-CT and histopathological evaluation results

LymphNode Station	Thorax-CT (Lymphnodeshortaxis cm)		PET-CT (SUVmax Value)		Pathological Evaluation	
	Benign(<1)	Malign(≥1)	Benign(<2,5)	Malign(≥2,5)	Benign	Malign
LN2	26	7	26	7	10	2
LN3	31	2	30	3	-	-
LN4	16	17	20	13	20	4
LN5	24	9	29	4	12	0
LN6	30	3	31	2	6	0
LN7	16	17	26	7	26	1
LN8	33	0	33	0	10	0
LN9	33	0	32	1	18	0
LN10	10	23	16	17	19	1
LN11	33	0	33	0	18	3

Of the 33 patients, 17 had lung resection and chest wall resection following EBUS LNBx, three had lung resection and chest wall resection without mediastinal lymph node sampling, six had mediastinoscopy, lung resection and chest wall resection, and seven had mediastinoscopy alone. Our clinical practice was primarily directed towards preoperative mediastinal lymphatic staging. Clinical/radiological staging was performed in only three cases since no pathological lymph node was observed radiologically and there was no pathological involvement in PET-CT. Of the 26 patients undergoing resection, 16 were stage IIb and 10 were stage IIIa. N2 lymph node and distant organ metastasis were not present in these patients. Twenty-three of these 26 cases were N0, three were N1, 19 were T3, and seven were T4. Among 33 cases, only two of the seven cases undergoing mediastinoscopy alone were stage IIb and five were stage IIIb. The resection phase could not be proceeded in five of these seven cases since metastases were detected in N2 lymph nodes. Two patients who did not have mediastinal lymph node metastasis and were suitable for surgery did not prefer surgical treatment. Complete resection (R0) was achieved in all of the 26 cases undergoing surgery.

The chest wall invasion was divided into three groups according to the radiological and pathological findings: parietal pleural involvement, soft tissue involvement (endothoracic fascia, intercostal muscle), and rib involvement. Compatible with the literature, the depth of invasion was considered to have progressed from the pleura to the rib. Thirty-three patients had pleural involvement, 19 had soft tissue involvement, 9 had rib involvement (Table 2).

Table 2. Parietal pleural, soft tissue and rib involvement

Parietal pleural involvement	Number	%
Negative	1	3
Positive	32	97
Total	33	100
Soft tissue involvement	Number	%
Negative	14	42.4
Positive	19	57.6
Total	33	100
Rib involvement	Number	%
Negative	24	72.7
Positive	9	27.3
Total	33	100

The correlation between pleural involvement and mediastinal lymph nodes was evaluated using binary logistic regression analysis. Lymph nodes with sufficient samples were detailly examined. A statistically negative correlation was observed between the depth of chest wall invasion and metastasis of lymph nodes 2,4,7,10 and 11 (p:0.041, p:0.006, p:0.011, p:0.025, and p:0.009 for LN 2, LN 4, LN 7, LN 10, and LN 11, respectively). As the invasion progresses towards the rib (periphery), the result of the histopathological evaluation of the lymph nodes numbered 2, 4, 7, 10 and 11 was found to be benign in 73.1% (1-0.269 = 0.731), 64.6% (1-0.354 = 0.646), 91.4% (1-0.086 = 0.914), 87.5% (1-0.125=0.875) and 64.6% (1-0.351=0.649), respectively. All results were statistically significant.

Discussion

In this study, surgery was performed on 33 (7.6%) of 431 patients with NSCLC. Chest wall invasion is reported to occur in about 5-8% of the cases undergoing surgery [5,6]. Before 1947, chest wall invasion was accepted as a criterion of inoperability, however, Coleman [7] in 1947, Grillo [5] in 1966, Peihler [9] in 1967, and Burnard [11] in 1974 reported an increase in survival rates among patients who underwent lung resection plus chest wall resection. Currently, chest wall invasion is not a contraindication for surgery. In our clinic, surgery is preferred if there is no N2 disease identified prior to resection and no comorbidity preventing the operation. Lymph node involvement, histopathological type, and R0 resection were found to be factors affecting prognosis in this study [4]. Sayar [12] reported that lymph node metastasis is one of the prognostic factors that negatively affect survival. In a study by Downey et al. involving 334 patients, the prognosis was reported to depend on complete resection, lymph node negativity, and the depth of invasion. Five-year survival was found to be 62% in T3N0M0 stage IIb cases with parietal pleural invasion alone and 35% in those with rib, soft tissue and muscle invasion. R0 resection was achieved in 175 cases and the five-year survival was found to be 32%. Survival was reported to be 4% in patients who underwent incomplete (R1-R2) resection. Patients who could not achieve R0 resection and those who did not undergo any surgery were found to have equal survival rates. Furthermore, N0 and N1 disease were reported to be similar in terms of survival, and depth of invasion was reported not to effect survival provided that complete resection was performed [3].

