Short-term Survival of Patients with Lung Metastases from Colorectal and Non-colorectal Cancer Who Underwent Pulmonary Metastasectomy*

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Abstract. *The lung is a common site of metastases, whose prevalence varies as a function of the primary tumor site, which is usually colorectal cancer (CRC), breast carcinoma, or genitourinary cancers, such as ovary, urinary bladder and renal cell carcinomas. The aim of the present study was to analyze whether the site of primitive tumor affects overall survival (OS) of patients with lung metastases (LMs) who underwent pulmonary metastasectomy. The data of 41 patients with surgically treated CRC (Group A=22 patients) and non-colorectal carcinomas (Group B=19 patients), who developed matachronous LMs and underwent pulmonary metastasectomy with curative intent, were analyzed. The origin of non-colorectal LMs was genitourinary cancer in nine and breast cancer in 10 patients. Overall, there were 22 men and 19 women, with a median age of 65 years (range=31-80); 18 patients had a solitary metastatic tumor, while 23 had two or more LMs. Twenty-nine patients underwent wedge resection, through thoracotomy or video-assisted thoracic surgery, while 12 underwent pulmonary lobectomy. Seventy-five LMs were resected with a 5-tear OS of 48.8%. No difference was found between elderly (≥65 year-old) and younger patients (p=0.26), and between those with solitary or multiple LMs (p=0.62) in terms of survival rate. The female patients had a worse OS (31.6% vs. 63.6%; odds ratio (OR)=3.79, 95% confidence interval (CI)=1.03-13.91, p=0.003) compared to males, independent of the origin of primary cancer. There was no difference in the cumulative survival rates (OR=1.65, 95%CI=0.48-5.69, p=0.42) between Groups and the log-rank test (p=0.75) was not significant. In conclusion, the main pathological characteristics of metastatic lesions and advanced age do not appear to be associated with a poor prognosis in patients with LMs, while the female gender is a negative prognostic factor. Thus, the primary tumor site should not be considered a major criterion in selecting patients for pulmonary metastasectomy.*

The lung is a common site of metastases, whose prevalence varies as a function of the primary tumor site, which is usually colorectal cancer (CRC), breast carcinoma, or genitourinary cancers, such as ovary, urinary bladder and renal cell carcinomas (1). CRC is the third cause of malignancy worldwide, accounting for 9-10% of all cancers, and the second cause of cancer-related death (2). CRC survival is highly dependent upon stage of disease at diagnosis, ranging from 10% to 90% in patients with advanced or early stage disease, respectively (2, 3). Breast cancer (BC) is the most common cancer in women, while urinary bladder and renal cell carcinoma, together, account for 12% of cases of cancer in men (4). Lung metastases (LMs) from recurrent breast cancer and renal cell carcinoma are not uncommon, with estimated prevalence rates as high as 70% in autopsy studies (5, 6). Unfortunately, the optimal treatment for patients with LMs is still controversial and several prognostic factors have been investigated. The aim of the present study was to analyze retrospectively whether the site of primitive tumor affects overall survival (OS) of patients with LMs who underwent pulmonary metastasectomy.

