Dissertation

Origin, histology and endoscopic findings of secondary tumors in the gastrointestinal tract

Ursprung, Histologie und Endoskopisches Erscheinungsbild sekundärer Tumoren im Gastrointestinaltrakt

Submitted by
Dr.in med. univ. Magdalena M. **GILG**

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at the **Institute of Pathology**

under the Supervision of

Univ. Doz. Dr. med. Cord Langner

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Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the "Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz".

Magdalena M. Gilg
Graz, April 16, 2018

Disclosures

Part of this thesis has been published in *Gastrointestinal Endoscop*y as: Gilg MM, Gröchenig H-P, Schlemmer A, Eherer A, Högenauer C, Langner C. Secondary tumors of the gastrointestinal tract: origin, histology, and endoscopic findings. Gastrointestinal Endoscopy (2018) [Epub ahead of print].

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All co-authors have explicitly agreed to the use of their data in this thesis.

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Abbreviations and Definitions

CD 68= cluster of differentiation 68

CGA= Chromogranin A

CK= cytokeratin

CUP= carcinoma of unknown primary

EK= [Ethikkomission] review board

GIT= gastrointestinal tract

H&E= hematoxylin and eosin

MEDOCS= hospital information system

MUC5AC= mucin 5AC

MUC6= mucin 6

NST= no special type

SATB2= Special AT-rich sequence-binding protein 2

STROBE= Strengthening the reporting of observational studies in epidemiology

TH 8= Thoracic vertebra number 8

WT1= Wilms-Tumor-Protein

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Abstract (German)

Hintergrund: Der Gastrointestinaltrakt (GIT) ist nur selten von sekundären Tumoren betroffen. Ziel dieser Studie war es klinische, endoskopische und pathologische Aspekte von sekundären Tumoren, die mittels Endoskopie diagnostiziert wurden, zu untersuchen.

Material und Methoden: Nach Durchführung einer retrospektiven Datenbankanalyse wurden 217 PatientInnen mit der Diagnose eines sekundären Tumors im GIT eingeschlossen. Bei allen PatientInnen wurde eine Gastro- und/oder Koloskopie durchgeführt und die histologische Diagnose am Institut für Pathologie, Medizinische Universität Graz, Graz, Österreich gestellt. PatientInnen mit systemischen Erkrankungen, wie Leukämien oder Lymphomen, wurden ausgeschlossen.

Ergebnisse: Malignes Melanom (n=33, 15%), Mammakarzinom (n=32, 15%) und Pankreaskarzinom (n=27, 12%) waren die häufigsten Primärtumoren. Ein Drittel der sekundären Tumoren wurden im Magen diagnostiziert (n=76, 35%), gefolgt von Dünndarm (n=54, 25%) und Rektum (n=53, 24%). Das Zeitintervall zwischen der Diagnose des primären und des sekundären Tumors war im Median 19 Monate (Bandbreite 0- 251), am längsten bei Nierenzellkarzinom und Mammakarzinom (Median jeweils 38 bzw. 45 Monate). Direkte Invasion (56%) durch extra- gastrointestinale Tumoren war häufiger als hämatogene Metastasierung (44%) und sowohl von der Lokalisation des sekundären Tumors als auch von der Histologie des dazugehörigen Primärtumors abhängig. Endoskopisch zeigten sekundären Tumoren des GIT heterogene, makroskopische Erscheinungsbilder. Bei PatientInnen mit bekanntem Primärtumor (n=168), wurde in nur 48% der Fälle ein sekundärer Tumor in die Differentialdiagnose miteinbezogen.

Conclusio: Sekundäre Tumoren des GIT können alle Abschnitte des GIT betreffen, Malignes Melanom, Mamma- und Pankreaskarzinom sind die häufigsten zugehörigen Primärtumoren. Die Hälfte aller Läsionen wurde endoskopisch als Primärtumor oder als benigne/entzündlich eingestuft. Um Fehldiagnosen zu vermeiden, ist die bioptische und histologische Verifizierung unabdingbar.

Abstract (English)

Background: Secondary tumors of the gastrointestinal tract (GIT) are a rare finding with a dismal prognosis because they are only found with advanced cancers. This study aimed to investigate clinical, endoscopic and pathological features of secondary tumors diagnosed during gastroscopy or colonoscopy.

Methods: A retrospective database search retrieved 217 patients with a secondary tumor of the GIT who had undergone endoscopy in 12 hospitals in southern Austria with histologically confirmed diagnosis from the Institute of Pathology, Medical University of Graz, Austria.

Results: Malignant melanoma (n=33, 15%), breast (n=32, 15%) and pancreatic cancer (n=27, 12%) were the most common corresponding primaries. The most frequent anatomical site was the stomach (n=76, 35%), followed by duodenum (n=54, 25%) and rectum (n=53, 24%). Time intervals between the initial diagnosis of a primary tumor and a secondary tumor ranged between 0 and 251 months (median 19 months). Fifty-six percent (n=122) of secondary tumors had invaded directly from extragastrointestinal sites (including peritoneal carcinomatosis), while 44% (n=95) of secondary lesions had spread via the vascular route, depending on both tumor site and corresponding primaries. When a definitive primary tumor was already known (n=168 patients), a secondary tumor was considered as a differential diagnosis in only 48% (n=80) of cases.

Conclusions: Malignant melanoma, breast cancer and pancreatic cancer are the most common underlying primary tumors of metastases within the GIT. As clinical presentation and endoscopic findings are highly unspecific, biopsies and histological workup are indicated for every suspicious lesion with the GIT to avoid diagnostic delay and misclassification.

1. Introduction

1.1 Definition

One hundred and twenty-eight years ago Stephan Paget introduced his “seed and soil” hypothesis describing the propensity of specific primary tumor cells to metastasize to distinct secondary tumor sites (1). He proposed that the primary tumor cells need to exhibit intrinsic factors that can “seed” new tumors , while target sites need to provide a suitable environment as “soil” for secondary tumor colonization (1).

We now know that metastatic dissemination of tumor cells consists of several steps including “ intravasation, survival in circulation, extravasation, and colonization and growth at a distant site” (2). Still, the exact mechanisms of metastatic pathways and organotropism have not yet been fully elucidated (2, 3). It seems that genes mediate organotropism and recently exosome integrins were found to affect organotropism (3). In general, breast cancer and its propensity to give rise to secondary tumors in the brain, lungs and bones is best investigated with respect to organotropism (2).

According to the WHO classification of tumors of the digestive system, secondary tumors of the gastrointestinal tract (GIT) “originate from extra-gastrointestinal sites or are discontinuous with a primary tumor elsewhere in the gastrointestinal tract” (4). Three different routes of cancer dissemination are known for the GIT. First, direct invasion by a primary tumor from an adjacent organ by continuous tumor growth, e.g. a pancreatic carcinoma infiltrating the small bowel. Second, hematogeneous or lymphatic spread, e.g. distant metastasis from breast cancer to the stomach (4, 5); Third, peritoneal dissemination, where cells detach from the original primary tumor, seed into the peritoneal cavity and are transported to distant peritoneal sites (6). Angiogenesis and tumor growth are promoted within the subperitoneum. These complex molecular processes have been described as the “peritoneal metastatic cascade” (7). Ovarian cancers as well as urinary bladder cancer typically spread via peritoneal carcinomatosis (8). Molecular mechanisms for GIT tropism of metastasis have not been investigated.

1.2 Epidemiology

Secondary tumors within the GIT are rare compared to metastases to lymph nodes, liver, lungs or bone. In a large study including data from nearly 4000 autopsies, the liver and lungs made up 22% of all metastatic target sites whereas the stomach accounted for only 0.6% of all secondary tumors detected (9).

Overall, breast, prostate and colorectal cancer showed the highest prevalence of all primary cancer subtypes diagnosed in 2012 among the Austrian population (10). In the past, breast cancer was identified as one of the most common corresponding primaries responsible for secondary tumors followed by malignant melanoma and lung cancer (11, 12). Breast cancer is also known for its potential to cause high numbers of secondary tumors, which has been calculated as 5.2 metastases per primary malignancy (9). In general, primary tumors originating in the GIT, such as colorectal cancer, only rarely disseminate metastases within the GIT (11).

In the absence of large clinical studies, the exact incidence of secondary tumors of the GIT has been difficult to estimate. Data derived from autopsy studies (13-15) tend to show higher incidences than those obtained from clinical studies, which are mostly restricted to case reports or small case series (16-19). Most studies focused on specific tumor entities, such as breast cancer, renal cell carcinoma or malignant melanoma (20-22), or specific anatomical sites. For instance, the ratio of secondary tumors within the stomach among all secondary lesions has been reported to vary between 0.2 and 1.7% (3,4,12).

1.3 Diagnosis of secondary tumors of the GIT

1.3.1 Clinical presentation and endoscopy

The diagnosis of a secondary tumor within the GIT can be a diagnostic challenge due to the rarity of disease and the variable presentation, as well as the similarity of clinical symptoms of primary and secondary tumors of the GIT.

Depending on the anatomical location, tumor extension and speed of tumor growth, secondary tumors to GIT may present with various acute to chronic clinical symptoms. Patients with secondary tumors located in the esophagus often present with dysphagia or bleeding (23). Intestinal tumor extension into the lumen may cause partial obstruction leading to abdominal pain, constipation, vomiting and ultimately to complete bowel obstruction, which

is an emergency situation (24, 25). In addition, patients may present with peritonitis following intestinal perforation as the tumor infiltrates through the bowel wall (26, 27).
Patients with either primary or secondary tumors of the GIT may present with signs of acute or sub-acute gastrointestinal bleeding, such as hematemesis or melena (28). Patients with acute GIT bleeding are usually assessed by endoscopy and when possible, bleeding is controlled in the same session (29). Information regarding the clinical and endoscopic presentation of secondary tumors is limited and endoscopic studies often do not distinguish between primary and secondary tumors (5, 7, 8).

1.3.2 Pathology

Biopsies are routinely taken during GI endoscopy and suspicious lesions are sent for histological workup. In general, the morphology of secondary tumors is variable, ranging from ulcers and submucosal thickening of the lumen to polypoid masses (30). For the stomach, a linitis plastica-like pattern has been described. Likewise, pigmentation has frequently been detected in secondary tumors originating from malignant melanoma. In the esophagus, submucosal tumor extension has been reported to be typical (4).
Histologically, secondary lesions of the GIT generally resemble the corresponding primary tumor. When there is no history of a primary tumor, i.e. a carcinoma of unknown primary (= CUP), a standardized algorithm including an immunohistochemistry panel is needed to establish a definitive diagnosis (Figure 1, Table 1).
Within the stomach it is important to differentiate the invasive lobular-type breast cancer from primary signet-ring cell carcinoma of the stomach. The most common differential diagnoses within the large bowel/rectum is to distinguish secondary lesions from primary colorectal cancer (31), while neuroendocrine and mesenchymal tumors are less frequent (30). In the small intestine, secondary tumors are much more frequent than primary neoplasms. There is no predilection for a specific corresponding primary tumor within the small bowel and metastatic spread occurs both via direct invasion and dissemination per continuitatem (32).

