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Improved staging using intraoperative ultrasound for mediastinal lymphadenectomy in non-small lung cancer surgery

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ABSTRACT

Background: Extent of lymph node involvement in patients with non-small cell lung cancer (NSCLC) is the cornerstone of staging and influences both multimodality treatment and final outcome. The aim of this study was to investigate accuracy and characteristics of intraoperative ultrasound guided systematic mediastinal nodal dissection in patients with resected NSCLC.

Methods: From January 2008 to June 2013, 244 patients undergoing intraoperative surgical staging after radical surgery for NSCLC were included in prospective study. The patients were divided in two groups according to systematic mediastinal nodal dissection: 124 patients in intraoperative ultrasound nodal dissection guided group and 120 in standard nodal dissection group. The lymph nodes were mapped by their number and station and histopathologic evaluation was performed.

Results: Operating time was prolonged for 10 min in patients with ultrasound guided mediastinal nodal dissection, but number and stations of evaluated lymph nodes were significantly higher ($p < 0.001$) in the same group. Skip nodal metastases were found in 24% of patients without N1 nodal involvement. Twelve (10%) patients were upstaged using US guided mediastinal lymphadenectomy. In US guided group 5-year survival rate was 59% and in the group of standard systematic mediastinal lymphadenectomy 43% ($p = 0.001$) Standard staging system seemed to be improved in ultrasound guided mediastinal lymphadenectomy patients. Complication rate showed no difference between analyzed groups.

Conclusion: Higher number and location of analyzed mediastinal nodal stations in patients with resected NSCLC using ultrasound is suggested to be of great oncological significance. Our results indicate that intraoperative ultrasound may have important staging implications.

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Introduction

Lung cancer is the leading cause of cancer mortality in most industrialized countries. Defining the stage of the disease is key for planning therapy, estimating prognosis and comparison of the results.[1] The extent of lymph node involvement in patients with non-small cell lung cancer (NSCLC) is the most important prognostic factor and influences multimodality treatment.[2,3] Radical surgical resection is the standard treatment for patients with NSCLC stage I, II and IIIA. Systematic dissection of hilar and mediastinal lymph nodes performed at thoracotomy is mandatory.[4] The 5-year survival depends primarily on TNM status and the overall medical status of the patient. Nodal involvement of the mediastinum decreases 5-year survival rate at 20%.[5,6] Accurate pathologic staging remains a basic recommendation for management of NSCLC, allows the estimation of prognosis and serves for defining the most adequate treatment strategy.[1] Medical imaging is unable to provide adequate staging and European Society of Thoracic Surgeons (ESTS) recommended a systematic nodal dissection (SND) in all cases.[1–4] Skip transfer and occult lymph node metastasis are two theoretical bases for SND.[5] The status of N2 lymph nodes and patterns of sub-N2 ($IIIA_1$–$IIIA_4$) determine the treatment strategies and prognosis of NSCLC.[6] There is evidence that lymph node dissection does not only improve staging, but also increases survival.[1] Different intraoperative diagnostical methods have been used to improve lymph node mapping and quality of the dissection, but with questionable success (Patent Blue V dye, radioisotope sentinel node mapping, polymerase chain reaction, etc.).[7–10]

In an attempt to achieve safety and improve accuracy, intraoperative ultrasound guided systematic mediastinal nodal dissection was studied in patients with resected NSCLC.

Materials and methods

Patients

From January 2003 to June 2013 a prospective trial of intraoperative surgical staging after radical surgery for NSCLC was carried out in 244 patients (164 (70%) males, 80 (30%) females) at the Department of Thoracic Surgery, Split University Hospital Centre. The patients were divided in two groups according to mediastinal nodal dissection. The groups were comparable according to extent of the disease and the cardiopulmonary reserve. In the group I (124 patients) intraoperative hand held ultrasound probe (7.5 MHz, Toshiba US device) (Fig. 1) was used during systematic mediastinal nodal dissection after radical surgery for NSCLC. In the group II (120 patients) radical surgery and standard systematic mediastinal nodal dissection was performed. The patient characteristics are presented in Table 1. Informed consent was obtained from all the patients and the Ethical Committee of Split University Hospital approved study protocol. Patients referred to surgery after neoadjuvant therapy were excluded from the study.

