The impact of location and amount of lung metastases in primary colorectal and renal cell cancer on prognosis : a retrospective observational study

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THE IMPACT OF LOCATION AND AMOUNT OF LUNG METASTASES IN PRIMARY COLORECTAL AND RENAL CELL CANCER ON PROGNOSIS: A RETROSPECTIVE OBSERVATIONAL STUDY

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LIST OF ABBREVIATIONS

HNPCC	-	Hereditary non-polyposis colorectal cancer (Lynch syndrome)
FAP	-	Familiar adenomatous polyposis
PTEN	-	Phosphatase and tensin homolog
KRAS	-	Kirsten Rat Sarcoma
NRAS	-	Neuroblastoma RAS viral oncogene homolog
anti-EGFR	-	Anti-epidermal growth factor receptor
BRAF	-	V-Raf murine sarcoma viral oncogene homolog B1
APC	-	Adenomatous polyposis coli
SMAD4	-	Mothers Against Decapentaplegic Homolog 4
MSI	-	Microsatellite-instability
HIV	-	Human immunodeficiency virus
HPV	-	Human papilloma virus
NSAIDs	-	Non-steroidal anti-inflammatory drugs
VHL-gene	-	Von-Hippel-Lindau-gene
CNS	-	Central nervous system
MRCCPS	-	Metastatic Renal Carcinoma Comprehensive Prognostic System
EMT	-	Epithelial-mesenchymal transition
WHO	-	World Health Organization
IBM SPSS	-	Statistical Package for the Social Sciences
CEA	-	Carcinoembryonic antigen
TNM	-	Tumor, nodes and metastases
R0-resection	-	Complete surgical resection of the tumor without remains of tumorous tissue at the border of resection

1. INTRODUCTION

1.1. Significance of pulmonary metastases

"Autopsies have demonstrated that 30% of all patients with malignancies develop pulmonary metastases" (1). Lung metastases are frequent with common cancers, for example, colorectal, renal cell, endometrium and breast cancer and therefore most studied in medical school. For purpose of this thesis, the focus is on primary colorectal and renal cell carcinoma as locus of primary cancer.

1.2. Anatomy of lungs

The lungs are arranged into the right lung and the left lung. The left and likewise also the right lung are composed of different lobes. Whereas the right lung features three lobes (superior, middle, inferior), the left lung has only two (superior, inferior) different lobes (Figure 1, 2).

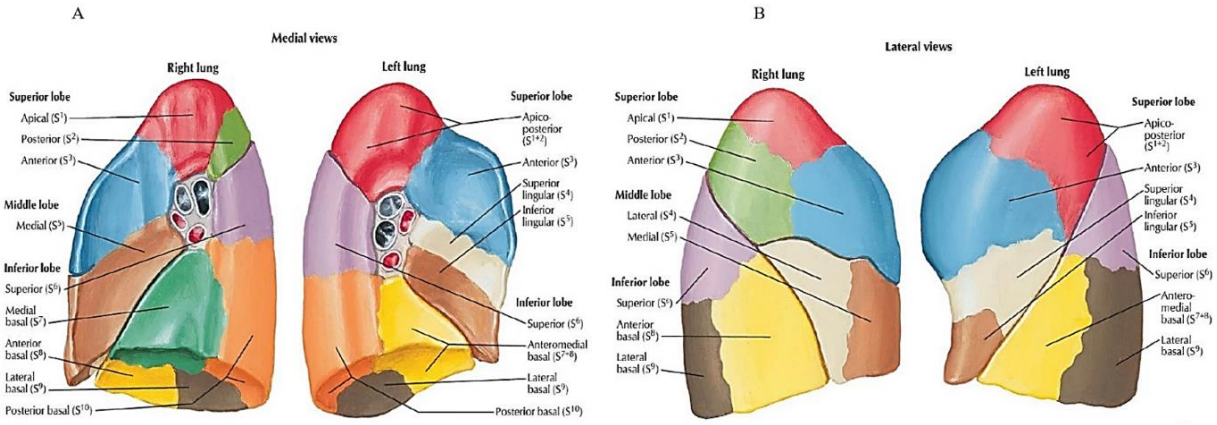

Figure 1. Medial (A) and lateral (B) view of lobes and segments of lungs (2)

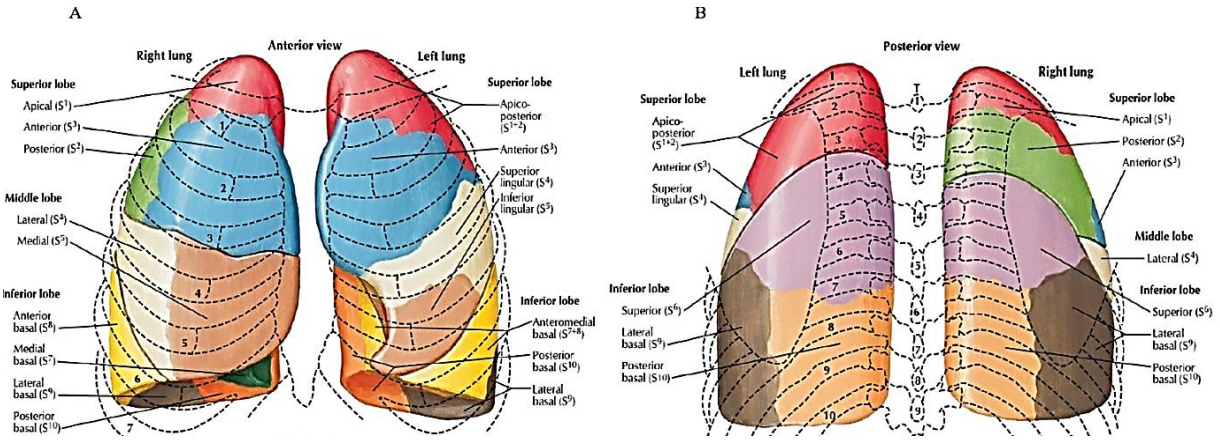

Figure 2. Anterior (A) and posterior (B) view of lobes and segments of lungs (2)

The left lung also often displays the lingula, a unique feature of the left lung and absent in the right lung, which is caused by the projection and localization of the heart in this area (3). Furthermore, the lobes of the lungs are subdivided into smaller “bronchopulmonary segments” (3), separated from each other by septa of connective tissue and supplied by individual bronchi and branches of the pulmonary artery together with pulmonary veins (Figures 1, 2). These segments, round about eighteen to twenty altogether, can be resected separately by surgery. The right lung contains ten different segments and the left lung round about eight to ten (3).

1.3. Definitions

1.3.1. Regiomed clinic association

In summer 2005, business executives of clinics of upper Franconia and southern Thuringia came together to discuss the question of how to secure the existence of different clinics in aforementioned regions (Figure 3). Up to now, the transitional cooperation resulting from this meeting remains unique. On the first of January 2008, this cooperation, composed of clinics in Coburg and the rural districts of Sonneberg, Lichtenfels, Hildburghausen and the town of Schleusingen, fused to “REGIOMED-Kliniken GmbH” to secure an affordable regional health care (4).

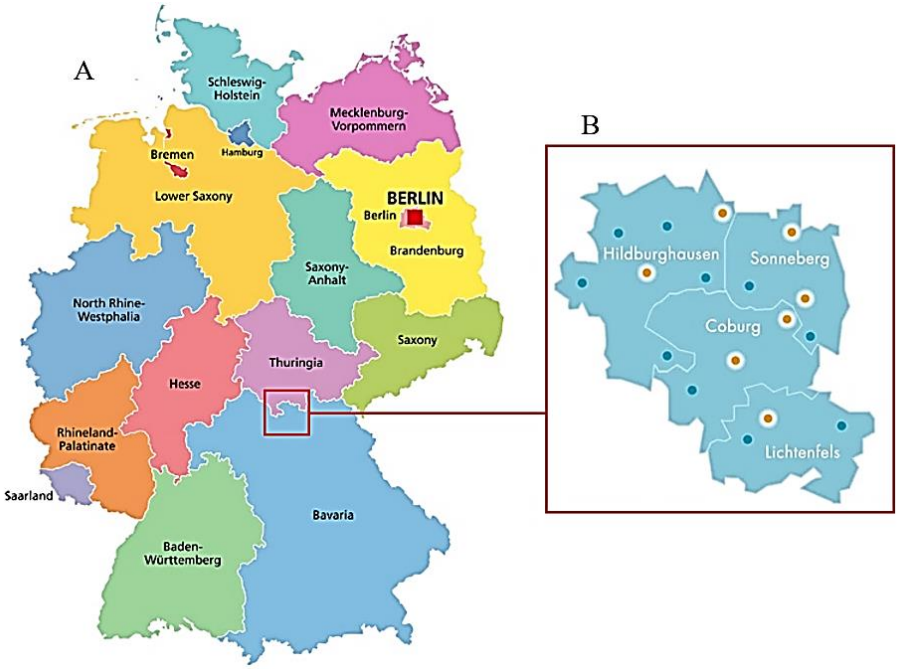

Figure 3. States of Germany (A) and localization of Regiomed clinical association (B) (5, 6)

"REGIOMED-Kliniken GmbH" is the first municipality and federal states overlapping clinical cooperation in upper Franconia and southern Thuringia and is composed of:

- sixteen different locations
- five acute clinics (six different locations)
- one rehabilitation clinic and one pain day-unit
- geriatric rehabilitation (two different locations)
- medical service centers / ambulatory healthcare centers (thirteen different locations with a broad spectrum of specialties)
- ground-based rescue services (rural district of Sonneberg and Hildburghausen)
- five retirement homes and two mental health care centers
- service company and training and development companies (Medical School and Regiomed-academy)

Therefore Regiomed provides professional expertise and regionwide health care (4).

1.3.2. Colorectal carcinoma

Colorectal carcinoma is defined as malignant tumor of colon and rectum (Figure 4) (7).

