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Visceral pleural infiltration as a negative prognostic factor in lung metastasis☆

József Furák[a,*], Imre Trojána[a], Tamás Szöke[a], László Tiszlavicz[b], József Eller[c], György Lázár[a]

[a]*Department of Surgery, University of Szeged, Pécsi u. 4. H-6720, Szeged, Hungary*
[b]*Department of Pathology, University of Szeged, Állomás u. 2. H-6725, Szeged, Hungary*
[c]*Department of Medical Informatics, University of Szeged, Korányi fasor 9. H-6720, Szeged, Hungary*

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Abstract

The prognostic value of visceral pleural infiltration in lung metastasis was analysed. Fifty-two patients (32 males and 20 females) were operated on for lung metastases. The locations of the primary tumours were as follows: 19 colon, 10 kidneys, 8 melanomas, 3 breast, 3 bladder, 2 uterus, 2 osteosarcomas, 1 testis, and 1 parotid, 1 haemangiopericytoma, 1 thyroid gland and 1 larynx. Explorative thoracotomies and incomplete resections were excluded from the study. Visceral pleural infiltration was present in 20 of the 52 cases. There was a significant correlation between the occurrence of pleural infiltration and multiple lesions ($P=0.019$). The overall five-year survival rate was 33.6%. In a subgroup of 38 patients with N0 and single metastases, the five-year survival rate was 73% and 12% in the cases without and with visceral pleural infiltration, respectively ($P=0.003$). Multivariate analysis of pleural infiltration, lymph node metastasis, multiple lesions and DFI revealed that only pleural infiltration ($P=0.003$) had a significant impact on survival. In one-third of the pulmonary metastases, visceral pleural infiltration appeared. There was a significant correlation between the occurrence of visceral pleural infiltration and multiple lesions. Visceral pleural infiltration in lung metastasis is a negative prognostic factor, and in these cases, survival was significantly reduced.

Keywords: Pulmonary metastasis; Visceral pleural infiltration; Prognostic factor

1. Introduction

Pulmonary metastasectomy is a standard procedure in selected cases to remove secondary malignant lesions from the lung parenchyma, and many studies have confirmed the indications, the technical principles, and the results of this surgical procedure [1–5]. Recently, emerging experiences, survival rates and prognostic factors after metastasectomies were evaluated. From an analysis of 5206 lung metastasectomies from 18 thoracic surgery departments in Europe, the United States and Canada, The International Registry of Lung Metastases has confirmed that the resectability, disease-free interval (DFI), and the number of metastases can predict the rate of survival after metastasectomy [1]. Furthermore, in cases of metastases from colorectal carcinoma, the unilateral or bilateral locations of metastases, the Dukes' status of the primary tumour, the carcinoembryonic antigen (CEA) level, and hilar or mediastinal lymph node involvement can be used as postoperative prognostic factors [2–5].

In primary lung cancer cases, the prognosis can be predicted from tumour (T), lymph node involvement (N), and metastasis (M) (TNM) data [6], but in pulmonary metastasis cases only the N and the M (multiple lesions) status were relevant prognostic factors.

In primary lung cancer staging, pleural infiltration upgrades the T status from T1 to T2, and leads to a poorer survival prognosis. The literature contains very little information on the influence of the loco-pathological status of the metastatic tumour upon survival, as has been detailed in primary lung cancer cases. In this retrospective study, we analysed the prognostic value of visceral pleural infiltration in lung metastasis and survival.

2. Material and methods

Fifty-two patients with pulmonary metastases underwent complete pulmonary metastasectomies in our thoracic department. There were 32 males and 20 females, and the mean age was 60.5 (20–86) years. Cases with explorative thoracotmies and incomplete resections were excluded from this study.

The four synchronous lesions were defined as those identified within three months of the primary tumour resection. The 48 metachronous lesions were identified as metastatic lesions that presented more than three months after the resection of the original malignant tumour [7].

The criteria for pulmonary metastasectomy were as follows: (1) the patient had to be able to tolerate the

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*Corresponding author. Tel.: +36-30-9955815; fax: +36-62-545 701.
E-mail address: jfurak@hotmail.com (J. Furák).

metastasectomy; (2) the primary tumour was controlled; (3) there were no other extrapulmonary metastasis, or, if this was present, it could be controlled by surgery or some other treatment modality; (4) the pulmonary metastasis was considered to be completely resectable; (5) no other effective treatment mode was available except resection [8].