Surgery

In all of the patients radical surgical resection was performed. Sites of mediastinal lymphadenectomies are shown in Table 2. The nodal stations were separately labeled and examined histologically. The number of involved lymph nodes and their stations and the status of the nodal capsule were documented according to recommendations of Naruke et al. modified by ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer.[4]

Histopathology and immunohistochemistry

Histopathology evaluation was performed by both macroscopic and microscopic examination. Each node was sectioned in 3–5 mm slices, and microscopically examined. For detection of possible metastases in the cases of microscopically negative N2 lymph nodes immunohistochemistry was used. Skip N2 metastases were defined as N2 lymph node metastases without any N1 node involvement.

Minimal N2 disease was defined as single-station lymph node involvement with microscopic disease, and those patients received cisplatin and gemcitabine based adjuvant chemotherapy. Patients with proven two or more station N2 (Bulky N2) disease received adjuvant concomitant chemo irradiation therapy according the Hospital medical policy. Post-operative treatment was not performed in 18 (8.5%) patients. Post-operative follow-up was scheduled every 6 months for the first three years and annually thereafter.

Statistical analysis

The data were analyzed using Microsoft Excel for Windows Version 11.0 (Microsoft Corporation, USA) and Statistica for Windows Release 12.0 (Statsoft Inc., Tulsa, OK, USA). The data were analyzed using Student's t-test, Wilcoxon rank-sum test, and Fisher's Exact test. Survival and patterns of failure were estimated using the Kaplan–Meier method with a log-rank test. All p values of less than 0.05 were considered to indicate statistical significance.

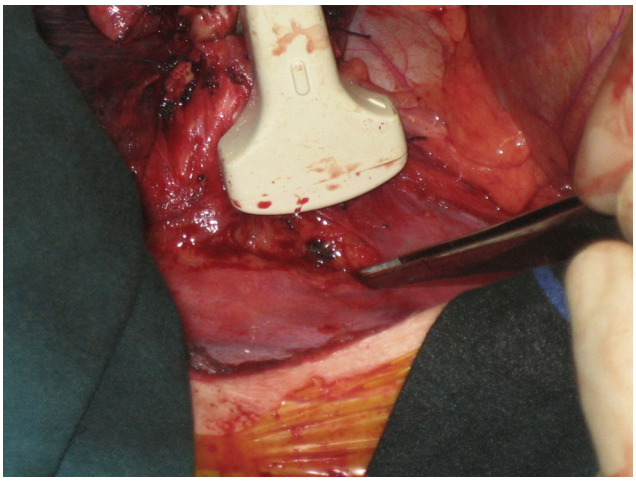

Fig. 1 – Ultrasound guided systematic mediastinal nodal dissection after radical surgery for NSCLC.

Table 1 – Comparison of patients characteristics with ultrasound guided (group I) and standard systematic mediastinal lymphadenectomy (group II).

	Group I		Group II		p
	n	(%)	*n*	(%)	
Gender	124		120		
Male	82	(58)	82	(60)	ns
Female	42	(42)	38	(40)	
Histology					
Adenocarcinoma	49	(39)	48	(40)	
Squamous cell	69	(55)	64	(53)	ns
Other	6	(5)	8	(7)	
Resection type					
Lobectomy	88	(71)	83	(69)	
Bilobectomy	9	(7)	11	(9)	ns
Pneumonectomy	27	(22)	26	(22)	
Localization					
Right	69	(56)	66	(55)	ns
Left	55	(44)	54	(45)	

Results

A total of 244 patients were included in the study, 124 in the first group and 120 in the second group. There were no significant differences between the groups regarding sex, age, comorbidity, tumor localization, surgical procedures or postoperative care (Table 1). Mean age at the time of surgery was 56 years (range, 28–79).

The surgical procedure depended on the extent of the disease, as well as the cardiopulmonary reserve of the patients and was comparable in both groups of patients. Operating time was prolonged for 10 (6–20) minutes in patients with US guided mediastinal nodal dissection, but number and stations of evaluated lymph nodes were significantly higher ($p < 0.001$) in the same group (Table 2). In the group with US guided mediastinal nodal dissection average number of harvested lymph nodes was 17 comparing to 14 in standard systematic mediastinal dissection ($p = 0.000$) (Table 3).

Table 2 – Number of extirpated lymph nodes for each mediastinal lymph node station depending on type of systematic mediastinal lymphadenectomy.

Stations	Right side		Left side	
	Group I	Group II	Group I	Group II
Highest mediastinal	184	131	–	–
Upper paratracheal	168	116	–	–
Prevascular and retrotracheal	169	124	–	–
Tracheobronchial	163	140	187	141
Sub-aortic (AP window)	–	–	105	115
Para-aortic (ascending aorta/phrenic)	–	–	148	118
Subcarinal	157	136	157	132
Para-oesophageal	168	129	156	109
Pulmonary ligament	172	148	175	141
Total	**1180**	**924**	**928**	**756**

Table 3 – An average total number of extirpated mediastinal lymph nodes (during single surgical procedure) depending on systematic mediastinal lymphadenectomy type.