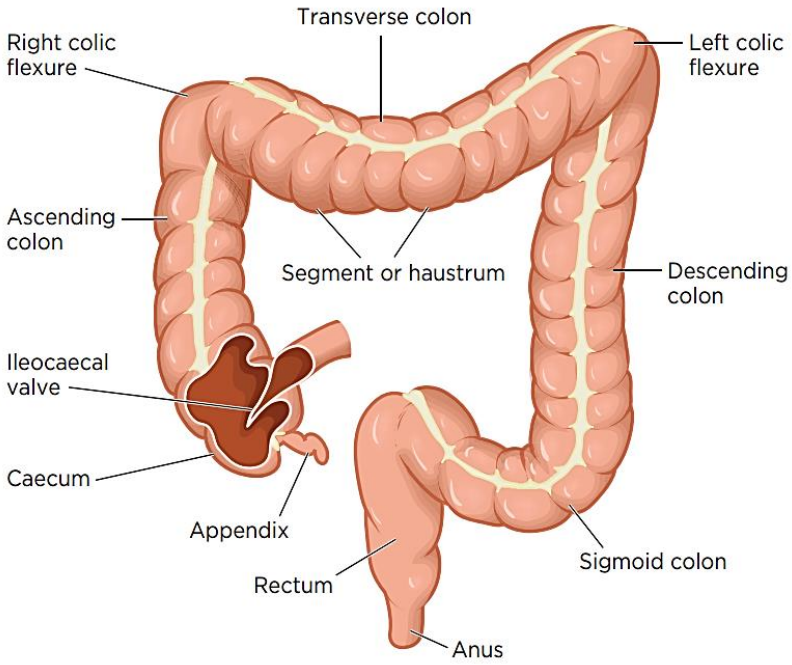

Figure 4. Anatomy of colon, rectum and anal canal (8)

Annual incidence of newly detected colorectal cancers is 30 to 40 cases per 100.000 persons in Europe, colorectal cancer accounts for 13% of all newly diagnosed cancerous diseases in Germany. This incidence increases with age with a total average of diagnosis between 70-75 years of age. 10% of all cases occur prior to the age of 55 and rarely occurrence is prior to 40 years of age. There is slightly higher incidence in males compared to females (7).

Risk factors are prior high-grade dysplastic colorectal adenomas above 10 mm, prior carcinomas within one´s own history or occurrence within one´s family. Furthermore, a higher risk for diagnosis of colorectal carcinoma exists for people with chronic-inflammatory diseases (like Crohn´s disease or ulcerative colitis) and is also connected with general lifestyle, for example, a high consumption of fat, raw meat, alcohol and smoking and also a low-fiber diet, adipositas, physical inactivity and a history of smoking. Also, prior radiation therapy of the abdomen shows higher risk for the development of colorectal carcinoma. Similarly, there is a higher risk for colorectal carcinoma in familial syndromes, for example, Hereditary Non-Polyposis Colorectal Cancer (HNPCC or Lynch-Syndrome) and familial adenomatous polyposis (FAP), hamartomatous polyposis (familial juvenile polyposis, Peutz-Jeghers-syndrome, PTEN hamartoma syndromes) and other polyposis syndromes caused by different mutations (7). In up to 60% the most common mutations in colorectal cancer are composed of mutations in KRAS or NRAS, which are biomarkers for resistance against anti-EGFR-therapy. In up to 15% activating BRAF-mutations are causative for colorectal cancer and responsible for a worse prognosis due to the more aggressive and therapy-resistant course of the disease. Additionally, mutations which cause deletion or inactivation of tumor-suppressor genes (APC, SMAD4, CDC4, p53) and multifactorial carcinogenesis via activation of oncogenes and microsatellite-instability (MSI) are causative mutations for colorectal cancer disease (7).

Overall, it is noteworthy that the most common type of colorectal cancer is caused by adenocarcinoma with the most common location in the sigma or the rectum itself.

Ways of metastases for colorectal cancer are lymphogenous, hematogenous or *per continuitatem,* which means a continuous spread of cancer cells along anatomical connected structures (9). In lymphogenous metastasis metastases proceed from regional lymph nodes and liver to lungs and peritoneum. In a total of 20% of all cases of primary colorectal cancer, metastases are detected synchronously (7).

Overall, survival of five years is stated from as high as up to 90% in low malignancy states to as low as below 10% in very high malignancy states (10).

1.3.3. Anal carcinoma

Anal carcinoma is defined as malignant tumor of the anal canal (Figure 5) (10).

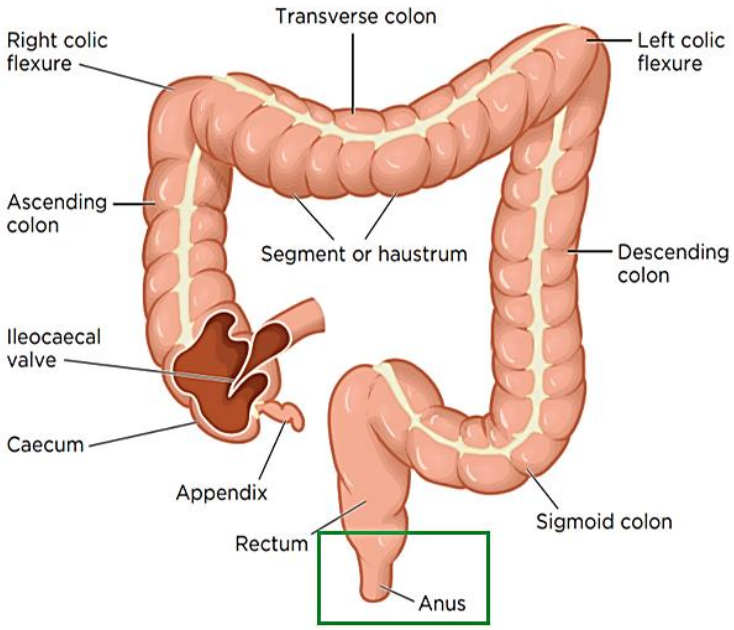

Figure 5. Visualization of localization of anal canal (8)

Since anal carcinoma has an incidence of 0.3 to 1 case per 100.000 and overall below 2% of all rectal carcinomas are carcinomas of anal canal, it is considered a rare disease. It is more common in females and most often diagnosed between the 50 and 60 decade (10).

Conspicuous is an increased incidence among homosexual men and HIV-infected individuals. Additional risk factors are further viral infections, for example, Condylomata accuminata (HPV-16 or HPV-18) and maybe herpes viruses. Furthermore, prior irradiation therapy and also a history of smoking are depicted as risk factors (10).

Carcinoma of anal canal is most commonly of squamous cell origin and defined as squamous cell carcinoma (10).

Metastasis of carcinoma of anal canal is mostly *per continuitatem* (9) via sphincter apparatus, vagina, bladder, urethra and prostate gland. Furthermore, lymphogenous (proximal to dentate line to pararectal and paravertebral lymph nodes) and hematogenous spread (especially in tumor localization above dentate line to liver, lung, skeletal system) is rare (10).

Five-year survival of carcinoma of anal canal is stated as 60 to 80% in low malignancy states and multimodal therapy, for surgery-only treatment around 50% (10).

1.3.4. Renal cell carcinoma

Renal cell carcinoma is defined as malignant disease of kidney (Figure 6), emerging from epithelial cells of renal tubuli (10).

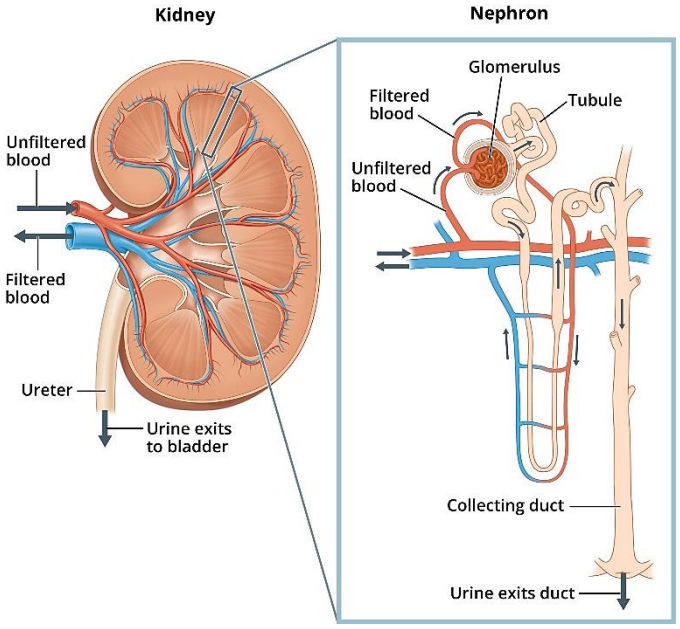

Figure 6. Anatomy of kidney and functional unit of kidney (11)

With an incidence of 10 to 22 cases per 100.000 of all malignant tumors, renal cell carcinoma accounts for 2 to 3% of all malignant tumors. Men are slightly more commonly affected and primary disease most commonly is diagnosed between 60 and 70 years of age (10).

Common risk factors are a history of smoking, adipositas, arterial hypertension as well as prior kidney disease (for example renal insufficiency and long-term dialysis or nephrolithiasis). Furthermore, hepatitis C, ionizing radiation and also exposure to cadmium, asbestos or trichlorethylene count as risk factors. Additionally, abusus of analgesics like Acetaminophen or NSAIDs (non-steroidal anti-inflammatory drugs) are also risk factors (10).

Round about 5 to 8% of all renal cell carcinoma are hereditary whereas 35% out of this group account for Von-Hippel-Lindau syndrome defined by multifactorial bilateral kidney carcinomas. Hereditary clear-cell, papillary and chromophil renal cell carcinoma, tuberous sclerosis and renal cell carcinoma within hereditary cystic kidneys are further entities with risk of malignancy of kidneys (10).

60% of all renal cell carcinomas are found in sonography as incidental findings (12).

Molecular changes and mutations responsible for renal kidney carcinomas are chromosomal aberrations (deletions, translocations, monosomy and trisomy) and changes of oncogenes (c-myc, c-fms, c-erbB, c-met). Changes in VHL-gene (chromosome 3p25) are prevalent in 80% of sporadic renal cell carcinomas (10).

In round about 30% of all renal cell carcinomas distant metastasis is present synchronously (whereas in tumor size below 3 cm diameter metastasis is rarely seen). Most commonly renal cell carcinomas metastasize hematogenously to lung, liver, bones and CNS (central nervous system) and less commonly lymphogenous metastasis (to pelvis and para-aortal) and local metastases emerge. Overall, the most common locations of metastasis in renal cell carcinoma are lungs and mediastinum, followed by regional lymph nodes, liver and skeletal system (10).

Overall, five-year survival in low-malignant stages of disease is round about 80%, decreasing to 50% in high-malignant stages. Different scores (for example Memorial Sloan-Kettering Cancer Center / Motzer-Score, MRCCPS, Glasgow Prognostic Score) are available for additional survival in metastasized disease and only named here for clarification (12).

1.3.5. Metastases

1.3.5.1. Metastases in general

Metastases overall are defined as resettlement of cells of a primary tumor on distant site within the same or other organs. Lung metastases are present in 10% of cases both in colorectal and in renal cell cancer. Most commonly they appear, in case of location within the lungs, with symptoms like cough, hemoptysis, dyspnea, thoracic pain (can be sign of invasion of pleura), general fatigue and weight loss. Nevertheless lung metastases are asymptomatic in most of the cases. Prognosis of metastatic disease depends on histology of primary cancerous disease and is more advantageous in long disease-free intervals, thus from the moment of the diagnosis of disease until the first symptoms of metastases emerge (12).

