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ORIGINAL ARTICLE

Factors related to local recurrence of non small cell lung cancer and its operability

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Summary

Purpose: *To analyze the correlation of primary tumor (PT) pathological characteristics (size, stage, type and grade) and the extent of initial surgical treatment of non small cell lung cancer (NSCLC) with the incidence and time to local recurrence (LR) and disease-free survival (DFS), as well as to determine in what way these parameters and LR localizations affect the possibility for surgical retreatment.*

Methods: *The research was conducted on 114 patients with NSCLC and LR that had initial surgery in two reference institutes in Serbia from January 2002 to December 2010. PT size and disease stage were defined according to the revised 2004 WHO classification. PTs were grouped by size into 3 categories. Due to great diversity, surgical procedures were sorted into 6 operation types. Standard statistical methods and tests were used for data analysis.*

Results: *Statistical analyses showed significant difference in DFS and LR reoperability that were related to PT size, disease stage and the extent of initial surgery. LR localization on the chest wall was favorable for secondary surgery due to LR.*

Conclusions: *Squamous cell lung carcinoma relapses locally more frequently than other lung tumor types, and the commonest LR site is the chest wall. This localization provides high possibility for surgical retreatment. Adequate staging, proper indications for surgical treatment and quality surgery provide longer DFS in patients with NSCLC. All these suggest that the surgeon may be considered as the most significant factor of prognosis.*

Key words: *local recurrence, lung cancer, prognostic factors, surgery*

Introduction

LR of surgically treated NSCLC can be localized in the bronchial stump, the remaining lung parenchyma, the mediastinal lymph nodes or in the chest wall [1-3]. Namely, factors related to local disease recurrence can be grouped into PT characteristics and quality of initial surgery, reflecting in the completeness of resection i.e. radicality and adequate lymphadenectomy [4-8]. The percentage of reoperable LRs of NSCLC varies in the relevant literature from 1 to 39% [9-12].

The purpose of this study was to analyze the correlation of PT pathological characteristics (size, stage, type and grade) and the extent of initial surgical treatment of lung cancer with the incidence and time to LR (i.e. DFS), as well as to determine in what way these parameters and LR localizations affect possibility for surgical retreatment.

Methods

Patients with LR of NSCLC, all of whom were initially surgically treated at the Institute for Lung Diseases of the Clinical Center of Serbia and the Institute for Oncology and Radiology of Serbia from January

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2002 to December 2010, were retrospectively registered and analyzed. In total, 114 patients with LR were included. A preliminary report was published in 2013, with 51 patients [12].

Data of interest were obtained from the patient medical records. Two groups of factors were analyzed in relation to LR incidence: (a) time to LR (i.e. DFS) and the possibility for surgical retreatment; and (b) PT pathological characteristics (size, stage, type and grade) and the extent of initial surgical procedures. PT size and disease stage were defined according to the revised 2004 WHO classification. PTs were grouped by size into 3 categories: T1 – from 0 to 30 mm, T2 – from 31 to 70 mm and T3 – over 70 mm in diameter. Due to their great diversity, surgical procedures were sorted into 6 operation (OP) types: OP type 1–conservative surgery (atypical and segmental resection), OP type 2–lobectomy or bilobectomy, OP type 3–extensive surgery (pneumonectomies or more extensive operations), OP type 4–conservative surgery with chest wall resection, OP type 5-lobectomy or bilobectomy with chest wall resection and OP type 6 - extensive surgery with chest wall resection. In addition, localizations of LRs were presented and classified in relation to their operability.

Statistics

Statistical analyses were based on standard statistical methods and tests. Frequencies, percentages, mean, median, standard deviation (SD) and range were used for the description of data. Depending on the parameters, Pearson x^2 test, Fisher's exact test and Wilcoxon rank sum test with continuity correction were used for testing the differences between treatment groups. The statistical significance level was set at α=0.05 and Bonferroni correction for α value was used in multiple testing over the same set of data. Curves of cumulative probabilities for DFS were constructed using the Kaplan-Meier product-limit method, described with median and 95% confidence interval (95%CI) and log-rank test was used for testing differences between curves with regard to parameters of relevance. Data analyses were performed using the statistical program R version 2.15.1 (2012-06-22); Copyright (C) 2012; The R Foundation for Statistical Computing ISBN 3-900051-07-0. Tables and Figures were constructed using Microsoft Office Word and Excel 2007.

