Original Article

The impact of the location, incidence and distribution of lung metastases in primary colorectal and renal cell cancer patients on prognosis: a retrospective observational study

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Background: Patients with distant metastases have an unfavourable prognosis, but patients with isolated pulmonary metastases should generally not be considered hopeless. Complete resection of metachronous and solitary metastases leads to prolonged survival; however, the influence of the location, distribution and bilaterality of pulmonary metastases needs to be investigated further. This article aimed to investigate the role of the distribution of lung metastases in primary colorectal and renal cell cancer patients on prognosis.

Methods: We retrospectively investigated the prognosis of patients with pulmonary metastases and colorectal or renal cell carcinoma, defined as the survival time of patients with different metastases. The types of metastases were unilobar, multilobar, unilateral, bilateral, diffuse, synchronous, or metachronous. The secondary outcome of this study was differences in prognosis according to additional criteria.

Results: Patients with metachronous metastases had significantly greater median survival than patients with synchronous metastases. There was a statistically significant difference in median survival between patients with unilateral (better survival) and patients with bilateral (worse survival) lung metastases. In patients with renal cell carcinoma, a statistically significant difference in median survival time was detected for patients with unilateral metastases. A significantly longer median survival time was observed in patients without diffuse metastases. A significantly greater median survival time was detected in patients with no thoracic nodal involvement. Moreover, there was no statistically significant difference in the median survival time for patients with colorectal versus renal cell carcinoma in general or for those with lung metastases. No statistically significant difference in median survival time was detected for patients according to single or multiple lung metastases, additional tumours or metastases during disease, the distance of residence from a specialized clinic in Coburg, sex, smoking or adipocytes, multimorbidity, immunosuppression or different cancer treatments.

Conclusions: For a minority of patients, pulmonary resection is a chance for prolonged survival. The perioperative mortality rate after metastasectomy is less than five percent. Patients with metachronous and unilateral lung metastases should be evaluated for surgery. Patients with diffuse metastases or lymph node involvement have a significantly shorter median survival time. Decision-making should be interdisciplinary.

Keywords: Pulmonary metastasis; metastasectomy; prognosis; thoracic surgery

Submitted Oct 23, 2023. Accepted for publication Mar 12, 2024. Published online May 29, 2024.
doi: 10.21037/tcr-23-1961
View this article at: https://dx.doi.org/10.21037/tcr-23-1961

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Introduction

Background

Patients with pulmonary metastasis have a poor prognosis; the median survival of all patients with pulmonary metastases and synchronous lung metastasis is only five months (1). Autopsies have demonstrated that 30–50% of all patients with malignancies develop lung metastases (2).

Rationale and knowledge gap

The benefits of surgery/ablation are limited, and only patients in a preselected group have an advantage from pulmonary metastasectomy; however, Tom Treasure and Fergus Macbeth mentioned that this procedure is framed by therapeutic opportunity and is not supported by strong evidence (3). Nevertheless, the analysis and publications about pulmonary metastasis have identified several prognostic factors. The effect on laterality and the number of pulmonary metastases has also been studied previously (4,5), and the prognostic evidence of laterality of pulmonary metastases is known to be incoherent. However, whether the exact location and pulmonary distribution of metastases have prognostic value has yet to be sufficiently investigated.

Objective

In this report, we aimed to evaluate whether the onset, pulmonary location, pulmonary distribution, and extent of lung metastasis in patients with colorectal (CRC) or renal cell cancer (RCC) can influence the prognosis of the disease. The secondary outcomes of this study were differences in prognosis concerning survival according to additional criteria (alcoholism, smoking status, further tumour/metastasis during disease, distance from residence to a specialized clinic, age at diagnosis, adiposity, multimorbidity, immunosuppression at diagnosis, point of first intervention, and different types of treatments).

The hypotheses are as follows:

(I) In CRC and RCC, patients with unilateral lung metastases have a better prognosis than patients with bilateral lung metastases.

(II) In CRC and RCC, patients with unilobar lung metastases have a better prognosis than patients with multilobar lung metastases.

(III) Patients with metastatic lung cancer and RCC have a better prognosis than patients with synchronous lung metastases.

(IV) In CRC and RCC, patients with solitary lung metastases have a better prognosis than patients with multiple or diffuse lung metastases.

We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1961/rc).

Highlight box

Key findings

- Patients with metachronous and unilateral lung metastases should be evaluated for surgery. Patients with diffuse metastases or lymph node involvement have a significantly shorter median survival time.

What is known and what is new?