1.3.5.2. Pathophysiology of metastasis

Organ metastases usually originate from dispersion of tumor cells either into blood stream (hematogenous) or lymphatic vessels (lymphogenous) and from spreading *per continuitatem* (along anatomically connected structures). This spread is influenced by cellular surface markers, genetic determinants and cytokines. The mechanism of metastasis requires multiple, defined steps and only takes place during the course of the disease (12). This pattern is described as "cascade of metastasis" and happens as the following scheme (Figure 7) explains:

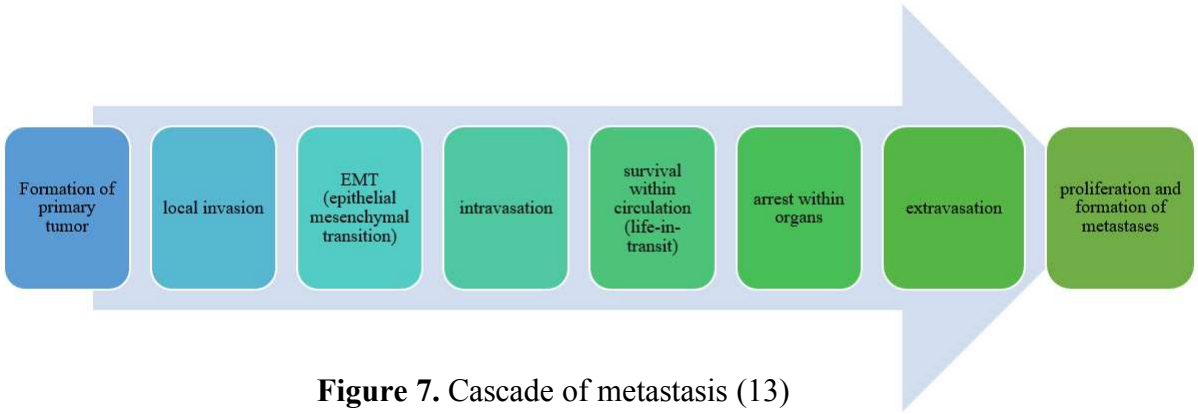

Figure 7. Cascade of metastasis (13)

In colorectal metastases primary destination of metastases is the liver through the portal venous circulation (Figure 8A), whereas the primary location of metastases of renal cell carcinoma lies within the lungs via the capillary network (Figure 8B).

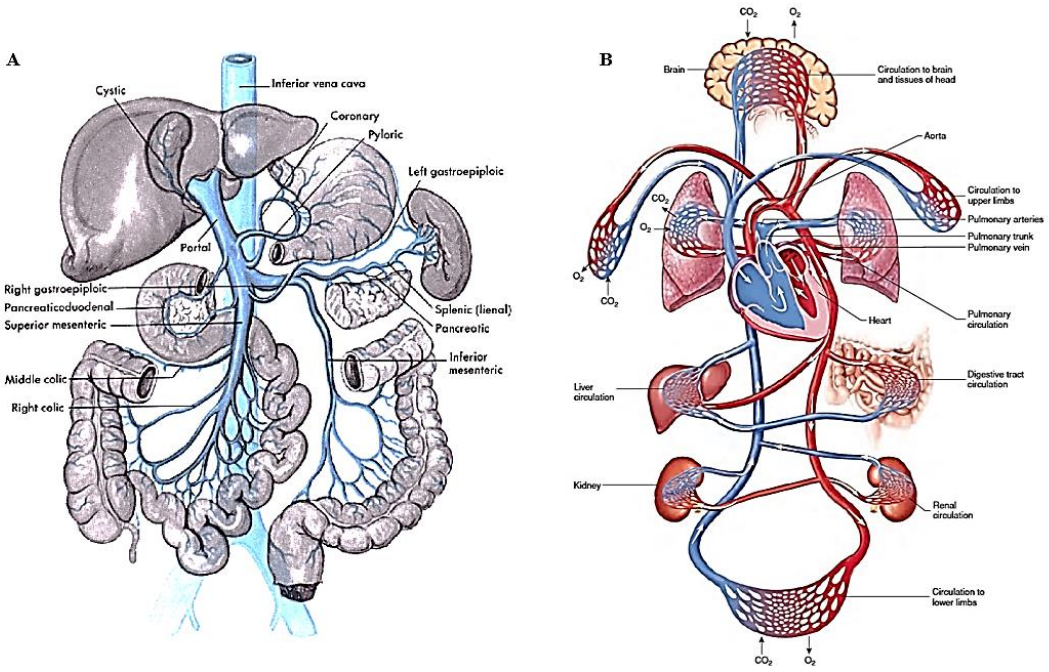

Figure 8. Portal venous system (A) and capillary network kidneys/lungs (B) (14, 15)

1.3.5.3. Types of metastases

Single metastasis is defined as only one solitary metastasis that is present in the entire lung organ.

Multiple metastases in this thesis are defined are bilateral (both of the lungs) but less than two lobes of the lungs are affected. There are different subgroups within the multiple metastases defined. In unilateral lung metastases just one side of the lungs (left or right) exhibits metastases, in bilateral lung metastases both sides of the lungs are affected. In unilobar lung metastases just one single lobe of the lung exhibits metastases. Multilobar lung metastases are defined as occurrence of metastases in more than two lobes of the lung (regardless of the affected site of the lungs).

Diffuse metastases are here defined as bilateral (both of the lungs affected) and more than one metastasis per lobe is present.

Synchronous metastases in general are defined as simultaneous appearance of metastases with primary tumor. These metastases are, for purpose of this thesis, here defined as metastases of primary carcinoma either at time of or within 6 months of diagnosis of primary tumor. Metachronous metastases are in general all metastases emerging later after diagnosis of primary tumor and are here defined as emergence of metastases 6 months or later after the diagnosis of the primary cancer (12).

Thoracic lymph node metastases affect any lymph node within the thoracic cavity or the mediastinum (Figure 9). In this thesis it is not distinguished between synchronous or metachronous appearance of lymph node metastases.

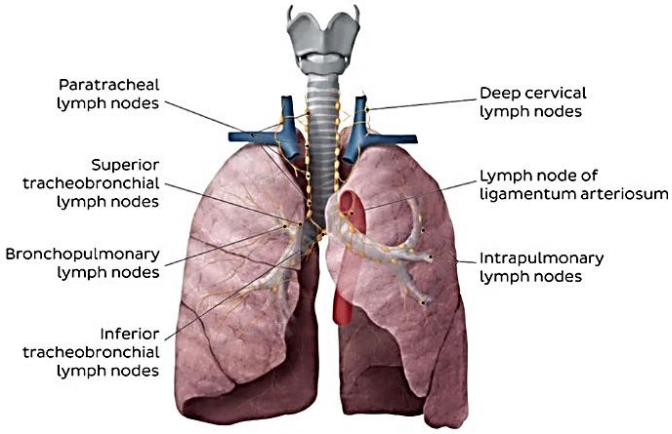

Figure 9. Lymph nodes of thoracic cavity and mediastinum (16)

1.3.6. Multimorbidity

Multimorbidity in this thesis is defined as more than 3 different chronic organ system diseases that require regular medical intervention/check-up and/or regular uptake of medication (for example, thyroid disease, cardiovascular disease, diabetes, epilepsy, hyperuricemia, anemia et cetera).

1.3.7. Immunosuppression

Immunosuppression in this thesis is specified as any condition that influences the action, reaction and therefore physiologic function of the immune system (for example diabetes, alcohol, medications, cachexia et cetera).

1.3.8. Survival

Survival is here defined as the time-span between diagnosis of primary carcinoma and either deceasing of the affected individual or survival of the individual beyond the time span of this study (beyond February 1, 2022).

1.3.9. TNM-classification

TNM-classification denotes an international standardized classification system that allows the staging and the follow-up of solid tumors. It is based on the tumor size (T), the lymph node affection (N) and the distant metastases (M) (17). All detailed TNM-stages of the patients of this thesis are attached in the supplement (Table 19).

2. OBJECTIVES

2.1. Aims

The purpose of this thesis is to evaluate whether localization and amount of only lung metastases can influence the prognosis of the disease.

Furthermore, if there is a difference in prognosis and therefore survival, this thesis can be used to eventually adapt therapeutic interventions in further studies for different subgroups of metastases and thereby, maybe, even help to create more favorable outcomes and thus increase survival in given groups of patients.

2.2. Hypothesis

In primary colorectal or renal cell carcinoma unilateral lung metastases have a better prognosis than bilateral lung metastases.

In primary colorectal or renal cell carcinoma unilobar lung metastases have a better prognosis than multilobar lung metastases.

In primary colorectal or renal cell carcinoma metachronous lung metastases have a better prognosis than synchronous lung metastases.

In primary colorectal or renal cell carcinoma single lung metastases have a better prognosis than multiple lung metastases.

3. SUBJECTS AND METHODS

3.1. Collection of data

Data collection was conducted in the Regiomed Clinic Coburg in the time span from October 1, 2021 to April 1, 2022. The sample of patients included in this study were all patients diagnosed with primary colorectal or renal cell carcinoma and only lung metastases in all prior defined clinics of Regiomed clinic association.

First of all, to collect the necessary data, all patients administered to hospitals within the Regiomed clinic association were separated by inclusion criteria primary colorectal carcinoma or primary renal cell carcinoma. After this initial step, patients with one of these two primary cancers were further sorted according to the type of metastases and filtered according to inclusion and exclusion criteria. After the collection of the sample of patients, data of each single patient were sighted for inclusion criteria according to medical reports, histopathological findings and medical imaging via computer tomography images at the time of diagnosis of primary cancer. Aforementioned data sources were also used to group patients corresponding to the localization and the amount of lung metastases.

Additional data collected were

- age at diagnosis and gender (female / male)
- distance of residence to specialized hospital Coburg
- history of smoking and alcohol
- obesity according to WHO: BMI > 30 (18)
- amount of pre-existing disease / multimorbidity
- immunosuppression at time of diagnosis
- time of first therapeutic approach
- initiated / implemented sort of therapy (chemotherapy, radiotherapy, surgery)
- further tumors / metastases during course of disease

3.2. Subjects

The sample of patients comprises of all the hospitalized population of the Regiomed clinic association between January 1, 2018 and February 1, 2022 with newly diagnosed primary colorectal or renal cell carcinoma and only lung metastases. The primary cancer of the patients was treated adapted to the stage of the disease according to the valid German S3-guidelines.