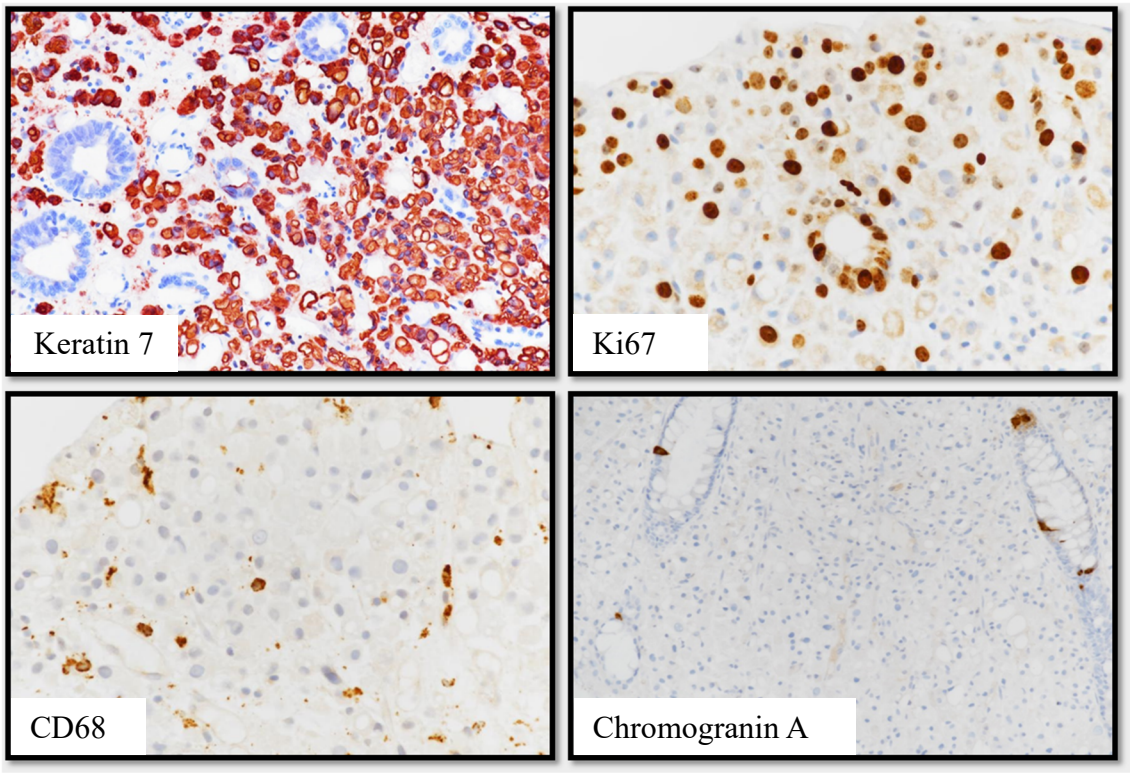


Figure 1: Example of an immunohistochemical panel from a patient with a rectal tumor secondary to invasive lobular breast cancer. Cells are positive for keratin 7, Ki67 proliferation markers are increased. The tumor is negative for CD 68 and neuroendocrine markers such as Chromogranin A.

Table 1: Example of an immunohistochemical profile of breast cancer metastases compared to primary colorectal cancer (CRC) and neuroendocrine tumors (NET) (+=positive, -= negative).

	CRC (4, 31)	NET (33)	Breast Cancer Metastases (31)
CK 7	**(+)**	**(+)**	+
CK 20	+	**(+)**	-
CDX2/SATB	+/+	-/+ / +/-	-/-
MUC 2	+	-	-
Chromogranin	-	-/**(+)**	-
Synaptophysin	-	+	-
Gata 3	-	-	+
Mammaglobin	-	-	+

1.4 Outcome and treatment of secondary tumors of the GIT

Since secondary tumors of the GIT are usually found only with an advanced primary tumor, the prognosis is poor and therapy is often limited to palliative treatment and supportive care. Data about prognostic factors for secondary tumors of the GIT are scarce and difficult to evaluate as multiple metastases are often diagnosed simultaneously. A median survival of three months was shown for gastric metastases (34), with the exception of secondary lesions from renal or lobular breast cancer as corresponding primary tumors (35, 36). For the entity of breast cancer metastases, the overall mortality risk has been calculated as 69% within the first to fifth year following initial diagnosis, independent of the metastatic site. Breast cancer patients with metastases to the brain only, liver only, or organs other than bones had the worst survival rates (37). It should be noted that there are no large series on breast cancer metastatic to the GIT.

Treatment will usually be palliative, aiming for relief of symptoms, particularly gastrointestinal obstruction, along with nausea, vomiting and malnutrition. Endoscopic implantation of stents for luminal obstruction is one treatment option (38). Acute bleeding may be treated endoscopically to stabilize the patient temporarily. Endoscopic or open abdominal surgery is usually not indicated in patients with secondary tumors of the GIT, except for specific anatomical sites or histological entities (20, 39) such as malignant melanoma with GIT metastases. In terms of overall survival and relief of symptoms, this patient group benefits from aggressive surgery if there are no further distant metastases and wide margins can be achieved (40).

1.5 Aim of the study

Most studies on secondary tumors of the GIT include only small numbers of patients, since they are usually retrospective analyses from single endoscopy units that include only limited information on underlying primary tumors, as well as clinical and endoscopic presentation (13, 41, 42). For a larger survey, a pathology-based retrospective observational study was designed to include all secondary tumors diagnosed at one pathology department serving hospitals in southern Austria, where patients had been biopsied at multiple endoscopy units within the last 30 years. Clinical presentation and endoscopic features, pathology diagnoses and the written communication between clinicians and pathologists were investigated (43).

2. Methods

2.1 Patients

We conducted a retrospective database analysis to identify all patients diagnosed with a secondary tumor of the GIT at the Institute of Pathology, Medical University of Graz, Austria, between 1985 and 2014. A systematic database review of "AURAWEB" and "MEDOCS" conducted by an employee of the Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, identified 502 patients. The eligibility criterion was the presence of a secondary GIT tumor diagnosed by endoscopy, biopsy, and histological analysis. After review of clinical records 139 patients had to be excluded as the definitive diagnosis was a primary tumor of the GIT; 33 further patients were excluded due to locally recurrent disease. Patients with systemic malignant disease (n=7) such as leukemia or lymphoma were excluded, as were patients with unclear pathology diagnosis (n=73), when the original slides or tumor material were not available for review. Another 33 patients were excluded due to incomplete endoscopic data (Figure 2) (43).

Data will be presented in accordance with the STROBE Statement, which intends to strengthen the reporting of observational studies (44). Basic demographic and clinical data, including symptoms and indication for endoscopy, were retrieved from the files, as was the time interval between diagnosis of primary and secondary tumors. The time interval was considered to be zero in patients with simultaneous diagnosis of the primary and secondary tumor. Additionally, pathology request forms were analyzed with regard to communication between clinicians and pathologists. This included information about the clinician's suspected diagnosis (primary and/or secondary tumor, ulcer/inflammatory process, benign tumor or unclear) and whether the clinician mentioned prior knowledge of an oncological disease. Since electronic files were not always available prior to 2006, hardcopy records were retrieved from hospital archives when necessary (43). As previously described (5, 45), routes of GIT involvement were classified as direct invasion (including direct invasion from peritoneal deposits) or vascular dissemination, i.e., hematogenous or lymphatic cancer spread. Metastatic cancer spread to extragastrointestinal sites was recorded if present (43).

The investigation was carried out in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board of the Medical University of Graz (EK 26-091 ex 13/14) (43).

2.2 Endoscopy

The upper GIT was defined as esophagus, stomach and duodenum (assessed by gastroscopy), the lower GIT as colon and rectum (assessed by colonoscopy). Endoscopic reports and images from twelve different endoscopy units were retrieved from the electronic patient record database or manually from the hospital archives, as appropriate. When images were not available, the endoscopy report was searched for a morphological description of the secondary tumor. Lesions were classified as non-classifiable when neither images nor a detailed morphological description were available (n=39). First, secondary tumors were assessed generally and either classified as "submucosa-like" or "primary carcinoma-like". "Submucosa-like" morphology reflected primary submucosal dissemination with or without secondary extension into the mucosal layer. In contrast − as has been suggested previously−"primary carcinoma-like" appearance resembles a primary gastrointestinal cancer, e.g. a polypoid or ulcerated tumor mass (13). Second, gross findings of secondary lesions were classified as follows: polypoid mass, nodule, intramural process, ulcer, or small black spot, as elsewhere (5, 13, 43) .In cases in which no lesions were identified during endoscopy, the mucosa was recorded as "normal". Lesions were further classified as "unifocal" (one secondary tumor visible) and "multifocal" (multiple secondary tumors visible). Finally, endoscopic reports were reviewed with regard to the examiners' interpretation of the findings (primary or secondary tumor, other or unclear lesion), without knowledge of the definitive histology (43).

As a rule, immunohistochemistry was part of the routine pathological workup to confirm the status as secondary tumors. A senior pathologist reviewed the histological diagnoses and reassessed the original slides from twelve patients with unclear or only descriptive diagnoses. Five of them required additional staining to classify the lesions, which provided definitive diagnoses in all cases. Immunohistochemical staining results were available in 116 (54%) out of 217 cases. Molecular analysis was not used in this dataset (43).

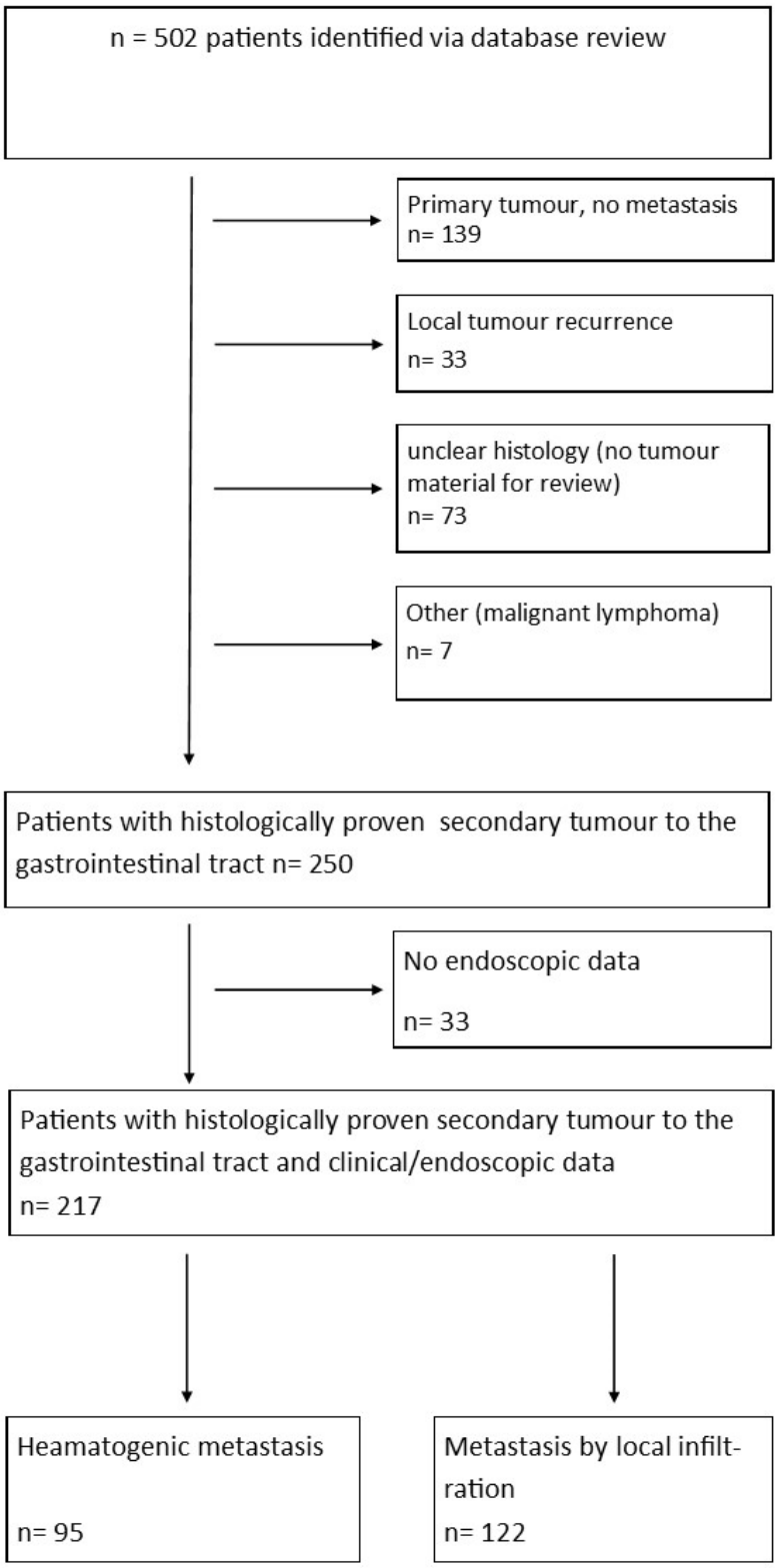


Figure 2: Flow diagram of the included patients, with reasons for exclusion.