- For a minority of patients, pulmonary resection is a chance for prolonged survival. The perioperative mortality rate after metastasectomy is less than five percent. Patients with metachronous metastases had significantly greater median survival than patients with synchronous metastases.
- There was no statistically significant difference in the median survival time for patients with colorectal versus renal cell carcinoma in general or for those with lung metastases. No statistically significant difference in median survival time was detected for patients according to single or multiple lung metastases, additional tumours or metastases during disease, the distance of residence from a specialized clinic in Coburg, sex, smoking or adipocytes, multimorbidity, immunosuppression or different cancer treatments. There was a statistically significant difference in median survival between patients with unilateral (better survival) and patients with bilateral (worse survival) lung metastases.

What is the implication, and what should change now?

- Decision-making should be interdisciplinary. Patients with metachronous and unilateral lung metastases should be evaluated for surgery.

Methods

The study design was a retrospective observational study. Part of the data in the method comes from the medical dissertation of Melissa Wieloch (6). The sample comprised all adult patients of the Regiomed Clinic Association (REGIOMED) between January 1, 2018, and February 1, 2022, with *de novo*-diagnosed primary CRC or RCC and only lung (synchronous/metachronous) metastases.

The exclusion criteria were prior cancerous disease, multiple cancer diseases at the time of diagnosis of CRC/RCC, and additional metastases other than lung metastases

at the time of diagnosis of RCC/CRC. Furthermore, patients from other institutions outside REGIOMED were recruited. The data of each patient met the inclusion criteria according to medical reports, histopathological findings, and medical imaging via positron-emission tomography (PET) or computer tomography (CT). The above data were also used to group patients according to the location and number of lung metastases.

The patients' primary cancer (primarius) was treated according to the valid German S3 guidelines but depended on the patient's performance status. Lung metastases were defined as circumscribed pulmonary nodules on dynamic CT scan (diameter ≥7 mm) or nodules with positivity on PET or nodules with histological confirmation.

We defined six types of metastases:

- Solitary lung metastasis was defined as multiple metastases with subgroups (unilobar, multilobar, unilateral, bilateral).
- Diffuse (bipulmonary and more than one metastasis per lobe) metastasis.
- Multilobar lung metastases were defined as metastases in more than two lobes of the lung (regardless of the lung's affected site).
- Diffuse metastases were defined as bilateral (both lungs affected) with more than one metastasis per lobe present.
- Synchronous metastases were defined as metastases of primary carcinoma within six months of diagnosis of the primary tumour; otherwise, they were considered metachronous metastases.
- Thoracic lymph node metastasis was considered lymphadenopathy on CT scan with progression, PET positivity, or histologic verification.

The additional data collected were age and sex, the distance (km) from residence to a specialized hospital in Coburg, history of smoking, alcohol consumption, and obesity according to the World Health Organization (body mass index >30 kg/m^2), number of preexisting diseases/multimorbidities, immunosuppression, duration of first therapeutic approach, initiation/implementation of therapy (systemic therapy, radiotherapy, surgery), and other tumours/metastases during disease. We defined multimorbidity as the presence of more than three chronic organ system diseases requiring regular medical intervention/checkups or medication uptake. Immunosuppression is a condition that influences the immune system's action, reaction, and physiologic function.

All patients were presented several times to the tumour board. The prerequisites for thoracic surgical intervention were as follows: the primarius was eliminated or controlled, all metastases were resectable with sufficient cardiopulmonary reserves after surgery, and the patient's wishes were met.

Survival was defined here as the period between the diagnosis of primary carcinoma and either the exitus letalis of the affected individual or the survival of the individual beyond the period of this study. Survival data were collected from our institutional cancer centre registry. The follow-up time in months was the median time between diagnosis of the primarius and February 2022. There was no loss to follow-up.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the International Ethics Board of the Medical School. REGIOMED approved this type of research based on §2 of the statutes (sign STWA/MICA, March 18, 2022, ID of the approval 2022-15), and informed consent was obtained from all individual participants.

Statistical analysis

The statistical significance of the results was analysed via IBM SPSS Statistics version 27. Kaplan-Meier analysis was used for survival analysis, and log-rank analysis was applied to compare groups. The level of significance was set at $P<0.05$. Observations are presented as the mean and median with additional usage of a 95% confidence interval (CI). For distinction and verification of the dependence of the variables, the Chi-square test was applied [chi-square test $\chi^2=\sum (O - E)^2/E$, where O is the observed frequency and E is the expected frequency]. Variables in the CRC cohort, such as initial therapy for primarius and alcohol abuse, were not analysed since the sample size was too small. Furthermore, in the RCC group, factors such as obesity, initial therapy for primarius, and the association between both kidneys and cancer were also not considered due to the small sample size.

