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Pattern of lung cancer recurrence after lung resection with bilateral lymph node dissection

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Introduction. Several studies have shown the survival benefit of bilateral lymph node dissection as part of curative-intent surgery for lung cancer. The pilot BML-1 study was the first randomized trial comparing bilateral with the standard (unilateral) systematic lymph node dissection.

Material and methods. Patients with non-small cell lung cancer stage I–IIIA, who underwent anatomical lung resection were randomised 1:1 to receive a bilateral or standard, unilateral lymphadenectomy. Data regarding the type of recurrence and time to recurrence were analysed.

Results. The rate of locoregional recurrence in the bilateral lymphadenectomy and the standard lymphadenectomy were 2.7% and 5.3% and those of distant relapse were 24.3% and 23.7% respectively ($p = 0.99$). The follow-up time was 87 months. The mean time from surgery to recurrence was 35.0 months and 22.8 months, respectively ($p = 0.83$).

Conclusions. There is no firm evidence that bilateral mediastinal lymphadenectomy (BML) is associated with a recurrence pattern that is different than that following the systematic lymph node dissection (SLND). We found a trend towards lower incidence of local recurrence and longer time to recurrence in the BML group, but the differences were statistically not significant. A large randomised study is warranted to further analyse this matter.

Keywords: lung cancer, mediastinum, lymphadenectomy, recurrence

Introduction

The rationale for bilateral lymph node dissection in patients with non-small cell lung cancer is the potential advantage of removal of contralateral mediastinal lymphatics harbouring metastatic deposits. Although it is not considered a standard, several studies have shown survival benefit [1–5]. The pilot BML-1 study was the first randomized trial comparing bilateral mediastinal lymphadenectomy (BML) with the standard systematic lymph node dissection (SLND), and its results regarding the effect of BML on survival were published elsewhere [1]. However, the effect of BML on the pattern of recurrence was not studied.

Material and methods

Clinical questions

Is the BML associated with a different pattern of cancer recurrence as compared with SLND?

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Study design

Follow-up of patients participating in a randomized, clinical trial. Data regarding cancer recurrence were derived from the BML-1 study [1].

Setting

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Patients

Following inclusion criteria were used:

- patients age 18–90, confirmed or suspected non-small-cell lung cancer (NSCLC) stage I–IIIA; accepted stage IIIA included only single-station, non-bulky N2 disease,
- preoperative staging included chest radiography, computed tomography, positron-emission tomography-computed tomography, abdominal ultrasonography, bronchoscopy, endobronchial ultrasonography, and endoscopic ultrasonography,
- general fitness enabling appropriate lung resection, assessed according to the European Respiratory Society and the European Society of Thoracic Surgery Guidelines [6].

The exclusion criteria were as follows:

- history of other malignancy, with the exception of non-melanoma skin cancer,
- induction chemo- or chemoradiotherapy,
- pathological confirmation of tumour other than NSCLC,
- ground-glass opacity lesions,
- lack of informed consent [1].

Intervention

Randomization was performed by the study coordinator (JK) using a computer-based random-digit generator (LUCASC, version 1.0, Morawski, Poland), with a 1:1 allocation ratio. The technique of lymph node dissection was described in detail elsewhere [1].

Data regarding cancer recurrence were obtained from the hospital database. In patients lost to follow-up, survival data form the national vital records (PESEL database) was used.

Endpoints

The primary endpoint was the recurrence type categorized as: no recurrence, locoregional and distant. The secondary endpoint was the time to recurrence.

Statistical analysis

Analyses were performed using Stata 13.1, StataCorp LP, TX, USA. At first the groups were compared using baseline characteristics represented by a proportion (percentile) for categorical and a mean with standard deviation (SD) or a median with inter-quartile range (IQR) for continuous variables. To reveal significant differences between groups, a chi-squared test (or the Fisher exact test if the chi-squared test assumptions were not met) were run for categorical variables. The Shapiro-Wilk test was used to verify whether the assumption of normal distribution was met. Next the t-test equal or unequal variance (depending on whether it was or was not confirmed by the F-test) was used if both groups met the assumption of normal distribution, otherwise the Mann-Whitney test was run. To answer a question on whether the type of recurrence was associated with the type of treatment, the multinomial logistic regression was used. Finally, as the sample size was small, to increase the precision of the assessment — especially for the impact of treatment on the risk of local recurrence — binomial logistic regression with bootstrap analysis was implemented. It was decided to use bootstrap as it leads to an increase in the precision of estimates, which was relatively low due to the sample size. The bootstrap model presents finally the point estimate [odds ratio (OR)] with normal-based 95% confidence interval (CI) for the OR, and the p value. There were some models with a different number of bootstrap repetitions run. It started with 10.000 and ended with 1.000.000 repetitions to observe the stability of estimates provided. Results with the p-value less than 0.05 were considered statistically significant.

