Scientific Research

In Surgical Treatment of Non-Small-Cell Lung Cancer a Minimum Number of Resected Mediastinal Lymph Nodes Is Mandatory for Accurate Staging

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Abstract

Objective: Increased numbers of removed lymph nodes (LN) are resulting in more accurate staging of the patient (Will-Rogers-Phenomenon). This study evaluates dependence of lymph node sample size to 1) Will-Rogers-Phenomenom, 2) influence of sample size on overall survival and in terms of 3) morbidity and mortality. Methods: 131 patients after pulmonary resection were retrospectively analysed concerning surgery, number of removed lymph nodes, stage, complications and survival. Patients were stratified according to the median number of lymph nodes in two groups (A <12 lymph nodes and B ≥12 lymph nodes). Results: 5% of the patients had only local lymphadenectomy and in 14% a systematic lymphadenectomy was performed. 17% of the patients showed skip metastasis. Lymph node positivity was correlated to the number of removed lymph nodes (p = 0.003). The approximated median survival for UICC (Union internationale contre le cancer) stage I was 511, stage II 521 and stage III 290 days. Subgroup analysis of survival data showed in group A an approximated median survival at stage I of 495 days, at II 537 days and at III 451.5 days. Group B showed at stage I 675 days, at II 521 days and at III 221 days. There was no difference in complications and mortality. Conclusion: A too low sample size leads to understaging due to skip metastasis. Obligatory mediastinal lymph node sampling would decrease the risk of understaging due to skip metastasis and does not increase morbidity or complications. Lymph node sampling is not inferior concerning morbidity and survival in our patient collective. This study cannot recommend a minimum number of LN to be resected. The evaluated limit of 12 LN proves to be suitable as a guideline.

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Keywords

Lung Cancer Surgery, Lymph Node, Lymphadenectomy, Lymph Node Sampling, Systematic Lymphadenectomy, Nsclc, Non-Small-Cell Lung Cancer

1. Introduction

Non small cell lung cancer (NSCLC) is characterized as a highly aggressive and early metastasizing malignant disease [1]. Staging is a complex and critical event, as clinical staging describes the extent of the disease, predicts prognosis and is crucial for optimal treatment and outcome of the patients [2] [3]. Accuracy of clinical staging before surgery in the pre PET-CT (positron emission tomography-computed tomography) era has been reported being only 35% - 55% [4] [5]. PET-CT has improved the diagnostic accuracy in the staging of NSCLC [6] [7]. However, the accuracy of PET-CT is still too low to replace invasive lymph node staging [8] [9]. Furthermore, after surgical treatment the lymph node status of the patient is important as to whether adjuvant treatment modalities are mandatory.

The benefits of a radical lymphadenectomy remain controversial. Studies comparing the outcome of NSCLC patients after surgical treatment with lymph node sampling versus radical lymphadenectomy revealed contradictory results [10]. Retrospective studies found a benefit in survival for UICC stage I patients [11] [12] whereas other analyses showed no advantage for either procedure [13]-[15]. In contrast to this survival benefit, increased perioperative morbidity and mortality due to extended lymph node dissection are discussed. A different study design counting total number of extirpated lymph nodes found a correlation with improved overall survival and increased disease free interval [15]. Those results were interpreted with the "Will-Rogers-Phenomenon", increased number of removed lymph nodes resulting in more accurate staging of the patient [16] [17].

Due to the lack of meaningful randomized controlled studies, there is no international consensus. In the US the systematic lymphadenectomy is prevalent. In Japan an extended lymphadenectomy to cervical and contralateral mediastinal lymph nodes was supported. In Europe, especially in the United Kingdom and in Germany, lymph node sampling was propagated by the majority. Berardi *et al*. already postulated at the American Society of Clinical Oncology (ASCO) 2011 annual meeting an adequate lymph node clearance with a minimum of 10 in order to receive an adequate staging [18].