The inclusion criteria comprised only lung metastases (synchronous or metachronous lung metastases), thoracic lymph node metastases and hospitalization in one of the clinics of the Regiomed clinic association. All patients were included regardless of gender, race and age.

Exclusion criteria were prior cancerous diseases, multiple cancer disease at time of diagnosis or additional metastases apart from lung metastases at time of diagnosis. Also excluded were patients with primary diagnosis prior to January 1, 2018 and after February 1, 2022. Furthermore, patients from other hospitals outside the hospitals of Regiomed clinic association were not taken into account.

3.3. Study description

3.3.1. Study design

Thesis design is a retrospective observational study composed of patients only from Regiomed clinic association with data processed from October 1, 2021 to April 1, 2022.

3.3.2. Primary outcomes

Primary outcome measure of this thesis is the difference in prognosis defined as survival over a given time period in different types of metastases in percent. Outcomes important for patients are described with p-value. Significance will be controlled via confidence interval in measuring unit of percentage.

3.3.3. Secondary outcomes

Secondary outcomes of this study are differences in prognosis with regard to survival over a given time period with respect to additional criteria (alcoholism, smoking, further tumor/metastasis during disease, distance of residence to specialized hospital Coburg, age at diagnosis, adipositas, multimorbidity, immunosuppression at diagnosis, point of first intervention, different types of treatments).

3.4. Ethics

The international review board of the Medical School Regiomed Coburg approved this type of research based on §2 of the statutes (sign STWA/MICA, Marc 18, 2022).

3.5. Statistical analysis, statistical significance values

Analysis of the results were conducted by IBM SPSS Statistics version 27. For survival analysis Kaplan-Meier analysis was used and for comparison of groups Logrank analysis has been applied. The level of significance was determined at $p < 0.05$.

Observations were described as mean and median with additional usage of 95% confidence interval.

For distinction and verification of dependence of variables the Chi-square test was applied (Chi-square test $\chi^2 = \sum \frac{(O-E)^2}{E}$, whereas O is observed frequency and E expected frequency).

Variables like initial therapy, alcohol abuse and chemotherapy as single treatment were not analyzed since the sample size therefore was too small. Furthermore, for renal cell cancer factors like adipositas and affection of both kidneys with cancer were also not taken into account due to the small sample size.

4. RESULTS

This thesis includes 35 patients (25/35 patients with primary colorectal carcinoma and 10/35 with renal cell carcinoma). Inclusion criteria were newly diagnosed primary colorectal or renal cell carcinoma with only lung metastases. Incorporated patients were hospitalized in Regiomed clinic association between January 1, 2018 to February 1, 2022.

The group of the primary colorectal cancer patients (25/35) with only lung metastases is composed of 11/25 females and 14/25 males. At time of the diagnosis of the primary colorectal cancer 5/25 patients were below the age of 60 and 20/25 were older than 60 years. Within the group of the primary colorectal cancer patients 10/25 patients exhibited synchronous metastases and 15/25 patients developed metachronous metastases. In 5/25 patients singular metastases were present, 20/25 patients exhibited multiple metastases. Within the group of multiple metastases 3/25 patients had unilobar and 16/25 patients multilobar metastases, 5/25 patients presented with unilateral and 14/25 patients manifested bilateral metastases, 12/25 patients showed diffuse metastases and in 11/25 patients the thoracic lymph nodes were affected. An additional tumor despite the primary cancer was detected in 4/25 patients and additional metastases were diagnosed in 17/25 patients during the course of the disease. At the time of the closure of the thesis 5/25 patients were still alive and 3/25 did not survive the first year after the diagnosis of the primary colorectal cancer. A total of 6/25 patients survived more than two years and 5/25 patients more than 3 years, 5/25 patients survived more than 5 years but less than 10 years and 1/25 patient survived more than 10 years after the diagnosis of the primary colorectal cancer. With reference to lifestyle 5/25 patients had a history of smoking, 1/25 patient a history of alcohol abuse and 11/25 patients were obese. A total of 7/25 patients were immunosuppressed at the time of the primary cancer diagnosis and 8/25 patients were multimorbid. All 25/25 patients received primary treatment within 30 days after the diagnosis of the primary cancer. According to the primary cancer 1/25 patient had only chemotherapy, 4/25 only surgery and 20/25 patients underwent both therapeutic interventions together.

The group of the primary renal cell cancer patients (10/35) with only lung metastases is composed of 4/10 females and 6/10 males. At the time of the diagnosis of the primary cancer 3/10 patients were below the age of 60 and 7/10 were older than 60 years when diagnosed with the primary renal cell cancer. Within this group, 6/10 patients exhibited synchronous and 4/10 patients developed metachronous metastases. In 2/10 patients singular metastases were present, 8/10 patients exhibited multiple metastases. Within the group of multiple metastases 2/10 patients had unilobar metastases, 8/10 patients multilobar metastases, 3/10 patients unilateral metastases and 7/10 patients manifested bilateral metastases. A total of 7/10 patients showed

diffuse metastases and in 6/10 patients the thoracic lymph nodes were affected. An additional tumor despite the primary cancer was detected in 3/10 patients and additional metastases were diagnosed in 7/10 patients during the course of the disease. At the time of the thesis closure 1/10 patient was still alive, 3/10 did not survive the first year, 3/10 patients survived less than 2 years and no patient survived between two to five years. A total of 2/10 patients survived more than 5 years and 1/10 patient survived more than ten years after diagnosis. With reference to lifestyle, 1/10 patient had a history of smoking, 0/10 patient had a history of alcohol abuse and 1/10 patient was obese at the time of the primary cancer diagnosis. A total of 3/10 patients were immunosuppressed at the time of the primary cancer diagnosis and 5/10 patients were multimorbid. In 8/10 patients primary treatment was within 30 days after the diagnosis of the primary cancer. According to the primary cancer 0/10 patient had only chemotherapy, 5/10 patients had only surgery and 5/10 patients underwent both therapeutic interventions together.

The total group of all patients (35/35) with only lung metastases is composed of 15/35 females and 20/35 males. At the time of the diagnosis of the primary cancer 8/35 patients were below the age of 60 and 27/35 were older than 60 years. In 16/35 patients synchronous metastases were present and 19/35 patients developed metachronous metastases. In 7/35 patients singular metastases were present, 18/35 patients exhibited multiple metastases. Within the group of multiple metastases 5/35 patients had unilobar metastases, 24/35 patients multilobar metastases, 8/35 patients unilateral metastases and 21/35 patients manifested bilateral metastases. A total of 19/35 patients showed diffuse metastases and in 17/35 patients the thoracic lymph nodes were affected. An additional tumor despite the primary cancer was detected in 7/35 patients and additional metastases were diagnosed in 24/35 patients during the course of the disease. At the time of the thesis closure 6/35 patients were still alive and 6/35 did not survive the first year after the diagnosis of the primary cancer, 3/35 patients survived more than 1 but less than 2 years, 6/35 patients survived more than 2 years, 5/35 patients survived more than 3 years, 7/35 more than 5 years and 2/35 patients more than 10 years after diagnosis of primary cancer. With reference to lifestyle, 6/35 patients had a history of smoking, 1/35 patient a history of alcohol abuse and 12/35 patients were obese. A total of 10/35 patients were immunosuppressed at time of primary cancer diagnosis and 13/35 patients were multimorbid. A total of 33/35 patients received primary treatment within 30 days after the diagnosis of the primary cancer. According to primary cancer 1/35 patient had only chemotherapy, 9/35 patients only surgery and 25/35 patients underwent both therapeutic interventions together. The detailed distribution of the specific characteristics is shown in the following tables (Table 1-3).

Table 1. Characteristics of patients with colorectal cancer

type / criteria	subtype	no. of patients
synchronous metastases		10
metachronous metastases		15
singular metastasis		5
multiple metastases	unilobar	3
	multilobar	16
	unilateral	5
	bilateral	14
diffuse metastases (bipulmonal + > 1 /lobe)		12
thoracic lymph nodes affected		11
additional tumor in course of disease		4
additional metastases in course of disease		17
survival after diagnosis	< 1 year	3
	< 2 years	0
	> 2 years	6
	> 3 years	5
	> 5 years	5
	> 10 years	1
	still alive at time of thesis closure (01-02-2022)	5
residence	< 10 km away from specialized center Coburg	5
	> 10 km away from specialized center Coburg	5
	> 20 km away from specialized center Coburg	14
	> 50 km away from specialized center Coburg	1
age at diagnosis	< 60 years of age	5
	> 60 years of age	20
gender distribution	females	11
	males	14
smoking		5
alcohol abuse		1
adipositas		11
multimorbidity		8
immunosuppression		7
primary treatment within 30 days after diagnosis		25
chemotherapy of only		1
surgery of primary cancerous disease only		4
radio-/chemotherapy and surgery		20
total no. colorectal cancer and only lung metastases		**25**

Data are presented as numeric values.

Table 2. Characteristics of patients with renal cell cancer

type / criteria	subtype	no. of patients
synchronous metastases		6
metachronous metastases		4
singular metastasis		2
multiple	unilobar	2
	multilobar	8
	unilateral	3
	bilateral	7
diffuse (bipulmonal + > 1/lobe)		7
thoracic lymph nodes affected		6
additional tumor in course of disease		3
additional metastases in course of disease		7
survival after diagnosis	< 1 year	3
	< 2 years	3
	> 2 years	0
	> 3 years	0
	> 5 years	2
	> 10 years	1
	still alive at time of thesis closure (01-02-2022)	1
residence	< 10 km away from specialized center Coburg	2
	> 10 km away from specialized center Coburg	1
	> 20 km away from specialized center Coburg	7
	> 50 km away from specialized center Coburg	0
age at diagnosis	< 60 years of age	3
	> 60 years of age	7
gender distribution	females	4
	males	6
smoking		1
alcohol abuse		0
adipositas		1
multimorbidity		5
immunosuppression		3
primary treatment within 30 days after diagnosis		8
chemotherapy only		0
surgery of primary cancerous disease only		5
radio-/chemotherapy and surgery		5
total no. renal cell cancer and only lung metastases		**10**

Data are presented as numerical values.