The preoperative evaluation in every cases included a chest X-ray, chest computed tomography (CT), bone scintigraphy, brain CT, bronchoscopy and spirometry for lung capacity. The site of the primary tumour was evaluated, e.g. via abdominal CT, mammography and colonoscopy.

The surgical approach was a posterolateral thoracotomy or sequential posterolateral thoracotomy with a 4–6-week interval. One VATS metastasectomy was performed on an 86-year-old patient. Parenchyma-sparing resections were carried out with complete mediastinal block dissections.

Twenty-four of the 52 patients received adjuvant therapy after the metastasectomies (6 irradiations and 18 chemotherapies).

All histological examinations were made by the same pathologist. Visceral pleural infiltration was diagnosed if the intraparenchymal metastasis invaded the visceral pleura.

The types of the primary tumours and the resections are shown in Table 1.

For statistical evaluation, the data were analysed with SPSS (Statistical Package for Social Science, SPSS Inc, Chicago, IL) software for Windows. With the Kaplan–Meier method, the survival was calculated from the time of the first metastasectomy to the last follow-up or the time of death. Significance was calculated with the log-rank test.

3. Results

There was no 30-day mortality. The mean DFI was 56.1 (1–377) months.

Table 1
Types of primary tumours and pulmonary resections

	No. of cases	Percentage
Patients	52	100
Primary tumour		
Colorectal	19	37
Renal	10	19
Melanoma	8	15
Breast	3	6
Bladder	3	6
Uterine	2	4
Osteosarcoma	2	4
Testicular	1	2
Parotid	1	2
Haemangiopericytoma	1	2
Thyroid gland	1	2
Laryngeal	1	2
Resection		
Total number of resections	52	100
Wedge resection	28	54
Lobectomy	22	42
Pneumonectomy	2	4
Unilateral resection	47	90
Bilateral resection	5	10

Twenty of the 52 cases involved visceral pleural infiltration (PL+) as intraparenchymal metastasis, and there were 32 non-pleural infiltration (PL0) cases. The pathology of the mestastases is detailed in Table 2.

There was no significant correlation between pleural infiltration and lymph node metastasis (0.235), or between pleural infiltration and DFI ($>$ or $<$ 36 months) ($P=0.575$), but the correlation between pleural infiltration and multiple metastases was significant ($P=0.019$).

There was no significant correlation between pleural infiltration and the cases with adjuvant therapy ($P=0.395$) (Table 3).

The overall five-year survival rate was 33.6%. Survival data are presented in Table 4.

To analyse the impact of pleural infiltration on the survival, a very homogeneous subgroup was made, which may be pathologically similar to stage I lung cancer (N0 status, complete resection, and single metastasis). There were 38 patients in this subgroup; the five-year survival was 73% and 12% ($P=0.003$) in the 27 PL0 and 11 PL+ cases, respectively. The survival distribution in this subgroup can be seen in Fig. 1.

The univariate analyses revealed that pleural infiltration ($P=0.001$), lymph node metastasis ($P=0.007$), and multiple metastases ($P=0.009$) had a significant impact on survival; the influence was not significant for DFI ($P=0.346$) and adjuvant therapy ($P=0.791$). Survival data are presented in Table 4. Multivariate analysis of pleural infiltration, lymph node metastasis, DFI, adjuvant therapy and multiple lesions indicated that only pleural infiltration ($P=0.003$) was a significant prognostic factor for survival,

Table 2
Pathology of metastases in 52 patients

	No. of cases	Percentage
Non-pleural infiltration (PL0)	32/52	62
Pleural infiltration (PL+)	20/52	38
Colorectal	9/19	
Renal	4/10	
Melanoma	2/8	
Breast	1/3	
Bladder	1/3	
Testicular	1/1	
Haemangiopericytoma	1/1	
Laryngeal	1/1	

PL0: non-pleural infiltration. PL+: pleural infiltration.

Table 3
Correlation between visceral pleural infiltration and lymph node involvement and adjuvant therapy and disease-free interval and number of metastases

	PL0	PL+	*P*-value
N0	29	15	
N+	3	5	0.235
DFI $<$ 36 months	14	7	
DFI $>$ 36 months	18	13	0.575
Single metastasis	30	13	
Multiple metastases	2	7	0.019
No adjuvant therapy	19	9	
Adjuvant therapy	13	11	0.395

N0: lymph nodes without metastasis; N+: Lymph nodes with metastasis; PL0: non-pleural infiltration; PL+: pleural infiltration; DFI: disease-free interval.