This analysis evaluates the outcome, morbidity and mortality of patients after pulmonary resection due to NSCLC based on the number and location of removed lymph nodes from the approach of the Will-Rogers-Phenomenon.

2. Material and Methods

From January 2006 through December 2010, 156 patients underwent surgery due to NSCLC in our department. 25 patients with carcinoma in situ, stage IV disease or neoadjuvant treatment were excluded from this analysis. The data of the remaining 131 patients was reviewed retrospectively from our records and analyzed in terms of surgery performed, number and level of removed lymph nodes (LN), pathological finding and stage, perioperative complications and mortality and survival data. Statistical analysis was performed using SPSS version 16.0 (SPSS Inc, Chicago, Illinois). Categorical variables were compared using X^2-Test and Fisher's Exact Test. All continuous variables were plotted on a histogram to determine the distribution of data points and select the appropriate statistical test to compare cohorts. Parametric continuous variables were expressed as mean (SD) and compared using an independent-samples t-test. Nonparametric continuous variables were expressed as median values with ranges and compared using the Mann-Whitney-U-Test. Correlation analysis was done using Spearman's rank correlation coefficient (Spearman's rho) for non-parametric measure of statistical dependence between two variables. Survival data were assessed by the method of Kaplan-Meier.

3. Results

The median age of the patients was 66 years (range 42 - 82) and 76% (n = 99) were male. Pathology report showed in 56% (n = 73) squamous cell carcinoma, in 42% (n = 55) adenocarcinoma and 2% (n = 3) other

NSCLC tumor entities. Surgical procedures performed were pneumonectomy 12% (n = 16), bilobectomy 7% (n = 9), lobectomy 72% (n = 94), wedge resection 5% (n = 7), sleeve resection 3% (n = 4) and segmental resection 1% (n = 1).

The performed lymphadenectomy was decided upon by the surgeon. In 5% (n = 6) of the patients a local lymphadenectomy was performed (LN taken: median 5.5, range 2 - 13), all other patients had at least one mediastinal LN removed (median 12, range 2 - 44). The pathological LN status was in 79 patients (60%) pN0, in 31 patients (24%) pN1, in 20 patients (15%) pN2 and one pN3. In 4 of the 79 pN0 patients (5%) only local lymphadenectomy without mediastinal LN sampling was performed, similar in 2 of the 31 pN1 patients (6%). In 9 of the 52 LN positive patients (17%) skip metastasis was found, distal LN were tumor infested whereas proximal LN were free of tumor. The analysis of Spearman's rank correlation coefficient for a connection between positive pathological LN status and number of removed LN showed that LN positivity correlates to the number of removed LN (rho = 0.254, p = 0.00343). A systematic lymphadenectomy was performed in 11% of the patients (n = 14) (median 13.5, range 8 - 22). In 131 patients a total of 1637 LN (median 12, range 2 - 44) were collected and evaluated.

4. Comparison <12 LN and ≥12 LN Lymphadenectomy

Patients were stratified according to the median number of removed LN in two comparable groups with 63 patients <12 LN (A) and 68 patients ≥12 LN (B). Median age of patients in A was 67 years, in B 66 years respectively. Groups were not different in gender distribution, tumor entity and patient ASA (American Society of Anesthesiologists) classification.

Group A contained more UICC (Union internationale contre le cancer) stage I patients (p = 0.009), group B contained more UICC stage II patients (p = 0.004) and the extent of pulmonary resection was different. 6 out of 7 (86%) wedge resections were located in A (p = 0.055) respectively 14 out of 16 (88%) pneumonectomies were located in B (p = 0.002). The other procedures were distributed equally.