Results

This study included 35 patients, 25 (71.4%) with primary CRC and 10 (28.6%) with RCC.

The CRC cohort included 11 females (44%) and 14 males (56%). Five patients (20%) were younger than 60 years, and 20 (80%) were older than 60 years. Ten patients (40%) exhibited synchronous metastases, and 15

Table 1 Characteristics of patients with colorectal cancer and only lung metastases (N=25)

Characteristics	N [%]
Synchronous metastases	10 [40]
Metachronous metastases	15 [60]
Singular metastasis	5 [20]
Multiple metastases	
Unilobar	4 [16]
Multilobar	16 [64]
Unilateral	5 [20]
Bilateral	15 [60]
Diffuse metastases (bipulmonal + >1/lobe)	12 [48]
Thoracic lymph nodes affected	11 [44]
Additional tumour in course of disease	4 [16]
Additional extrapulmonary metastases in course of disease	17 [68]
Survival after diagnosis	
<1 year	3 [12]
<2 years	0
>2 years	6 [24]
>3 years	5 [20]
>5 years	5 [20]
>10 years	1 [4]
Still alive at time of thesis closure (01-02-2022)	5 [20]
Residence	
<10 km away from specialized centre Coburg	5 [20]
>10 km away from specialized centre Coburg	5 [20]
>20 km away from specialized centre Coburg	14 [56]
>50 km away from specialized centre Coburg	1 [4]
Age at diagnosis	
≤60 years	5 [20]
>60 years	20 [80]
Gender	
Female	11 [44]
Male	14 [56]
Smoking	5 [20]
Alcohol abuse	1 [4]
Obesity	11 [44]
Multimorbidity	8 [32]
Immunosuppression	7 [28]
Primary treatment within 30 days after diagnosis	25 [100]
Systemic therapy of only	1 [4]
Surgery of primary cancerous disease only	4 [16]
Radio-/systemic therapy and surgery	20 [80]

(60%) developed metachronous metastases. In 5 patients (20%), singular metastases were present, and 20 patients (80%) exhibited multiple metastases. Four patients (16%) had multiple unilobar metastases, 16 patients (64%) had multiple multilobar metastases, 5 patients (20%) presented with multiple unilateral metastases, 15 patients (60%) had multiple bilateral metastases, 12 patients (48%) had diffuse metastases, and 11 patients (44%) had metastatic thoracic lymph nodes. Despite the primary cancer and course of the disease, an additional tumour was detected in four patients (16%), and additional metastases were diagnosed in 17 patients (68%) during the disease course. At the time of closure, only five patients were still alive, and three patients did not survive the first year after the diagnosis of primary CRC. The median follow-up time was 60 months, ranging from 12–158 months. Patient characteristics are summarized in *Table 1*. All patients received primary treatment within 30 days after the primary cancer diagnosis. According to the primary cancer, one patient had only systemic therapy, four patients had only surgery, and 20 patients underwent therapeutic interventions together. Eight patients underwent pulmonary metastasectomy, but only one patient had a solitary pulmonary metastasectomy.

There were four primary RCC patients (10/35) with only lung metastases (40%, 4/10), six males (60%), three patients (30%) younger than 60 years, and seven (70%) older than 60 years. Six patients (60%) exhibited synchronous metastases, and four (40%) developed metachronous metastases. In two patients (20%), singular metastases were present; eight of ten (80%) exhibited multiple metastases. Among the patients with multiple metastases, two patients (20%) had unilobar metastases, six patients (60%) had multilobar metastases, two patients (20%) had unilateral metastases, and six patients (60%) had bilateral metastases. Seven patients (70%) had diffuse metastases, and the

Table 2 Characteristics of patients with renal cell cancer and only lung metastases (n=10)

Characteristics	N [%]
Synchronous metastases	6 [60]
Metachronous metastases	4 [40]
Singular metastasis	2 [20]
Multiple metastases	
Unilobar	2 [20]
Multilobar	6 [60]
Unilateral	2 [20]
Bilateral	6 [60]
Diffuse (bipulmonal + >1/lobe)	7 [70]
Thoracic lymph nodes affected	6 [60]
Additional tumour in course of disease	3 [30]
Additional metastases in course of disease	7 [70]
Survival after diagnosis	
<1 year	3 [30]
<2 years	3 [30]
>2 years	0
>3 years	0
>5 years	2 [20]
>10 years	1 [10]
Still alive at time of thesis closure (01-02-2022)	1 [10]
Residence	
<10 km away from specialized centre Coburg	2 [20]
>10 km away from specialized centre Coburg	1 [10]
>20 km away from specialized centre Coburg	7 [70]
>50 km away from specialized centre Coburg	0
Age at diagnosis	
≤60 years	3 [30]
>60 years	7 [70]
Gender	
Female	4 [40]
Male	6 [60]
Smoking	1 [10]
Alcohol abuse	0
Obesity	1 [10]
Multimorbidity	5 [50]
Immunosuppression	3 [30]
Primary treatment within 30 days after diagnosis	8 [80]
Systemic therapy only	0
Surgery of primary cancerous disease only	5 [50]
Radio-/systemic therapy and surgery	5 [50]