Results

The BML-1 study enrolled 102 patients. 13 patients met the exclusion criteria, so survival analysis data of 89 patients were available: 40 in the BML group and 49 in the SLND group [1]. Data regarding the type of recurrence in 14 patients were not available, so the recurrence pattern was analysed in 37 patients in the BML group and 38 in the SLND group.

Both groups were comparable regarding age, sex, location of the tumour, histology, clinical stage, type and side of resection and number of lymph nodes removed (Tab. I).

Survival analysis in the BML-1 study was reported elsewhere [1].

The 5-year recurrence-free survival was 64.9% in the BML group and 60.5% in the SLND group. The rate of locoregional recurrence in the BML and the SLND group were 2.7% and 5.3% and those of distant relapse were 24.3% and 23.7% respectively (Tab. II). Multinomial logistic regression did not show significant difference between the BML and the SLND group regarding the recurrence pattern ($p = 0.99$) (Tab. III). As the OR for observing local/regional recurrence in the BML was considerably lower, the binomial logistic regression with bootstrap analysis was additionally implemented to increase the precision of the estimate, however, no significant effect has been observed (Tab. IV). The follow-up time was 87 months. The mean time from surgery to recurrence was 35.0 months in the BML group *vs.* 22.8 months in the SLND group ($p = 0.83$).

Discussion

As the BML study was the first randomised trial to compare BML with the standard systematic lymph node dissection, there is no literature data that could be used for comparison with our results. The published evidence pertains to recurrence in patients who underwent standard treatment, i.e., SLND.

Table I. Baseline characteristics of the study groups

Patients' characteristics	BML (n = 37)	SLND (n = 38)	p value
Age			0.678
Mean (SD)	61.5 (6.9)	62.1 (6.0)	
Median (IQR)	61.0 (6.0)	62.5 (6.0)	
Sex (M) — n (%)	26 (70.3)	27 (71.0)	0.941
Tumour location — n (%)			
RUL	10 (27.0)	8 (21.1)	
RML	0 (0.0)	1 (2.6)	
RLL	10 (27.0)	9 (23.7)	
CUL	5 (13.5)	9 (23.7)	
LUC	2 (5.4)	5 (13.2)	
LLL	8 (21.6)	5 (13.2)	
LC	2 (5.4)	1 (2.6)	
Histology — n (%)			
SCC	19 (51.4)	25 (65.8)	
ADC	16 (43.2)	9 (23.7)	
LCC	0 (0.0)	1 (2.6)	
ASC	2 (5.4)	2 (5.3)	
OTH	0 (0.0)	1 (2.6)	
cTNM — n (%)			
			0.925
T1aN0M0	4 (10.8)	3 (7.9)	
T1aN1M0	1 (2.7)	0 (0.0)	
T1bN0M0	3 (8.1)	4 (10.5)	
T1bN1M0	2 (5.4)	0 (0.0)	
T1bN2M0	1 (2.7)	2 (5.3)	
T2aN0M0	12 (32.4)	10 (26.3)	
T2aN1M0	1 (2.7)	1 (2.6)	
T2aN2M0	2 (5.4)	1 (2.6)	
T2bN0M0	4 (10.8)	8 (21.1)	
T2bN1M0	2 (5.4)	2 (5.3)	
T2bN2M0	2 (5.4)	2 (5.3)	
T2bN3M0	1 (2.7)	0 (0.0)	
T3N0M0	1 (2.7)	2 (5.3)	
T3N2M0	1 (2.7)	3 (7.9)	
Type of resection — n (%)			
			0.935
LBL	3 (8.1)	2 (5.3)	
UBL	1 (2.7)	1 (2.6)	
LLL	6 (16.2)	4 (10.5)	
RLL	6 (16.2)	5 (13.2)	
LUL	6 (16.2)	11 (28.9)	
RUL	9 (24.3)	7 (18.4)	
RML	0 (0.0)	1 (2.6)	
LPN	5 (13.5)	6 (15.8)	
RPN	1 (2.7)	1 (2.6)	
Extent of resection — n (%)			
Bilobectomy	4 (10.8)	3 (7.9)	
Lobectomy	27 (73.0)	28 (73.7)	
Pneumonectomy	6 (16.2)	7 (18.4)	
Side — n (%)			
Left	17 (45.9)	21 (55.3)	
Right	20 (54.1)	17 (44.7)	
Upper/lower lobes — n (%)			
			0.440
Upper*	16 (51.6)	20 (64.5)	
Lower	15 (48.4)	11 (35.5)	
N2 sum			< 0.001
Mean (SD)	24.9 (9.2)	14.7 (8.7)	
Median (IQR)	24.0 (12.0)	14.0 (9.0)	
N1 sum			0.865
Mean (SD)	10.1 (8.0)	8.7 (4.7)	
Median (IQR)	7.0 (7.0)	8.0 (7.0)	