Results

Demographic characteristics of the analyzed sample are given in Table 1. Patients were aged from 37 to 75 years (median 57.5), dominantly male (78%), passionate smokers (93%), without (88%) positive family history for lung cancer (75%), and from urban environment (79%). Most patients had moderately differentiated squamous cell carcinoma, 31 to 70 mm in diameter, and disease stage III or II. One patient had operable solitary brain metastasis (stage IV), previously removed. All PT characteristics are shown in Table 2. Initial complete resection with macroscopically negative margins (R0 or R01 resection) was achieved in the whole group. The extent of initial surgical procedures ranged from atypical resections to pneumonectomies with chest wall resection and mediastinal lymphadenectomies, which are presented in Table 3. In 18 (15.79%) patients, staged IIIb or IV, neoadjuvant treatment was administered prior to surgical treatment: chemotherapy alone in 17 (14.91%) patients, combined with radiotherapy in one patient (0.88%). Postoperative adjuvant chemotherapy was administered to 91 (79.82%) patients.

Postoperative check-ups with chest CT were performed quarterly in the first 2 years and 6-monthly thereafter. All patients had LR within 1 to 51 months from initial surgery, with a median DFS of 13 months (range 10-14) (Figure 1). Pathological confirmation of LR was obtained by bronchoscopic biopsy, percutaneous fine-needle biopsy or secondary surgery.

Analysis showed no statistically significant difference in DFS and LR incidence among different pathological types of PT. On the other hand, there was statistically significant difference in DFS in regard to pathological grade of PT (log-rank test; p=0.0333), with a median DFS increas-

Table 1. Patient characteristics

Characteristics	*N (%)*
Age (years)	
Mean±SD	57.93±8.27
Median (range)	57.5 (37-75)
Gender	
Male	89 (78.07)
Female	25 (21.93)
Cigarette smoking	
Yes	106 (92.98)
No	3 (2.63)
No data	5 (4.39)
Professional exposure*	
Yes	7 (6.14)
No	100 (87.72)
No data	7 (6.14)
Positive family history	
Yes	13 (11.40)
No	86 (75.44)
No data	15 (13.16)
Environment	
Urban	90 (78.95)
Rural	24 (21.05)
Total	114 (100.00)

SD: standard deviation
*dyes, varnishes, asbestos, mining, etc.

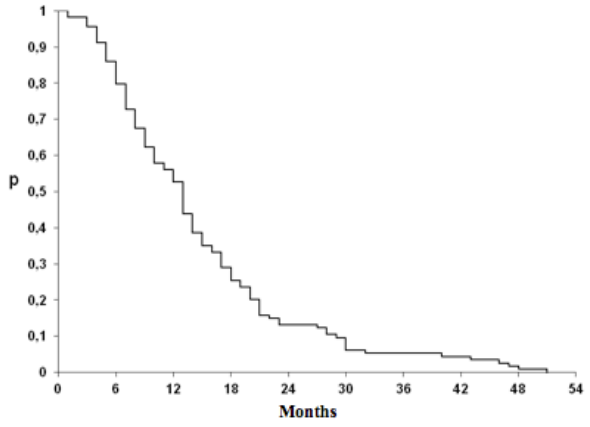

Figure 1. Kaplan Meier disease-free survival (DFS) curve describing time from initial operation to local recurrence in months (N=114). All patients had local recurrence within 1 to 51 months from initial surgery, with a median DFS of 13 months (range 10-14).

