To cite this article: Ağaoğlu Şanlı B, Ulugün FI, Mutlu F, Dinçtürk UA, Karaçam V, Akçalı O, Şanlı A. Factors affecting clinical follow-up of patients who had extended resection due to non-small cell lung cancer with vertebral invasion. Curr Thorac Surg 2024; 9(1): 13-19.

Original Article

Factors affecting clinical follow-up of patients who had extended resection due to non-small cell lung cancer with vertebral invasion

Bahar Ağaoğlu Şanlı[1]*, Fatma İlknur Ulugün[2], Fatma Mutlu[2], Üstün Andaç Dinçtürk[3], Volkan Karaçam[2], Ömer Akçalı[3], Aydın Şanlı[1]

[1]Department of Thoracic Surgery, Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital, İzmir, Turkey
[2]Department of Thoracic Surgery, Dokuz Eylül University, Faculty of Medicine, İzmir, Turkey
[3]Department of Orthopedics and Traumatology, Dokuz Eylül University, Faculty of Medicine, İzmir, Turkey

ABSTRACT

Background: Chest wall involvement or vertebral invasion can be detected in 8-15% of patients with non-small cell lung cancer. We aimed to evaluate the surgical treatment outcomes and factors affecting overall survival (OS) in those patients who underwent en-bloc resection due to vertebral and chest wall invasion.

Materials and Methods: The study encompassed 15 patients with locally advanced non-small cell lung cancer who underwent anatomical lung resection and various vertebral and/or chest wall resections because of vertebral invasion at our institution between 2007 and 2019. Demographic, clinical, and pathological data of these patients were collected retrospectively and the effects of these factors on surgical outcomes and survival were evaluated.

Results: The mean age of the 15 patients was 59.1 ± 10.2 years. Among the patients, six had adenocarcinoma (40%), five had squamous cell carcinoma (33.3%), one had large cell neuroendocrine carcinoma (6.7%), two had a combination of large cell neuroendocrine and adenocarcinoma (13.3%), and one had pleomorphic cell carcinoma (6.7%). Simultaneous to lung resection, hemicorpectomy in four patients (26.6%), total vertebrectomy in one patient (6.6%), partial corpectomy in three patients (20.0%), en-bloc transversectomy in five patients (33.3%), hemilaminectomy in two patients (13.3%) were performed. Two patients underwent only vertebra resection, while 13 patients underwent partial rib resection along with the vertebra. The median overall survival (OS) was 26.3 months (14.7-37.8). The postoperative survival rates were 93%, and 33% for 30-day, and 3-year respectively. When comparing OS among histopathological subgroups, no statistically significant difference was observed (p = 0.473). The median OS was 9.2 months for patients who underwent only vertebra resection, while it was 26.3 months for those who underwent vertebra and rib resection (p = 0.534). Other clinical features such as neoadjuvant treatment status, surgical margin positivity, and presence of recurrence did not exhibit a statistically significant impact on the patients' survival.

Conclusions: En-bloc resection is a treatment alternative that can be successfully applied in patients with primary lung malignancies together with vertebral invasion. Nonetheless, chemotherapy, radiotherapy, or immunotherapy is advised for disease management during the postoperative period.

Keywords: vertebral invasion, non-small cell lung cancer, extended resection

Corresponding Author*: Bahar Ağaoğlu Şanlı, MD. Department of Thoracic Surgery, Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital, İzmir, Turkey
E-mail: drbaharagaoglu@hotmail.com Phone: +90 5412121299
Doi: 10.26663/cts.2024.003
Received 12.11.2023 accepted 21.02.2024

Introduction

Eighty percent of all lung cancer cases are attributed to non-small cell lung cancer (NSCLC). Approximately 50% of these patients have metastasis. In 8-15% of cases, chest wall involvement (T3) or vertebral invasion (T4) can be detected. Vertebra surgery has been performed by neurosurgeons for many years with the logic of decompression surgery and was not aimed at oncological complete surgery. Special orthopedic spinal surgeons' focus on this field together with thoracic surgeons has led to more radical surgical interventions [1]. This study aimed to assess surgical treatment outcomes and the factors that impact overall survival (OS) in NSCLC patients who underwent en-bloc resection because of vertebral and chest wall invasion.