thoracic lymph nodes were affected in six (60%) patients. Despite the primary cancer, an additional tumour was detected in three patients (30%), and additional metastases were diagnosed in seven patients (70%) during the disease course. Four patients (40%) survived more than five years, and one (10%) survived more than 10 years after diagnosis. Patient characteristics are summarized in *Table 2*. The median follow-up time was 52 months, ranging from 19–289 months. In eight patients (80%), primary treatment was given within 30 days after the primary cancer diagnosis. Five patients (50%) had undergone surgery only, and five (50%) had undergone therapeutic intervention together. Two patients (20%) underwent pulmonary metastasectomy, whereas only one patient (10%) was solitary. Additional metastases in both groups appeared within 12 months after pulmonary metastasis was detected. If metastasectomy was indicated, we preferred open surgery and the palpation technique.

Survival analysis of patients with CRC and pulmonary metastasis

No patient died perioperatively. Overall, the median survival time in the CRC cohort was 52 months (95% CI: 37.2 to 66.8 months). The median survival time of patients with synchronous metastases was significantly lower than that of patients with metachronous metastases (P=0.04) (*Figure 1*). There was no significant difference in the median survival between patients with single metastases and those with multiple metastases (P=0.82). No significant difference in median survival was found between patients with unilobar and multilobar metastases (P=0.87). Furthermore, patients with bilateral metastases did not exhibit inferior survival; therefore, bilateral metastases had no statistical relevance for survival (P=0.08). Additionally, lymph node metastases

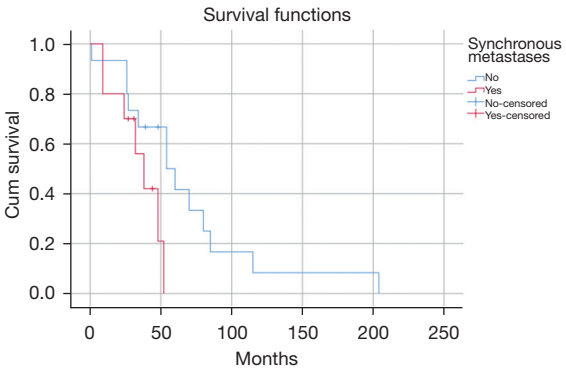

Figure 1 Survival of patients with synchronous/metachronous metastases among those with colorectal cancer (P=0.04).

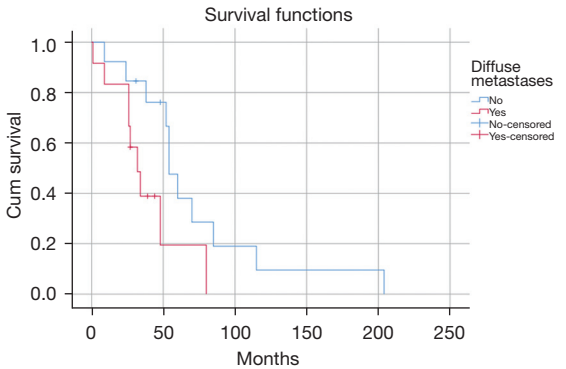

Figure 2 Survival functions of diffuse/nondiffuse lung metastases in colorectal cancer patients (P=0.045).

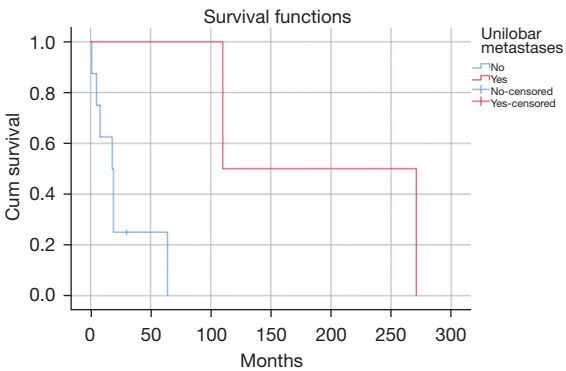

Figure 3 Survival functions of renal cell carcinoma patients with unilobar or multilobar metastases (P=0.045).