	Right		Left	
	Group I	Group II	Group I	Group II
min	14	12	15	14
max	25	21	26	19
mean	17.23	14.43	17.87	14.38

Skip nodal metastases were found in 24% of patients without N1 nodal involvement comparable in both groups of patients (Table 4). In the first group 12 (10%) patients were upstaged using US guided mediastinal lymphadenectomy and they received adjuvant treatment that would not be administrated otherwise. Median follow-up was 42 (range 5–66) months. Estimated mean 5-year survival showed that higher number of harvested mediastinal lymph nodes influences survival rate. In US guided group 5-year survival rate was 59% and in the group of standard systematic mediastinal lymphadenectomy 43% ($p = 0.001$) (Fig. 2).

Standard staging system seemed to be improved in US guided mediastinal lymphadenectomy patients. Complication rate showed no difference between analyzed groups of patients.

Discussion

Identifying pathological N2 disease is of paramount concern because its presence significantly affects prognosis and therapeutic implications.[5] Over the last several years, different techniques have emerged, which vary in accuracy and procedure–related morbidity.[11] Even with improvements in preoperative staging, there is still a group of patients over or under staged preoperatively. For example, the pathological $IIIA_1$ and $IIIA_2$ cases after thoracotomy are clinical stage I or stage II by imaging.[6] Because of that, SND is recommended in all cases to ensure complete resection and accurate staging and to define the most adequate treatment strategy.[12]

The myth of increased complications following systematic node dissection is swept away by two recent studies. Lardinois et al. showed that there was no significant difference in terms of morbidity, duration of drainage, and duration of hospital stay when comparing sampling to dissection.[13] Doddoli et al. showed that there was no difference in complications except left laryngeal nerve palsy, which was more frequent following systematic lymphadenectomy.[14]

Table 4 – Skip metastases and multi-level and one-level mediastinal lymph node involvement.

	Group I		Group II	
	N	(%)	N	(%)
Multi-level involvement	14	(12)	13	(11)
Three stations	2		2	
Two stations	12		11	
One-level involvement	18	(14)	16	(13)
Total	32	(26)	29	(24)

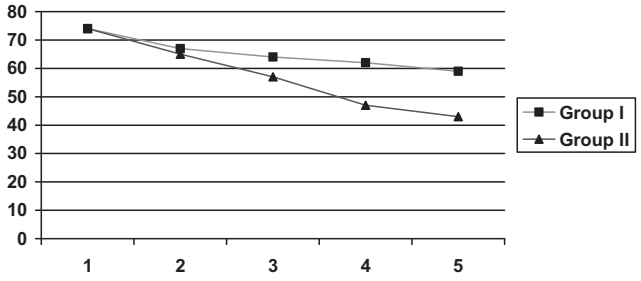

Fig. 2 – Five-year survival rate after operation according to type of mediastinal dissection.

Different methods have been used to improve lymph node mapping and SND, but are not widely accepted yet. Several studies used technitium[99] for intraoperative sentinel node mapping, but after initial promising results they concluded that it yielded worse accuracy than expected and attempt for validation of this technique was unsuccessful.[8,15] Bustos et al. tried intraoperative detection of sentinel node using Patent Blue V dye, but the black coloration of the lymph node interfered with the visualization of the dye and identification rate was low.[7] Menconi et al. have used videothoracoscopic staging with ultrasound color Doppler to evaluate T and N staging.[16] Their preliminary results on 10 patients indicated that it should be applied to diagnosis of patients in stage IIIA and particularly valuable for patients in stage IIIB.[8]

Our results indicate that intraoperative US may have important staging implications. The number of evaluated lymph nodes and upstaged patients was significantly higher in the group of patients with intraoperative ultrasound guided systematic mediastinal nodal dissection.

Operating time was not significantly prolonged. Intraoperative US during systematic mediastinal lymph node dissection is helpful in avoiding possible damage to mediastinal structures. The procedure is simple, safe and highly accurate. A possible disadvantage is the need for experience in ultrasound diagnostics. After the initial layout for ultrasound equipment the method is inexpensive.

Systematic mediastinal lymph node dissection put no patients in any risk by unnecessarily prolonging operative time, but at the same time, information gathered by these methods seemed to bring survival benefit for some patients. Our results indicate that intraoperative US may have important staging implications. Further clinical studies should be carried out in order to improve intraoperative staging in NSCLC patients.

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