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Evaluation of the Effect of Intraoperative Frozen Section on Overall Timeliness and Survival in Lung Cancer Surgery

Akciğer Kanseri Cerrahisinde İntraoperatif Frozen Section Uygulamasının Genel Zamanlama ve Sağkalım Üzerine Etkisinin Değerlendirilmesi

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Abstract

Aim: We aimed to find out whether there is any delay in the management of the process in patients operated for lung cancer and to understand the effect of intraoperative frozen section on this process.

Material and Method: A total of 176 patients were examined. The dates of admission, diagnosis, operation and postoperative pathology results were noted. Five intervals were defined as time to first evaluation to diagnosis, first evaluation to surgery, diagnosis to surgery, first evaluation to the day of postoperative pathology report and diagnosis to the day of postoperative pathology report.

Results: The majority of patients (81.8%) were male and the median age was 63 years (iqr=11). The median time between the first assessment to final pathological examination result were 62 days (iqr=70). The time from initial presentation to surgery was significantly shorter (p<0.001) and the time from diagnosis to final pathology was also significantly shorter (p<0.001) in patients diagnosed by frozen section. However, there was no significant difference in the time from initial evaluation to diagnosis between the two groups (0.052). There was no significant difference in survival between patients diagnosed by frozen and patients diagnosed by other methods (p=0.508).

Conclusion: Solutions to increase the timeliness of care for patients with lung cancer can be designed with a better understanding of delays. Intraoperative frozen section diagnosis improves overall timeliness but has no effect on survival in lung cancer patients undergoing surgery.

Keywords: Timeliness, lung cancer, thoracic surgery, frozen section

Öz

Amaç: Akciğer kanseri nedeniyle ameliyat edilen hastalarda sürecin yönetiminde herhangi bir gecikme olup olmadığını bulmayı ve intraoperatif frozen incelemenin bu süreçteki etkisini anlamayı hedefledik.

Gereç ve Yöntem: Toplam 176 hasta analiz edildi. Başvuru tarihleri, tanıları, yapılan ameliyatlar ve ameliyat sonrası patoloji sonuçları kaydedildi. İlk başvurudan histopatolojik tanının konulmasına, cerrahi gününe ve ameliyat sonrası patolojinin sonuçlandığı güne kadar olan 3 zaman dilimi, histopatolojik tanının konulduğu günden cerrahiye kadar olan interval ve cerrahi gününden ameliyat sonrası patolojinin sonuçlandığı güne kadar olan gün olmak üzere toplam 5 interval tanımlandı.

Bulgular: Hastaların çoğunluğu (%81,8) erkekti ve ortanca yaş 63 (IQR=11) idi. İlk değerlendirmeden nihai patolojik inceleme sonucuna kadar geçen ortanca süre 62 gündü (iqr=70). İntraoperatif frozen inceleme ile tanı konulan hastalarda ilk başvurudan ameliyata kadar geçen süre anlamlı olarak daha kısaydı (p<0.001) ve tanıdan nihai patolojiye kadar geçen süre de anlamlı olarak daha kısaydı (p<0.001). Ancak, ilk değerlendirmeden tanıya kadar geçen süre açısından iki grup arasında anlamlı bir fark yoktu (0,052). İntraoperatif frozen ile tanı konulan hastalar ile preoperatif diğer yöntemlerle tanı konulan hastalar arasında sağkalım açısından anlamlı bir fark bulunmadı (p=0,508).

Sonuç: Akciğer kanserli hastaların bakımının zamanında yapılmasını sağlayacak planlar ancak gecikmelerin daha iyi anlaşılmasıyla tasarlanabilir. Akciğer kanseri nedeniyle cerrahi uygulanan hastalarda tanının intraoperatif frozen inceleme ile koyulması tüm sürecin hızlanmasına katkı sağlar ancak sağkalım üzerinde bir etkisi yoktur.

Anahtar Kelimeler: Akciğer kanseri, frozen kesit, göğüs cerrahisi, zamanındalık

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INTRODUCTION

In developed countries, lung cancer is the leading cause of cancer-related deaths because it is often not diagnosed until late stages.[1] In 2018, 52.7% of newly diagnosed lung malignancies in Turkey had distant metastases at the time of diagnosis.[2] It seems that, although there are many factors that directly affect the results, such as the type of cancer, the stage of the malignancy, and the treatment method the most critical step toward effective lung cancer treatment is a reliable early identification.[3] Delays in lung cancer detection and treatment can cause severe emotional anguish, decreased quality of life, higher use of health-care resources, and, arguably, increased costs of care.