had no statistically significant influence on survival (P=0.17). Nevertheless, a significantly greater median survival time was noted in patients without diffuse metastasis (P=0.045) (*Figure 2*). In addition, it is noteworthy that, regarding survival, no statistically significant differences were found for factors such as additional tumours (P=0.98), the appearance of additional metastases during disease (P>0.99), or the distance from residence to the specialized centre in Coburg (P=0.07). Additionally, sex (male or female) did not significantly affect survival (P=0.78), nor did smoking status (P=0.26), adiposity (P=0.38), multimorbidity (P=0.10), or immunosuppression (P=0.88). Likewise, the type of therapy applied was also not a statistically significant factor for survival (P=0.63).

Survival analysis of patients with RCC and pulmonary metastasis

The median survival of patients diagnosed with RCC and metastases was 19 months (95% CI: 17.5 to 20.5 months). For RCC patients, there was no statistically significant difference between factors such as synchronous and metachronous appearances of lung metastases (P=0.052) or singular compared to multiple metastases (P=0.35). Moreover, there was no statistically significant difference in survival between patients with bilateral metastases (P=0.15) and patients with diffuse metastases (P=0.15). Additionally, lymph node metastases had no relevant influence on survival (P=0.16). Furthermore, the appearance of an additional tumour (P=0.09) or metastasis (P=0.34) did not significantly impact survival. Additionally, the distance from residence to the specialized centre in Coburg had no significant statistical value (P=0.07). Similarly, sex (male or female) had no significant influence on survival (P=0.24), smoking status (P=0.18), multimorbidity status (P>0.99), or immunosuppression status at the time of diagnosis of primary RCC (P=0.11). Moreover, data were collected to evaluate whether cancer involving the renal pelvis influenced survival, but this was not the case (P=0.45). Additionally, the presence of one or both kidneys did not significantly affect survival (P=0.97). However, within this group of patients with RCC and metastases, there was a statistically significant difference in median survival between patients with unilobar lung metastases and those with multilobar lung metastases (P=0.045) (*Figure 3*).

Comparison of the CRC and RCC and overall survival

A comparison of CRC and RCC as primary cancers (n=35) revealed that the median survival time was greater in patients with CRC (48 months, 95% CI: 30.1 to 65.9 months)

Table 3 Patient characteristics of the complete sample (cohort) and only lung metastases (n=35)

Characteristics	N [%]
Synchronous metastases	16 [46]
Metachronous metastases	19 [54]
Singular metastasis	7 [20]
Multiple metastases	
Unilobar	6 [17]
Multilobar	22 [63]
Unilateral	7 [20]
Bilateral	21 [60]
Diffuse (bipulmonal + >1/lobe)	19 [54]
Thoracic lymph nodes affected	17 [49]
Additional tumour in course of disease	7 [20]
Additional metastases in course of disease	24 [69]
Survival after diagnosis	
<1 year	6 [17]
<2 years	3 [9]
>2 years	6 [17]
>3 years	5 [14]
>5 years	7 [20]
>10 years	2 [6]
Still alive at time of thesis closure (01-02-2022)	6 [17]
Residence	
<10 km away from specialized centre Coburg	7 [20]
>10 km away from specialized centre Coburg	6 [17]
>20 km away from specialized centre Coburg	21 [60]
>50 km away from specialized centre Coburg	1 [3]
Age at diagnosis	
≤60 years	8 [23]
>60 years	27 [77]
Gender	
Female	15 [43]
Male	20 [57]
Smoking	6 [17]
Alcohol abuse	1 [3]
Obesity	12 [34]
Multimorbidity	13 [37]
Immunosuppression	10 [29]
Primary treatment within 30 days after diagnosis	33 [94]
Systemic therapy only	1 [3]
Surgery of primary cancerous disease only	9 [26]
Radio-/systemic therapy and surgery	25 [71]

Table 3 *(continued)*

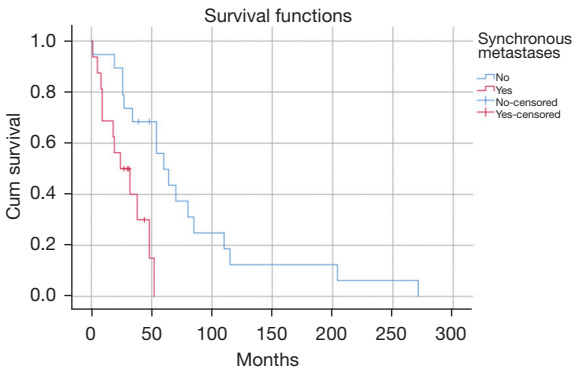

Figure 4 Survival functions of patients with synchronous/metachronous lung metastases (P=0.002).