*Right middle lobe combined with right upper lobe; ADC — adenocarcinoma; ASC — adenosquamous carcinoma; BML — bilateral mediastinal lymphadenectomy; CUL — culmen/culmenectomy; IQR — inter-quartile range; LBL — lower bilobectomy; LCC — large cell carcinoma; LC — left central; LIN: lingula/lingulectomy; LLL — left lower lobe/lobectomy; LPN — left pneumonectomy; LUC — left upper central; LUL — left upper lobe/lobectomy; M — male; OTH — other; RLL — right lower lobe/lobectomy; RML — right middle lobe/lobectomy; RPN — right pneumonectomy; RUL — right upper lobe/lobectomy; SCC — squamous cell carcinoma; SD — standard deviation; SLND — systematic lymph node dissection; UBL — upper bilobectomy

Table II. Pattern of recurrence

Pattern of recurrence n (%)	BML	SLND	
No recurrence	24 (64.9)	23 (60.5)	0.999
Local/regional	1 (2.7)	2 (5.3)	
Distant	9 (24.3)	9 (23.7)	

BML — bilateral mediastinal lymphadenectomy; SLND — systematic lymph node dissection

Yamaouchi et al. [7] reported recurrence in 501 patients out of 1,374 operated on for lung cancer. Among them, 25% were local, 62.3% were distant and 11.2% of patients developed both local and distant recurrence at the same time. Similarly, in a large study published recently, the most common type of relapse was distant (56%), however this cohort included both small-cell and non-small cell lung cancer [8]. Jeong et al. [9] analysed recurrence patterns in 949 patients with early-stage lung cancer. As expected, the relapse rate was low (20.4%), but the distant recurrence rate was almost twice as high as the locoregional one (13.1% *vs.* 7.3%). These data are in line with our results, showing distant metastases to be the most common type of relapse. In our cohort, the rate of distant relapse was similar in the BML and the SLND group (24.3% and 23.7% respectively). On the other hand, the rate of locoregional

Table III. The risk estimate (odds ratio) of different recurrence types bilateral mediastinal lymphadenectomy (BML) *vs.* systematic lymph node dissection (SLND) groups (multinomial univariable logistic regression)

Pattern of recurrence	Odds ratio	95% CI		p value
		LL	UP	
No recurrence	1 (ref.)			
Local/regional	0.48	0.04	5.65	0.559
Distant	0.96	0.32	2.84	0.939

CI — confidence interval; LL — lower limit for 95% CI; UP — upper limit for 95% CI

Table IV. Odds ratios (ORs) for observing local/regional recurrence in the bilateral mediastinal lymphadenectomy (BML) as compared to the systematic lymph node dissection (SLND) group in the bootstrap analyses (binomial univariable logistic regression)

Odds ratio	Normal based 95% CI		p value	No of bootstrap repetitions
	LL	UP		
0.48	0.11	2.12	0.333	10 000
0.48	0.11	2.13	0.334	100 000
0.48	0.11	2.13	0.334	300 000
0.48	0.11	2.13	0.333	1 000 000

CI — confidence interval; LL — lower limit for 95% CI; UP — upper limit for 95% CI

recurrence was two times lower in the BML group (2.7% *vs.* 5.3%), however the difference was statistically not significant. The lack of significance is probably due to the small number of patients available for analysis. The BML-1 trial was a pilot study, with one of its main weaknesses being the limited number of patients. It is also probably the reason for the lack of significance of difference in the time to relapse (35.0 months in the BML group *vs.* 22.8 months in the SLND group).

Conclusions

There is no firm evidence that BML is associated with a recurrence pattern different than the SLND. We found a trend towards lower incidence of local recurrence and longer time to recurrence in the BML group, but the differences were statistically not significant. A large randomised study is warranted to further analyse this matter.

Article information and declarations

Data availability statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics statement

The protocol of the BML-1 study has been approved by the Bioethical Committee of the Jagiellonian University (K/ /ZDS/002337.

Authors contributions

Jakub Szadurski — project development, data collection, data analysis, manuscript editing.
Łukasz Trybalski — project development, data collection, data analysis, manuscript writing.
Jarosław Kużdżał — project development, data collection, data analysis, manuscript writing.
Aleksander Galas — data analysis, manuscript writing.
Janusz Warmus — data collection, manuscript writing.
Zbigniew Grochowski — data collection, manuscript writing.
Mirosław Janczura — data collection, manuscript writing.
Katarzyna Żanowska — data collection, manuscript writing.
Piotr Kocoń — project development, data analysis, manuscript writing.

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Conflicts of interest

None declared.

Supplementary material

None.

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