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Patients and Methods

Data of 41 patients with surgically-treated CRC (Group A=22 patients) and non-colorectal carcinomas (Group B=19 patients), who developed matachronous LMs and underwent pulmonary metastasectomy with curative intent, were analyzed. The origin of non-colorectal LMs was genitourinary cancer in nine (21.9%) and BC in 10 (24.4%) patients. Overall, there were 22 (53.7%) men and 19 (46.3%) women, with a median age of 65 years (range=31-80 years). The two Groups were sex- and age-matched. The median interval from primary tumor resection and LMs resection was 31 months (range=8-98), and the follow-up period after first metastasectomy was 31±24 months. Only seven (17.1%) patients had pulmonary lesion-related symptoms, such as cough, shortness of breath, and chest or rib pain.The local institutional ethics committee obtained written informed consent from all participants before surgery and the study had full ethical approval. We decided to perform metastasectomy based on the location, size and number of LMs detected on computed tomography (CT) scan, which appeared surgically resectable. The presence of regional mediastinal or hilar lymph node involvement represented an exclusion criterion. Eight (19.5%) patients received systemic chemotherapy before pulmonary surgery, and four (9.8%) received chemotherapy after LMs resection. The data are expressed as mean±standard deviation (SD) or as median (range). Student's t-test and the chi-square (χ^2) test were used for inter-group comparison. Relationships between parameters were assessed using the Pearson's correlation coefficient (R) calculation. The odds ratio (OR) calculation was also obtained and the 95% confidence interval (CI) was used to estimate the precision of the OR. OS was analyzed with the Kaplan-Meier method and a stratified log-rank test. A *p*-value <0.05 was considered statistically significant. Statistical calculations were performed with the Statistica software (StatSoft, Tulsa, OK, USA).

Results

No correlation was found between age of the patients and size (R=–0.02, p=0.91) or number (R= –0.18, p=0.29) of the LMs. No difference was observed between Groups in terms of age, male to female ratio, interval from primary tumor resection, number and size of the LMs or length of follow-up (Table I). Eighteen (43.9%) patients had a solitary metastatic tumor, while 23 (56.1%) patients had two or more LMs. Twenty-nine (70.7%) patients underwent wedge resection through thoracotomy (N=20, 48.8%) or video-assisted thoracic surgery (VATS), while 12 (29.3%) underwent pulmonary lobectomy. Seventy-five (median=1.5, range=1-7 per patient) LMs (mean size of 1.7±0.8 cm) were resected. A second pulmonary metastasectomy was required in four (9.7%) patients. The 5-year OS was 48.8%. No difference was found between elderly (≥65 year-old) and younger patients (56.5% *vs*. 38.9%, p=0.26) and between those with solitary or multiple LMs (52.2% *vs*. 44.4%, p=0.62) in terms of survival rate. The female patients had a worse 5-year OS (31.6% *vs*. 63.6%; OR=3.79, 95% CI 1.03-13.91, p=0.003) compared to males, independent of the origin of primary cancer. There was no difference in the cumulative survival rates (OR=1.65, 95% CI 0.48-5.69, p=0.42) between Groups (A *vs*. B: 54.5% *vs*. 42.1%), and the log-rank test (p=0.75) was not significant (Figure 1).

Table I. *Comparisons between Groups (mean±standard deviation) in patients with lung metastases (LMs) from colorectal (Group A) and non-colorectal cancer (Group B).*

Parameter	Group A	Group B	*p*-Value
No. of patients (%)	22 (53.7%)	19 (46.3%)	-
Age (years)	65.8±9.5	61.4±14.2	0.24
Males *vs*. females	14 *vs*. 8	8 *vs*. 11	0.17
Interval (months)	32.3±24.1	29.2±23.4	0.68
No. of the removed LMs	1.8±1.1	2.3±1.9	0.30
Single *vs*. multiple LMs	10 *vs*. 12	8 *vs*. 11	0.82
Size of the LMs	1.9±1.0	1.6±0.7	0.28
Follow-up (months)	31.9±28.0	27.8±22.6	0.61

Interval, interval from primary tumor resection.