2.3 Statistical analysis

All data were entered in a prospective joint database. Categorical variables are presented as absolute and relative frequencies, and numerical variables as means and ranges, as well as medians. Differences in categorical variables were examined using the chi-square test or Fisher's exact test, as appropriate. Differences in continuous variables between groups were analyzed with the Mann-Whitney U-Test (43). All statistical calculations were performed using IBM SPSS (22) and Microsoft Excel (version 2010). All reported P values were 2-sided with significance at $p<0.05$.

3. Results

3.1 Basic demographic data

Overall, 217 secondary tumors were diagnosed in 214 patients (103 male, 114 female, ratio 1.1:1), as three patients had gastroscopy as well as colonoscopy, which revealed secondary tumors in both the upper and the lower GIT. Mean age at the time of diagnosis of a secondary tumor was 67 years (median 66, range 24-91) (Table 2) (43).

Table 2: Patient characteristics.

		n	%
Sex	Male	103	48
	Female	114	52
Primary tumor known	Yes	168	77
	No	49	23
Primary cancer	Malignant melanoma	33	15
	Breast	32	15
	Pancreas	27	12
	Prostate	25	12
	Ovaries	17	8
	Stomach	15	7
	Kidneys	14	7
	Lung	10	5
	Colorectum	6	3
	Cervix	6	3
	Uterus	6	3
	Liver	4	2
	Gallbladder	4	2
	Urinary bladder	4	2
	Other	13	6
Number of metastases	Unifocal	135	62
	Multifocal	48	22
	Unknown	34	16

3.2 Clinical presentation and anatomical distribution of secondary tumors

For 132/214 (62%) patients, information was available on clinical symptoms for which endoscopy was indicated. The most frequent were abdominal discomfort, weight loss, change of bowel habits, abdominal distension, nausea and vomiting in more than half of the patients (n=53, 40%), followed by acute or subacute gastrointestinal bleeding, including iron deficiency anemia of unknown cause, hematemesis and melena in about one-fourth of patients (n=31, 24%), and symptoms of gastrointestinal obstruction (bowel obstruction, constipation) (n=16, 12%). In 29/132 (22%) patients, endoscopy was performed in the course of the search for a primary tumor (43). Differences in clinical indications for gastroscopy and colonoscopy are shown in Figure 3.

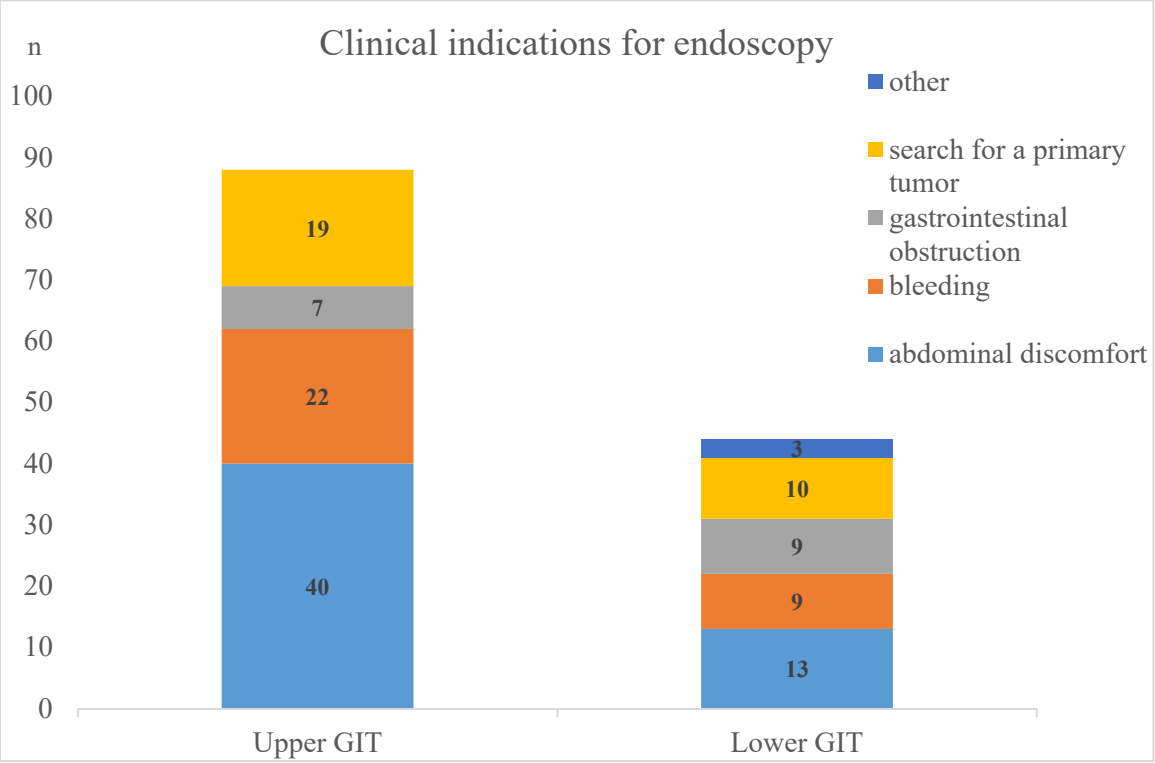


Figure 3: Clinical indications for endoscopy according to upper and lower GIT.

For 82% of secondary tumors (n=178), data were available on the endoscopic appearance of secondary tumors. Endoscopic images were included in 130/178 (73%) reports. Regarding general assessment, 88 (50%) of secondary tumors were categorized as submucosa-like (secondary tumor-like) and the remainder (n=77, 43%) as primary carcinoma-like, except for six cases (3%) in which a definitive classification was impossible; seven further specimens (4%) were classified as completely normal mucosa (Figure 4) (43).

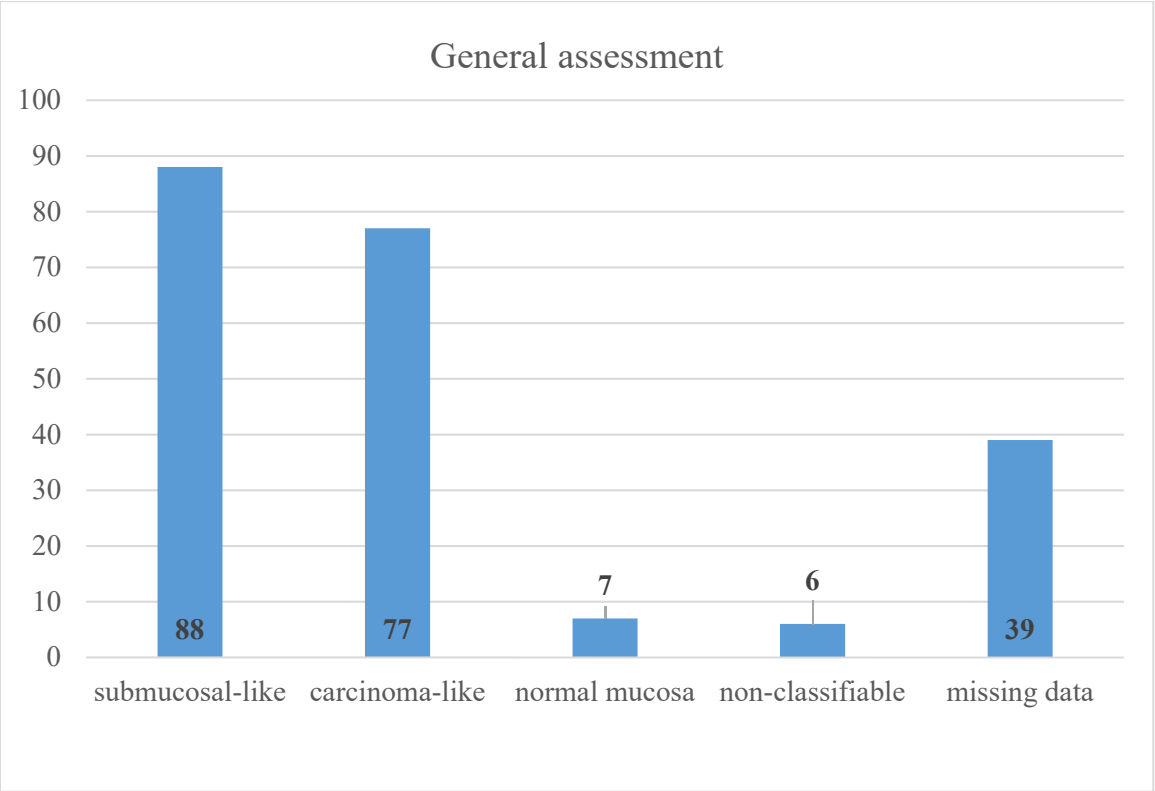


Figure 4: Endoscopic appearance and general assessment (submucosa-like vs. primary carcinoma-like) of secondary tumors of the GIT.

In detail, secondary tumors were classified as “intramural processes” in about one-third of cases (n=66), followed by a “polypoid mass” (n=51) or “mucosal ulceration” (n=29) (Figure 5). So-called volcano-like lesions were detected in only 11% (n=19) of secondary tumors. Notably, 7 out of 33 (21%) patients with metastatic malignant melanoma presented with “small black spots” in this series (43) (Figure 6). Further endoscopic examples of gross findings of secondary tumors are shown in Figure 7. Details on the endoscopic appearance of secondary tumors stratified according to corresponding primary tumors are shown in Figure 8 and 9.