Materials and Methods

This study included 15 locally advanced patients diagnosed with T3-T4/N0/M0 lung cancer with chest wall and transverse process (T3) and vertebral (T4) invasion between 2007 and 2019 at our clinic. The patients did not exhibit mediastinal lymph node involvement or distant organ metastasis during their invasive staging, and therefore, they were classified as operable according to the International Association for the Study of Lung Cancer (IASLC) 2017 criteria. All surgeries were performed by the same spine and thoracic surgeon. The study excluded patients with distant metastatic involvement in the vertebra and chest wall. The primary objective of the study was to explore the prognostic impacts of resection type, histopathological type, and the utilization of neoadjuvant/adjuvant chemotherapy or radiotherapy on survival outcomes.

All patients underwent preoperative evaluation encompassing cardiac and pulmonary physical examinations, routine blood tests, chest X-rays, fiberoptic bronchoscopy (FOB), and pulmonary function tests (PFTs). In clinical staging, computerized tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) were utilized.

Patients with an FEV1 value above 1.5 liters were deemed appropriate candidates for lobectomy, whereas those with an FEV1 value above 2 liters were considered suitable for pneumonectomy. Patients with an FEV1 value falling within the range of 1.5 to 2 liters (equivalent to less than 80%) underwent a reevaluation that included additional tests such as carbon monoxide diffusing capacity measurement (DLCO), ventilation-perfusion scintigraphy, and cardiopulmonary exercise tests.

Patients with mediastinal lymph nodes that had a short axis longer than 1 cm on chest CT or showed suspicious FDG uptake on PET/CT underwent lymph node sampling and, to rule out metastasis, either endobronchial ultrasound (EBUS) or mediastinoscopy was performed. In each case, guided by neuromonitoring (Medtronic®), anatomical resection of the lung, vertebra, and/or chest wall was carried out through posterolateral thoracotomy or high posterior incision (Paulson-J incision) based on the lesion's location. Anatomical lung resection was performed first in all cases, followed by surgical intervention directed at the vertebra to achieve complete resection. The ethics committee of Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital (CREC 2022/22-44) approved the protocol for the current study. All patients gave written informed consent for surgical treatment and were aware that all information could be used anonymously for scientific purposes only.

Statistical Analyses

Statistical analyses were conducted using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). In descriptive statistics, continuous variables were represented as mean ± standard deviation, while categorical variables were presented as counts and percentages. Survival analysis was performed using the Kaplan-Meier method and assessed using the log-rank test. Survival times were presented along with the median and 95% confidence intervals (CI). Statistical significance was determined as $p < 0.05$ in all tests.

Results

The average age of the 15 patients, consisting of 12 males and 3 females, was determined to be 59.1 ± 10.2 years. The mean tumor diameter was 46.4 ± 20.7 mm. Among the patients, six had adenocarcinoma (40%), five had squamous cell carcinoma (33.3%), one had large cell neuroendocrine carcinoma (6.7%), two had a combination of large cell neuroendocrine and adenocarcinoma (13.3%), and one had pleomorphic cell carcinoma (6.7%) (Table 1).

The postoperative pathological stages were as follows: T3N0 (Stage 2B) for five patients, T4N0 (Stage 3A) for seven patients, T4N1 (Stage 3A) for two patients, and TxN0 for one patient. The patient who underwent PTx had received a diagnosis of adenocarcinoma (T4N0M0) and had regressed to T3N0 after neoadjuvant chemo-radiotherapy, followed by resection. The final pathology report did not reveal any viable tumor tissue.

Among the patients with T4N1, one had tumor tissue detected in a hilar lymph node, which was not observed in the preoperative evaluation, as there was no FDG uptake in mediastinal tissues on the patient's PET/CT scan. Additionally, due to the lymph node's size being larger than 1 cm, it was evaluated with EBUS, and no tumor tissue was found. In the case of another patient with T4N1, the lymph node containing the observed tumor was surgically removed from the lobectomy material.