A tissue biopsy is the gold standard for confirming the presence of malignancy. Lung tissue biopsy samples must contain enough tissue material to allow histopathology processes to determine the subtype of lung cancer. The initial biopsy is crucial for confirming an early diagnosis and preventing the need for a repeat biopsy, which increases the risk of complications and delays in treatment commencement.[4] There are numerous procedures that are frequently used to diagnose lung cancer, such as fiber optic bronchoscopy with or without transbronchial needle aspiration, endobronchial ultrasound (EBUS), image-guided trans-thoracic needle aspiration, mediastinoscopy, pleural fluid analysis (thoracentesis), thoracoscopy, and other surgical methods.

Despite comprehensive investigations, some patients with suspected lung cancer may undergo surgery without prior histological evidence of malignancy. Intraoperative frozen section is one of the key tools for directing surgical methods for pulmonary nodules since it is an important way for rapid intraoperative assessment of the benignity or malignancy and histological type of pulmonary nodules.[5,6]

Our goal was to find out if there were any delays between the initial presentation and the diagnosis or between the diagnosis and the treatment. Also, if there are delays in patient care, if these delays affect overall survival and what variables contribute to these delays. Our ultimate goal was to determine how the time from admission to the finalization of the postoperative pathologic diagnosis was affected in patients with intraoperative frozen diagnosis.

MATERİAL AND METHOD

In this retrospective study, patients from 1 March 2019 to 30 January 2023 who underwent surgical resection due to non small cell lung cancer were evaluated. The study was approved by Bilkent City Hospital Ethics Committee (Date: 25.06.2020, Decision no: E1-20-817). All participants provided informed consent. All procedures employed in this investigation were in conformity with the appropriate standards and regulations, as well as the Helsinki Declaration.

Patients who underwent more than one surgery, who were metastatic at the time of diagnosis and who were lost to follow-up and those whose records could not be accessed were excluded. Patients with incompatible preoperative and postoperative diagnoses were also excluded (2 patients).

Age, gender, preoperative diagnosis method, operation information, pathologic stage of the patients information was noted. Operative records, survival information and tumor characteristics were accessed through the Hospital and National medical records system. The dates of admission, diagnosis, operation day and the day of postoperative pathology result confirmed were also noted.

Thus 5 time intervals were defined as;

- from date of admission to diagnosis,
- from date of admission to surgery day
- from diagnosis to surgery date of
- from surgery day to postoperative pathology result confirmed
- from date of admission to postoperative pathology result confirmed

The date of admission was based on the day of presentation with the relevant complaint to any of pulmonology, thoracic surgery or medical oncology. Patients hospitalized in other clinics were considered to be admitted on the day of consultation to the same disciplines. For patients with a pathologic diagnosis obtained by any method, the date of the final pathology of the material obtained in the procedure was determined as the date of diagnosis. For patients diagnosed by intraoperative frozen, the date of diagnosis was determined to be the same as the date of operation. Twenty four patients came to our hospital for operation after being diagnosed at an external center. In these patients, unlike the patients diagnosed in our hospital, the date of admission was after the date of diagnosis. The date when the postoperative pathology was confirmed was taken as the date when the treatment plans of the patients were finalized.

Patients were divided into two subgroups: patients with preoperative diagnosis by any method and patients with intraoperative diagnosis by intraoperative frozen section. Those who underwent rebiopsy due to inadequate diagnosis were noted. In addition, the preoperative diagnosis obtained by EBUS, bronchus biopsy or trans thoracic needle biopsy was compared with the postoperative diagnosis.

The Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corp., Armonk, NY, USA) was used for all analyses. The variables were investigated using visual and analytical methods to determine whether or not they are normally distributed. Continuous variable descriptive analysis is expressed as a median (interquartile range [IQR]) for not normally distributed variables and mean (standard deviation), or a number (percentages) for normally distributed variables. Numbers and percentages are used to represent categorical variables. The Mann-Whitney U test was used to compare time invervals and survival between the groups. A p value of less than 0.05 was considered to show a statistically significant result.