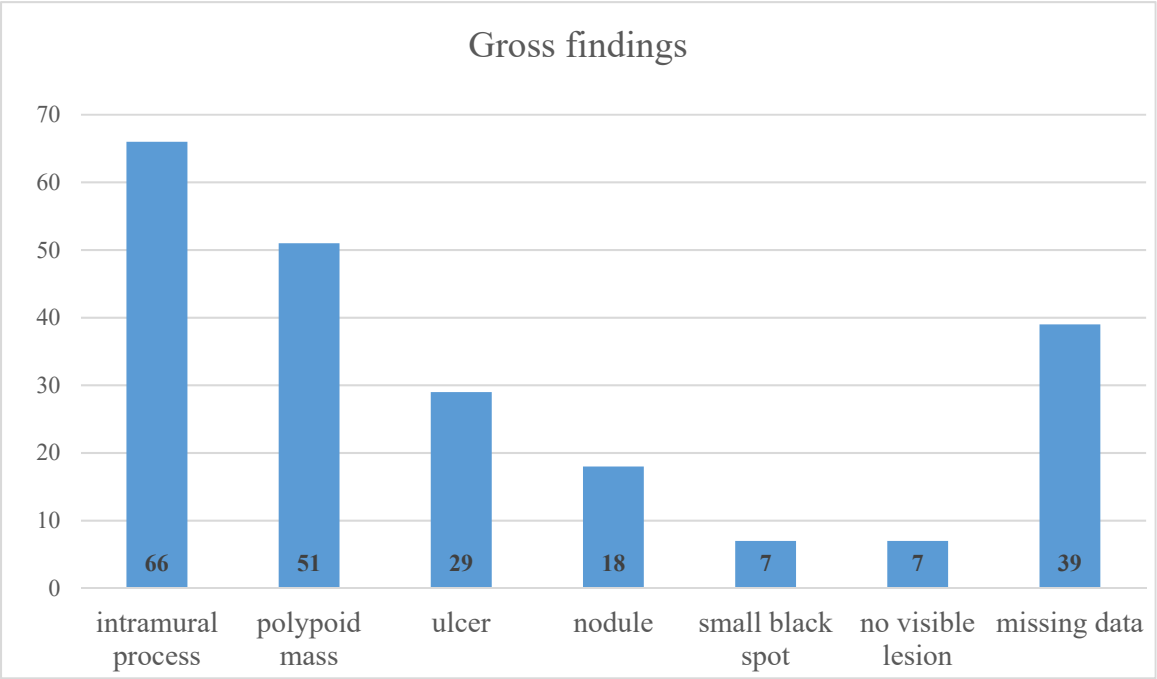


Figure 5: Endoscopic appearance of secondary tumors within the GIT – detailed assessment and analysis of morphological patterns.

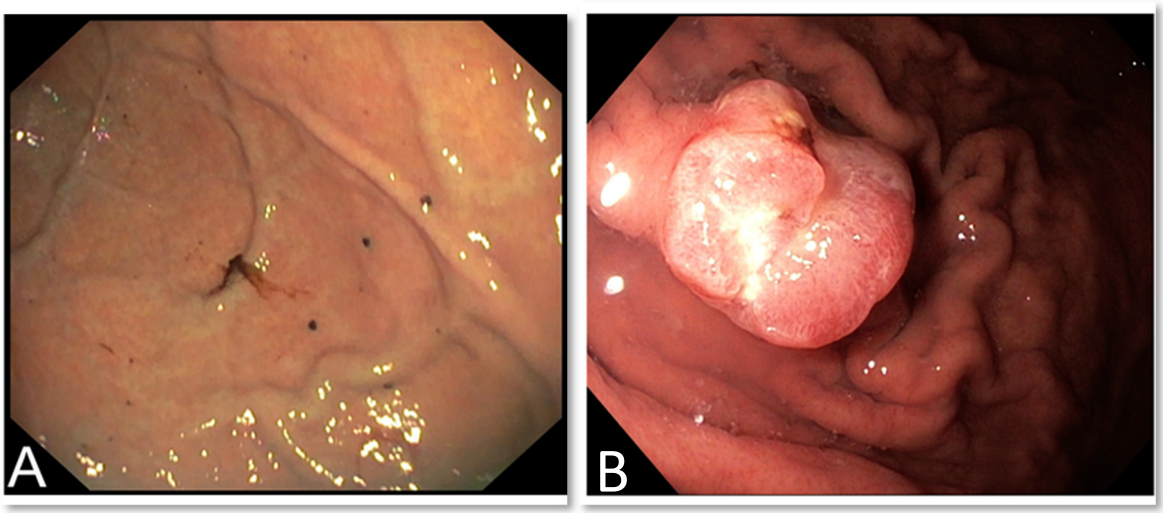


Figure 6: Two tumors secondary to malignant melanoma metastatic to the stomach. Notably, only Figure 6A shows phenotypical "small black spot", whereas 6B presents with a polypoid mass.

Endoscopists provided a provisional diagnosis in 107 cases. Specifically, 59 (55%) lesions were correctly interpreted as secondary tumors, whereas 31 (29%) lesions were misinterpreted as a primary tumor of the GIT, and further 17 (16%) lesions were assessed as benign, e.g. inflammation or ulcer. There was no difference in the rate of correct assessment of the lesions following endoscopy with regard to the time intervals since diagnosis of the primary lesion. For the group of patients in whom a secondary tumor of the GIT was correctly

suspected, the mean interval was 28 months (median 19 months, range 0-105). For the remainder of patients the mean interval was 38 months (median 16, range 0-251) (p=0.83) (43). Notably, a clinical and/or endoscopic diagnosis was not routinely reported to the pathologist on the pathology request form. In detail, in patients with a prior diagnosis of cancer (n=168), a secondary tumor was mentioned as a possible differential diagnosis in only half of the cases (n=81). In as many as 66 (39%) patients, no information at all was provided on preexisting malignancy. For the remaining cases, the pathology request forms were not available (43).

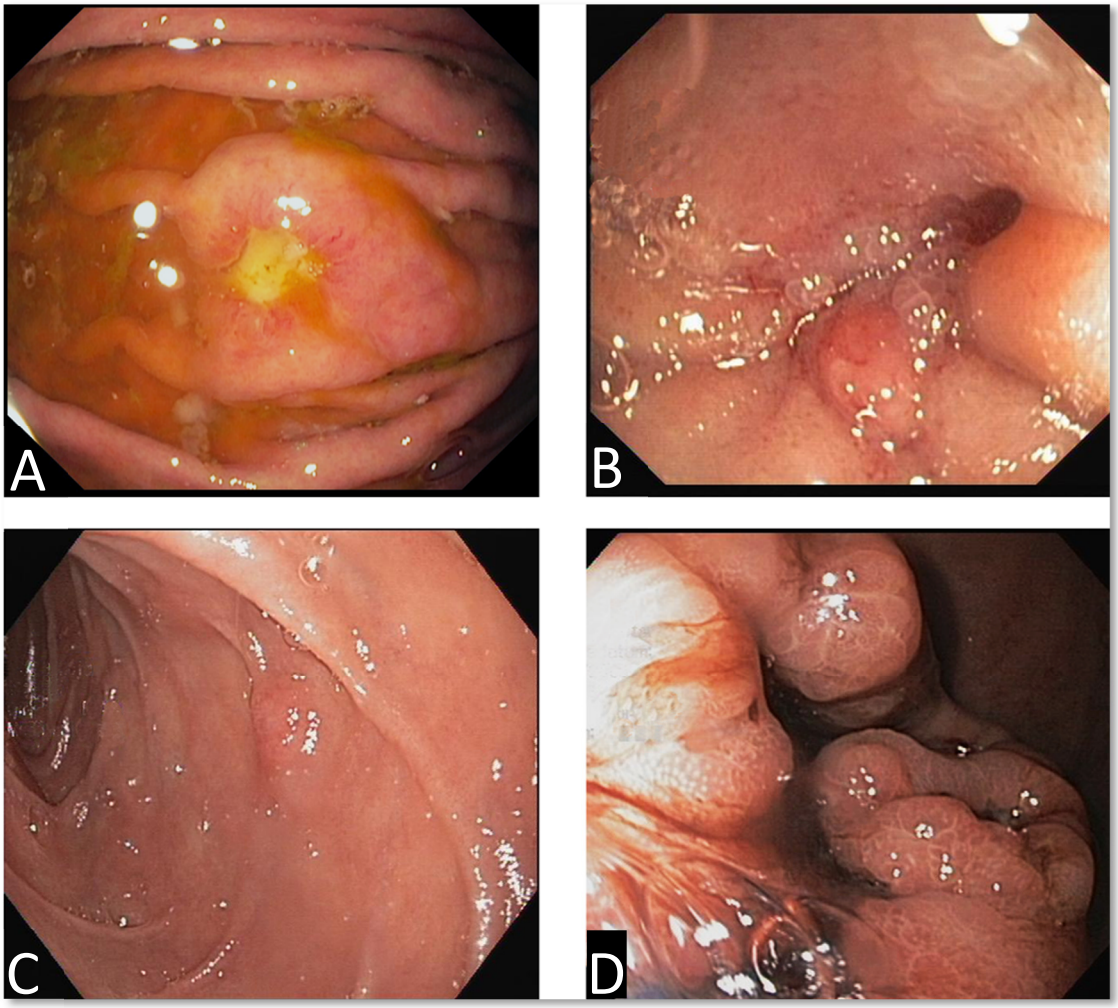


Figure 7: Examples of typical endoscopic findings for secondary tumors:

A "Ulcer": female patient with a known history of breast cancer and upper GIT bleeding. Upon gastroscopy, this ulcer was detected in the stomach; multiple biopsies were taken and confirmed breast cancer metastatic to the stomach.

B "Intramural process": female patient with a known history of cholangiocellular carcinoma and large bowel obstruction undergoing colonoscopy. Histological workup of the intramural process revealed a secondary tumor metastatic to the colon from the gallbladder.

C "Polypoid mass": male patient who presented with unexplained weight loss. On gastroscopy, a flat polypoid mass was detected in the duodenum. Histological workup of the polypoid mass revealed a tumor within the duodenum secondary to a malignant peripheral nerve sheath tumor.