Table 3. Characteristics of complete sample of patients

type / criteria	subtype	no. of patients
synchronous metastases		16
metachronous metastases		19
singular metastasis		7
multiple	unilobar	5
	multilobar	24
	unilateral	8
	bilateral	21
diffuse (bipulmonal + > 1/lobe)		19
thoracic lymph nodes affected		17
additional tumor in course of disease		7
additional metastases in course of disease		24
survival after diagnosis	< 1 year	6
	< 2 years	3
	> 2 years	6
	> 3 years	5
	> 5 years	7
	> 10 years	2
	still alive at time of thesis closure (01-02-2022)	6
residence	< 10 km away from specialized center Coburg	7
	> 10 km away from specialized center Coburg	6
	> 20 km away from specialized center Coburg	21
	> 50 km away from specialized center Coburg	1
age at diagnosis	< 60 years of age	8
	> 60 years of age	27
gender distribution	females	15
	males	20
smoking		6
alcohol abuse		1
adipositas		12
multimorbidity		13
immunosuppression		10
primary treatment within 30 days after diagnosis		33
chemotherapy only		1
surgery of primary cancerous disease only		9
radio-/chemotherapy and surgery		25
total no. renal cell cancer/colorectal cancer and only lung metastases		**35**

Data are presented as numerical values.

4.1. Analysis colorectal carcinoma

In total, 25 patients (N = 25) with colorectal carcinoma were analyzed. In this group, 20 patients died within the observational time span and 5 patients survived. Overall, the median survival within the colorectal carcinoma group was 52 months (95% confidence interval: 37.2 to 66.8 months). Number of events were here 20 (5 censored) and 20.0%.

Median time of survival of patients with synchronous metastases was significant lower compared to that of patients with metachronous metastases (p = 0.040).

Table 4. Synchronous metastases in colorectal carcinoma: Chi-square-test

Synchronous metastases	Total N	N of Events	Censored	
			N	Percent
no	15	13	2	13.3%
yes	10	7	3	30.0%
overall	25	20	5	20.0%

N = absolute rate

Table 5. Survival in synchronous lung metastases in colorectal carcinoma

Synchronous metastases	Mean[a] 95% Confidence interval	Median 95% Confidence interval
no	39.446 – 96.087	26.088 – 81.912
yes	24.123 – 45.877	23.191 – 52.809
overall	36.987 – 78.720	37.196 – 66.804

[a] Estimation limited to largest survival time if it is censored
P-value: Logrank test = p-value 0.040

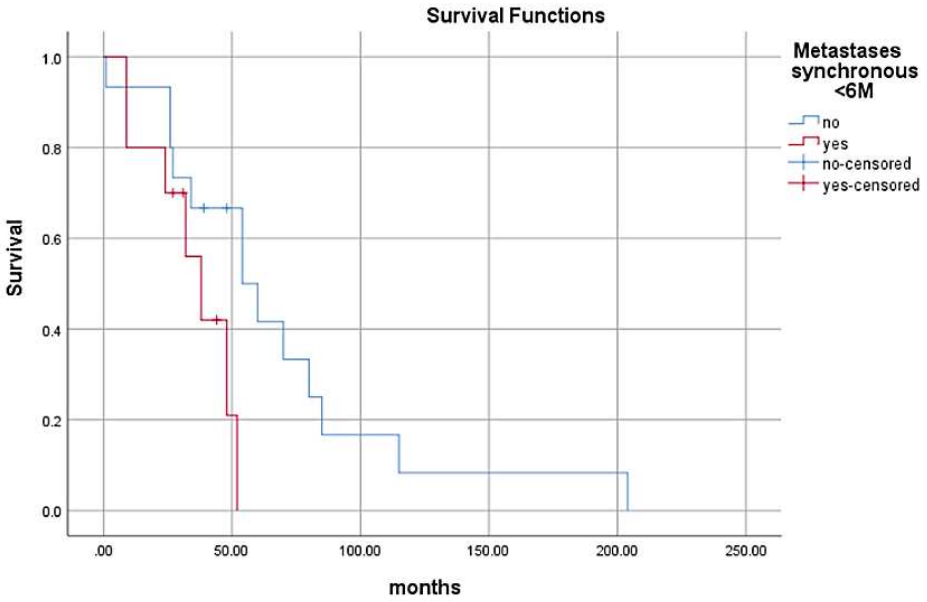

Figure 10. Synchronous/metachronous metastases in colorectal carcinoma

Comparing survival of patients with singular to those with multiple metastases, there was no significant difference in median survial between both groups (p = 0.821). Comparing patients with unilobar and multilobar metastases, no significant difference in median survival between both groups was revealed (p = 0.873). Furthermore, patients with bilateral metastases did not show any inferior survival and therefore bilateral metastases were of no statistical relevance in respect to survival (p = 0.079). Additionally, lymph node metastases did not have any statistically relevant influence on survival either (p = 0.174).

Nevertheless, a statistically higher median survival time was noted in non-presence of diffuse metastasis (p = 0.045).

Table 6. Diffuse lung metastases in colorectal carcinoma: Chi-square-test

Diffuse metastases	Total N	N of Events	Censored	
			N	Percent
no	13	11	2	15.4%
yes	12	9	3	25.0%
overall	25	20	5	20.0%

N = absolute rate

Table 7. Survival in diffuse lung metastases in colorectal carcinoma

Diffuse metastases	Mean[a] 95% Confidence interval	Median 95% Confidence interval
no	40.64 – 102.99	45.73 – 62.27
yes	22.41 – 55.03	21.55 – 42.45
overall	36.98 – 78.72	37.20 – 66.80

[a] Estimation limited to largest survival time if it is censored
P-value: Logrank test = p-value 0.045

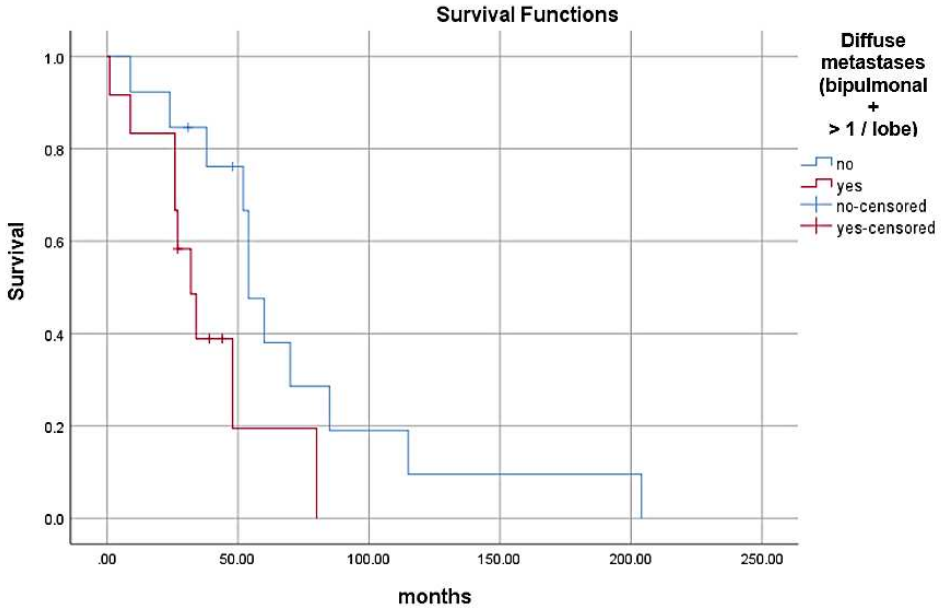

Figure 11. Survival functions of diffuse lung metastases in colorectal carcinoma

In addition, it is noteworthy that with regard to survival no statistically significant differences were found for factors like additional tumors (p = 0.977), appearance of additional metastases during disease (p = 0.996) or distance of residence to specialized center Coburg (p = 0.068). Also sex (male or female) does not make a statistically significant difference in survival (p = 0.776), neither does smoking (0.263), adipositas (p = 0.379), multimorbidity (p = 0.103) or immunosuppression (p = 0.880). Likewise, the type of therapy applied was also not a statistically significant factor for survival (p = 0.631).

4.2. Analysis renal cell carcinoma

In total, 10 patients (N = 10) with renal cell carcinoma were included in this thesis. During the interval of observation 9 patients died (N of events = 9) and one survived (N censored = 1). Median survival of patients with diagnosed renal cell carcinoma and metastases was 19 months (95% confidence interval: 17.5 to 20.5 months).

For renal cell carcinoma patients there was no statistically significant difference between factors like synchronous compared to metachronous appearance of lung metastases (p = 0.052) or singular compared to multiple metastases (p = 0.345). There was also no statistically relevant difference in survival between patients with bilateral metastases (p = 0.147) and diffuse metastases (p = 0.147). Additionally, lymph node metastases also showed no relevant influence on survival (p = 0.158). Furthermore, the appearance of an additional tumor (p = 0.089) or of metastases (p = 0.338) did not constitute a significant impact on survival. Also, the distance of residence to the specialized center Coburg had no significant statistical value (p = 0.068). Likewise did sex (male or female) have no significant statistical influence on survival (p = 0.235), neither did smoking (p = 0.176), multimorbidity (p = 0.996) or immunosuppression at time of diagnosis of primary renal cell carcinoma (p = 0.109). Moreover, data were collected to evaluate whether cancer involvement of renal pelvis influenced survival but this was not the case (p = 0.452). Also, affection of one or both kidneys did not make a statistically relevant difference in survival (p = 0.972).

But within this group of patients with renal cell carcinoma and metastases there was a statistically significant difference in median survival between patients with unilobar and those with multilobar lung metastases (p = 0.045).

Table 8. Unilobar metastases in renal cell carcinoma: Chi-square-test

Unilobar metastases	Total N	N of Events	Censored	
			N	Percent
no	8	7	1	12.5%
yes	2	2	0	0.0%
overall	10	9	1	10.0%

N = absolute rate

Table 9. Survival in unilobar and multilobar lung metastases in renal cell carcinoma

Unilobar and multilobar metastases	Mean[a] 95% Confidence interval	Median 95% Confidence interval
no	7.14 – 42.36	7.84 – 28.16
yes	32.72 – 348.28	.
overall	4.96 – 127.71	17.48 – 20.52

[a] Estimation limited to largest survival time if it is censored.
P-value: Logrank test = p-value 0.045

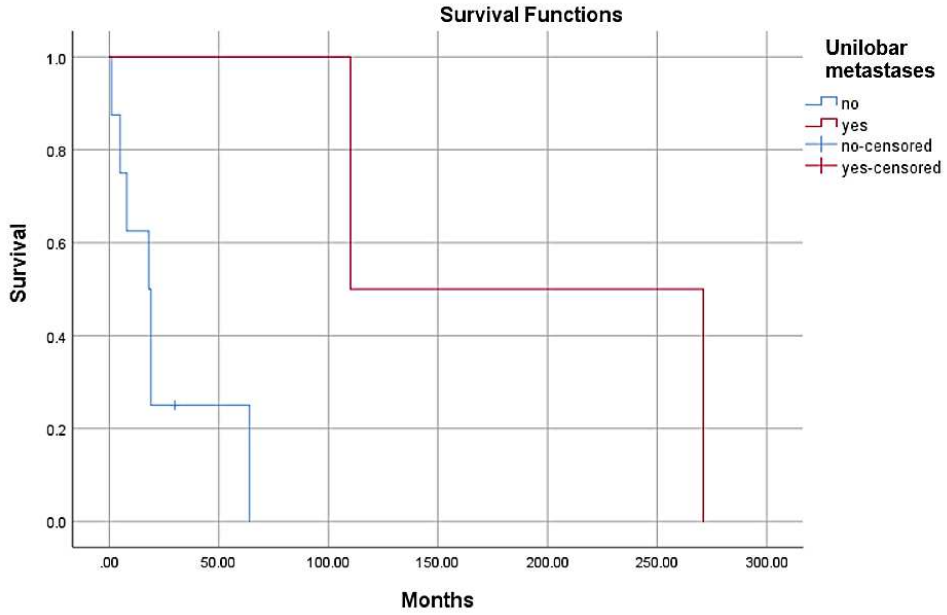

Figure 12. Survival functions of uni-/multilobar metastases in renal cell carcinoma

4.3. Association of colorectal carcinoma and renal cell carcinoma

In association and comparison of colorectal carcinoma and renal cell carcinoma as primary cancers (N = 35) it appeared that median survival in colorectal cancer would be higher (48 months with confidence interval: 30.1 to 65.9 months) than median survival in renal cell carcinoma (19 months with confidence interval: 17.5 to 20.5 months). However, the difference between the groups of colorectal and renal cell carcinoma did not turn out statistically significant (p = 0.802).

