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Sentinel lymph node mapping in early stage non-small cell lung carcinoma

Erken evre küçük hücreli dışı akciğer kanserinde sentinel lenf nodu haritalaması

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Background: This study aims to assess the accuracy and feasibility of intraoperative sentinel lymph node (SLN) mapping in patients with clinical early stage (stage I-II) non-small cell lung carcinoma (NSCLC).

Methods: A total of 22 patients with pathologically proven clinically early stage NSCLC (2 females, 20 males; mean age 57.62 years; range 45 to 76 years) were included. During thoracotomy, tumor and nodal stations were surveyed with a hand-held gamma counter. Serial-section histological examination and immunohistochemistry were performed to confirm the presence of metastatic disease.

Results: According to preoperative results of fluorine-18-deoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) scan and mediastinoscopy, all of the 22 patients were clinical stage 1A (n=7), stage 1B (n=7), stage 2A (n=7) and stage 2B (n=1). A total of 422 lymph nodes were harvested in 22 patients undergoing thoracotomy and histological examination was performed (mean 19.2±1.8, range 6 to 37 lymph nodes). Metastatic involvement was detected in three of 22 SLNs (13.63%) in 22 patients. The identification rate of SLN was 81.81% and accuracy and sensitivity rate were 100%, while false negativity ratio was 0%.

Conclusion: Intraoperative SLN mapping can be performed in patients with NSCLC with a high accuracy and sensitivity rate. The knowledge of tumor lymphatic drainage by intraoperative SLN mapping in NSCLC may help the surgeon to perform a better lymphadenectomy and encourage the use of more sensitive pathological and molecular techniques to discover occult or micrometastatic disease.

Key words: Early stage; mediastinoscopy; mediastinum; non-small cell lung cancer; sentinel lymph node.

Amaç: Bu çalışmada klinik erken evre (evre I-II) küçük hücreli dışı akciğer kanserli (KHDAK) hastalarda ameliyat sırası sentinel lenf nodu (SLN) haritalamasının doğruluk ve uygulanabilirliği değerlendirildi.

Çalışma planı: Çalışmaya tanısı patolojik olarak konulmuş 22 klinik erken evre KHDAK hastası (2 kadın, 20 erkek; ort. yaş 57.62 yıl; dağılım 45-76 yıl) dahil edildi. Torakotomi sırasında tümör ve lenf nodu istasyonları taşınabilir gama sayıcı ile incelendi. Metastatik hastalığın varlığını kanıtlamak için seri kesitlerde histolojik inceleme ve immünohistokimya kullanıldı.

Bulgular: Cerrahi öncesi fluorine-18-deoksiglukoz (FDG) poszitron emisyon tomografisi (PET)/bilgisayarlı tomografi (BT) ve mediastinoskopi sonuçlarına göre, 22 hastanın tamamı klinik evre 1A (n=7), evre 1B (n=7), evre 2A (n=7) ve evre 2B (n=1) idi. Torakotomi yapılan 22 hastadan toplam 422 lenf nodu elde edildi ve histolojik inceleme yapıldı. (ortalama 19.2±1.8, dağılım 6-37 lenf nodu). Yirmi iki hastada bulunan 22 SLN'den üçünde (%13.63) metastatik tutulum saptandı. Sentinel lenf nodu saptanma oranı %81.81, doğruluk ve duyarlılık %100, yanlış negatiflik oranı ise %0 idi.

Sonuç: Küçük hücreli dışı akciğer kanser hastalarında ameliyat sırası SLN haritalaması yapılabilir ve yüksek bir doğruluk ve duyarlılığa sahiptir. Küçük hücreli dışı akciğer kanserinde ameliyat sırası SLN haritalaması ile tümörün lenfatik drenajı ile ilgili bilgi, daha iyi bir lenfadenektomi yapma konusunda cerraha yardım eder ve gizli ve mikrometastatik hastalığın saptanmasında daha hassas patolojik ve moleküler tekniklerin kullanılmasını teşvik eder.

Anahtar sözcükler: Erken evre; mediastinoskopi; mediasten; küçük hücreli dışı akciğer kanseri, sentinel lenf nodu.