RESULTS

In total, we identified 176 patients. The majority of patients (81.8%) were male, the median age was 63 (iqr=11), and squamous cell carsinoma was the most frequent histology (47.1%). The most common comorbidity was chronic obstructive pulmonary disease (n=56, 31.8%). While there were 56 patients (31.8%) diagnosed by bronchus biopsy or EBUS, 64 patients (36.3%) were diagnosed by transthoracic biopsy. There were 54 patients (30.7%) in the frozen group and 122 patients (69.3%) in the non-frozen group. The tumors characteristics are listed in **Table 1**.

Table 1. Tumor Characteristic in 176 patients

	No. of tumors n (%)
Histologic type	
squamous cell	83(47.1%)
adenocarcinoma	55(31.2%)
large cell	11(6.2%)
nos	9(5.1%)
carsinoid	8(4.5%)
adenosquamous	4(2.3%)
malign mesenchimal tumor	3(1.7%)
malign epithelial tumor	1(0.6%)
snovial sarcom	1(0.6%)
karsinosarcoma	1(0.6%)
Stage	
IA1	11(6.3)
IA2	20(11.4%)
IA3	16 (9.1%)
IB	17(9.7%)
IIA	15(8.5%)
IIB	45(25.6%)
IIIA	39(22.2%)
IIIB	7(4%)
IIIC	2(1.1%)
IVA	4(2.3%)

Of the 54 patients in whom the diagnosis was made by intraoperative frozen section, 34 (62.9%) underwent bronchus biopsy or transthoracic needle biopsy as a preoperative diagnostic procedure with negative results (16 bronchus biopsy and 18 transthoracic needle biopsy).

Wedge resection or segmentectomy was performed in 8 cases (4.5%), lobectomy in 99 cases (56.2%), bilobectomy in 12 cases (6.8%), lobectomy plus thoracic wall resection in 9 cases (5.1%), sleeve lobectomy in 8 cases (4.5%), pneumonectomy in 31 cases (17.6%), and extended pneumonectomy in 9 cases (5.1%).

The median time between the first assessment to diagnosis were 19 days (iqr=34.7), first assessment to surgery day were 40 days (iqr=67.2) and first assessment to final pathological examination result were 62 days (iqr=70). The median time between the diagnosis to surgery day were 20 days (iqr=42) and diagnosis to final pathological examination result were 42 days (iqr=40.7). The median time between the surgery day to final pathological examination result were 19 days (iqr=16).

The time from initial presentation to surgery was significantly shorter (p<0.001) and the time from diagnosis to final pathology was also significantly shorter (p<0.001) in patients diagnosed by frozen section. In addition, the whole process progressed faster in patients diagnosed perioperatively by frozen section (p<0.001). However, there was no significant difference in the time from initial evaluation to diagnosis between the two groups (p=0.052). In addition, the time from surgery to the postoperative pathology result was not affected by whether the diagnosis was made by frozen section or not (p=0.464). The timeliness of entire cohort is summarized in **Table 2**.

Table 2. Median time intervals for frozen and non-frozen groups

	frozen median day (iqr)	non-frozen median day (iqr)	p value
	21.5 (30.2)	16(43.5)	0.052
from date of admission to surgery day	21.5 (26.5)	55(75.2)	<0.001
from diagnosis to surgery day	0(0)	31.5(39.7)	<0.001
from diagnosis to the postoperative pathology	19.5(18.2)	53(40.2)	<0.001
from surgery day to the postoperative pathology	19.5(18)	19 (13.2)	0.464
from date of admission to the postoperative pathology	46 (47.7)	73(68.2)	<0.001

Median survival was 15.66 months (min 0.17- max 41.96 months, iqr=22.1). In patients who underwent lung resection, there was no significant difference in survival between patients diagnosed by frozen and patients diagnosed by other methods (p=0.508).

DISCUSSION

Screening for early lung cancer development is essential for early treatment, which can improve the disease's outcome. Because most modern tools and methodologies can only detect cancer in its advanced stages, when therapy may be ineffective in controlling the disease, early diagnosis of lung cancer remains challenging. There are numerous effects that can affect how long it takes to reach a diagnosis and how long it takes for the treatment plan to be finalized. Despite all of the multiple variables, it is possible to argue that decreasing this interval will benefit the sickness. Clinicians can propose measures to speed up the lengthiest phase if they can pinpoint it.