D "Polypoid mass": male patient with a previously unknown secondary tumor from malignant melanoma metastatic to the stomach presenting with a polypoid mass upon

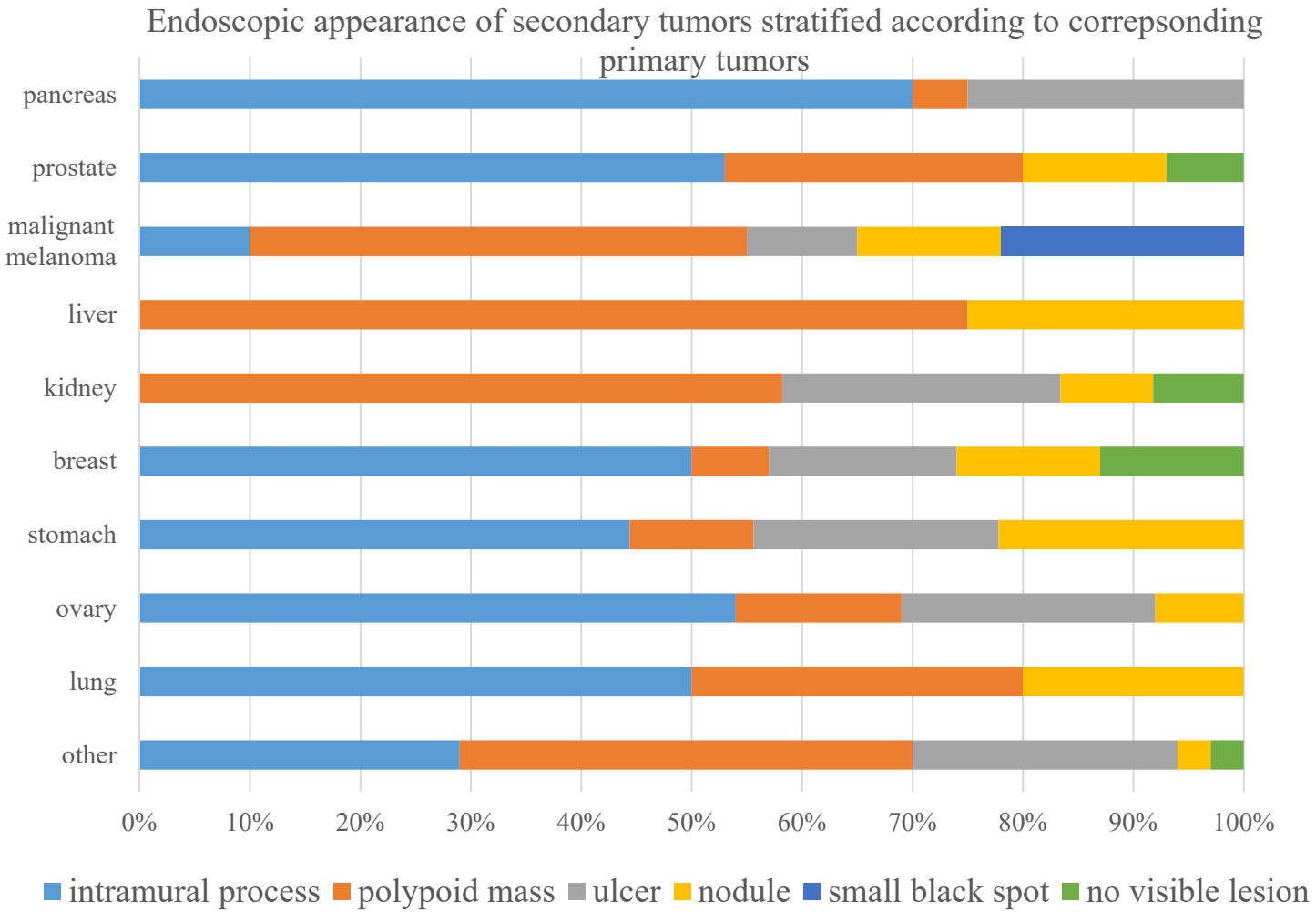


Figure 8: Details of the endoscopic appearance of secondary tumors according to the histology of the corresponding primary tumor (in %) and gross findings.

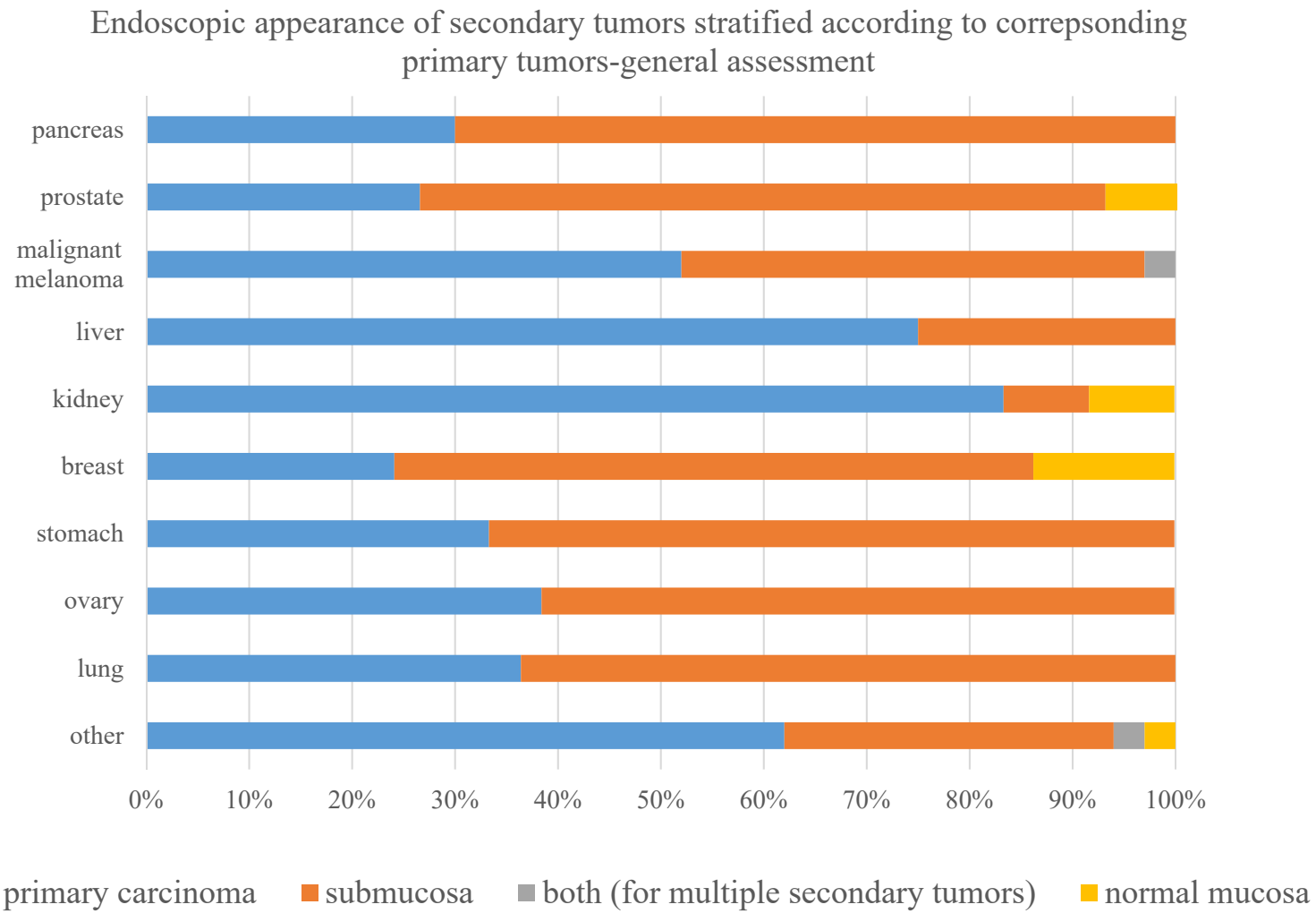


Figure 9: Details of the endoscopic appearance of secondary tumors according to the histology of the corresponding primary tumor (in %) and general assessment.

3.4 Corresponding primary tumors

At the time of endoscopy, corresponding primary tumors were known in 168 (77%) patients and unknown in 49 (23%) (Table 1). With pancreatic carcinoma, the primary tumor was significantly more often unknown (19/49, 39%) prior to the diagnosis of a secondary tumor ($p<0.001$) than in the remaining histological entities (43) (Table 3).

Malignant melanoma (n=33, 15%) and breast cancer (n=32, 15%) were the most common primaries, followed by pancreas (n=27, 12%), prostate cancer (n=25, 12%) and renal cell carcinoma (n= 14, 7%) (Figure 10). About one-fourth of lesions were secondary to rare corresponding primary tumors. In detail, secondary tumors from lung cancer (4.6%, n=11), soft tissue (3.2%, n=7), colorectum (2.8%, n=6), cervix (2.8%, n=6), uterus (2.8%, n=6), liver (1.8%, n=4), gallbladder (1.8%, n=4), urinary bladder (1.8%, n=4), vagina (0.9%, n=2), testicles (0.5%, n=1), tonsils (0.5%, n=1), fallopian tube (0.5%, n=1), and the oral cavity (0.5%, n=1) were present in this database (43).

Comparing absolute numbers of secondary tumors of the upper to the lower GIT, malignant melanoma (n=27, 22%, p=0.002), breast (n=26, 21%, p=0.01) and pancreatic cancer (n=23, 19%, p=0.001) were significantly more frequent in the upper GIT, whereas prostate (n=24, 26%, $p<0.001$), gastric (n=14, 15%, $p<0.001$), and ovarian cancer (n=13, 14%, p=0.005) were the most common corresponding primaries in the lower GIT (Figure 10) (43).

The mean time between diagnosis of primary and secondary tumors was 31 months (median 19, range 0-251) in our series. Patients with secondary tumors from renal cell carcinoma were diagnosed at the latest at a mean of 62 months following primary diagnosis (median 38, range 0-251). The second-longest intervals were found in breast cancer patients (mean 56 months, median 45, range 0-178). In contrast, patients with pancreatic (mean 0.4 months, median 0, range 0-5) and colorectal cancer (mean 8, median 6, range 0-20) had the shortest time intervals. In detail, the three longest time intervals in this dataset were reported for one patient with a secondary tumor from renal cell carcinoma (251 months following diagnosis of the corresponding primary), another with cervical cancer (213 months) and one patient with malignant melanoma (202 months) (Figure 11) (43).

Data on extragastrointestinal cancer spread were available for 159 (74%) patients. Of these, 109 (69%) had evidence of additional metastatic disease, preferentially to the lungs (n=26, 24%), liver (n=39, 36 %), peritoneum (n=37, 34%), bone (n=19, 17%) and other sites (lymph nodes n=18, 17%), skin (n=13, 12%), brain (n=6, 6%), other (n=27, 25%).

Table 3: Differences in knowledge of an underlying primary tumor depending on histological entity (using Fisher's exact test).

Primary tumor	**Lung**	**Breast**	**Kidney**	**Liver**	**Malignant melanoma**	**Gall-blad-der**	**Prostate**	**Uterus**
unknown	4	5	1	0	5	0	7	0
known	7	27	13	4	28	4	18	6
total	11	32	14	4	33	4	25	6
p-value	p=0.27	p=0.38	p=0.2	0.58	p=0.37	p=0.58	p=0.46	p=0.58
Primary tumor	**Pancreas**	**Ovary**	**Colo-rectum**	**Cervix**	**Stomach**	**Urinary bladder**	**Other**	**Total**
unknown	19	4	1	0	1	0	2	49
known	8	13	5	6	14	4	11	168
total	27	17	6	6	15	4	13	217
p-value	**p<0.001**	p=1	p=1	p=0.34	p=0.20	p=0.58	NA	NA