Discussion

The lung is the most common extra-abdominal site of metastases from CRC and it has been estimated that between 10% and 20% of patients with CRC may develop LMs (7, 8). Unfortunately, the 5-year survival of patients with stage IV CRC and untreated metastatic disease is approximately 10%, while the resection of isolated pulmonary metastases (PM) increases survival rates up to 40% and, in selected cases, metastasectomy can be curative (9, 10). However, in certain studies, the relapse rate following pulmonary metastasectomy may reach 70% (11). A Danish cohort study reports that 7.5% of patients with CRC developed synchronous LMs, and 2.8% had metastases exclusively in the lung (12). Their survival was higher than that of patients with metachronous metastases. In several studies, usually performed on patients with LMs from CRC cancer, the 5-year OS following pulmonary metastasectomy, ranges from 35% to 61% (Table II). The main factors related to worse survival were the number of LMs and preoperative carcinoembryonic antigen (CEA) serum levels (15, 17, 18, 20). Other reported poor prognostic factors are disease-free intervals related to the time of adjuvant chemotherapy, young age and the presence of multiple *vs*. solitary LMs (21). We did not find similar results because the 5-year OS of patients aged <65 or ≥65 years was similar and the number of LMs did not affect significantly the outcome. In patients with CRC, factors associated with LMs are advanced tumor stage, nodal involvement (N2) and lymphovascular invasion in the primary tissue cancer (22). However, the weight of all prognostic factors should be interpreted carefully and periodic follow-up examinations are suggested for excluding

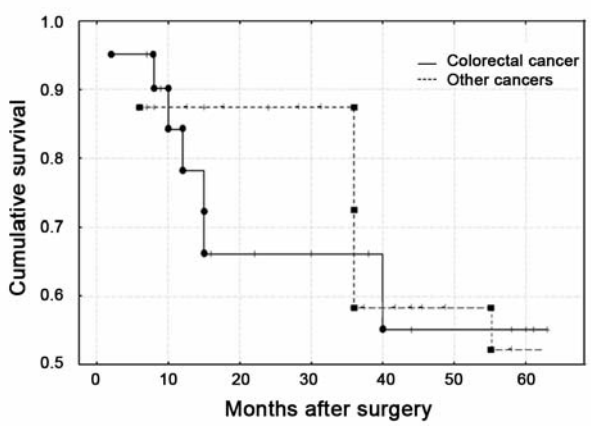

Figure 1. *Kaplan–Meyer survival curves for patients with lung metastases from colorectal and non-colorectal cancer who underwent pulmonary metastasectomy.*

Table II. *Results of metastasectomy in patients with lung metastases (LMs) from colorectal cancer (*3-year survival).*

Author (ref.)	5-year survival	Main prognostic factors related to survival
Suzuki *et al*. (13)	45.5%	No. of LMs, PTPA
Javed *et al*. (14)	61.0%*	Size of the LMs
Vodika *et al*. (15)	45.0%	PCEA
Younes *et al*. (16)	34.7%	Unilateral LMs, NCT
Rama *et al*. (17)	71.0%	No. of LMs, PCEA, DFI
Iizasa *et al*. (18)	41.3%	No. of LMs, PCEA
Inoue *et al*. (19)	45.3%	No. of LMs, PCEA, LNI
Saito et al. (20)	39.6%	PCEA, LNI

PTPA, Preoperative tissue polypeptide antigen level; PCEA, preoperative carcinoembryonic antigen level; NCT, neoadjuvant chemotherapy; DFI, disease-free interval; LNI, lymph node involvement.

pulmonary recurrence (16, 19). Also, in patients with CRC and both hepatic and pulmonary metastases, the OS was similar to those with LMs only, regardless of whether they are synchronous or metachronous, although patients with LNs as the first location had a worse outcome (23). In patients with LMs from renal cell carcinoma, the 5-year OS is usually shorter (33-37%) but independent of the number of LMs, while those with synchronous metastases have a significant worse prognosis (6, 24). The 4-year OS of patients with BC who underwent metastasectomy of LM is significantly longer (82% *vs*. 32%) than that of those with non-pulmonary metastases (5).

In conclusion, in this short-term study, the main pathological characteristics of metastatic lesions, including the site of primitive tumor, do not appear to be important prognostic determinants for survival. Our results also support that advanced age is not associated with a poor prognosis in patients with LMs and that the female gender is a negative prognostic factor. Thus, the origin of LMs should not be considered a major criterion in selecting patients for pulmonary metastasectomy.

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