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ORIGINAL ARTICLE

Correlation of tumor size as independent factor and disease stage with local recurrence of non-small cell lung carcinoma and its operability

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Summary

Purpose: *To analyze the correlation of non-small cell lung carcinoma (NSCLC) primary tumor size, independently, and the initial disease stage with the incidence of local recurrence (LR) and disease-free survival (DFS), as well as the LR operability.*

Methods: *The research was conducted on 114 patients operated due to NSCLC at the Institute for Lung Diseases of the Clinical Center of Serbia and the Institute for Oncology and Radiology of Serbia from January 2002 to December 2010, who developed LR during the 5-year follow-up. Diagnostic methods and surgical approaches were standard, defined by protocols. Standard statistical methods and tests were used for data analysis.*

Results: *Statistical analysis showed significant difference in DFS and LR incidence in first 2 postoperative years related to primary tumor size and stage. Patients with T1 tumors (vs T2 vs T3), as well as in earlier disease stage, had significantly longer DFS. LR in the first and second year after primary tumor operation occurred more frequently with larger primary tumors. Significant correlation was registered between LR operability and primary tumor size, as well as LR operability and primary tumor stage.*

Conclusions: *This research highlights size of the primary tumor as independent prognostic factor for patients with NSCLC. The likelihood of LR increases with larger primary tumor and higher primary tumor stages, while DFS decreases. Because larger tumors are more frequently understaged, with occult mediastinal metastases, their LR is not possible to be surgically treated.*

Key words: *local recurrence,non-small cell lung carcinoma,prognosis,size,stage*

Introduction

NSCLC represents 85-90% of all lung cancers, with a 5-year survival rate less than 15%, all stages included [1].During 2011, the Institute of Public Health of Serbia recorded 6254 new cases of lung carcinoma in Serbia [2], while the Statistical Office of the Republic of Serbia registered 4989 lung carcinoma-related deaths [3]. The incidence and mortality rates of lung carcinoma in Serbia are higher than the European average (40 countries) ranking third in men and eighth in women [4].

Many authors have indicated mediastinal lymph nodes as the most frequent site of LR of NSCLC [5,6], while others cite the lung parenchyma [7]. Patients with LR can be re-operated, treated with chemotherapy, radiotherapy or combined chemoradiotherapy, or, in case of inoperability, treated symptomatically.

Many studies analyzed the prognostic significance of certain factors in LR. Data show that LR is associated with the primary tumor characteristics [8-10], inadequate assessment of the true disease stage [11-15], as well as radicality of the initial surgical treatment [16]. This renders the surgeon an important prognostic factor.

Several studies analyzed the relationship between primary tumor size, nodal status and patients' survival, but no data exist on isolated cor-

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relation of primary tumor size and LR, as well as LR incidence and primary NSCLC disease stage.

The aim of this study was to analyze the correlation of primary tumor size, independently, and initial disease stage with the incidence of LRand DFS, as well as the LR operability.

Methods

All patients with NSCLC surgically treated at the Institute for Lung Diseases of Clinical Center of Serbia and the Institute for Oncology and Radiology of Serbia from January 2002 to December 2010 were followed up for 5 years from the initial operation, with special focus in local disease recurrences. Check-ups were quarterly in the first 2 years and 6-monthly there after. During follow-up, 114 patients developed LR without distant metastases, and further analysis was conducted in this group of patients.

Data on patient characteristics, primary tumor features and treatment and characteristics of LR were collected from the patient medical records of the two institutions. Parameters of interest for statistical analysis included the primary tumor size and stage since a great number of patients were clinically understaged (concordance of 75.44% among clinical and pathological tumor size; 52.63% for tumor stage). These data were taken from the official pathology reports and defined based on the revised 2004 TNM classification. Primary tumors were divided into 3 categories according to size: T1 – from 0 to 30 mm, T2 – from 31 to 70 mm and T3 – over 70 mm in diameter. Encountered were all stages, from Ia to IV (one patient had operable solitary brain metastasis that was treated with metastasectomy prior to primary NSCLC operation). The incidence of LR, DFS and LR operability were analyzed in relation to the primary tumor size and stage.