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Lung cancer is the most common cause of cancer death, and it accounted for 28% of all estimated cancer deaths in the United States in 2009.[1] Complete surgical resection for localized disease is the most viable option for obtain sustained remission or a cure.[2,3] When there are no distant metastases, mediastinal lymph node (LN) involvement is the most important prognostic factor in non-small cell lung cancer (NSCLC), and it influences therapeutic strategies.[4] Nonetheless, the five-year survival rate after a complete resection of stage 1 tumors is only 60-70%. Furthermore, patients who relapse after a complete resection of stage 1 LN-negative tumors by definition had occult disease at the time of their initial surgery, and nearly 40% of node-negative patients will develop recurrent disease and die within two years.[5] Improvement in the LN staging of lung cancer would facilitate the selection of patients for novel therapeutic approaches in either neoadjuvant or adjuvant settings.

The sentinel node (SN) concept can be used when the lymphatic flux from a primary tumor first flows into the sentinel lymph node (SLN) before flowing into more distal LNs. If lymphatic metastasis occurs, these nodes most likely will harbor metastasizing cancer cells along the path of the lymphatic drainage of the tumor tissues. The technique employs a lymphatic tracer (most commonly a radioisotope or blue dye)[6] that is injected into the tumor. This is followed by visualization or gamma counter measurements of individual LNs to determine the first site of efferent lymphatic drainage from a tumor. If this concept is correct, then when metastasis is not found in a SLN, it most likely will also not be present in the more distal node. The primary benefit of the SN concept is that it enables surgeons to avoid non-therapeutic LN dissection and the complications that may follow. Sentinel lymph node assessment has become the standard of care in melanoma and breast cancer surgery.[6,7] Although there is also evidence of the existence of SLN in NSCLC, SLN mapping is not widely used in the management of this disease.[8-10]

The objective of this study was to assess the feasibility and accuracy of intraoperative SLN mapping, which reflects the patients who are positive for SLNs, and determine how it relates to metastatic disease in patients with clinical early-stage NSCLC.

PATIENTS AND METHODS

A total of 22 patients with pathologically proven clinical early-stage (stage 1-2) NSCLC (2 females, 20 males, mean age 57.6 years; range 45 to 76 years) were enrolled prospectively in this study between November 2007 - April 2009 at the Eskişehir Osmangazi University School of Medicine, Department of Thoracic Surgery. Approval was obtained from the institutional ethics committee of the university. Before surgery, all enrolled patients had a conventional diagnostic work-up, including a thorough history, physical examination, routine biochemical laboratory tests, contrast-enhanced diagnostic chest computed tomography (CT), and a flexible bronchoscopy. In addition, an integrated positron emission tomography (PET)/CT scan, whole body bone scintigraphy, and cranial magnetic resonance imaging (MRI) were performed in all patients to exclude the presence of a distant metastasis. A standard cervical mediastinoscopy and extended mediastinoscopy (for sample stations 5 and 6) were also performed for invasive mediastinal staging. The mediastinoscopy was performed concurrently with the resection. The patients who received induction chemotherapy and/or radiation therapy were excluded, and informed consent was obtained from all of the participants.

Intraoperative SLN mapping technique

In this prospective study, the intraoperative SLN mapping technique involved the direct injection of the lung tumor with 0.25 mCi of technetium-99m (Tc-99m) pertechnetate (Eczacıbaşı-Monrol Nuclear Products, Kocaeli, Turkey), which was labeled as "Colloidal rhenium sulphide, Nano-colloid" (Nanocis®, IBA SA, Louvain-la-Leuve, Belgium). This was filtered once through a sterile 200 nanometer filter. After the initial thoracotomy, the tumor was injected with the Tc-99m nano-colloid that had been divided perioperatively into four equal doses. The migration time was recorded, and during the time allowed for the migration of the radioactivity through the lymphatics, care was taken to avoid disrupting the peribronchial tissues where the majority of lymphatic channels reside. The tumor and nodal stations were initially surveyed in the thorax intraoperatively with a hand-held gamma counter (EUROPROBE, Lyon, France) after the injection for an average of 45 minutes (range, 30-60 minutes), and background levels were recorded within the mediastinum, distant from the primary tumor *(in vivo)* and after *(ex vivo)* dissection. The radioactivity count was recorded for a period of 10 seconds. The lobar and intralobar LNs were not evaluated due to the shine-through effect of the injection site. Since background activity from the heart, major vessels, and primary tumor created a radioactive signal, the SNs frequently could not be identified in vivo using radioactivity alone. However, radioactivity was useful ex vivo for distinguishing the SNs from the non-SNs. This examination of the excised LNs was performed by the operating surgeon away from the operative field

after the conclusion of the procedure. The nodes with the highest counts per second and with ex vivo measurements three times higher than the intrathoracic background were classified as SLNs, and the migration of the Tc-99m nano-colloid was considered to be successful.