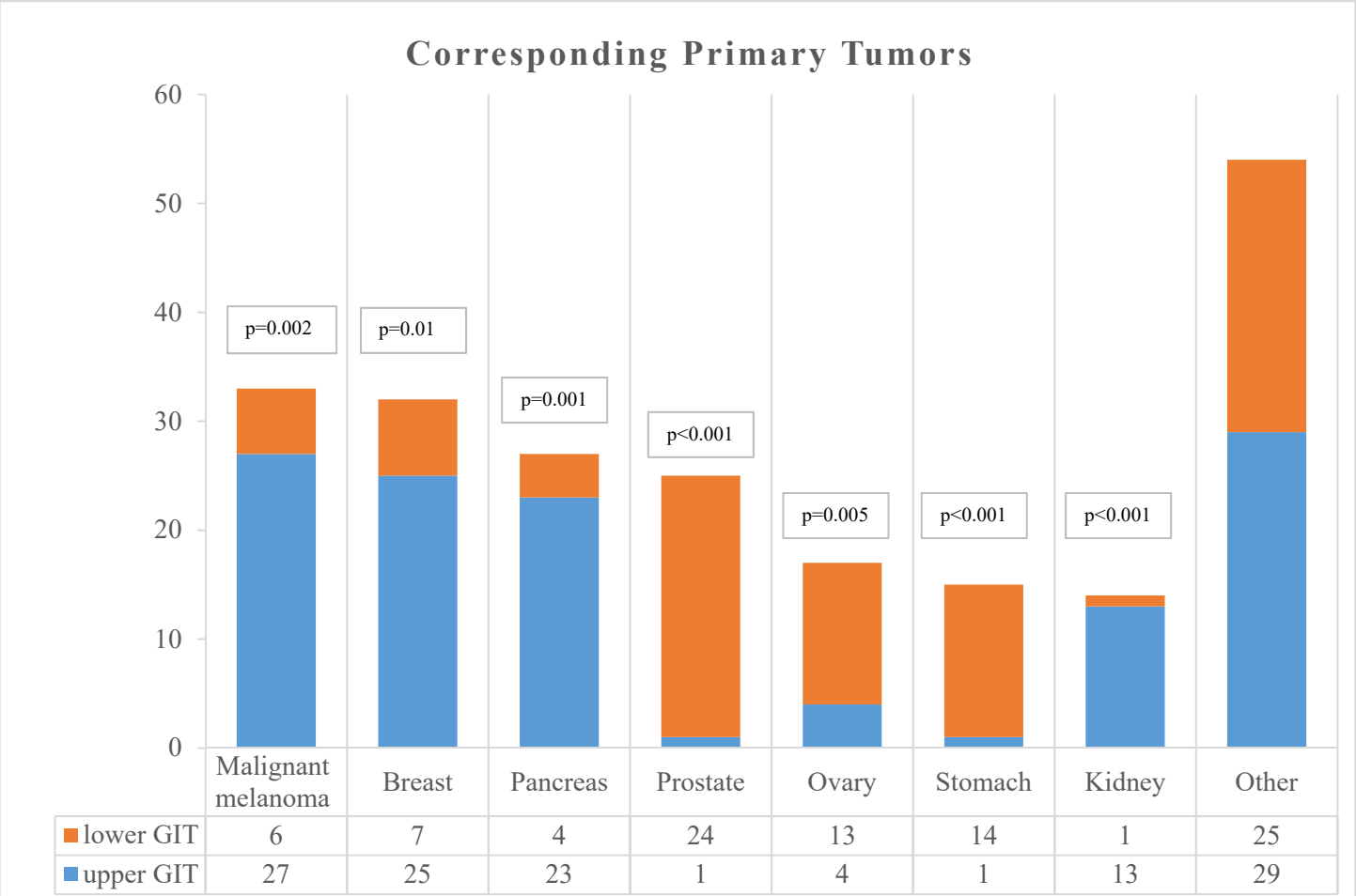


Figure 10: Corresponding primary tumors according to upper and lower GIT localization. Differences were calculated with Fisher's exact test (Data reproduced and modified from Gilg et al. (43) with permission of publisher (Elsevier)).

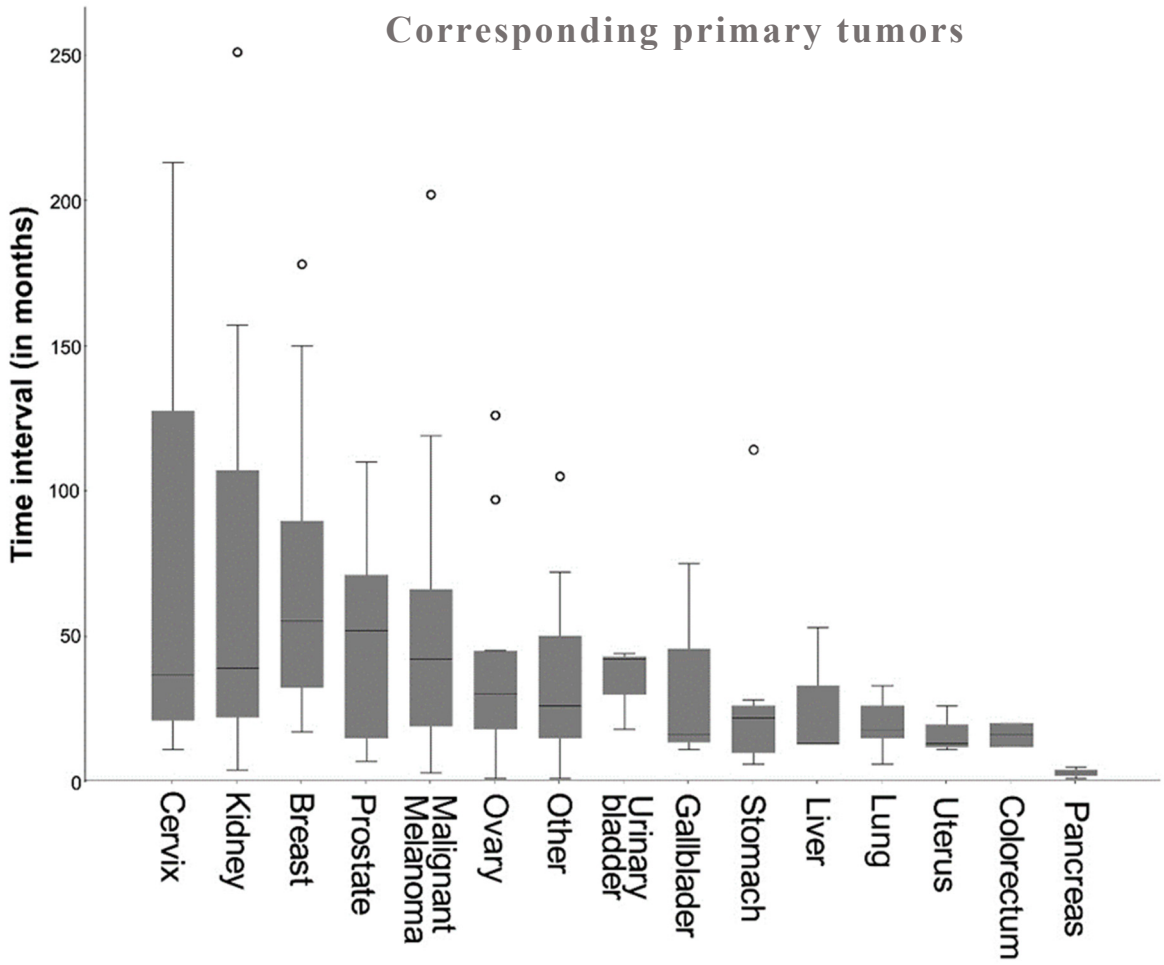


Figure 11: Boxplots showing median time intervals of specific corresponding primary tumors within the GIT (in months) (Data reproduced and modified from Gilg et al. (43) with permission of publisher (Elsevier)).

3.4.1. Breast cancer as corresponding primary tumor

In this dataset the most common histological subtype was invasive lobular type breast cancer in 24/32 patients (75%), including one patient with a lobular-tubular subtype, whereas the remainder (n=8, 25%) was of the invasive carcinoma NST subtype. Regarding the route of cancer dissemination, all tumors spread hematogenously (Figure 12) (Table 4) (43).

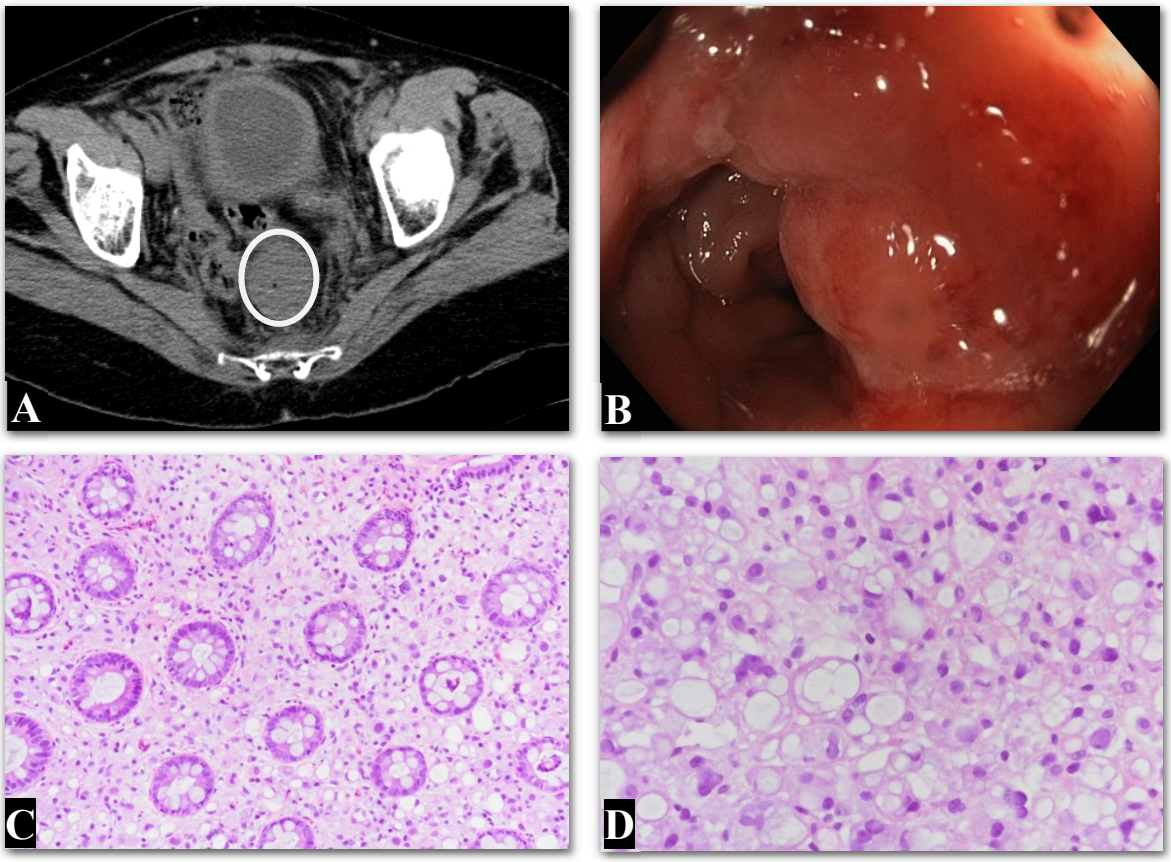
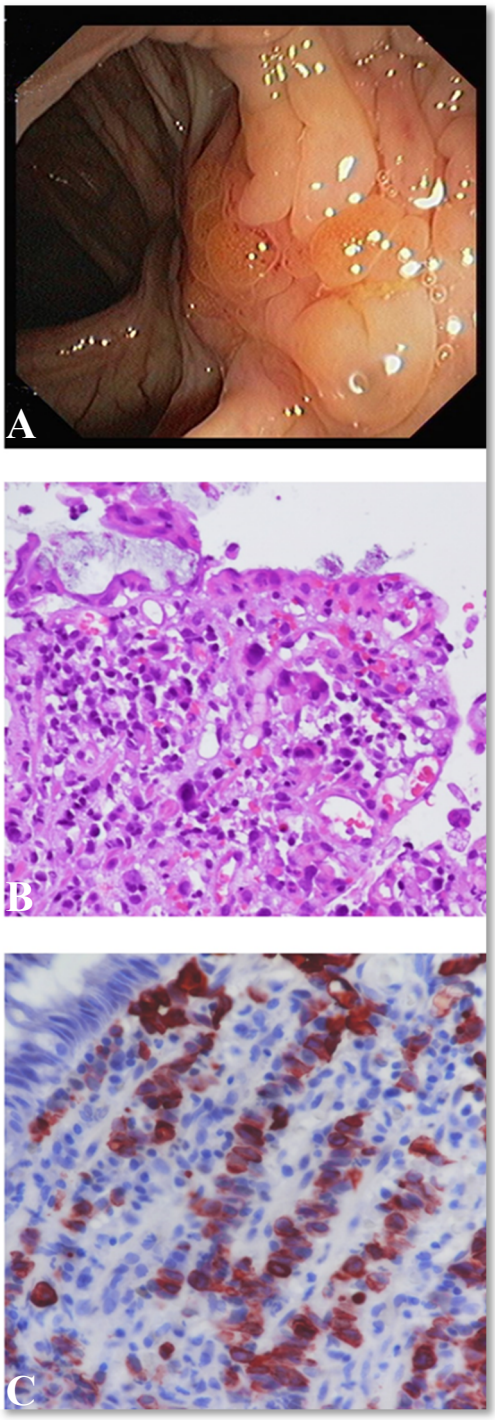