than in patients with RCC (19 months, 95% CI: 17.5 to 20.5 months). However, the difference between the CRC and RCC groups was not significant (P=0.80). If we subgrouped our CRC and RCC patients (shortened to "cohort" in *Table 3*), a significant difference was detected concerning the median survival of patients with synchronous and metachronous appearances of metastases (P=0.002) (*Figure 4*). A statistically significant difference in survival (P=0.01) was also detected between patients with bilateral and unilateral metastases (*Figure 5*). Moreover, in the absence of diffuse metastasis (*Figure 6*), meaning in the case of the presence of metastases in all lobes, a significant difference in the survival time was detected between patients with diffuse metastasis and patients with non-diffuse metastases (P=0.007). It is also noteworthy that there was a statistically significant difference in median survival between patients with or without lymph node metastases (P=0.02) (*Figure 7*). Overall, we found no other statistically significant factors for primary CRC with lung metastases or primary RCC with lung metastases.

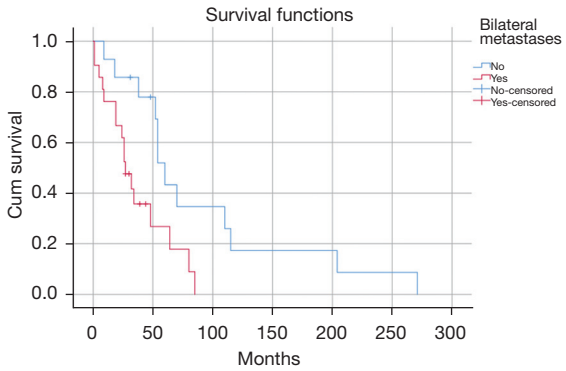

Figure 5 Survival functions of uni-/bilateral metastases in all patients (P=0.01).

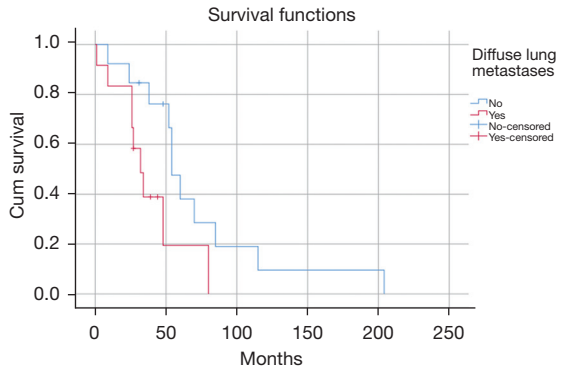

Figure 6 Survival functions of diffuse lung metastases in all patients (P=0.007).

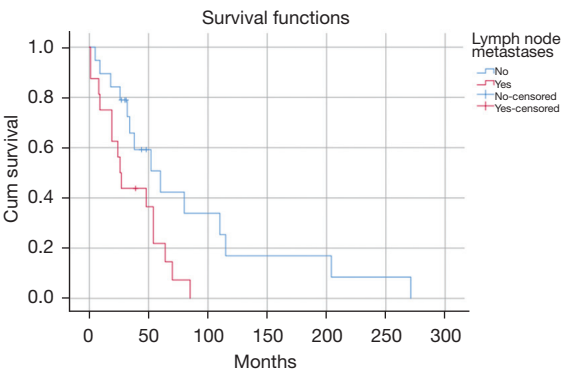

Figure 7 Median survival time between patients with and without lymph node involvement (P=0.02).

Discussion

Patients selected for complete resection of colon or renal cell metastases in the lung have a survival advantage (1-3). This, in turn, means that we should safely and effectively detect them. Araujo-Filho and colleagues stated that CT scans are superior to chest radiographs for detecting lung metastases (7). According to German guidelines, our patients underwent a CT scan as part of the staging process. Even so, for verification of the existence of lung metastases, chest computed tomography scans were used in our study for proof of lung metastases, but medical records, CT dynamics, PET, and histopathological evidence were included as data sources.

The International Registry of Lung Metastases investigators described solitary metastasis as a favourable prognostic factor; in their study, 2,383/5,206 (45.8%) patients with solitary metastasis were resected. In comparison, in our study, metastasectomy was performed on only 10/35 (28.6%) patients, and only two patients (5.7%) had a solitary metastasis. It is essential to remember that only 32% and 20% of our patients with CRC and RCC, respectively, underwent thoracic surgery. Of these, only 4% and 10% presented a single metastasis, representing the best possible scenario to benefit from pulmonary metastasectomy. Currently, metastasectomy is generally offered only to patients with controlled underlying disease, no widespread extrapulmonary metastases, completely resectable lung metastases, or sufficient cardiopulmonary reserve (4); therefore, few patients meet these requirements.