The lung resections were performed concurrently with the complete mediastinal LN dissection, which consisted of the resection of all accessible LNs in the mediastinum and hilum according to the tumor-node-metastasis (TNM) classification for malignant tumors.[11] All resected specimens were examined by experienced pulmonary pathologists.

Pathologic evaluation

All harvested LNs, including the SLNs identified during the operation, were first examined using standard histology with hematoxylin and eosin (H-E) utilizing conventional bi-valving techniques. If the initial histological examination was negative for metastases, at least three serial (step) sections at 30 to 40 μm intervals were evaluated. Afterward, each block was stained immunohistochemically with the cytokeratins AE1/AE3/PCK26 according to standard protocol (AE1MS-341-P and AE3MS-342-P (Neomarkers Inc., Fremont, California, USA). Appropriate tumor cell morphology with brown granular cytoplasmic positivity was considered as a positive result.

Statistical analysis

The identification rate was defined as the percentage of patients with detected SLNs among the whole analyzed group. The false-negative rate for SLN identification was assessed by the presence of metastatic LNs not identified as SLNs with the labeled SLNs appearing uninvolved histologically.

RESULTS

Preoperatively, according to the results of an fluorine-18-deoxyglucose (FDG)-PET CT scan and a mediastinoscopy, seven of the 22 patients were at clinical stage 1A, seven were at stage 1B, seven were at stage 2A, and one was at stage 2B. The scan and mediastinoscopy detected no N_1 metastatic involvement in the three patients at the clinical early-stage (stage 1-2). After surgery, one patient was moved from stage 1A ($T_1bN_0M_0$) to stage 2A ($T_{1b}N_1M_0$), one was moved from stage 1B ($T_{2a}N_0M_0$) to stage 2A ($T_{2a}N_1M_0$), and one was moved from stage 2A ($T_{2b}N_0M_0$) to stage 2B ($T_{2b}N_1M_0$). The histological types included 14 squamous cell carcinomas (65%) and eight