Statistics

Statistical analyses were based on standard statistical methods and tests. Frequencies, percentages, mean, median, 95% confidence intervals (95% CI), standard deviation (SD) and range were used for description of the data. The statistical significance level was set at $p<0.05$ and Bonferroni correction for α value was used in multiple testing over the same set of data. For testing the significance of differences between repeated measurements of parameters of interest within treatment groups Wilcoxon signed rank test with continuity correction was used. For testing the differences between treatment groups depending on the parameters Pearson x2 test, Fisher's exact test and Wilcoxon rank sum test with continuity correction were used. Curves of probabilities for time from initial surgical treatment to LR diagnosis were constructed using the Kaplan-Meier product-limit method with Log-rank test for testing differences between curves with regard to parameters of relevance.

Results

Of the 114 patients, 78% (89/114) were male and 22% (25/114) female. The patient mean age was 57.9 ± 8.27 (SD) years with median 57.5 years (range 37-75). Surgical treatment ranged from atypical resections to pneumonectomies with chest wall resection and mediastinal lymphadenectomies.

Primary tumors were most often squamous cell carcinomas, moderately to well-differentiated in 74% of the cases. All pathological data of primary tumors (size, type, grade and distribution by TNM T parameter and stage) are shown in Table 1. Primary tumors were mostly classified as T2 or T3 in disease stages II or III.

In all patients LR occurred within 4 years from the initial operation. Median DFS was 13 months (95% CI 10-14). Most frequent isolated localizations of LR were chest wall (28.95%, 33/114 patients), mediastinal lymph nodes (23.68%, 27/114 patients) and lung parenchyma (19.30%, 22/114 patients). Concordance among pathological types of primary tumor and LR was verified in 97.14% (68/70) of the patients. Most frequent LR histological type was squamous cell carcinoma of

Table 1. Primary tumor histological characteristics of the primary tumor in 114 patients with local recurrence

Primary tumors characteristics	*N (%)*
Tumor size (mm)	
Mean (±SD)	55.29 (±27.89)
Median (range)	50 (10-190)
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)
T stage	
T1	16 (14.04)
T2	44 (38.60)
T3	37 (32.46)
T4	17 (14.91)
TNM disease stage§	
I	24 (21.05)
II	38 (33.33)
III	47 (41.23)
IV †	1 (0.88)
no data	4 (3.51)

SD:standard deviation, *bronchioalveolar mucinous, large cell, large cell neuroendocrine, sarcomatoid, §revised 2004 TNM classification, †operable solitary brain metastasis

Table 2. Distribution of NSCLC local recurrences in postoperative years by primary tumor size and stage

	NSCLC primary tumor size categories				
NSCLC-LR	*T1 ** N(%)*	*T2§ N(%)*	*T3† N(%)*	*no data N(%)*	*p value*
1st year					
no	18 (69.2)	34 (55.7)	6 (26.1)	2 (50)	0.0082!
yes	8 (30.8)	27 (44.3)	17 (73.9)	2 (50)	
2nd year					
no	9 (34.6)	5 (8.2)	0 (0)	1 (25)	
yes	9 (34.6)	29 (47.5)	6 (26.1)	1 (25)	0.0102∞
already LR*	8 (30.8)	27 (44.3)	17 (73.9)	2 (50)	
3rd year					
no	5 (19.2)	1 (1.6)	0 (0)	0 (0)	
yes	4 (15.4)	4 (6.6)	0 (0)	1 (25)	0.3007∞
already LR*	17 (65.4)	56 (91.8)	23 (100)	3 (75)	
4th year					
no	1 (3.8)	0 (0)	0 (0)	0 (0)	
yes	4 (15.4)	1 (1.6)	0 (0)	0 (0)	1.0
already LR*	21 (80.8)	60 (98.4)	23 (100)	4 (100)	
Total	26 (100)	61 (100)	23 (100)	4 (100)	-