In general, incomplete resection (R1 or R2) is thought to have a limited therapeutic effect regardless of the nodal state [3,10,13]. The long-term survival rates of patients who underwent incomplete resection and those who do not undergo resection are quite similar. Three-year survival was 4% in patients who underwent R1-R2 resection, while it was 0% in patients without resection [6]. Obtaining a negative surgical margin is the main approach in all patients with chest wall invasion.

In our clinic, a good prognosis is observed in patients who undergo complete resection unless there is N2 disease. Patients with no N2 positivity and who have the possibility to undergo complete resection determined radiologically and clinically should have surgery. In this study, no further surgical procedure was performed in patients who were found to have N2 disease through mediastinoscopy prior to resection.

Residual tumor after chest wall resection has a negative impact on survival [13]. In chest wall resection, an upper and lower rib, along with the invasive rib, should be removed bilaterally, together with the intact area, as much as possible [14]. Chapelier [4] reported the ideal surgical margin as at least 3 cm. Morbidity and mortality rates in large resections performed to increase the success of surgery are 20% and 3.8%, respectively [3,15]. No chest wall reconstruction is usually performed in small chest wall defects whereas anterior or lateral defects larger than 5 cm should be repaired with the help of various prostheses as they can impair respiratory physiology [16]. In this study, chest wall reconstruction with prolene mesh was performed in three patients undergoing anterior chest wall resection, six patients undergoing lateral chest wall resection, and three patients undergoing posterior chest wall resection.

General approach to NSCLC with chest wall invasion has been identified in many studies since 1947; however, no study was performed investigating the association of the depth of invasion and lymph node metastasis. The surgical technique to be applied according to the depth of invasion and its effects on survival have not been adequately studied. For instance, no consensus has been established regarding the surgical technique to be performed in the presence of pleural invasion alone; the personal experience of surgeons has been leading. Many studies have stated that the depth of invasion is a prognostic factor for survival [9,14]. In a study involving 104 cases, Facciolo [17] investigated the association between the depth of chest wall invasion and survival rates and reported that survival was significantly better in patients with parietal pleural involvement than those with soft tissue and rib involvement. In similar studies, complete resection rather than the depth of invasion has been emphasized to be an adequate evaluation criterion for long-term survival [5,9].

Downey [3] similarly showed that regardless of the nodal state, the depth of tumor invasion had no significant effect on prognosis. The presence of mediastinal lymph node metastasis significantly reduces five-year survival. In a series reported by Facciolo [17], the survival rate was 67.3% and 17.9% in cases with N0 and N2 disease, respectively, whereas in Piehler's [9] study it was 53.7% in patients with N0 disease and 7.4% in patients with N2 disease.

In tumors with chest wall invasion, people who benefit most from surgical treatment are those with N0 disease. If complete resection can be achieved in these patients, en bloc resection is

recommended to be performed as the standard surgical procedure. The five-year life expectancy in patients undergoing complete resection is around 40%. A five-year survival rate of up to 54% has been reported in chest wall resections performed for N0 disease [3]. Surgical resection is not recommended in patients with positive N2 lymph nodes due to poor five-year survival and higher morbidity rates [18].

As in all patients with NSCLC, survival is negatively affected by the presence of lymph node metastasis in patients with chest wall invasion [13,17]. While survival rates are reported to be high in patients with N0 disease, the prognosis is poor in N1 and N2. Patients with N2 positivity have a very poor survival rate [12,19]. Sayar [12] reported that multiple N1 and single N2 have similar survival rates and that N1 disease should be evaluated as single and multiple separately and taken into consideration in staging. In a 2017 study conducted by Sehitogullari [20], five-year survival rates were reported as 38.6%, 23.4%, and 0% in N0, N1, and N2, respectively. In a 2020 study reported by Jones [21], pathological nodal state and stage were shown to be significant determinants of disease-free and overall survival [21].

Since the importance of lymph node metastasis on the prognosis is known, we have statistically analyzed the negative correlation between the depth of invasion and lymph node metastases in detail. The metastasis rate in the intrathoracic lymph nodes was statistically significantly lowered with the depth of invasion progressing towards parietal pleura to the ribs in this study. A negative correlation was observed between the depth of invasion of the chest wall and metastasis of lymph nodes 2,4,7,10 and 11. As the invasion progresses towards the periphery, the result of the histopathological evaluation of the lymph nodes number 2, 4, 7, 10 and 11 was found to be benign in 73.1%, 64.6%, 91.4%, 87.5% and 64.9%, respectively. In the literature, the relationship between the depth of chest wall invasion and lymph node metastasis has not been specifically studied, and the studies have generally evaluated all prognostic factors.

Conclusions

Negative prognostic effect of depth of chest wall invasion seems to disappear in patients undergoing complete resection. It should be remembered that an advanced chest wall invasion does not increase lymph node metastasis, which is an important prognostic marker. We believe that larger series and multi-center trials to be conducted in the future will support our results and that there is a need for a new evaluation method for tumor size according to the anatomical location in staging systems.