In group A, 17 patients (27%) had only LN up to station 1 removed, in 4 patients (6%) only a local lymphadenectomy was performed, 5 patients (8%) were lymph node positive (N+). In group B 10 patients (15%) had surgery up to station 1 lymph nodes, 2 patients (3%) only local, 6 patients (9%) were N+. In group A, 15 (24%) patients were N+, in B 36 (53%) respectively (p = 0.0007). In group A the pathological lymph node status was in 48 patients (76%) pN0, in 8 patients (13%) pN1 and in 7 patients (11%) pN2. Group B had 31 patients (46%) with pN0, 23 (34%) pN1, 13 (19%) pN2 and one pN3. Group A presented more pN0 patients (p = 0.0003), group B presented more pN1 patients (p = 0.019), pN2 and pN3 patients were equally distributed (**Table 1**).

Analysis of the postoperative period showed that the in-patient care duration of group A in median was 15 days (range 8 - 52) of group B 16 days (range 9 - 36): In both groups the ICU time was in median 2 days. No difference was presented between the groups. Complications and morbidity were equally distributed. Postoperative pneumothorax, pleural effusion and pneumonia presented a total of 10 occasions in group A, 13, 16 and 4 occasions in group B respectively. Blood transfusion was necessary in 10 patients in A and 13 patients in B. Pulmonary fistula was evident, 5 times in group A and 9 times in group B. All 3 re-intubations and all 3 re-operations presented in group A (**Table 2**).

Subgroup analysis of survival data showed patients of group A to have an approximated median survival at stage I of 495 days, at stage II of 537 days and at stage III of 451.5 days. Patients of group B showed at stage I 675 days, at stage II 521 days and at stage III 221 days. The pN0 patients of group A had an approximated median survival of 527 days, group B 5285 days, pN1 2785 days, pN1 373 days, pN2 4515 days and 216 days respectively. There was no statistical evaluation possible due to small number of patients.

The duration of in-patient care was in mean 17.5 ± 7.2 days (range 8 - 52), 3.3 ± 3.8 days were spent on the ICU. In the perioperative period 23 patients received blood transfusions, on 26 occasions they presented with pleural effusion, 23 with residual pneumothorax, 14 cases of pneumonia, 14 fistula, on 3 occasions the patient had to be re-intubated due to respiratory insufficiency and on 3 occasions a re-operation was necessary. The perioperative in-patient care mortality was zero, in the follow up period (8 to 68 month) 34 patients (26%) died. A median survival could not be calculated, due to lack of events for all patients and for the subgroups UICC stage I and II. The approximated median survival in total for all patients was 414 days (range 55 - 1437). For UICC stage I patients 511, for stage II 521 and stage III 290 days. There was no difference in survival between stage I and stage II (p = 0.4408), survival of stage III patients showed a decrease in comparison to stage I and II (p <

Table 1. Patient data were stratified according to the median number of removed LN in two comparable groups with <12 LN (A) and ≥12 LN (B). Differences were labeled with "*".

		Group A	Group B	Total	p value
n		63	68	131	-
Age (median)		67	66	66	-
Gender	Male	43	56	99	0.069
	Female	20	12	32	
Histology	Adenocarcinoma	31	24	55	0.115
	Squamous Cell Carcinoma	29	44	73	
	Other	3	0	3	0.108
ASA	I	1	1	2	1
	II	9	8	17	0.796
	III	51	57	108	0.819
	IV	2	2	4	1
Surgery	Wedge Resection	6	1	7	0.055
	Segmental Resection	1	0	1	0.481
	Sleeve Resection	3	1	4	0.351
	Lobectomy	48	46	94	0.333
	Bilobectomy	4	5	9	1
	Pneumonectomy	2	14	16	0.002*
UICC Stage	I	38	25	63	0.009*
	II	8	24	32	0.004*
	III	17	19	36	1
Lymphadenectomy	Local	4	2	6	0.427
	Systematic	5	9	14	0.403
	1 Station	17	10	27	0.089
	2 Stations	29	20	49	0.070
	3 Stations	13	22	35	0.167
	4 Stations	4	13	27	0.0376*
	5 Stations	0	2	2	0.497
	pN0	48	31	79	0.0003*
	pN1	8	23	31	0.019*
	pN2	7	13	20	0.23
	pN3	0	1	1	1

Table 2. Incidence of morbidity and complications. There was no difference between the groups.