Table 4
Survival data (univariate analysis)

	Patients (No.)	Five-year survival (%)	*P*-value
Overall survival	52	33.6	
Pleural infiltration (PL+)	20	6	
Non-pleural infiltration (PL0)	32	59	0.001
Lymph node metastasis (N+)	8	0	
Lymph node-negative (N0)	44	41	0.007
Multiple metastases	9	0	
Single metastasis	43	45	0.009
DFI>36 months	31	38	
DFI<36 months	21	25	0.346
Adjuvant therapy	24	30	
No adjuvant therapy	28	38	0.791

N0: lymph nodes without metastasis; N+: lymph nodes with metastasis; PL0: non-pleural infiltration; PL+: pleural infiltration; DFI: disease-free interval.

and lymph node metastasis ($P=0.055$), DFI ($P=0.058$), adjuvant therapy ($P=0.661$) and multiple metastases ($P=0.665$) had no significant impact on survival. Data in multivariate analysis are presented in Table 5.

4. Discussion

Pulmonary metastasectomy should be a parenchyma-sparing resection of secondary malignant lesions, and this principle is supported by the data from three multicentral studies [1, 9, 10]. In our practice, the rate of sublobar resection was 54%, lobectomy was 42% and pneumonectomy was 4%, which are very similar to the corresponding data from the above-mentioned studies: 75%-62%-73%, 21%-35%-24%, 2.5%-1.8%-1.3%, respectively. Our approach is a posterolateral thoracotomy; in bilateral cases we prefer sequential, posterolateral thoracotomies, as recommended by Saito et al. [9].

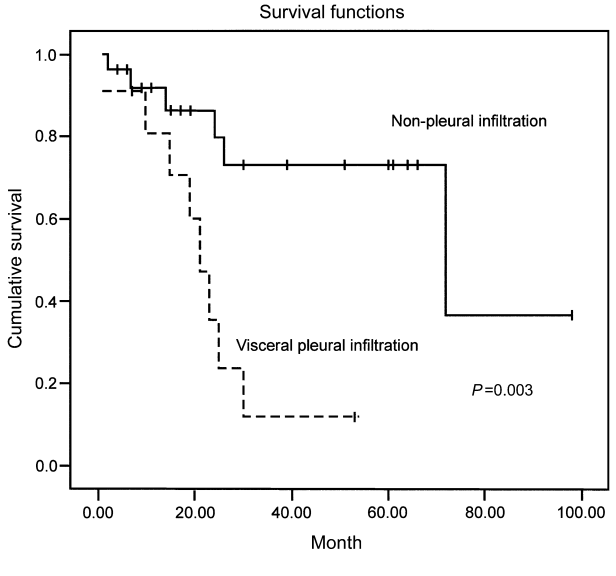

Fig. 1. Survival in the N0-single metastasis subgroup.

Table 5
Multivariate analysis (Cox Regression)

	Wald sig.	Odds ratio	95.0% CI	
			Lower	Upper
Pleural infiltration	0.003	4.262	1.617	11.233
Lymph node metastasis	0.055	2.830	0.977	8.197
Multiple metastases	0.665	1.263	0.184	1.028
DFI	0.058	0.435	0.439	3.633
Adjuvant therapy	0.661	0.830	0.362	1.907

DFI: disease-free interval; Sig.: significance; CI: Confidence interval.

The stage and prognosis of a primary tumour can be given in terms of the TNM system, and this is well detailed in lung cancer cases [6]. However, in cases with resectable pulmonary metastases, the pathological structure of the secondary pulmonary tumour has not been widely detailed. Few studies have been published on visceral pleural infiltration in pulmonary metastasis cases. In the study by Shiono et al. [11], the rate of pleural infiltration by the pulmonary metastases from colorectal carcinoma was 7%. There was no local recurrence among the pleural infiltration cases, but the survival was not analysed in that study. In our series, the rate of visceral pleural infiltration was 38%, and 47% (9/19) among colorectal metastases. Mori et al., presented a case-report with two osteosarcoma metastases with parietal pleural migration [12].