Table 10. Metastases in colorectal and renal cell carcinoma: Chi-square-test

Type	Total N	N of Events	Censored	
			N	Percent
colorectal	25	20	5	20.0%
renal cell	10	9	1	10.0%
overall	35	29	6	17.1%

N = absolute rate

In association of colorectal and renal cell carcinoma (shortened to "in association" in the following tables) a significant statistical difference was detected with regard to median survival of patients with synchronous and those with metachronous appearance of metastases (p = 0.002).

Table 11. Synchronous lung metastases in association: Chi-square-test

Synchronous metastases in association	Total N	N of Events	Censored	
			N	Percent
no	15	13	2	13.3%
yes	10	7	3	30.0%
overall	25	20	5	20.0%

N = absolute rate

Table 12. Survival in synchronous lung metastases in association

Synchronous metastases in association	Mean[a] 95% Confidence interval	Median 95% Confidence interval
no	46.39 – 112.79	41.06 – 78.94
yes	18.40 – 37.22	4.40 – 43.60
overall	37.29 – 84.05	30.14 – 65.86

[a] Estimation limited to largest survival time if it is censored.
P-value: Logrank test = p-value 0.002

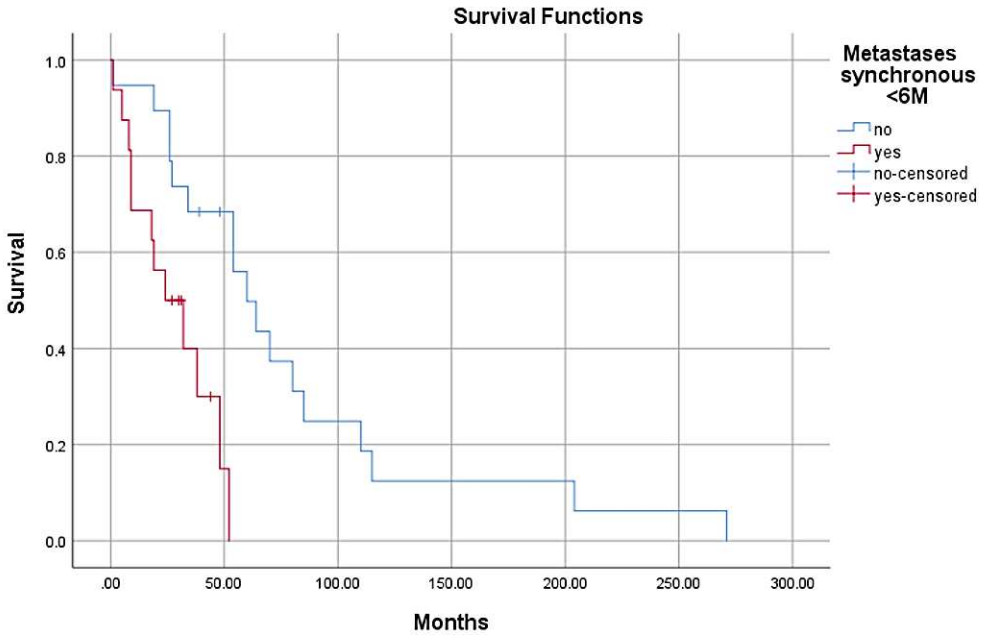

Figure 13. Survival functions synchronous lung metastases in association

A statistically significant difference in survival (p = 0.011) was also detected in comparison of bilateral and unilateral metastases.

Table 13. Bilateral lung metastases in association: Chi-square-test

Bilateral metastases in association	Total N	N of Events	Censored	
			N	Percent
no	14	12	2	14.3%
yes	21	17	4	19.0%
overall	35	29	6	17.1%

N = absolute rate

Table 14. Survival in bilateral lung metastases in association

Bilateral metastases in association	Mean[a] 95% Confidence interval	Median 95% Confidence interval
no	46.54 – 134.67	51.34 – 68.66
yes	23.68 – 49.36	18.56 – 35.44
overall	37.29 – 84.05	30.14 – 65.86

[a] Estimation limited to largest survival time if it is censored.
P-value: Logrank test = p-value 0.011

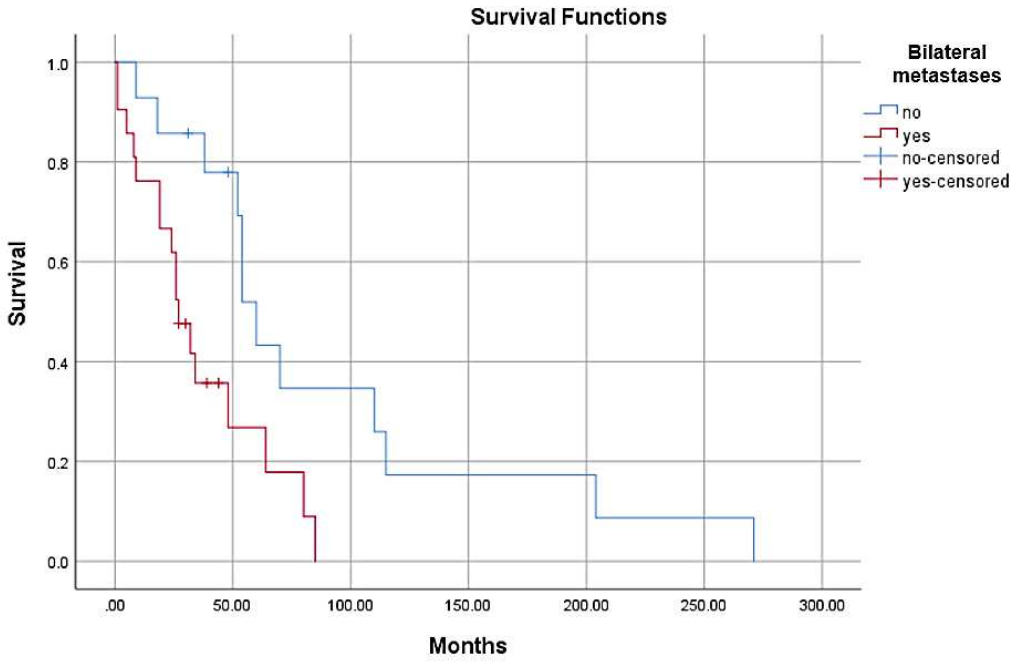

Figure 14. Survival functions uni-/bilateral metastases in association

Moreover, in the absence of diffuse metastases, which means, in case of bipulmonal metastases and presence of less than one metastasis per lobe, a significant difference in time of survival of patients in comparison to those patients with diffuse metastases was detected ($p = 0.007$).

Table 15. Diffuse lung metastases in association: Chi-square-test

Diffuse metastases in association	Total N	N of Events	Censored	
			N	Percent
no	16	14	2	12.5%
yes	19	15	4	21.1%
overall	35	29	6	17.1%

N = absolute rate

Table 16. Survival in diffuse lung metastases in association

Diffuse metastases in association	Mean[a] 95% Confidence interval	Median 95% Confidence interval
no	47.16 – 124.49	50.66 – 69.34
yes	21.09 – 45.99	14.06 – 39.94
overall	37.29 – 84.05	30.14 – 65.86

[a] Estimation limited to largest survival time if it is censored.
P-value: Logrank test = p-value 0.007

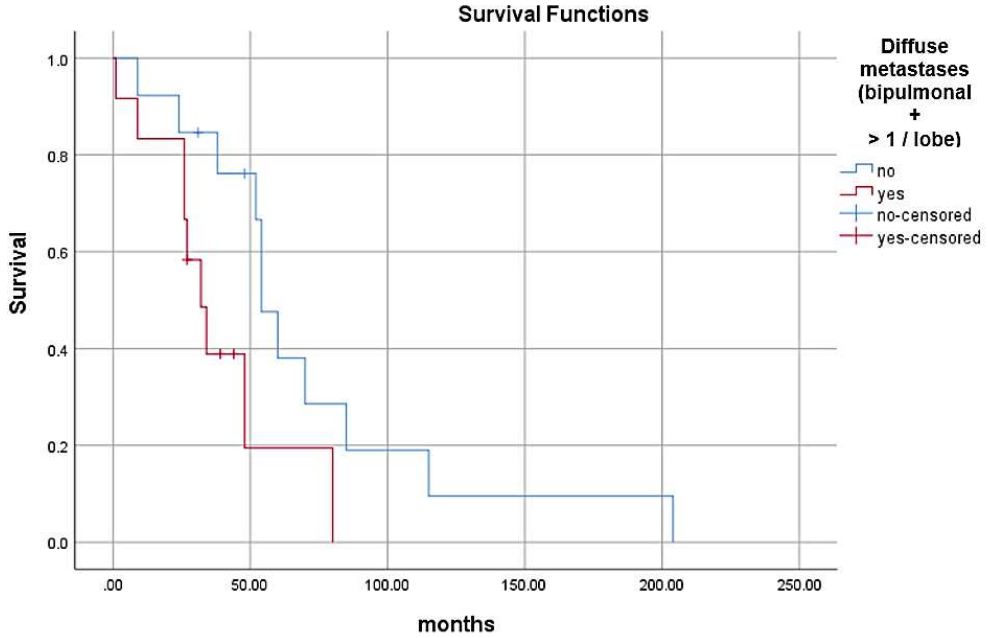

Figure 15. Survival functions of diffuse lung metastases in association

It is also noteworthy that median survival in patients with or without lymph node metastases showed statistically significant difference in survival (p = 0.024).