Table 2. Primary tumors' characteristics

Characteristics	*N (%)*
Tumor size (mm)	
Mean±SD	55.29±27.89
Median (range)	50 (10-190)
Tumor size*	
T1	26 (22.81)
T2	61 (53.51)
T3	23 (20.17)
No data	4 (3.51)
Tumor type	
Squamous cell	72 (63.16)
Adenocarcinoma	35 (30.70)
Other**	7 (6.14)
Tumor grade	
1	24 (21.05)
2	60 (52.63)
3	26 (22.81)
4	2 (1.75)
No data	2 (1.75)
TNM disease stage§	
I	24 (21.05)
II	38 (33.33)
III	47 (41.23)
IV†	1 (0.88)
No data	4 (3.51)
Total	114 (100.00)

SD : standard deviation,
*T1 – from 0 to 30 mm, T2 – from 31 to 70 mm and T3 – over 70 mm in diameter,
**: bronchioloalveolar mucinous carcinoma, large cell carcinoma, large cell neuroendocrine carcinoma, sarcomatoid carcinoma,
§ revised 2004 TNM classification,
†operable solitary brain metastasis

ing in more differentiated tumors (14.5 vs 13 vs 12 vs 5.5 months for grade 1 vs 2 vs 3 vs 4, respectively). In addition, statistical analysis showed significant correlation between DFS and PT size categories (log-rank test; $p=5.4*10^{-4}$), with a median DFS increasing in smaller PTs (17 vs 19 vs 9 months for T1 vs T2 vs T3, respectively). Also, a statistically significant difference was noticed in LR incidence in the first and second year after the operation related to PT size (Wilcoxon rank sum test with continuity correction; $p[1yr]=2.6*10^{-4}$, $p[2yr]=1.23*10^{-3}$), with higher LR incidence in larger tumors. Statistically significant difference was noticed in DFS (log-rank test; $p=2.02*10^{-4}$) and LR incidence in the first 2 postoperative years (Fisher Exact Test; p[1yr]=0.0454, p[2yr]=0.0290) related to PT stage. Comparing patients without neoadjuvant treatment (stages I, II or IIIa) and those with specific anticancer therapy prior to surgery (stages IIIb and IV), a statistically significant difference was observed in these two groups regarding LR incidence in the first postoperative year (43 vs 71% of patients, respectively), as well as in DFS (median 13 vs 8 months, respectively).

Statistical analysis showed significant difference in DFS related to the extent of initial operation (log-rank test; $p=6.56x10^{-3}$). After multiple testing, it was shown that lobectomies or bilobectomies (only), compared to more extensive surgery with additional chest wall resection, provided longer DFS (log-rank test; Bonferroni correction for α value:=0.0033). Median DFS with corresponding 95%CI for all primary surgery types are listed in Table 3. In addition, there was no statistically significant difference in DFS and LR incidence between patients in different disease stages who were administered adjuvant treatment and those with only curative surgery.

Local recurrences were surgically treated in 42 (36.84%) patients. Most frequent localization of LRs was the chest wall, followed by mediastinal lymph nodes (Table 4). Statistical analysis showed that chest wall localization was the most favorable for reoperation (Fisher exact test; $p<0.001$). LRs in mediastinal lymph nodes were treated with non-surgical methods in all but 2 cases. Possibility for surgical treatment of LR was higher in patients who were initially treated with lobectomies or bilobectomies with or without chest wall resection (70/114, 61.40%), in comparison to patients treated with other surgical procedures (44/114, 38.60%) (Pearson x^2 test; p=0.0446). Analysis of PT characteristics in relation with LR operability showed that patients with squamous cell pathological type more often had operable LR (Pearson x^2 test; $x^2_1=4.6886$; p=0.030363), as well as those with smaller PT size (Wilcoxon rank sum test

Table 3. Patient distribution by initial surgery extent and median disease-free survival with corresponding 95%CI for all primary operation types

Primary operation types	*N (%)*	*Median (95%CI)*
Conservative surgery *	10 (8.77)	17.5 (>12)
Lobectomy or bilobectomy	52 (45.61)	14 (12 - 20)
Extensive surgery +	25 (21.93)	10 (8 - 17)
Conservative surgery with chest wall resection	4 (3.51)	9 (>9)
Lobectomy or bilobectomy with chest wall resection	18 (15.79)	9 (7 - 14)
Extensive surgery with chest wall resection	5 (4.39)	13 (>13)