Figure 12: 72-year-old female patient with invasive lobular type breast cancer metastatic to the rectum; A: transverse CT scan showing rectal stenosis (circle); B: Colonoscopy showing subtotal stenosis of the rectum due to a polypoid tumor mass; C: In between normal colonic crypts H&E stain shows atypical cells within the stroma with discohesive growth pattern; D: On high power magnification atypical nuclei can be seen with areas of histiocytic morphology, along with signet ring cells.

Table 4: Details on tumors secondary to breast cancer (data reproduced and modified from Gilg et al. (43) with permission of publisher (Elsevier)).			
		Invasive lobular (n=24)	Invasive carcinoma NST (n=8)
Primary tumor	known	21	6
	unknown	3	2
Localization (multiple localizations possible)	stomach	16	7
	small intestine	2	1
	colon	5	0
	rectum	3	0
Route of cancer dissemination	hematogenous	24	8
	direct invasion	0	0
Clinical evaluation by endoscopist	primary tumor	5	2
	secondary tumor	2	2
	benign	2	2
	inflammatory	1	1
	unclear/ no diagnosis	3	0
	missing data	11	1
General morphology assessment	carcinoma-like	5	3
	submucosa-like	15	3
	normal mucosa	2	2
	missing data	2	0
Gross findings	intramural process	14	1
	polypoid mass	1	1
	ulcer	3	2
	nodule	2	2
	small black spot	0	0
	no visible lesion	2	2
	missing data	2	0

3.4.2 Gastric cancer as a corresponding primary tumor



Tumors secondary to primary gastric tumors included gastric cancer of the intestinal subtype (n=4, 27%) and of the poorly cohesive (diffuse type according to the Lauren classification) subtype (n=9, 60%). In two cases (13%), the pathology database did not permit a retrospective histological classification. Regarding the route of cancer dissemination, all secondary tumors spread via direct invasion. Details are shown in Figure 13 and Table 5.

Figure 13: Example of a male patient with direct invasion of metastatic gastric cancer infiltrating the transverse colon. **A:** colonoscopy showing a polypoid mass with primary carcinoma-like appearance; **B**: H&E stain shows atypical cells diffusely infiltrating the stroma. **C**: Expression of keratin 7 within the cytoplasm.

Table 5. Details on tumors secondary to gastric cancer.			
		intestinal (n=4)	poorly-cohesive (n=9)
Primary tumor	known	4	9
	unknown	0	0
Localization (multiple localizations possible)	small intestine	1	1
	colon	1	6
	rectum	2	2
Route of cancer dissemination	hematogenous	0	0
	direct invasion	4	9
Endoscopist's evaluation	primary tumor	0	1
	secondary tumor	1	0
	benign	0	1
	inflammatory	0	0
	unclear/ no diagnosis	2	2
	missing data	1	5
General morphologic assessment	carcinoma-like	1	3
	submucosa-like	3	2
	normal mucosa	0	0
	missing data	0	4
Gross findings	intramural process	3	1
	polypoid mass	0	1
	ulcer	1	2
	nodule	0	1
	small black spot	0	0
	no visible lesion	0	0
	missing data	0	4

3.4.3 Malignant melanoma as a corresponding primary tumor

Table 6. Details of tumors secondary to malignant melanoma.

		n
Primary tumor	known	28 (85%)
	unknown	5 (15%)
Localization (multiple localizations possible)	stomach	20 (61%)
	duodenum	9 (27%)
	colon	2 (6%)
	rectum	2 (6%)
Route of cancer dissemination	hematogenous	33 (100%)
	direct invasion	0 (0%)
Clinical evaluation endoscopist	primary tumor	6 (18%)
	secondary tumor	17 (52%)
	benign	1 (3%)
	inflammatory	1 (3%)
	unclear/ no diagnosis	5 (15%)
	missing data	3 (9%)
General morphology assessment	carcinoma-like	16 (49%)
	submucosa-like	14 (42%)
	both	1 (3%)
	missing data	2 (6%)
Gross findings	intramural process	3 (9%)
	polypoid mass	14 (42%)
	ulcer	3 (9%)
	nodule	4 (12%)
	small black spot	7 (21%)
	no visible lesion	0 (0%)
	missing data	2 (6%)

Secondary tumors originating from malignant melanoma were the most common histological subtype in our series, compromising 33 out of 217 lesions (17%). The primary tumor was known in the majority of patients (n=28, 85%) and all of the tumors spread hematogenously. The typical “small black spot” morphology was present in one-fifth of patients (n= 7); further

details on endoscopic findings are shown in Table 6. Endoscopists correctly suggested a secondary lesion for 17/33 (52%) patients. Nearly all secondary tumors (29/33, 88%) were diagnosed when there was already further distant metastatic spread of malignant melanoma.

3.5 Routes of cancer dissemination

Overall, direct invasion (n=122, 56%) from extragastrointestinal neoplasms was slightly more common than vascular cancer spread (n=95, 44%). Direct invasion, including invasion via peritoneal carcinomatosis, depended on the anatomical site of the secondary tumors as well as on the underlying primary tumor type. Typically, esophagus, colon, and rectum were directly invaded by secondary neoplasms, whereas vascular spread was more frequent in the stomach (Table 7). In detail, tumors secondary to pancreatic cancer (n=27, $p< 0.001$, directly infiltrating the duodenum), gastric cancer (n=15, $p< 0.001$ directly infiltrating duodenum and colon), ovarian (n=17, $p< 0.001$) and prostate cancer (n=25, $p< 0.001$) (directly infiltrating the colorectum) significantly more often infiltrated the target region directly per continuitatem (Figure 14). Notably, none of the aforementioned tumors included in our series disseminated via vascular spread (43). In contrast, malignant melanoma (n=33, $p< 0.001$) and breast cancer (n=32, $p< 0.001$) spread only via the vascular route. Together, 82% (n=78) of secondary tumors with this route of cancer dissemination comprised malignant melanoma, breast cancer and renal cell cancer (n=13, $p< 0.001$).

When a primary cancer was unknown prior to endoscopy (n=49, 23%), secondary tumors significantly more often invaded the GIT directly (p=0.02) (Table 7).Patients whose tumors directly invaded metastatic target sites presented with significantly shorter time intervals between diagnosis of a primary and secondary tumor (mean 35 months, median 18, range 0-151) than patients with vascular spread (mean 48 months, median 36, range 0-202, p=0.005) (43).

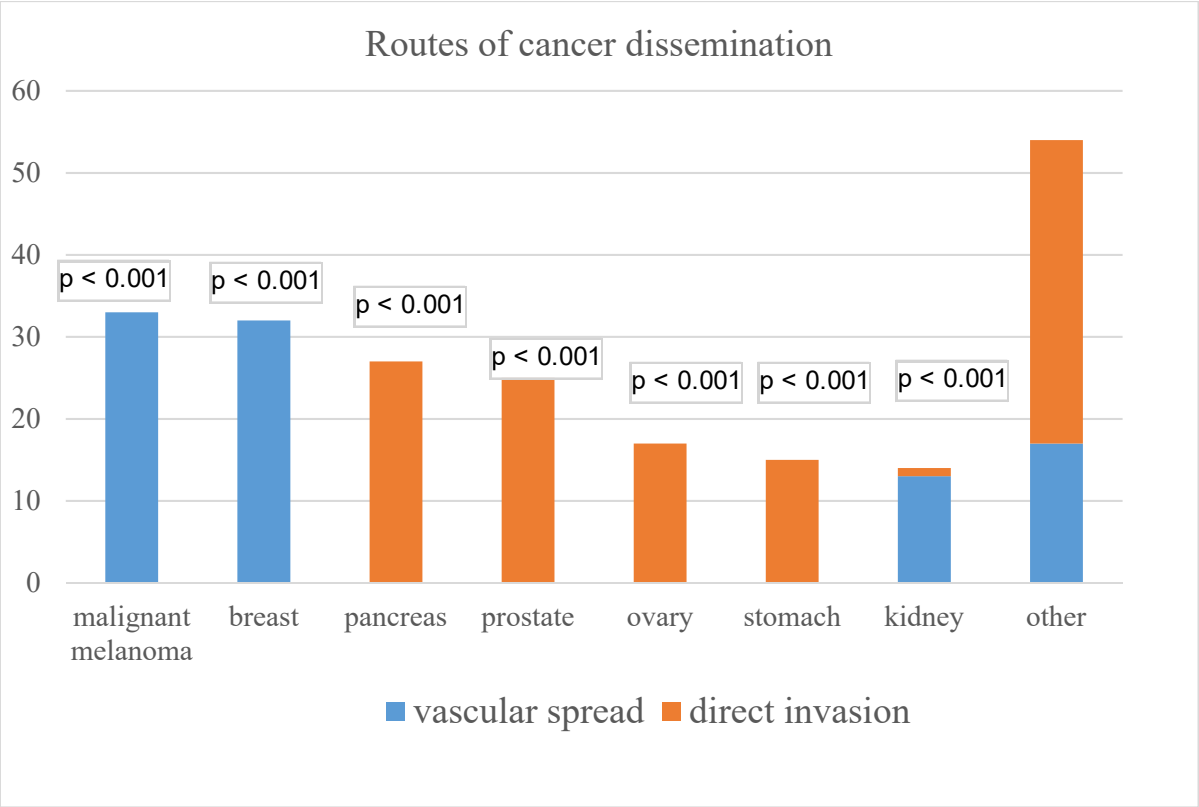


Figure 14: Differences in routes of cancer dissemination (vascular spread versus direct invasion) according to distinct histological entities (data reproduced and modified from Gilg et al. (43) with permission of publisher (Elsevier)).

Table 7: Details of secondary tumors of the GIT according to route of cancer dissemination (vascular spread versus direct invasion) for 217 lesions (data reproduced and modified from Gilg et al. (43) with permission of publisher (Elsevier)).