	Group A	Group B	Total	p value
Pneumothorax	10	13	23	0.162
Pleural Effusion	10	16	26	0.097
Fistula	5	9	14	0.142
Pneumonia	10	4	14	0.058
Blood Transfusion	10	13	23	0.162
Re-operation	3	0	3	0.108
Re-intubation	3	0	3	0.108

0.05) (**Figure 1**). Dividing the patient collective in subgroups concerning the pathological nodal status pN0 patients had overall survival in median 529 days, pN1 patients 293.5 and pN2 340 days. pN0 groups overall survival was longer than pN1 ($p = 0.0351$) and pN2 ($p < 0.0001$). There was no difference between pN2 and pN3 patients (**Figure 2**).
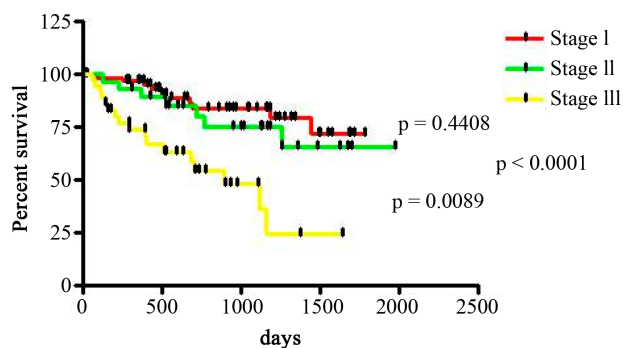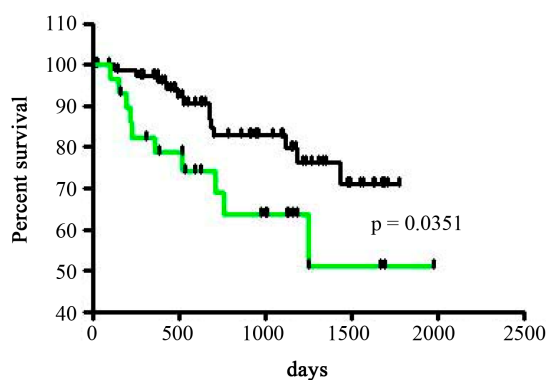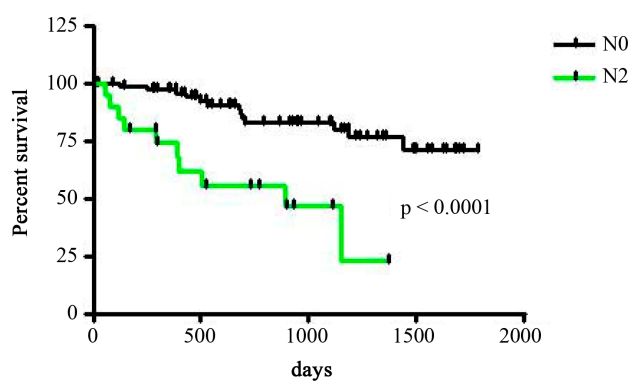

Figure 1. Median survival for UICC stage I patients was 511 days, for stage II 521 days and stage III 290 days respectively. There was no difference between stage I and stage II ($p = 0.4408$), survival of stage III patients showed a decrease in comparison to stage I and II ($p < 0.0001$ and $p = 0.0089$).

(a)

(b)

Figure 2. Dividing the patient collective in subgroups in terms of pathological lymph node status. pN0 patients had an overall survival in median 529 days, pN1 patients 293.5 and pN2 340 days. pN0 groups overall survival was longer than pN1 ($p = 0.0351$) and pN2 ($p < 0.0001$). There was no difference between pN2 and pN3 patients.