Table 17. Lymph node metastases in association: Chi-square-test

Lymph node metastases in association	Total N	N of Events	Censored	
			N	Percent
no	19	14	5	26.3%
yes	16	15	1	6.3%
overall	35	29	6	17.1%

N = absolute rate

Table 18. Survival in lymph node metastases in association

Lymph node metastases in association	Mean[a] 95% Confidence interval	Median 95% Confidence interval
no	42.82 – 127.87	26.09 – 93.91
yes	22.40 – 49.04	20.12 – 31.88
overall	37.29 – 84.05	30.14 – 65.86

[a] Estimation limited to largest survival time if it is cencored.
P-value: Logrank test = p-value 0.024

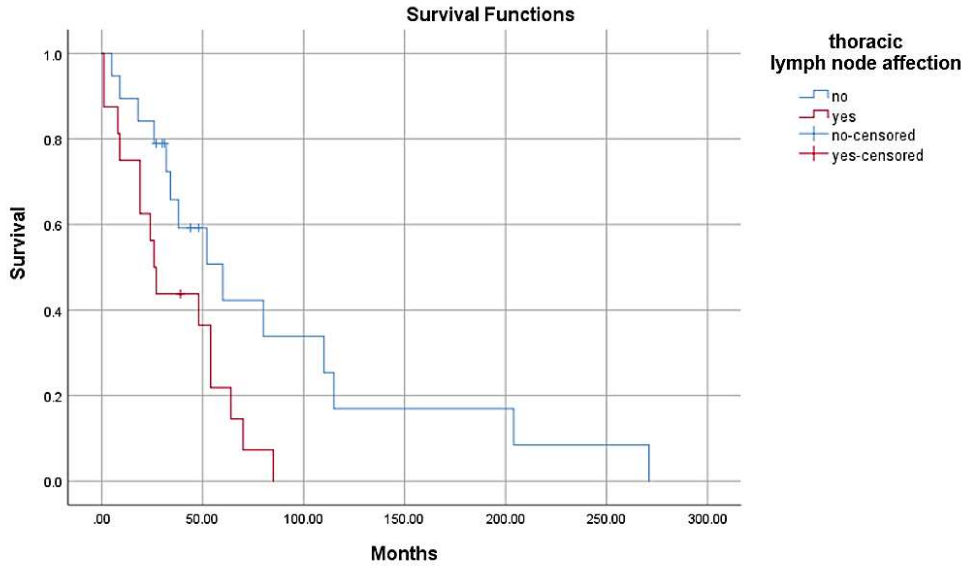

Figure 16. Thoracic lymph node affection in association

Overall, regarding both primary colorectal carcinoma with lung metastases and primary renal cell carcinoma with lung metastases there were factors that were not statistically significant. First of all, there was no statistically relevant difference in survival neither in comparison between singular and multiple lung metastases ($p = 0.447$) nor unilobar compared to multilobar metastases ($p = 0.141$). Also, the appearance of additional tumors ($p = 0.201$) or metastases ($p = 0.724$) during the course of disease was not identified as a statistically significant factor of survival. Furthermore, the distance of residence to the specialized clinic Coburg did not have a statistically relevant influence on survival ($p = 0.331$). Additionally, neither did the cofounding factor of sex (male or female) have a statistical relevance ($p = 0.336$) nor were factors like smoking ($p = 0.573$), adipositas ($p = 0.108$), multimorbidity ($p = 0.297$) or immunosuppression ($p = 0.527$) decisive for a statistically significant difference in median survival. Finally, the type of therapy, for example radio-/chemotherapy plus surgery ($p = 0.584$) or only surgery ($p = 0.368$) did not have a statistical relevance or make a difference in median survival.

5. DISCUSSION

Up to now, the biggest published study related to pulmonary metastases is a retrospective multicenter study by the International Registry of Lung Metastasis. In this study 5206 patients were analyzed and the results identified a row of prognostic factors as for example the histology of the primary cancer, the R0-resection of the primary tumor and the metastases, the disease-free intervals between the primary cancer and metastases and the number of metastases. However, influence of localization and bilaterality of metastases was insufficiently investigated in this study (19).

In September 2021, the thirtieth annual conference of German association of Thoracic Surgery (Deutsche Gesellschaft für Thoraxchirurgie) took place in Erfurt (Germany). During this conference new publications were presented and one of them, a study of two clinics in Regensburg in Germany, showed that emerging pulmonary metastasis of colorectal carcinoma might not be influenced by localization of primary tumor (20). During the discussion of the results of the study of Loch and colleagues also discussion of amount of lung metastases emerged and the question was raised whether the localization and the amount of lung metastases in colorectal cancer might influence the prognosis of the disease in general.

In 2003 the University of Heidelberg in Germany conducted the study "Prognostic factors and survival after complete resection of pulmonary metastases from colorectal carcinoma: Experiences in 167 patients" (21). In total, 167 patients were included and the study was carried out in the time span from 1985 to 2000 (21). According to this study post-surgical survival was significantly higher in patients with solitary metastasis. In the conclusion, it is stated that the "number of pulmonary metastases were identified as prognosis-related criteria for surgery" (21). Also mentioned was synchronous and metachronous appearance of metastases with no difference in prognosis in both groups. Additionally, better prognosis for patients without lymph node metastases was observed (21). Since the previously mentioned study depicts a difference in survival related to the amount of lung metastases, our study tried to find out whether the localization of metastases itself can influence the rate of survival of affected patients. Therefore, it was aimed not only at studying affection of one or more lobes of the lung predicts a difference in prognosis, but also it was to investigate whether unilateral or bilateral affection of the lungs could also make a difference in survival. As the prior study included only patients with primary cancer of colorectal region, it was also necessary to compare a group of patients with colorectal cancer to other groups of cancerous diseases.

Therefore, the decision was made to also include patients with primary renal cell carcinoma in this thesis since this kind of cancer also spreads regularly to the lungs via hematogenous route, which constitutes a plausible criterion for the inclusion in this thesis. The purpose of this thesis was to investigate whether the localization and the amount of lung metastases can influence the prognosis of the disease. Furthermore, if there was a difference in prognosis and therefore survival, this thesis could be used to encourage further studies in defined subgroups of metastases in the future and thereby eventually help to create favorable outcomes and thus increase survival in patients.

Lien and colleagues stated that CT scans are superior in detection of lung metastases compared to chest radiographs (22). Notwithstanding, for verification of existence of lung metastases, not only chest computed tomography scans were used in this thesis for the prove of lung metastases but also medical records, CT dynamics and histopathological evidence as data sources were included.

Our study has shown that there are some statistically significant differences in survival especially in association of colorectal and renal cell carcinoma. Foremost, metachronous metastases, unilateral metastases, lack of diffuse metastases and absence of lymph node metastases showed statistically significant difference in median survival time when compared to synchronous metastases, bilateral metastases, existence of diffuse metastases and presence of lymph node metastases. These results are divergent to some findings of other published studies.

A better survival of patients with unilateral metastases correlates with outcomes of Schott and coworkers whereupon “patients with pulmonary metastases < 2 cm in diameter and limited to one site had prolonged survival compared with other patients” (23) particularly in patients with primary renal cell carcinoma (23). Additionally, superior median survival seems to be present in patients with primary renal cell carcinoma and unilobar metastases compared to patients with multilobar affection.

Our findings partially correlate with prior studies, especially with the aforementioned German study “Prognostic factors and survival after complete resection of pulmonary metastases from colorectal carcinoma: Experiences in 167 patients” (21) which revealed that survival after metastasectomy in “patients with up to 4 lung metastases (139/167) showed a significantly better overall survival compared with patients with more than 4 metastatic lesions” (21).

In our group of patients ten times metastasectomy was performed. All ten patients survived more than two years after diagnosis of primary cancer which supports the theory of Pfannschmidt and colleagues. Detailed TNM-stages and information according surgical treatment of every included patient is attached in the supplement (Table 19).

The lack of thoracic lymph node metastases was also a factor for better median survival, which correlates with findings of the study of the Department of Thoracic Surgery Heidelberg (21) according to which there was "only a 6% survival rate at 4 years" (24) for "patients with hilar or mediastinal lymph node metastases" (24). But in contrast to the referred study from Heidelberg, which showed no statistically relevant difference in survival between synchronous and metachronous metastases (21), our thesis detected a better median survival in metachronous metastases as mentioned before.

Despite initial presumption of better survival of patients with colorectal carcinoma and lung metastases (median survival 52 months, 95% confidence interval 37.2 – 66.8 months) in comparison to patients with renal cell carcinoma and lung metastases (median survival 19 months, confidence interval 17.5 – 20.5 months), there was no statistically significant benefit in survival confirmed here.

It seems advisable to investigate whether specific types of treatment for different subgroups of metastases can improve overall survival. Therefore, as stated by Shields and colleagues, "combinations of chemotherapy and surgery may be considered and may offer more patients the potential for optimal local and systemic control of their disease process" (24), although no significant difference in distinct types of therapy could be confirmed in our thesis. Overall, since complete resection of lung metastases in colorectal cancer led to a statistically relevant survival benefit, the very same thing should be realized (25), equal actions also account for given criteria and renal cell carcinoma as described by Pfannschmidt and colleagues (21). Nevertheless, Ike and colleagues stated that the follow-up of patients with colorectal cancer and lung metastases with "radiographic examinations and serum CEA" (27) is a useful investigation to control the course of the disease (27).

It is noteworthy in regard to our study that Regiomed clinic Sonneberg exhibited the highest death rate of all patients with colorectal cancer (including those patients that were not included in this thesis because they did not fit the given criteria) compared to those patients from other clinics of Regiomed clinic association. This conspicuity needs further investigation but, for purpose of this thesis, this finding is just noted.

In our retrospective observational study, problems lay in the collection of medical data since only medical history records were used to gain information about included patients. Since the amount of smoking and possible alcohol abuse were minor details in the patients' medical history, it cannot be ruled out that there is a lack of detailed information about these factors in this study. Furthermore, in the case of one patient no information about prior health status could be included in this study because the primary cancer diagnosis was that far in the past that no medical records of this time period were available. Furthermore, data collection and search for relevant information regarding lung metastases gained limited findings since official research on this topic is scarce.

Since this study only includes patients from Regiomed clinic association, it became apparent after the data collection for colorectal cancer that the sample size of included patients would not be sufficient for the conduction of an appropriate thesis. Therefore, renal cell carcinoma data were added on so that the study sample contained 35 patients. However, this study sample is still limited so that there´s clear advice for repetition of this type of study with bigger sample sizes to gain broader and more specific results and also to confirm the aims of this study. It is also suggested to include more different primary cancers with preference of lung metastases to detect even differences in prognosis for different types of primary cancers as well.