	NSCLC primary tumor stage categories					
NSCLC-LR	*Stage I N(%)*	*Stage II N(%)*	*Stage III N(%)*	*Stage IV N(%)*	*no data N(%)*	*p value*
1st year						
no	18 (75)	19 (50)	21 (44.7)	0 (0)	2 (50)	0.0454∞
yes	6 (25)	19 (50)	26 (55.3)	1 (100)	2 (50)	
2nd year						
no	9 (37.5)	3 (7.9)	3 (6.4)	0 (0)	0 (0)	
yes	9 (37.5)	16 (42.1)	18 (38.3)	0 (0)	2 (50)	0.0291∞
already LR*	6 (25)	19 (50)	26 (55.3)	1 (100)	2 (50)	
3rd year						
no	6 (25)	0 (0)	0 (0)	0 (0)	0 (0)	
yes	3 (12.5)	3 (7.9)	3 (6.4)	0 (0)	0 (0)	0.0613∞
already LR*	15 (62.5)	35 (92.1)	44 (93.6)	1 (100)	4 (100)	
4th year						
no	1 (4.2)	0 (0)	0 (0)	0 (0)	0 (0)	
yes	5 (20.8)	0 (0)	0 (0)	0 (0)	0 (0)	1∞
already LR*	18 (75)	38 (100)	47 (100)	1 (100)	4 (100)	
Total	24 (21.1)	38 (33.3)	47 (41.2)	1 (0.9)	4 (3.5)	-

LR: local recurrence. *patients having already LR, **primary tumors < 30mm in diameter; §primary tumors from 31 to 70mm in diameter; †primary tumors > 70mm in diameter; !Pearson x^2 test 9.612; ∞Fisher's exact test

moderately differentiated grade.

Local recurrence and NSCLC primary tumor size

Analysis of LR incidence and primary tumor size showed statistically significant difference in LR incidence in the first and second year after operation (Wilcoxon rank sum test with continuity correction; $p[1]=2.6x10^{-4}$, $p[2]=1.23x10^{-3}$). Patients who developed LR within the first two postoperative years had larger primary tumor size in comparison to patients without LR. In the T3 category (primary tumor >70mm), all patients had LR within first two postoperative years (Table 2).

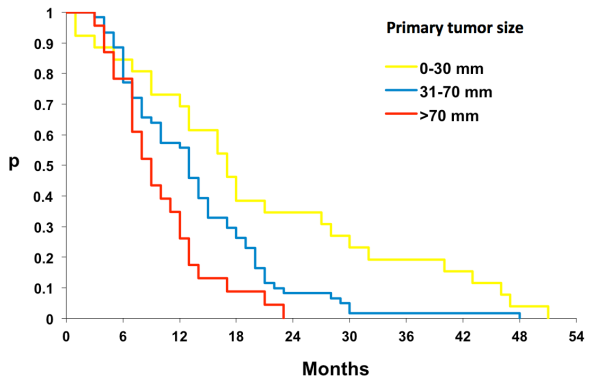

Figure 1. Kaplan-Meier disease-free survival in NSCLC primary tumors' size categories (Log rank, $p=5.4x10^{-4}$).

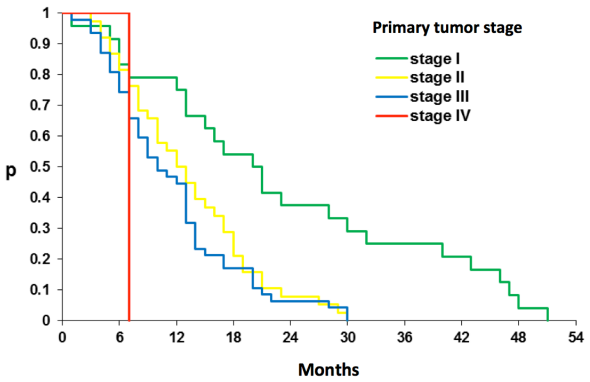

Figure 2. Kaplan-Meier disease-free survival in NSCLC primary tumors' stages (Log-rank, $p=2.02x10^{-4}$).