*atypical or segmental resection, + pneumonectomies or more extensive operations

Table 4. Localization of lung cancer local recurrences and applied retreatment

Localization of local recurrence	*Surgery N (%)*	*Other* N (%)*	*Total N (%)*
Chest wall	20 (60.61)	13 (39.39)	33 (28.95)
Mediastinal LN	2 (7.41)	25 (92.59)	27 (23.68)
Lung parenchyma	10 (45.45)	12 (54.55)	22 (19.30)
Bronchial stump	7 (41.18)	10 (58.82)	17 (14.91)
Bronchial stump and mediastinal LN	1 (14.29)	6 (85.71)	7 (6.14)
Lung parenchyma and mediastinal LN	1 (20.00)	4 (80.00)	5 (4.39)
Chest wall and mediastinal LN Bronchial stump	1 (50.00)	1 (50.00)	2 (1.75)
and chest wall	0 (0)	1 (100)	1 (0.88)
Total	42 (36.84)	72 (63.16)	114 (100)

*chemotherapy, radiotherapy, combination chemo/radiotherapy or palliative treatment, LN: lymph nodes

with continuity correction; p=0.0436) and lower disease stage (Pearson x^2 test; $p=5.423*10^{-3}$).

Discussion

The median DFS in this series of patients was 13 months (range 10-14). Reasons for this slightly shorter DFS compared with literature [13-15] can be initial under-staging of patients and inadequate radicality during initial surgical treatment [4,5,7,8].

As mentioned in methodology, the initial research was published in 2013, with a series of 51 patients [12]. Distribution of patients in the present larger series (114 patients) was roughly the same regarding age, gender, smoking habits and living environment, as well as regarding PT characteristics and initial surgical treatment extent. The most frequent pathological types of PTs were squamous cell carcinomas (63%), locally relapsing on the chest wall, and adenocarcinomas (31%), producing skip metastases to the mediastinal lymph nodes, which correlates with data available in the literature [16,17]. LRs of squamous cell carcinomas on the chest wall were more frequent, probably due to patient's under-staging and lower quality of surgery due to unreliable intraoperative pathological assessment of the resection margins. However, no statistically significant differences in DFS and LR incidence among PT types were registered. The same conclusion was reported by Martini et al. as well [18,19], while Jung et al. showed higher LR incidence in squamous cell PTs [2]. PT size and disease stage were distinguished as factors statistically significant for DFS and LR incidence in first 2 postoperative years and these results correlate with available literature data [14,19-24]. Patients who were initially treated surgically (stages I, II and IIIa) had longer DFS than those who, prior to surgery, received specific anticancer therapy, which suggests well-chosen indications for surgery. Some authors examined survival and LR incidence in patients with disease stage I subjected to lobectomies vs atypical resections [25,26], as well as the effects of selective vs systemic lymph node dissection [27], with almost the same prognostic results. This analysis showed that the extent of initial operation affected DFS, being significantly longer in patients treated with lobectomies and bilobectomies comparing to those with more extensive surgery. These results could explained by the completeness of surgical

resection, i.e. quality of the performed surgical procedure. What is important to mention is that adjuvant postoperative treatment did not provide longer DFS or lower LR incidence for patients who received it. However, no reliable comparisons and comments can be made between our results and other, somehow similar studies, due to their unavailability in the literature.

Literature data suggest lung parenchyma and mediastinal lymph nodes as the most frequent LR site [1-3], while chest wall was highly represented in our series (29%), followed by mediastinal lymph nodes (24%). In total, 37% (42/114) of our patients with LRs were retreated surgically, while in the previously published paper [12], 39% (20/51) of the patients were reoperable. These figures are significantly higher compared to some reported series that had 1-6% of secondary operations due to LR [10,11]. A probable explanation would be the localization of LR, i.e. chest wall LRs were more amenable to surgical resection. This correlation was also confirmed by statistical analysis. The lowest possibility for secondary operation was observed in patients with LR in mediastinal lymph nodes or the bronchial stump, which correlates with literature data [9].

Squamous cell type of PT, smaller PT size, lower disease stage, LR localization on the chest wall, as well as initial surgical treatment consisting of lobectomies or bilobectomies with or without chest wall resection, were recognized as factors favorable for LR reoperability. In addition, better tumor grade of differentiation, smaller PT size, lower disease stage (with emphasis on stages I, II and IIIa) and initially performed lobectomies or bilobectomies, were proven as factors that provide longer DFS. It can be concluded that adequate staging, proper indications for surgical treatment and quality surgery provide longer DFS in patients with lung cancer. All these suggest that the surgeon may be considered as the most significant factor of prognosis.

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