Additionally, despite study results of this thesis, it is recommended to add more detailed questions concerning alcohol abuse and tobacco smoking to case history forms or questionnaires used in clinics (at least in the Regiomed clinic association). Since the anamnestic data seemed incomplete in conduction of this study, this would bring about an improvement of quality of anamnesis in general.

6. CONCLUSION

Implications of this study are:

- Patients with metachronous lung metastases (> 6 months after primary diagnosis of cancer) in colorectal and renal cell carcinoma have statistically significant higher median survival than patients with synchronous metastases.
- There was a statistically significant difference in median survival between patients with unilateral (better survival) versus bilateral (worse survival) lung metastases in colorectal and renal cell carcinoma. In patients with renal cell carcinoma a statistically significant difference in median survival time was detected in case of unilateral metastases (but the results are based on a very low sample size).
- In absence of diffuse metastases (bipulmonal + > 1/lobe) in colorectal and renal cell carcinoma a statistically higher median survival time was observed.
- If thoracic lymph node metastases in colorectal and renal cell carcinoma were absent, a statistically significant higher median survival time was detected.
- There was no statistically significant difference in median survival time for patients with colorectal versus renal cell carcinoma in general and lung metastases.
- No statistically significant difference in median survival time was detected for patients with singular versus multiple lung metastases, additional tumors or metastases during course of disease, distance of residence to specialized clinic Coburg, sex (female, male), smoking and adipositas, multimorbidity and immunosuppression or different treatments (surgery, radio-/chemotherapy or both).
- Anamnestic notes for smoking and alcohol consumption in forms of medical history taking or medical questionnaires should be implemented within Regiomed clinic association.

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8. SUMMARY

Objectives: Aim of this study was to figure out whether localization and amount of lung metastases can influence the prognosis of the disease.

Materials and methods: In this retrospective observational study all patients with newly diagnosed primary colorectal or renal cell carcinoma and only lung metastases administered to Regiomed clinic association between January 1, 2018 and February 1, 2022 were included. In total 35 patients were classified into groups according to primary type of cancer, amount and localization of lung metastases and presence of thoracic lymph node metastases.

Results: Patients with metachronous lung metastases (> 6 months after primary diagnosis of cancer) in colorectal and renal cell carcinoma have a statistically significantly higher median survival than patients with synchronous metastases. There was a statistically significant difference in median survival between patients with unilateral versus bilateral lung metastases in colorectal and renal cell carcinoma. In case of a lack of diffuse metastases (bipulmonal + > 1/lobe) in colorectal and renal cell carcinoma a statistically higher median survival time was observed. In absence of thoracic lymph node metastases in colorectal and renal cell carcinoma a statistically significantly higher median survival time of patients was detected. In renal cell carcinoma a statistically significant difference in median survival time was detected in case of unilateral metastases (but results based on a very low sample size). There was no statistically significant difference in median survival time for patients with colorectal versus renal cell carcinoma in general and lung metastases. No statistically significant difference in median survival time was detected for patients with singular versus multiple lung metastases, patients with additional tumors or metastases during the course of the disease, those with varying distance of residence to the specialized clinic of Coburg, patients of a certain gender (female, male), different smoking habits and those with or without adipositas, multimorbidity and immunosuppression or different treatments (surgery, radio-/chemotherapy or both).

Conclusion: Although there might be an association between localization and amount of lung metastases and time of survival, additional research and especially studies with bigger sample sizes are needed for more precise evidence.

9. CROATIAN SUMMARY

Naslov: Utjecaj lokalizacije i količine plućnih metastaza u primarnom kolorektalnom karcinomu i karcinomu bubrežnih stanica na prognozu: retrospektivna opservacijska studija.

Ciljevi: Cilj ovog istraživanja bio je utvrditi mogu li lokalizacija i količina plućnih metastaza utjecati na prognozu bolesti.

Materijali i metode: U ovu retrospektivnu opservacijsku studiju uključeni su svi bolesnici klinike Regiomed kojima je u periodu između 01.01.2018. i 01.02.2022 bio novodijagnosticiran primarni kolorektalni karcinom ili karcinom bubrežnih stanica te su imali samo plućne metastaze. Ukupno 35 bolesnika podijeljeno je u grupe prema vrsti primarnog tumora, količini i lokalizaciji plućnih metastaza i prisutnosti metastaza u torakalnim limfnim čvorovima.

Rezultati: Razvoj metakronih metastaza u plućima (> 6 mjeseci nakon primarne dijagnoze tumora) u kolorektalnom karcinomu i karcinomu bubrežnih stanica ima statistički značajno veći medijan preživljavanja u odnosu na prisutnost sinkronih metastaza. Utvrđena je statistički značajna razlika u medijanu preživljavanja kad se uspoređuju unilateralne u odnosu na bilateralne plućne metastaze. U slučaju odsutnosti difuznih metastaza (bipulmonalnih ili više od jedne metastaze u jednom plućnom režnju) u kolorektalnom karcinomu i karcinomu bubrežnih stanica uočen je statistički značajno veći medijan preživljavanja. Utvrđen je statistički značajno veći medijan preživljavanja ukoliko nisu prisutne metastaze u torakalnim limfnim čvorovima. U karcinomu bubrežnih stanica uočena je statistički značajna razlika u medijanu preživljavanja kod jednostranih metastaza (ali rezultati su temeljeni na vrlo malom uzorku). Nije utvrđena statistički značajna razlika u medijanu preživljavanja za kolorektalni karcinom u odnosu na karcinom bubrežnih stanica općenito ili s prisutnim plućnim metastazama. Nije uočena niti statistički značajna razlika u medijanu preživljavanja kod prisutnosti singularnih u odnosu na multiple metastaze, u slučaju razvoja dodatnih tumora ili bolesti za vrijeme trajanja primarnog karcinoma, u slučaju udaljenosti od specijalizirane klinike Coburg, kod muškog ili ženskog spola, kod pušača i adipoznih bolesnika, kod bolesnika s dodatnim komorbiditetima i imunosupresivnih bolesnika, ili kod različitih vrsta liječenja (kirurgija, radioterapija, kemoterapija ili kombinacija radioterapije i kemoterapije).

Zaključak: Iako može postojati povezanost između količine i lokalizacije plućnih metastaza i preživljavanja, potrebno je provesti dodatna istraživanja, naročito na većem uzorku bolesnika kako bi rezultati bili precizniji.

10. CURRICULUM VITAE

Name, Surname:	Melissa Tanja Wieloch
Date of birth:	October 8, 1991
Marital status:	married
Formal education:	1998 – 2002 Elementary school ”Am Markt” Lichtenfels 2002 – 2008 Middle school “Viktor-von-Scheffel Realschule“ Bad Staffelstein 2009 – 2012 Vocational School for nursing Lichtenfels 2012 – 2015 College of further education “Regiomontanusschule“ Coburg since 2016 University of Split – School of medicine / Medical School Regiomed
Graduations:	2008 High-school diploma 2012 State examination – registered nurse 2014 Subjected-linked eligibility of university admission (“Fachabitur”) 2015 Higher education entrance qualification (“Abitur”) 2015 Emergency medical technician (“Rettungssanitäterin”) 2022 Expected graduation Medical School
Apprenticeships:	2009 – 2012 Apprenticeship nurse 2015 Apprenticeship paramedic

Occupational career:	2009 – 2012	Apprenticeship nurse
	2012 – 2014	Part-time nurse in nursing home for elderly at "BRK-Pflegeheim" Bad Staffelstein
	2015	Apprenticeship paramedic
	2015 – 2016	Full-time paramedic rescue service German Red Cross Lichtenfels
	since 2016	Medical Studies in English University of Split
	since 2019	Part-time paramedic rescue service German Red Cross Lichtenfels
	2020	Part-time nurse at Regiomed Clinic Coburg (during COVID-19 pandemic for 4 months)
	since 2020	Part-time nurse in COVID-19 vaccination center Lichtenfels
	2022	Expected graduation Medical School

Additional Qualifications: Diverse seminars of German Red Cross,
truck driver license

Languages: German (first language)
English (TOEFL-Test)
French (level B2)

Other activities: music, drawing, reading

11. SUPPLEMENT

Table 19. TNM-stages and interventions of included patients

Patient	TNM-stage	surgery primary tumor	surgery metastasectomy
1	G1, pT1a, L0, V0, Pn0, R0	yes	yes
2	T3, M0, M1	yes	no
3	not available	no	no
4	pT3, N1, M1, G3	yes	no
5	pT3a, L0, V0, Pn0, R0	yes	no
6	pT3a, pN0 (0/6), L0, V0, Pn0, R1, G3	yes	no
7	pT2, pN0 (0/1), pMX, L0, V0, Pn0, R0	yes	no
8	pT3a, pN0 (0/4), L0, V0, Pn0, G3, R0	yes	no
9	pT3a, pN0 (0/1), L0, V0, n0, R1	yes	no
10	pT3a, L0, V0, Pn0, R0	yes	no
11	Tx, N0, M0, G3	yes	yes
12	uT4, uN+, M0	yes	yes
13	pT1, sM1	no	no
14	G3, cT4, Nx, M1	yes	no
15	not available	yes	yes
16	T3-4, N+, M1 (pul)	no	no
17	pT3a, Pn1 (1/3), M0, R0, L1, V0, Pn1	yes	yes
18	pT3, pN2a, L1, V0, Pn0, R0	yes	no
19	cT4, cN2	yes	no
20	not available	yes	no
21	ypT3, ypN0, cM1 (pul), L0, V0, R0	yes	no
22	cT4, cN2, cM1	yes	no
23	uT3, uN1, M0 (2018)	no	no
24	cT3, N0, M1 (pul), G2	no	no
25	cT4, cN2, cM1 (pul), G2	yes	yes
26	cT4, N2b, MX	yes	yes
27	pT3, pN0 (0/20), L0, V0, Pn0, R0	yes	no
28	pT4b, pN2b (7/30), cM0, R0, G2	yes	no
29	pT3, pN0 (0/15), L0, V0, R0, G2	yes	no
30	pT3, pN2a (4/21), L1, V0, Pn0, R0, G2	yes	no
31	pT3, pN0	yes	yes
32	pT3, pN1 (1/13), cM0, L0, V0, R0	yes	yes
33	pT3, pN0, L0, V0, Pn1, R0, M0	yes	yes
34	pT3, pN2b (28/32), cM1	yes	no
35	T3c	not available	no

Tumor stages of every included patient according to TNM-classification and interventions