Table 1. Clinical data of the patients

Histological typs	Clinical stage	Operation	Number of Harvested LNs	Harvesting station	Pathological stage
Adenocarcinoma	IA ($T_{1b}N_0M_0$)	L Lower lobectomy	17	4,5,6,7,9,10,11	IA ($T_{1b}N_0M_0$)
Squamous cell carcinoma	IA ($T_{1a}N_0M_0$)	R Upper lobectomy	11	4,7,9,10,11	IA ($T_{1a}N_0M_0$)
Squamous cell carcinoma	IIA ($T_3N_0M_0$)	L Lower lobectomy	10	5,6,7,8,10	IIA ($T_3N_0M_0$)
Adenocarcinoma	IB ($T_{2a}N_0M_0$)	R Middle lobectomy	23	2,4,7,9,10,11,12	IB ($T_{2a}N_0M_0$)
Squamous cell carcinoma	IB ($T_{2a}N_0M_0$)	R Upper lobectomy	20	4,7,9,10,11	IB ($T_{2a}N_0M_0$)
Adenocarcinoma	IB ($T_{2a}N_0M_0$)	L Lower lobectomy	24	4,5,6,7,9,10,11,12	IIA ($T_{2a}N_1M_0$)
Squamous cell carcinoma	IIA ($T_{2b}N_0M_0$)	L Pneumonectomy	19	5,6,7,8,9,10	IIA ($T_{2b}N_0M_0$)
Squamous cell carcinoma	IB ($T_{2a}N_0M_0$)	R Upper lobectomy	22	4,7,9,10,11,12	IB ($T_{2a}N_0M_0$)
Squamous cell carcinoma	IB ($T_{2a}N_0M_0$)	R Upper lobectomy	20	2,4,7,10,11	IB ($T_{2a}N_0M_0$)
Squamous cell carcinoma	IIA ($T_3N_0M_0$)	L Pneumonectomy	21	5,6,7,9,10,11	IIA ($T_3N_0M_0$)
Squamous cell carcinoma	IA ($T_{1b}N_0M_0$)	R Upper lobectomy	22	2,4,7,9,10,11	IA ($T_{1b}N_0M_0$)
Squamous cell carcinoma	IIA ($T_{2b}N_0M_0$)	R Pneumonectomy	20	2,4,7,8,9,10,11	IIA ($T_{2b}N_0M_0$)
Squamous cell carcinoma	IIB ($T_3N_0M_0$)	L Pneumonectomy	17	5,6,7,8,9,10	IIB ($T_3N_0M_0$)
Squamous cell carcinoma	IA ($T_{1b}N_0M_0$)	R Upper lobectomy	17	4,7,8,10,11,12	IA ($T_{1b}N_0M_0$)
Adenocarcinoma	IIA ($T_{2b}N_0M_0$)	R Upper lobectomy	22	4,7,8,9,10,11	IIB ($T_{2b}N_1M_0$)
Adenocarcinoma	IB ($T_{2a}N_0M_0$)	L Upper lobectomy	6	5,6,7,10,11	IB ($T_{2a}N_0M_0$)
Adenocarcinoma	IA ($T_{1b}N_0M_0$)	R Lower lobectomy	14	2,4,7,9,10,11	IIA ($T_{1b}N_1M_0$)
Squamous cell carcinoma	IIA ($T_3N_0M_0$)	R Lower lobectomy	20	4,7,9,10,11	IIA ($T_3N_0M_0$)
Squamous cell carcinoma	IA ($T_{1b}N_0M_0$)	L Upper lobectomy	13	5,6,7,9,10,11	IA ($T_{1b}N_0M_0$)
Adenocarcinoma	IA ($T_{1b}N_0M_0$)	R Middle lobectomy	24	2,4,7,10,11,12	IA ($T_{1b}N_0M_0$)
Squamous cell carcinoma	IIA ($T_3N_0M_0$)	R Pneumonectomy	37	2,4,7,9,10,11	IIA ($T_3N_0M_0$)
Adenocarcinoma	IB ($T_{2a}N_0M_0$)	L Lower lobectomy	23	5,6,7,9,10,11	IB ($T_{2a}N_0M_0$)

adenocarcinomas (35%), and the mean size of the primary tumors was 5±2.6 cm (range 1.5-13 cm). We performed 17 lobectomies and five pneumonectomies (Table 1).

No complications were observed during the SLN mapping procedure. The mean time interval between the intraoperative injection and the first measurement of radioactivity with a hand-held gamma probe was 45 minutes (range 30-60 minutes). Successful migration was observed in 18 of the 22 patients (81.8%), and the LNs were successfully identified. In 14 of the 18 patients (77.9%), a single SLN was identified, whereas in the four others (22.2%), two LNs were found. A total of 422 LNs were harvested and histologically evaluated in the 22 patients who underwent a thoracotomy (mean 19.2±1.8, range 6-37 LNs), and metastatic involvement was detected in three of the participants (13.63%) The SLNs obtained from the patients and the nodes were localized in the N_1 areas. All of the three metastatic SLNs were detected by routine H-E staining, and the other SLNs did not reveal any additional metastases via either H-E or immunohistochemical staining. There was also no skip metastasis. In our series, the identification rate of SLN was 81.81%, the accuracy and sensitivity were 100%, and the false-negative ratio was 0%.

DISCUSSION

Mediastinal lymph node dissection (MLND) is an effective procedure for complete local control of NSCLC. Subsequent improvement in the prognosis of patients as well as nodal staging can also be seen. On the other hand, LN dissection is not therapeutic and may even be harmful for patients without LN metastasis. Although major complications comparable to the arm edema seen in breast cancer or the lymphedema and nerve injury seen in melanoma are not seen with mediastinal LN dissection, an MLND can cause other problems such as recurrent laryngeal nerve palsy, chylothorax, arrhythmia, or other cardiac complications.[12] In addition, the procedure can produce potential immunological effects from the extensive lymphatic ablation, longer operative time, and greater amount of total chest tube drainage.[13]