In 4 cases, a posterolateral thoracotomy was conducted, while a Paulson incision was performed in 11 patients. The most important indication for making a Poulson incision is the proximity of the lesion to the superior sulcus structures and the depth of invasion. Therefore, it is not a certain level of elevation that determines the shape of the incision, but the depth of invasion. Among the surgical procedures, right upper lobectomy was carried out in 10 cases, left upper lobectomy in three cases, left pneumonectomy in one case, and left lower lobe superior segmentectomy in one case. Besides lung resection, hemi corpectomy in four patients (26.6%), total vertebrectomy in one patient (6.6%), partial corpectomy in three patients (20%), en-bloc transversectomy in five patients (33.3%), hemilaminectomy in two patients (13.3%) were performed. All patients were preoperatively scored for spinal instability using the Neoplastic Spinal Instability Score (SINS), with an average SINS score of 4.93. Furthermore, to achieve complete resection because of local invasion, partial rib excision was conducted in 13 cases. The average number of ribs removed was 3.2 (ranging from 1 to 5 ribs). Instrumentation was applied to include one healthy vertebra below and above in 6 patients. Two patients underwent only vertebra resection, while 13 patients underwent partial rib resection along with the vertebra (Table 1). In the postoperative period, one patient experienced prolonged air leakage, another had cerebrospinal fluid leakage, and one patient developed pneumonia. None of the patients experienced neurological damage. The diagnosis of CSF leaks is usually made by looking at the color of the incoming fluid. Because the examinations to be performed are far from practical and open to complications. The discharge of white fluid in a patient whose drainage is interrupted is considered a void leak, and it usually disappears spontaneously. In our case, it also resolved spontaneously.

Table 1. Demographic and clinical characteristics.

Age (years) mean±sd (min-max)	59.1±10.2 (43.0-78.0)
Gender n (%)	
Male	13 (86.7)
Female	2 (13.3)
Histopathology n (%)	
Adenocarcinoma	6 (40.0)
Squamous cell carcinoma	5 (33.3)
Large cell neuroendocrine carcinoma	1 (6.7)
Pleomorphic cell carcinoma	1 (6.7)
Combined large cell + adenocarcinoma	2 (13.3)
Stage at diagnosis n (%)	
T3N0	4 (26.7)
T4N0	11 (73.3)
Neoadjuvant therapy n (%)	6 (40.0)
Tumor size (mm) mean±sd (min-max)	46.4±20.7 (15.0-100.0)
Incision n (%)	
Posterolateral thoracotomy	4 (26.7)
Paulson	11 (73.3)
Resection n (%)	
Vertebral resection	2 (13.3)
Vertebra + chest wall resection	13 (86.7)
Surgical margin n (%)	
Positive	7 (46.7)
Negative	8 (53.3)
Recurrence n (%)	4 (26.7)
3-year survival n (%)	5 (33.3)
Postoperative mortality (30-day) rate (%)	93
Follow-up time (month) mean±sd (min-max)	31.3±31.4 (0.9-126.5)

Preoperatively, neoadjuvant treatment was administered to six patients, with only chemotherapy (CT) given to two patients and chemotherapy combined with radiation therapy (CRT) given to four patients. Additionally, 14 patients received adjuvant treatment, with CT alone given to three patients and CRT given to 11 patients. The only patient who did not receive adjuvant treatment had postoperative pathology reported as pTx. Among the patients, 4 (26.6%) experienced recurrence, with brain metastasis occurring in two cases, lumbar vertebral metastasis in one case, and contralateral lung and rib metastasis in one case (Table 1). Among the cases with recurrence, three had the histological subtype of adenocarcinoma, and one had a combination of large cell neuroendocrine carcinoma and adenocarcinoma. One of the recurrent patients (Tx) did not receive adjuvant treatment, while the other two did not receive neoadjuvant treatment.