In one of the most extensive epidemiologic studies, with more than two million cases between 2010 and 2015, Chen *et al.* demonstrated that 5% and 8% of patients with CRC and RCC, respectively, had synchronous metastases (1). The incidence increased over time. Synchronous metastasis occurred more frequently in our study (40% in the CRC group and 24% in the RCC group); we explain this trend by referring to radiologic advancements (CT and PET) and accurate staging procedures. Like others, our study showed that metachronous metastases led to statistically significant differences in median survival time compared to synchronous metastases.

Despite increasing knowledge about the prognostic value of pulmonary metastasis characteristics, the impact of the amount, localization, and intrapulmonary distribution of metastases are equally contentious (4). To date, one of the most published surgical studies on pulmonary metastases is a retrospective multicentre study by the International Registry of Lung Metastases (8). In this study, 2,383 patients had solitary metastasis, and 2,726 patients had multiple lesions resected. The results revealed several favourable prognostic factors, for example, the histology of the primary

cancer, the pulmonary R0 resection, the disease-free interval (DFI), and the number of metastases. However, this study did not investigate the influence of the location or laterality of metastases.

On the other hand, Younes *et al.* reported that the impact of differences in the laterality of the nodules according to univariate analysis did not reach statistical significance (5). In our patient cohort, unilateral metastases and lack of diffuse metastases led to statistically significant differences in median survival time compared to bilateral metastases and the existence of diffuse metastases. In the CRC subgroup, even patients with unilobar metastases had a better prognosis than patients with multilobar metastases (P=0.045).

After the recruitment of the patients constituting our study cohort, additional extrapulmonary metastases were diagnosed in 17 patients with CRC (68%) and 7 with RCC (70%). We only observed numbers that were high in the epidemiological report of Chen *et al.*; in 54.5% of cases, they found the presence of bone, brain, or liver metastasis at diagnosis of synchronous lung metastasis (1). These observations emphasize that in most cases, an already metastatic tumour disease remains unisolated, so continuing tumour follow-up care is essential.

Pastorino and associates reported (8) a median follow-up of 46 months and a survival of 36% at five years. We lost 20/35 (57.1%) patients in the first five years, and six patients had yet to reach the limit of five years. Thus, we expect similar overall survival rates. Thus, overall survival is comparable despite the absence of resection. Nevertheless, our patients with diffuse pulmonary metastases had a poor prognosis. Unlike others, no statistically significant difference in median survival time was detected in our study for patients with single versus multiple lung metastases; we explain this abbreviation with the small sample size.

We investigated only CRC and RCC patients with pulmonary metastasis without previous extrapulmonary manifestations. On the other hand, Saito *et al.* (9) noted that patients with previous hepatic metastasis had survival rates similar to those of patients with only pulmonary metastasis. Additionally, the appearance of additional tumours in our study or extrapulmonary metastases during disease was not identified as a statistically significant survival factor.

In the study by Pfannschmidt *et al.* on metastatic RCC (10), the overall 5-year survival rate was 36.9%. Similarly, most patients (6/10, 60%) did not survive within the first five years. Survival in Heidelberg Province was significantly greater for patients with solitary metastasis and complete resection than for those with incomplete resection and multiple metastases. The authors also noted that the number of metastases, regional thoracic lymphomatous metastasis, and the DFI were overall predictors of survival (10). Schott *et al.* (11) reported that patients with smaller pulmonary metastases (less than 2 cm in diameter) and unilateral manifestations had prolonged survival. Since the previously mentioned studies depict a difference in survival related to the number of lung metastases, we tried to determine whether metastasis localization could influence the survival rate of affected patients. Therefore, we aimed not only to study the ability of one or more lung lobes to predict a difference in prognosis but also to investigate whether unilateral or bilateral effects on the lungs could also affect survival. In comparison, there was a statistically significant difference in median survival between patients with unilobar lung metastases and those with multilobar lung metastases (P=0.045). Interestingly, we found no additional differences.

We did not investigate the value of systematic therapy. Seitlinger *et al.* (12) recently published a review evaluating the benefit of pulmonary metastasectomy in RCC and the role of different modern systemic approaches. The authors summarized that different multimodal treatment combinations were being used, but pulmonary metastasectomy should be considered for a median survival of 37 months.