The application of the SLN mapping technique to NSCLC was initially reported by Little et al.[14] in a series of 36 patients in which they used isosulfan blue dye in an attempt to identify SLNs in patients with resectable NSCLC. In the end, they successfully identified SLNs in 47% of their patients. The specificity of their technique was excellent (100%), but the low sensitivity was primarily due to the frequent appearance of black, anthracotic LNs that made detection of the blue dye in those nodes quite challenging. In an attempt to overcome this difficulty, Liptay et al.[15] began the use of Tc-99m as a radiotracer for SLN mapping in lung cancer. They demonstrated successful migration of Tc-99m in 120 of 148 patients (81%). Sentinel lymph nodes were identified in 104 of the 120 patients (87%) and in 104 of the total number of 148 (70%). The SLN harbored cancer in 32% of their patients, and upstaging occurred in eight of the 104 patients (5.5%). In a recent study by Kim et al.,[16] 42 patients who were candidates for lobectomies with mediastinal LN dissection for stage 1 NSCLC were evaluated, and SLNs were identified in 40 of them (95.2%), with the number representing 2.3 + or - 1.1 stations (range 1-5) per patient. Furthermore, 10 out of the 40 patients (25.0%) had metastases in 11 SLNs, and three of these 11 SLNs (27.3%) had skip metastases. In addition, no false-negative SLNs were detected in any of the 10 patients with N_1 or N_2 disease (0%). Sentinel lymph node mapping may lead to improved prognostic separation of patients based on the number and degree of nodes involved,[17,18] and the intraoperative identification of skip metastases in the mediastinum may allow for a more accurate characterization of this unique pattern of lymphatic drainage.[19,20]

Different studies have reported 54.2-96.1% SLN detection rates in NSCLC.[10,21-24] In our study, successful migration was observed in 18 of the 22 patients (81.8%), and the LNs were successfully identified. In 14 of the 18 patients (77.9%), a single SLN was identified, but in the other four (22.2%), two LNs were found. Metastatic involvement was detected in three of the 22 (13.63%) SLNs obtained from the 22 patients, and these nodes were localized in the N_1 LN areas. All of the metastatic SLNs were found via H-E staining, and the other SLNs revealed no any additional metastases after immunohistochemical examination. In addition, no skip metastasis was detected.

The SLN mapping technique evaluates the first echelon of LNs that drain from primary lung cancer. However, accurate staging of NSCLC requires an evaluation of all of the sites of potential thoracic LN metastasis, which requires an assessment of more than the first echelon of draining LNs. The regional lymphatic system of the lung is complex and tends to drain in different directions, including the contralateral mediastinal LNs.[25] Detection of LN involvement beyond the first echelon can increase the patient's tumor stage from 2 to 3. In our study, we performed the preoperative FDG-PET/CT scan in addition to a mediastinoscopy for mediastinal staging, and only the patients who were diagnosed as being in the clinical early-stage were enrolled in the study. We believe that the staging of the mediastinum with an FDG-PET CT scan

and a mediastinoscopy preoperatively can contribute significantly to a more accurate identification of patients in the early-stage of NSCLC. It can also decrease the false-negative results of the SLN procedure.

The sentinel lymph node study results are more reliable when using a well-selected group of patients in the clinical early-stage of NSCLC. The absence of skip metastases and micrometastases in our study may be explained by the use of this type of patient population along with the small number of subjects in our series.

In four of the 22 patients in our study, migration was not observed, and in two patients, there was post-obstructive inflammation due to significant narrowing of the bronchi. Although LNs can be found in the subpleural space, most of them are intraparenchymal.[26] Adjacent parenchymal inflammation deteriorates the lymphatic flow, and the flow of the radiopharmaceuticals into the LNs could be decreased as a result. Tumor necrosis is another problem involved with migration.

In conclusion, intraoperative SLN mapping has high sensitivity and accuracy rates and is feasible for patients with NSCLC. Mediastinal LN dissection in lung cancer patients usually does not require a long time to perform and is not usually associated with postoperative morbidity. However, intraoperative knowledge of tumor lymphatic drainage could help the surgeon perform a better lymphadenectomy. A secondary benefit of SN identification is the focus on more sensitive pathological and molecular techniques to discover occult or micrometastatic diseases.

Declaration of conflicting interests

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