The intersections that patients must pass through between diagnosis and the choice of a treatment plan are described by standardized definitions of time points and intervals, some of which are objective (such as the date of diagnosis or the date of surgery), while others, such as the date of initial presentation, are subjective.[4]

The reliability and applicability of globally applicable approaches to assessing the timing of cancer diagnosis in each center is questionable, as the dates of some decisive

milestones are uncertain and multifactorial. Accurate estimates of the timing of cancer diagnosis and understanding the factors affecting the diagnostic process require methods that are independent of this uncertainty. In this sense, it is important for each center to evaluate its own process and see where it stands and to take delaying measures. Our findings are consistent with those of numerous other research conducted around the world. The time to diagnosis ranged from 1 to 35.5 days in various studies.[7] They commented that there was a higher than average delay, especially in veteran hospitals, but suggested that this may be due to differences in care processes.[7-9] However, the median time to diagnosis in this study was 19 days, which is within the guidelines recommended by the RAND Corporation.[9]

Similarly, there have been numerous studies on the time interval between diagnosis and treatment. Times ranging from 22 to 66 days have been reported.[10,11] In our study, the treatment time was found to be 20 days. Compared to other studies, this short interval may be due to the high number of patients diagnosed with intraoperative frozen section. Because intraoperative frozen section makes it possible to diagnose and treat the patient on the same day.

In the RAND Corporation guideline, it was pointed out that the time until diagnosis should not exceed 42 days.[9] When global data on the subject are analyzed, inter-country variations are noteworthy.[11] Access to timely health treatments is not the same in all nations, and there are variances even within the same country's centers and regions. If the center determines in its own evaluation that the most time loss occurs in the period from diagnosis to surgery, it should not hesitate to diagnose appropriate cases with intraoperative frozen section. In this way, it may be possible to minimize the impact of center-specific factors on patient care. Our study showed that in patients undergoing lung resection, frozen section diagnosed patients were prepared for surgery faster from the first admission. Ultimately, this acceleration, which is due to the fact that diagnosis and treatment are offered on the same day, shortens the time from initial presentation to final pathology in patients undergoing lung resection. In our study, this time was approximately one and a half times between the two groups.

Some studies have reported mixed findings on whether mortality is affected by delays in diagnosis or treatment. While some attributed the decrease in mortality to shorter delays, other studies actually found a statistically significant relationship between shorter delays and increased mortality.[9-11] In our study, in support of these conflicting data, we concluded that this time advantage provided by intraoperative frozen section did not affect survival as a result of the comparison between the groups. Therefore, we think that it is not possible to definitively determine whether the delays experienced have a positive or negative effect on long-term outcomes.

In our study, it was determined that the interval from surgery to the final postoperative pathology report was not affected by whether intraoperative frozen section was performed or not. This interval is independent of surgeons and is pathology managed. It is also the least open to external influence in the entire timeline. In the goal of improving patient care, it would be wise to focus on services that are within the sphere of influence.

Many studies have aimed to identify and correct inefficiencies in all aspects of patient care, from initial contact to final follow-up. Recommendations include creating a dedicated team for each cancer, providing a patient navigator to help schedule appointments, diagnostic and treatment algorithms, and using outpatient care instead of hospitalization for minor diagnostic or treatment procedures.[7,13] We believe that these types of system improvement steps will be the focus of attention in the future. It is critical to continue working toward improving cancer timelines so that we can keep up with developments in lung cancer diagnosis and therapy.

This study has some limitations. First of all, it is a retrospective and single-center study. The facilities of the center may be different in other parts of the country, so generalizing the data to Turkey in general may be misleading. Moreover, the period covered by the study includes the COVID-19 pandemic period when access to hospitals with other complaints was limited. The sample size is small, and larger studies with more centers and cases are required. It was also observed that due to some personal preferences, patients hesitated to reach the center where they could receive treatment despite knowing their diagnosis.

CONCLUSION

In lung cancer, reducing the time between diagnosis and definitive treatment plan provides a survival advantage. From initial evaluation to postoperative pathologic examination of patients, it has been found that the most time lost is the time spent in deciding on and preparing for surgery. Intraoperative frozen section shortens both times but is not effective in achieving a survival advantage.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Bilkent City Hospital Ethics Committee (Date: 25.06.2020, Decision no: E1-20-817).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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