The median OS was 26.3 months (95% CI, 14.7-37.8). The postoperative survival rates at different time intervals were 93%, 33% for 30-day, and 3-year respectively. Among the surviving patients, one had undergone right upper lobectomy, partial resection of the 3rd rib, and T3 transversectomy, with a pathological report indicating T4N1 adenocarcinoma. The other patient had undergone left upper lobectomy, partial resection of the 2nd, 3rd, and 4th ribs, and T3 total vertebrectomy, with a pathological report indicating T3N0 combination of large cell neuroendocrine and adenocarcinoma.

When comparing OS among histopathological subgroups, no statistically significant difference was found (p = 0.473). The median OS for each subgroup was as follows: 26.3 months for adenocarcinoma, 15.7 months for squamous cell carcinoma, 4.6 months for large cell neuroendocrine carcinoma, 31.1 months for pleomorphic cell carcinoma, and 58.3 months for the combination of large cell neuroendocrine and adenocarcinoma (Table 2). Out of the 6 patients who received neoadjuvant treatment, 5 (83%) were assessed as T4 in the preoperative evaluation, while 1 (16%) was T3. The median overall survival (OS) was calculated as 22.0 months. Among the 9 patients who did not receive neoadjuvant treatment, 6 (67%) were evaluated as T4 in the preoperative assessment, while 3 (33%) were T3, and the median OS was 31.1 months (p = 0.307) (Table 2). Regarding the surgical approach, the median OS was 9.2 months for patients who underwent only vertebra resection, while it was 26.3 months for those who underwent vertebra and rib resection (p = 0.534) (Table 2). The comparison of OS based on clinical and pathological characteristics of the patients is presented in table 2.

Table 2. Overall survival analyses of patients according to clinical and pathological characteristics.

	Overall survival (months) 95% CI	P value (Log Rank test)
Histopathology		0.473
Adenocarcinoma	26.3 (15.3-37.2)	
Squamous cell carcinoma	15.7 (0.0-42.3)	
Large cell neuroendocrine carcinoma	4.6 (-)	
Pleomorphic cell carcinoma	31.1 (-)	
Combined large cell + adenocarcinoma	58.3 (-)	
Stage at diagnosis		0.637
T3N0	15.6 (0.0-51.7)	
T4N0	26.3 (16.4-36.2)	
Neoadjuvant therapy		0.307
Yes	22.0 (0.0-48.0)	
No	31.1 (0.0-70.1)	
Resection		0.534
Vertebra	9.2 (-)	
Vertebra+chest wall	26.3 (14.7-37.8)	
Surgical margin		0.153
Positive	22.0 (0.0-66.7)	
Negative	26.3 (7.7-44.8)	
Recurrence		0.462
Yes	17.7 (0.0-38.9)	
No	26.8 (10.1-43.6)	

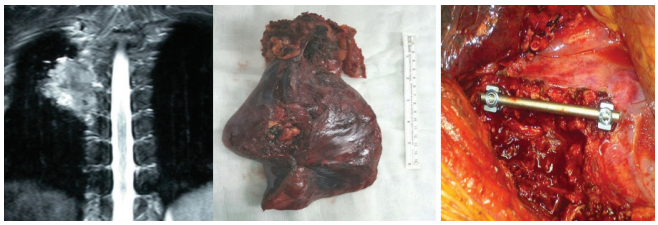

Figure 1. Preoperative MRI image of en bloc resection and lung carcinoma with vertebral invasion **(a)**, intraoperative image after anterior hemi corpectomy **(b)**, hemicorpectomy with instrumentation placement **(c)**.

Discussion

In patients diagnosed with NSCLC, over 50% are initially found to have distant organ metastasis at the time of diagnosis, whereas only around 15% are confined to the primary site. The axial skeleton is one of the regions where bone metastases are frequently faced with its rich venous webwork clearing out lung, pelvis, and thorax. Several studies have reported vertebral invasion in approximately 8-15% of lung cancer cases [1]. Invasion of the vertebra can occur through direct adjacency or via the Batson plexus hematogenously [2,3]. Vertebral invasion is viewed as a locally advanced stage and is associated with a poor prognosis; however, it is not regarded as an indicator of inoperability. Advances in surgical equipment and the availability of multidisciplinary surgical approaches with spine surgeons have increased the chances of surgical treatment [4]. Nevertheless, metastatic vertebral involvement should be accepted as a systemic disease, and surgery should not be aspired.