Lung cancer is one of the most common cancers worldwide. For this reason, November is recognised as "Lung Cancer Awareness Month" and November 17 as "Lung Cancer Awareness Day" all over the world [22]. Diagnosing lung cancer at an early stage is very important for the treatment. Thus, early diagnosis should be a priority and treatments including multidisciplinary team approach should be expanded. For early and the most effective treatment of lung cancer, country-specific risk factors should be identified and public awareness raising programmes should be developed.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

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Ethical approval

Ankara City Hospital Ethics Committee of the Ministry of Health Provincial Health Directorate on 25/06/2020 (No: E1-20-817).

References

1. Elia S, Griffo S, Gentile M, et al. Surgical treatment of lung cancer invading chest wall: A retrospective analysis of 110 patients. *Eur J Cardiothorac Surg.* 2001;20:356–60.
2. Pairolero PC. Extended resections for lung cancer. How far is too far? *Eur J Cardiothorac Surg.* 1999;16:48-50.
3. Downey RJ, Martini N, Rusch VW, et al. Extent of chest wall invasion and survival in patients with lung cancer. *Ann Thorac Surg.* 1999;68:188-93.
4. Chapelier A, Fadel E, Macchiarini P, et al. Factors affecting long-term survival after en-bloc resection of lung cancer invading the chest wall. *Eur J Cardiothorac Surg.* 2000;18:513-8.
5. Grillo HC, Greenberg JJ, Wilkins EW Jr. Resection of bronchogenic carcinoma involving thoracic wall. *J Thorac Cardiovasc Surg.* 1966;51:417-21.
6. McCaughan BC, Martini N, Bains MS, et al. Chest wall invasion in carcinoma of the lung: Therapeutic and prognostic implications. *J Thorac Cardiovasc Surg.* 1985;89:836-41.
7. Coleman F.P. Primary Carcinoma of lung with invasion of the ribs. Pneumonectomy and simultaneous bloc resection of the chest wall. *Ann Surg.* 1947;126:156-68.
8. Patterson GA, Ilves R, Ginsberg RJ, et al. The value of adjuvant radiotherapy in pulmonary and chest wall resection for bronchogenic carcinoma. *Ann Thorac Surg.* 1982;34:692-7.
9. Piehler JM, Pairolero PC, Weiland LH, et al. Bronchogenic carcinoma with chest wall invasion: Factors affecting survival following en bloc resection. *Ann Thorac Surg.* 1982;34:684-91.
10. Allen MS, Mathisen DJ, Grillo HC, et al. Bronchogenic carcinoma with chest wall invasion. *Ann Thorac Surg.* 1991;51:948-51.
11. Burnard RJ, Martini N, Beattie EJ Jr. The value of resection in tumors involving the chest wall. *J Thorac Cardiovasc Surg.* 1974;68:530-5.
12. Sayar A, Turna A, Kilicgun A, et al. Prognostic significance of surgical-pathologic multiple-station N1 disease in non-small cell carcinoma of the lung. *Eur J Cardiothorac Surg.* 2004;25:434-8.
13. Albertucci M, DeMeester TR, Rothberg M, et al. Surgery and the management of peripheral lung tumors adherent to the parietal pleura. *J Thorac Cardiovasc Surg.* 1992;103:8–13.
14. Magdeleinat P, Alifano M, Benbrahem C, et al. Surgical treatment of lung cancer invading the chest wall: Results and prognostic factors. *Ann Thorac Surg.* 2001;71:1094-9.
15. Matsuoka H, Nishio W, Okada M, et al. Resection of chest wall invasion in patients with non-small cell lung cancer. *Eur J Cardiothorac Surg.* 2004;26:1200-4.
16. Koizumi K, Haraguchi S, Hirata T, et al. Surgical treatment of lung cancer with vertebral invasion. *Ann Thorac Cardiovasc Surg.* 2004;10:229-34.
17. Facciolo F, Cardillo G, Lopergolo M, et al. Chest wall invasion non-small cell lung carcinoma: A rationale for en bloc resection. *J Thorac Surg.* 2002;121:649-56.
18. Cicero JL, Ponn RB, Daly DT. Surgical treatment of nonsmall cell lung cancer in: T.W.Shields, editor. *General Thoracic Surgery*, 5th ed. Philadelphia: Lippincott, Williams&Wilkins: 2000. p. 1311-41.
19. Watanabe Y, Hayashi, Shimizu J, et al. Mediastinal nodal involvement and the prognosis of nonsmall cell lung cancer. *Chest.* 1991;100:423-8.
20. Sehitogullari A, Aydemir Y, Sayir F. Factors affecting survival in non-small cell lung cancer invading the chest wall. *Biomed Res.* 2016;28:1-6.
21. Jones GD, Caso R, No JS, et al. Prognostic factors following complete resection of non-superior sulcus lung cancer invading the chest wall. *Eur J Cardiothorac Surg.* 2020 1;58:78-85.
22. Bakar C. Epidemiology of cancer in the world and Turkey. *Turkiye Klinikleri J Med Genet-Special Topics.* 2017;2:49-59.