This group had statistically significant increased LR incidence in the first postoperative year in comparison to patients with T1 category - primary tumor <30mm (73.91 vs 30.77%). In addition, patients with T2 category (31-70 mm) had significantly more frequent LR in the second postoperative year in comparison to patients with T1 tumors (47.54 vs 34.62%).

A decrease in median DFS was noticed in patients with larger primary tumors (Figure 1). By 13th postoperative month, all patients with T3 tumors had LR, with a median DFS of 9 months, while in 31% of T1 patients with LR the median DFS was 17 months. Analysis showed significant correlation between DFS and primary tumor size (Log-Rank test; $p=5.4x10^{-4}$). Patients with T1 tumors (vs T2 vs T3) had longer DFS.

Local recurrence and NSCLC disease stage

Analysis of the incidence of LR and primary tumor stage showed statistically significant difference in the first two postoperative years (Table 2). Yet, it could not be statistically concluded whether there were more NSCLC LRs in stage I, II, III or IV in these years due to insufficient number of patients observed in these categories for the given parameter.

Table 3. Distribution of NSCLC local recurrence treatment modalities in 114 patients by primary tumor size and stage

NSCLC-PT	*NSCLC-LR treatment modality*		
	Operation (N%)	*Other§ (N%)*	*Total (N%)*
Size			
T1*	14 (53.85)	12 (46.15)	26 (100)
T2**	19 (31.15)	42 (68.85)	61 (100)
T3***	7 (30.44)	16 (69.56)	23 (100)
no data	2 (50.00)	2 (50.00)	4 (100)
Stage			
I	15 (62.50)	9 (37.50)	24 (100)
II	15 (39.47)	23 (60.53)	38 (100)
III	11 (23.40)	36 (76.60)	47 (100)
IV	1 (100)	0 (0)	1 (100)
no data	(0)	4 (100)	4 (100)
Total	42 (36.84)	72 (63.16)	114 (100)

*primary tumors < 30mm in diameter; **primary tumors from 31 to 70mm in diameter; ***primary tumors > 70mm in diameter.§chemotherapy, radiotherapy or both, PT: primary tumor, LR: local recurrence

There was also statistically significant difference in DFS in relation to primary tumor stage (Log-Rank test; $p=2.02x10^{-4}$). DFS, as shown in Figure 2, was longer in stage I patients (median 20.5 months) compared to stage II and III patients (median 12.5 and 10 months, respectively). These results, however, should not be taken without considering that there was only one patient in stage IV, with a DFS of 7 months.

Patients were grouped into two categories: category 1 with potentially operable disease (stages I, II or IIIa), and category 2 with inoperable disease, which was initially treated with neoadjuvant therapy (stages IIIb or IV). Analysis of these categories showed significantly higher incidence of LR in category 2 (vs category 1) in the first postoperative year (71 vs 43% of patients), and longer DFS in category 1 (vs category 2), with median 13 and 8 months, respectively.

Operability of local recurrence

The possibility for surgical treatment of LR was assessed in relation to primary tumor size

and stage. Surgical removal of LR was possible in 36.84% (42/114) of the patients; in most cases it included resection of the chest wall (ribs and muscles). Symptomatic treatment was offered to 12.28% of the patients with poor general condition. The remaining were administered chemotherapy, either alone (33.33%) or combined with radiotherapy (4.39%), or radiotherapy alone (13.16%). The distribution of surgically and non-surgically treated patients by primary tumor size and stage is displayed in the Table 3. In surgically treated patients, the average primary tumor size was 48.7 mm vs 59.1 mm in the other group. Statistical analysis showed significant difference between primary tumor size and LR operability (Wilcoxon rank sum test with continuity correction; p=0.0436), but could not precisely determine which primary tumor size category was more favorable for operation. As shown in Table 3, most operated patients had PT less than 30 mm in diameter (53.85%). Patients with larger tumors (31-70 mm or over 70 mm) were not operable in 70% of the cases and received some other treatment. There was also significant difference in the prevalence of certain primary tumor stages between surgically and non-surgically treated patients (Pearson x^2 test; p=5.423x10-3). One patient with operable brain metastasis and stage IV disease was excluded from statistical analysis although he had operable LR. As shown in Table 3, most patients with stage I primary tumor were operable, while stage II and III patients were typically treated with chemotherapy, radiotherapy or both.