On a standard X-ray (direct radiograph), metastatic lesions in the vertebrae from lung cancer are typically observed as lytic lesions. However, it has been noted that for these lesions to become visible on direct radiographs, invasion of nearly 50% of the vertebral body is usually required. For that reason, when there is suspicion of vertebral metastasis, additional imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) is suggested. CT may offer information about the localization and number of metastases; however, it may not always clearly distinguish between infectious and tumoral lesions. Therefore, the combination of CT with radionuclide scanning techniques is recommended [2]. On the other hand, magnetic resonance imaging (MRI) allows for a more detailed evaluation of the relationship and boundaries of the mass with surrounding tissues so provides a clearer picture of the lesion's adjacency and extent.

When evaluating NSCLC by their subtypes, it has been reported that squamous cell carcinoma is the subtype that most frequently invades the vertebrae and has the most aggressive course. It often leads to massive vertebral destruction. Surgery is typically performed as a salvage procedure with a focus on preserving movement and neurological function. In the case of small cell carcinomas, radiotherapy is prioritized due to the tumor's radiosensitivity, and surgery does not have a role [3]. In our study, although the squamous cell carcinoma's median OS was found to be shorter than that of adenocarcinomas, no statistically significant difference was observed among histopathological subgroups. The limited patient population in the study may have hindered the statistical significance of this difference from being reflected in the results.

SINS criteria are the initial evidence-driven guidelines for evaluating instability in spinal metastases, and if the score is 7 or higher, the patient is recommended to be evaluated for surgery [5]. In our cases, the average SINS score was 4.93. Only one patient had vertebral corpus involvement of more than 50%, while in the remaining cases, it was less than 50%. In addition, in the classification of NSCLC according to IASLC 8th edition, T3 is considered as chest wall invasion and T4 is considered as vertebral invasion. There is no specific T classification for isolated transverse process involvement of the vertebra; it is generally considered as T3 [6]. The ribs articulate with the vertebrae through the tuberculum costae to the transverse process and through the costal head to the vertebral corpus. In this study, the involvement of the ribs that included both articulations were classified as T3, and complete removal was interpreted as unblock transversectomy.

Postoperative complications can vary and may include pulmonary complications such as pneumonia, prolonged air leakage, bronchopleural fistula, empyema, chylothorax, hemothorax, surgical site infection, and respiratory failure. Additionally, according to the vertebra resection applied there can be neurological complications such as medulla spinalis injury and neurological sequelae, cerebrospinal fluid leakage, and in cases of superior sulcus tumors, Horner syndrome [7-9]. In our study, three cases experienced pneumonia, prolonged air leakage, and cerebrospinal fluid leakage as complications.

Due to the observed correlation between resection type and prognosis, it is recommended to perform the broadest possible resection and en-bloc excision. A favorable impact is observed on survival in NSCLC with vertebral invasion when complete resection is achieved [8,10]. For cases of NSCLC with vertebral invasion 5-year survival rate of 65% have been reported following complete resection [9]. In our research, the 1-year and 3-year survival rates were 53% and 33% respectively.

In this study, performing chest wall resection along with vertebrae resection prolonged the median OS of the patients compared to patients who underwent only vertebral resection, but there was no statistically significant difference between the groups. The reason why no statistical difference could be demonstrated may be the limited number of patients in this study. However, this result may be a guide for future studies that will be better planned.

Surgical approaches may involve either the Paulson incision or thoracotomy. In the Paulson incision, an incision is made along the line between the posterior edge of the scapula and spinal processes and can extend up to the upper border of the scapula or even to the level of C7. This approach provides visibility of the vertebra, thoracic nerves, posterior chest wall, transverse processes, and brachial plexus roots [11]. In our cases, 4 patients underwent posterolateral thoracotomy, while 11 patients received the Paulson incision.