Our study did not reveal a significant correlation between visceral pleural infiltration of the metastasis and lymph node metastasis, or between visceral pleural infiltration and DFI, but a significant correlation was demonstrated between visceral pleural infiltration and multiple metastases ($P=0.019$). By univariate analysis, multiple metastases had a significant impact on survival compared to solitary metastasis (0% vs. 45%) ($P=0.009$), but the multivariate analysis did not indicate a significant impact of multiple lesions on survival. In the breast cancer metastasis study by Friedel et al., on behalf of the International Registry of Lung Metastases, no significant difference in the five-year survival rate was found between solitary metastases (44%) and multiple metastases (25%) [10], whereas Hofmann et al., found a significant difference in five-year survival between single (54.7%) and multiple metastases (29.8%) in renal cell carcinoma [13]. Okumura et al., reported a significant difference in five-year survival between the

solitary (52.5%) and multiple (25.5%) metastases in colorectal cases [2], but Sakamoto et al., did not confirm this (51% vs. 47%) [14].

The incidence of lymph node metastasis in our series was 15.4%. It was 15% in the investigation of colorectal cases by Okumura et al. [2], and 5% in the Pastorino and the International Registry of Lung Metastases study [1]. In our work, the five-year survival rate in lymph node metastasis cases (N+) was 0%, and in cases without lymph node metastasis (N0) was 41% ($P=0.007$). Only the univariate analysis indicated that lymph node involvement had a significant impact on the survival, but by multivariate analysis, the lymph node metastasis was not a significant prognostic factor for survival ($P=0.055$). This finding is similar to that in the study by Ercan et al., who recommended complete mediastinal lymph node dissection, which was a standard procedure in our practice too [15].

The five-year overall survival rate in our patients was 33.6%, which is similar to the 32.4% reported in colorectal [4] and 38% in breast cancer [10] metastasectomies, 30% in colon tumours with hepatic and pulmonary metastasectases [7].

In primary lung cancer, visceral pleural infiltration is associated with an upgrade of the tumour from T1 to T2, and the survival is reduced from 67% in pathologic stage I/A to 57% in pathologic stage I/B [6]. Our study with completete metastasectomies has revealed the same tendency. The five-year survival rate in a homogeneous subgroup of patients with N0 and single metastasis, pathologically very similar to stage I lung cancer cases, was 73% and 12% in non-pleural infiltration and in visceral pleural infiltration cases, respectively ($P=0.003$).

We can conclude that in one-third of the pulmonary metastases, visceral pleural infiltration could be found. The visceral pleural infiltration from pulmonary metastasis, significantly reduces the survival rate in patients who have undergone metastasectomy. Multivariate analysis demonstrates that only the visceral pleural infiltration has significant effects on the survival rate. The presence of pleural infiltration should be considered in any assessment of the prognosis after pulmonary metastasectomy.

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Conference discussion

Dr P. Van Schil (*Antwerp, Belgium*): Was visceral pleural invasion a significant independent prognostic factor in the multivariate analysis?

***Dr Furak*:** Yes.

***Dr Van Schil*:** And did you look at the local recurrences?

***Dr Furak*:** We had 8.5% of local recurrence.

***Dr Van Schil*:** In those patients with visceral pleural invasion?

***Dr Furak*:** Yes, I mean almost half of them local and lymph node recurrence.

Dr Van Schil: So the question remains whether those patients are dying of local recurrence or other distant metastases.

Dr Furak: Systemic, because there was a very close correlation between multiple lesions and pleural infiltration.

Dr A. End (*Vienna, Austria*): Do you perform lymph node dissection in any case?

Dr Furak: It's a routine procedure in our surgery.

Dr End: Do you also perform mediastinoscopy?

Dr Furak: No. During the surgery we performed block dissection.

Dr End: In case of pleural infiltration, do you consider a more aggressive adjuvant therapy?

Dr Furak: That's it. I think this is the most important message of this statement.

Dr A. Tcherveniakov (*Sofia, Bulgaria*): Yesterday we had a discussion about the locations of the metastatic lung lesions. Do you have any specific data about the localizations of the metastatic tumors? In my opinion the upper lobes are more frequent site of recurrence than the lower lobes.

Dr Furak: The tendency was that one! The metastasis was a little bit more frequent in the upper part of the lung, but I cannot tell you the correct data currently.