Discussion

Lymphatic drainage variations, frequent (31-74%) skip metastases and micrometastases undetectable by PET/CT in N1-N2 stages lead to omission of distant metastases at initial surgery and to patient understaging [12-15]. Inadequate preoperative assessment of the disease contributes to inappropriate operational radicality during primary surgical treatment. Incomplete resection, with microscopically positive resection margins and inadequate lymphadenectomy, is associated with disease relapse [16]. Some authors found nodal metastases outside the lobe where the primary tumor was localized in approximately 30% of the operated patients with N1 disease, which may be the cause of disease relapse as well [11]. Several publications point out the importance of the primary tumor characteristics in relapse. Presence of lung symptoms, squamous cell histology, tumor size over 3 cm, vascular invasion and metastases in multiple lymph nodes result in more frequent disease relapses [8-10].

All patients in this series had LR in the first 4 postoperative years, most often within the first 2 years. In patients with tumors over 70 mm in size, all LR occurred in the first 2 postoperative years. Research showed statistically significant difference in DFS and incidence of LR in the first and second postoperative year in relation to primary tumor size (<30 mm vs 31-70 mm vs >70 mm), that is, with increasing tumor size the median DFS becomes shorter (17; 95% Cl;13-30 vs 13; 95% Cl;10-15 vs 9; 95% Cl;7-13 months, respectively), while the incidence of LR was higher (30.77 vs 44.26 vs 73.91% for the first postoperative year; 34.62 vs 47.54 vs 26.09% for second postoperative year). The percentage in the group with primary tumors over 70 mm was lower than in the other two groups because 74% of these patients already had recurrence in the first postoperative year.

Koike et al. [17] cite that tumor size is independent postoperative prognostic factor for survival of patients in clinical stage I. Several publications list tumor size as significant prognostic factor for disease relapse [18-21]. Some authors indicate that each centimeter of increase in tumor size triples the risk for disease progression to stage II or III [22]. Others double the risk for presence of occult mediastinal metastases (N2) in tumor increase from under 1cm to over 2 cm in size [23]. Subotic et al. confirmed more frequent mediastinal lymph node involvement in larger tumors, in comparison to tumors with smaller diameter (40.6 vs 22.2%) [21].

The median DFS in this research was 13 months (95% Cl;10-14), for all disease stages. In other series [20,24,25], DFS was 20 months. This study showed statistically significant difference in DFS and incidence of LR in relation to primary tumor stage. DFS was significantly longer in stage I patients (median 20.5 months) in comparison to stages II and III (medians 12.5 and 10 months, respectively). In a clinical study by Goodgame et al. relapse occurred 20 months after initial operation of stage I NSCLC [26]. There was a statistically significant difference in local recurrence incidence in the first and second postoperative year, but analysis could not reveal for which disease stages, due to the small number of patients observed in these categories for a given parameter.

Statistical analysis showed significant differ-

ence between primary tumor size and the operability of LR, but could indicate significance of a certain tumor size category. As expected, increase of primary tumor size correlated with decrease in LR operability. An explanation may be the understaged patients, that is patients with occult mediastinal metastases which is 2-fold more frequent in tumors over 2 cm in size, in comparison to tumors less than 1 cm in diameter [21,23]. In addition, as mentioned earlier, increase in tumor size for a centimeter triples the risk for disease progression to stages II and III [22].

Inadequate preoperative assessment of the disease extent minimizes the radicality required in the initial surgical treatment, but microscopically positive resection margins and inadequate lymphadenectomy renders the surgeon as an important factor for patients' prognosis.

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