Our findings in the CRC cohort partially correlate with prior studies, especially with the second German study of Pfannschmidt *et al.* (13). The overall 5-year survival in Heidelberg was 32.4%; in our study, 14/25 (56%) patients died within the first five years. Their study involved 167 patients with CRC and revealed that survival after less metastasectomy (≤4) was significantly better overall than that after resection of more metastatic lesions (13). In our cohort of patients, metastasectomy was performed only eight times. All those patients survived more than two years after the primary cancer diagnosis, supporting the theory of Pfannschmidt and colleagues. The lack of thoracic lymph node metastases was also a factor for improved median survival, correlating with findings of the study of the Department of Thoracic Surgery Heidelberg (13), according to which there was only a 6% survival rate at four years for patients with hilar or mediastinal lymph node metastases. However, in contrast to the findings of the referenced study from Heidelberg, which showed no statistically significant difference in survival between patients with synchronous and metachronous metastases (13), our study detected a better median survival in patients with metachronous

metastases as mentioned before.

Despite the initial presumption of better survival in patients with CRC and lung metastases (median survival 52 months, 95% CI: 37.2–66.8 months) than in patients with RCC and lung metastases (median survival 19 months, 95% CI: 17.5–20.5 months), there was no statistically significant improvement in survival. These findings were previously reported (14).

A negative prognostic factor identified in many articles is lymph node involvement, which considerably worsens survival (4). Moreover, the inclusion of primary tumours did not influence the independent survival analysis in our study; however, the presence of both primary tumours was an adverse prognostic factor for overall survival.

It seems advisable to investigate whether specific types of treatment for different subgroups of metastases can improve overall survival. Image-guided thermal ablation and stereotactic radiotherapy are alternatives to pulmonary metastasectomy, but good evidence to justify their use is lacking (3). Therefore, as stated by Shields and colleagues, combinations of systemic therapy and local ablation may be considered and may offer more patients the potential for optimal local and systemic control of their disease process (15). However, no significant difference in the distinct types of therapy was confirmed in our thesis.

Limitations

In our retrospective observational study, there were problems in collecting medical data since only medical history records were used to obtain information about the included patients. Furthermore, data collection and searches for relevant information on lung metastases have yielded limited findings since official research on this topic is scarce. The selected sample was small and heterogeneous, and the patients were treated oncologically in different ways, both medically and surgically. An additional limitation is the failure to study the value of systematic therapy. Metastatic disease from two primary tumours, such as those observed here, should be considered a systemic disease regardless of the tumour burden of each selected patient.

On the other hand, selection bias is possible because patients who underwent surgery exhibited good surgical tolerance and good performance status and may have had a better prognosis. Because of these limitations, we need to take a critical look at our survival data. This sample size is still limited; therefore, repeating this type of study with larger sample sizes to obtain broader and more specific results and advance the objectives is well advised. It is also suggested that more primary cancers with a disposition to lung metastases be included for possible detection of differences in prognosis according to different types of primary cancers. Additionally, despite the results of this study, more detailed questions concerning alcohol abuse and tobacco smoking should be added to case history forms or questionnaires used in our clinics. The anamnestic data seemed incomplete during the execution of this study, and this approach could improve the quality of anamnesis in general.

Conclusions

For some patients, pulmonary metastasectomy is associated with prolonged survival. The perioperative mortality rate after metastasectomy is less than five percent. A minority of patients with metachronous and unilateral manifestations have a better prognosis. Patients with RCC and unilobar metastasis also have extended survival. Patients with diffuse metastases or lymph node involvement have a significantly shorter median survival time. Moreover, there was no statistically significant difference in the median survival time for patients with CRC versus RCC or lung metastases. No statistically significant difference in median survival time was detected for patients with additional tumours or metastases during the disease, distance from residence to the specialized clinic in Coburg, sex, smoking and obesity, multimorbidity, immunosuppression or different treatments (surgery, radio-/systemic therapy or both). Patients with pulmonary metastases should be presented and evaluated for surgery. However, only a minority of these tumours are operable.

Acknowledgments

Part of the data in this article comes from the medical dissertation of Melissa Wieloch.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1961/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1961/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1961/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1961/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the International Ethics Board of the Medical School. REGIOMED approved this type of research based on §2 of the statutes (sign STWA/MICA, March 18, 2022, ID of the approval 2022-15), and informed consent was obtained from all individual participants.

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Cite this article as: Wieloch M, Hammoudeh S, Stange S, Orban K, Sziklavari Z. The impact of the location, incidence and distribution of lung metastases in primary colorectal and renal cell cancer patients on prognosis: a retrospective observational study. Transl Cancer Res 2024;13(5):2346-2356. doi: 10.21037/tcr-23-1961