5. Discussion

Finding the answer to the important question to which extend lymphadenectomy in NSCLC patients has to be performed, the data of 131 patients consecutively operated on NSCLC was analyzed. In our study patient data showed normal distribution of gender, tumor entity and ASA classification. Also the vast majority of single lobectomy as performed surgical procedure indicates a very homogeneous cohort. The perioperative morbidity and mortality was lower compared to the literature. In similar patient cohorts perioperative mortality is reported being 1.3% - 5.6% [19] [20]. The low number of systematic lymphadenectomies (n = 14) may be responsible for the moderate perioperative morbidity and mortality. A statement concerning increased morbidity due to extended surgical procedure is very limited but also low in comparison [20].

All 1637 lymph nodes were allocated to their origin. In 4 out of 79 pN0 patients (5%) and in 2 out of 31 pN1 patients (6%) only a local lymphadenectomy was performed. A closer look at the origin sites of the tumor infested lymph nodes showed in 9 patients skip metastasis. About 17% of the tumors in our patient cohort have not continuously metastasized. Mediastinal skip lymphatic metastasis is reported in about 25% of the patients depending on the localization of the primary tumor and is important for the extent of the mediastinal lymph node dissection [21] [22]. Therefore, for these 6 patients we have to assume a certain rate of incorrect staging due to a lack of removed lymph nodes.

In addition, the present survival data suggests an inaccuracy in staging due to too low number of resected lymph nodes. This study showed no difference in overall survival between UICC stage I and stage II (511 vs. 521 days) patients. 5-year survival for stage I patients ranges between 60% - 80%, at stage II between 35% - 55% [23]-[25]. The difference to stage III (290 days) was as expected. Analysis of subgroups dividing the patient collective comparing pN0 and pN1 patients with and without mediastinal lymph node sampling presented unfortunately no difference in survival due to a very small number of events.

The patient cohort was divided according to the median number of removed LN in two comparable groups, group A < 12 LN taken and group B ≥ 12 LN removed. The number of 12 LN as a benchmark also seemed suitable according to the postulation at ASCO 2011 annual meeting that an adequate lymph node clearance requires a minimum of 10 LN in order to receive an adequate staging [18]. Comparing lymph node status showed increased N+ patients in group B. Especially the pN1 subgroup presented an increase, indicating to early lymphadenopathy. Spearman rho correlation showed a connection between positive pathological LN status and number of removed lymph nodes. Higher number of removed lymph nodes increases the probability to find diseased lymph nodes. Those results correlate with the interpretation as the "Will-Rogers-Phenomenon", increased number of removed lymph nodes resulting in more accurate staging [16] [17].

Subgroup analysis of survival data showed UICC stage I patients of group A had an approximated median survival of 495 days, patients of group B of 675 days. Survival analysis on base of pathological LN status survival curves were as expected (**Figure 2**). This may be a result of inaccurate staging due to a small number of lymph nodes removed for evaluation. Unfortunately, this was not statistically different due to a small number of events.

When comparing the groups regarding morbidity and complications, no difference was found. Group B was also containing mainly patients treated with lymph node sampling, only 14 patients in total had a radical lymphadenectomy. Statements to the comparable low morbidity and complications rate are very limited, but there was no difference in morbidity, complications and mortality in patients with increased lymph node sample size.

6. Conclusion

NSCLC is early metastasizing to lymph nodes, frequently also skipping the first lymph node station. Taking a predetermined number of lymph nodes would decrease the risk of understaging. Obligatory mediastinale lymph node sampling would decrease the risk of understaging due to skip metastasis and does not increase morbidity or complication rates. A radical lymphadenectomy would eliminate the problem of inaccurate staging, eventually in exchange to increased complication rates. This study shows limitations in finding an answer to a possible increased occurrence of perioperative morbidity and mortality due to radical lymphadenectomy. Furthermore, this study cannot recommend a minimum number of LN to be resected. The evaluated limit of 12 LN proves to be suitable as a guideline.

Conflict of Interest

None declared.

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