Koizumi et al [8] have recommended total vertebrectomy when more than 50% of the vertebra is destroyed due to apical chest tumors. For cases with less than 30% involvement, partial vertebrectomy can be considered, but defining clear surgical margins with partial tumor resection can be challenging. Therefore, several studies have suggested that combining complete resection ensuring surgical margin safety with preoperative or postoperative chemoradiotherapy reduces the local recurrence rate and achieves extended survival in patients receiving neoadjuvant or adjuvant treatment [8,9]. However, it's worth noting that neoadjuvant chemoradiotherapy can lead to an increase in tumor invasion depth during the treatment period and may result in the progression of neurological symptoms related to local invasion. Additionally, preoperative radiotherapy has been suggested to potentially reduce bone density and may pose stabilization concerns in post-resection bone instrumentation procedures [4,9]. For this reason, in our cases, we targeted adjuvant radiotherapy rather than preoperative radiotherapy.

The main limitation of our retrospectively designed study is the small number of patients since this surgical method is performed rarely and requires a multidisciplinary approach. Nevertheless, it provides preliminary findings that may guide prospective studies planned with a larger patient population in the future.

In conclusion, patients with primary lung malignancies associated with vertebral invasion have the opportunity for successful surgical intervention through en-bloc resection while preserving safe surgical margins. However, in the postoperative period, chemotherapy, radiotherapy, or immunotherapy is recommended to achieve the control of disease and enhance treatment effectiveness.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

Ethics approval

The study was approved by Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital Ethical Committee (CREC 2022/22-44).

Authors' contribution

BAS,AS; conceived and designed this study, BAS,FM; made the analysis of data, FIU,UAD; made the creation of new software used in the work, VK,OA; have drafted the work, BAS,AS contributed to interpretation and revision. All authors have read and approved the final manuscript.

References

1. Ozturk S, Erol FS. Vertebral Resection in Invasive Tumors to Vertebrae, Turkiye Klinikleri J Thor Surg-Special Topics 2018; 9: 175-80.
2. Akcalı O. Spinal Metastasis of Lung Tumor. Diagnosis and Treatment of Spine and Spinal Cord Tumors. Ed. Ufuk Aydinli. Bölüm 14, S209-S216.Ankara, 4/2016.
3. Aydinli U, Ozturk C, Bayram S, Sarihan S, Evrensel T, Yilmaz HS. Evaluation of lung cancer metastases to the spine. Acta Orthop Belg 2006; 72: 592-7.
4. Sanli A. The ability of surgery in T4 lung cancer. Eur J Ther 2018; 24; S33-9.
5. Civan M, Eralp L. Diagnostic algorithms in metastatic patients. TOTBID 2019; 18: 523-33.

6. Lim W, Ridge CA, Nicholson AG, Mirsadraee S. The 8th lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. Quant Imaging Med Surg 2018; 8: 709-18.
7. Aydin AL, Emel E, Sasani M, Gomleksiz C, Oktenoglu T, Ozer AF. Lung Cancer Metastasıs to the Spıne. Turk Neurosurg 2016; 26: 635-642.
8. Koizumi K, Haraguchi S, Hirata T, Hirai K, Mikami I, Yamagishi S et al. Surgical treatment of lung cancer with vertebral invasion. Ann Thorac Cardiovasc Surg 2004; 10: 229-34.
9. Sanli A, Onen A, Yucesoy K, Karacam V, Karapolat S, Gökçen B et al. Göğüs duvarı (T3) ve vertebra (T4) tutulumu olan küçük hücreli dışı akciğer kanseri olgularında cerrahi tedavi. Tüberküloz ve Toraks Dergisi 2007; 55: 383-9.
10. Chadeyras JB, Mazel C, Grunenwald D. Résection Vertébrale monobloc pour cancer pulmonaire: 12 ans d'expérience. Annales de Chirurgie 2006; 131: 616-22.
11. Citak N, Metin M. Superior sulcus tümörlerinde (Pancoast) güncel yaklaşım. Güncel Göğüs Hastalıkları Serisi 2013; 1: 70-84.