	Vascular spread	**Direct infiltration**
	n	n
Total number of lesions	95 (44%)	122 (56%)
Primary cancer known	81 (37%)	87 (40%)
Primary cancer unknown	14 (7%)	35 (16%)
Anatomical site (multiple sites possible)		
Esophagus	1 (1%)	5 (4%)
Stomach	66 (65%)	10 (8%)
Duodenum	21 (21%)	33 (26%)
Colon	9 (9%)	31 (24%)
Rectum	5 (5%)	48 (38%)

3.6 Anatomical distribution of secondary tumors

Gastroscopy identified 123/ 217 (57%) secondary tumors while 94/217 (43%) lesions were detected during colonoscopy. Thirty-five percent of secondary tumors were detected in the stomach (n=76), followed by the duodenum (25%, n=54) and rectum (24%, n=53) (Table 8) (43).

Table 8: Spatial distribution of secondary tumors within the GIT (data reproduced and modified from Gilg et al. (43) with permission of publisher (Elsevier)).

Localization of secondary tumors		**n**	**%**
	Esophagus	6	3
	Stomach	76	33
	Duodenum	54	24
	Colon	40	17
	Rectum	53	23

3.6.1 Secondary tumors of the stomach

With respect to gastric localization of secondary tumors, the majority of lesions was detected in oxyntic mucosa (59/76, 78%) and 23/76 (30%) patients had multifocal gastric lesions; seven (9%) further patients had additional metastatic lesions in the duodenum. The corresponding primary tumor was known for 64 lesions (84%) prior to gastroscopy. A majority of secondary lesions disseminated via hematogenous spread (n=65, 86%). The most common secondary tumors within the stomach originated from breast cancer (n=24, 32%), followed by malignant melanoma (n=20, 26%) and renal cell carcinoma (n=10, 13%). Clinical symptoms and indications for gastroscopy were available for 53 (70%) patients, of whom 27 (51%) showed signs of abdominal discomfort, 15 (28%) presented with bleeding, nine (17%) with vomiting/obstruction and in a further 11 (21%) patients, gastroscopy was performed in search of a primary tumor (43).

3.6.2 Secondary tumors of the rectum

The rectum was the site of 53/217 (24%) secondary lesions. In 43 (81%) patients a corresponding primary tumor was already known upon diagnosis of the secondary tumor. In a majority of cases (n=23, 43%), the underlying corresponding primary tumor was prostate cancer. Details of the remaining primary lesions are shown in Table 9.

Table 9: Corresponding primary tumors of secondary rectal tumors.

Histology	**n**	**%**
Prostate	23	43.4%
Ovary	7	13.2%
Stomach	4	7.5%
Breast	3	5.7%
Cervix	3	5.7%
Malignant melanoma	2	3.8%
Urinary bladder	2	3.8%
Uterus	2	3.8%
Pancreas	1	1.9%
Other	6	11.3%
Total	**53**	**100.0%**

Ninety-one percent (n=48) of secondary tumors invaded the rectum directly. Rarely (n=5, 9%), we detected secondary lesions that metastasized to the rectum via vascular spread. There is a notable case of a 72-year-old female patient who presented with a three-month history of constipation, diffuse abdominal pain and mild anemia (Figure 12). There was no relevant past medical history, except for osteoporosis and chronic kidney failure. Subtotal stenosis of the rectum was detected upon colonoscopy and multiple biopsies were taken. Histology revealed atypical cells in between normal colonic crypts within the stroma with a discohesive growth pattern. On high power magnification, atypical nuclei could be seen. In addition, there were areas with histiocytic morphology and signet ring cells. Upon immunohistochemistry, cells were positive for keratin, particularly keratin 7; proliferation markers were positive (MIB) and cells were negative for CD 68 and CGA. Furthermore, the tumor was negative for CDX 20, but diffusely positive for estrogen receptor, which excluded a colorectal primary and confirmed a secondary tumor from invasive lobular breast cancer.

Staging including mammography revealed a 7 mm large mass in the left breast and a bone metastasis in the 8th thoracic vertebra. Core needle biopsy of the breast confirmed lobular breast cancer as the primary corresponding tumor. Notably, peritoneal cancer dissemination was neither clinically nor radiologically evident at the time of initial diagnosis, so that the metastasis was classified as hematogenous. The patient underwent palliative chemotherapy and died of progressive disease nine months after initial diagnosis.

3.6.3 Case Report: Secondary tumor of the ampulla of Vater

This retrospective database analysis included a 57-year-old patient who presented with gastrointestinal bleeding 39 months after diagnosis of clear cell renal carcinoma and nephrectomy. This case report including a review of the literature was published in the Journal of *Molecular and Clinical Oncology* (46). Upon gastroscopy, the ampulla was irregularly distended, but the rest of the GIT was unremarkable. Histology revealed renal clear cell carcinoma within the submucosa and "secondary ulceration of the mucosal surface" (46). On high power magnification **"**well differentiated cancer cells [were] arranged in typical alveolar pattern with clear cytoplasm and hyperchromatic nuclei" (46) . When staging showed no further metastatic lesions, the patient underwent a Whipple procedure for the papillary metastasis with wide resection margins and tumor negative lymph nodes. The patient underwent routine follow-up and there was no evidence of disease four years after diagnosis of the secondary tumor (46).

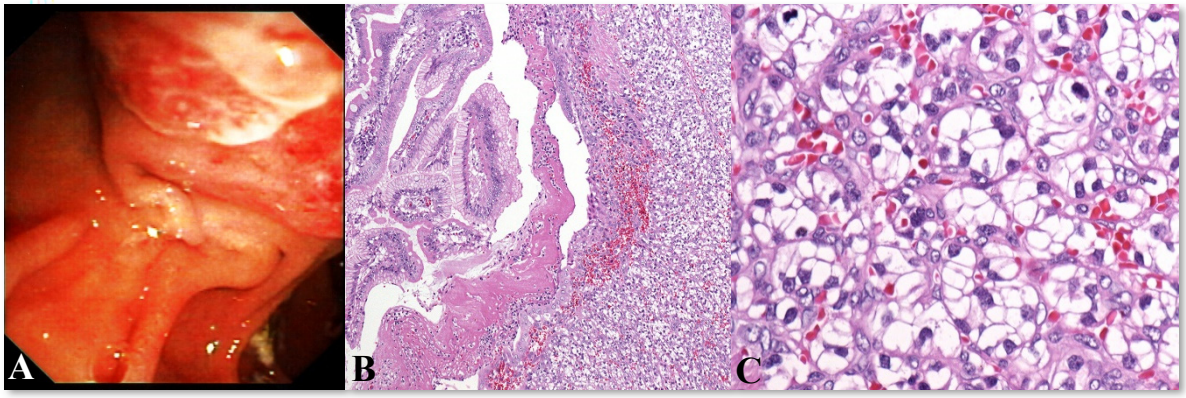


Figure 15: "A, irregular enlargement of the ampulla. B, renal clear cell carcinoma which is developed mainly in the submucosa with secondary ulceration of the mucosal surface (original magnification, ×100) C, well differentiated cancer cells arranged in typical alveolar pattern (original magnification, ×250)" (46). Figure reproduced from Sarocchi et al. (46) with permission of publisher (Spandidos Publications).

4. Discussion

This series provides a thorough overview of the largest cohort of secondary tumors of the GIT ever analyzed. Secondary tumors may occur in all parts of the GIT; however, specific preferences for anatomical distribution as well as routes of cancer dissemination were identified for corresponding primary tumors. In summary, vascular cancer spread was typical for gastric lesions, in contrast to duodenal or rectal lesions, which most frequently were invaded directly. Three out of four patients included in this study had a known corresponding primary tumor prior to detection of the secondary GIT lesion. Our study showed that malignant melanoma, breast cancer and pancreatic cancer were the most common corresponding primaries in the upper GIT, while prostate, gastric and ovarian cancer most frequently disseminated to the lower parts of the GIT. This study further revealed that time intervals between the initial diagnosis of primary and secondary tumors are highly variable, with the longest intervals in renal cell and breast cancer patients (43).

Secondary tumors of the GIT are rare compared to other metastatic sites (9, 36, 47). A quantitative analysis of patterns of metastatic cancer spread by Disibio et al. (20) covered 3827 autopsies. The most common metastatic sites were lymph nodes, lungs, liver and bone, independent of the corresponding primary tumor. In contrast, testes, vagina, stomach, skeletal muscle and prostate were the most infrequent metastatic target sites in their analysis. With respect to the GIT, secondary tumors of the stomach the small and large intestines accounted for less than 3% of lesions altogether (9).

4.1 Clinical presentation and endoscopic correlation

Like previous studies, our attempt also failed to detect endoscopic features that would allow differentiation between primary or secondary tumors (13, 34, 41, 43, 48, 49). To this end, lesions were classified as “submucosa-like” (i.e., secondary tumor-like) or “primary carcinoma-like” (5). However, only 50% of secondary tumors were located in the submucosal parts of the GIT in this series, while the remainder was not classifiable or exhibited primary carcinoma-like patterns. This two-tier classification thus is not useful in the differentiation between primary and secondary tumors of the GIT. Similarly, distinct endoscopic appearance, i.e. morphology and quantity, of secondary tumors of different histological origin was unspecific in our cohort. In detail, “polypoid masses” are typically seen in primary

carcinomas as well as intramural processes, but the secondary tumors most frequently encountered in this cohort were also described as such. Furthermore, volcano-like morphology had been described as typical for secondary tumors of the GIT in the past (11, 15, 35, 50, 51). We could not confirm this pattern as specific for secondary tumors in our series, as less than 10% of lesions showed this morphology. Equally, only one out of five melanoma metastases in this series presented with brownish or black spots; the remaining melanoma lesions were amelanotic and endoscopically indistinguishable from other secondary tumors (43, 52).

In accordance with the literature, indications for endoscopic intervention varied from mild abdominal discomfort to acute bleeding or bowel obstructions (5, 41). Among all diagnoses made at an endoscopy unit, the diagnosis of a secondary tumor is a rare event. It has been estimated that 3847 gastroscopies and 1871 colonoscopies have to be performed until one secondary tumor of the stomach or lower GIT is found (41). The low incidence as well as unspecific morphology and clinical presentation of secondary tumors of the GIT may account for the low awareness of secondary tumors and misinterpretation as primary or benign lesion in approximately 50% of lesions investigated in this series (43).

Histology thus is crucial for accurate diagnosis and classification of secondary gastrointestinal tumors. Still, clinicians need to bear in mind that pathologists can only diagnose lesions they are aware of, that is, lesions they know about and/or have already seen. Here, “expectation” is a contributing factor that should not be underrated. Due to the rarity of cases, pathologists do not “expect” a neoplastic lesion to be secondary.

It is important that the pathologist is made aware of any underlying primary tumor, even diagnosed many years ago, as otherwise, the risk of misdiagnosis or incorrect classification of secondary tumors is rather high. Unnecessary diagnostic delay or even surgical procedures, especially in poorly differentiated lesions, may be avoided by improved communication among clinicians and pathologists so that the appropriate set of immunohistochemical markers can be chosen (43).

4.2 Corresponding primary tumors

Comparing the most frequent secondary tumors detected in this dataset, i.e. from malignant melanoma, breast and pancreatic cancer, to published series in the literature, geographic differences can be noted. In a series of 42 Taiwanese patients diagnosed with secondary tumors of the GIT, a high proportion of secondary tumors from hepatocellular carcinoma (12%) was notable upon endoscopy, possibly reflecting the high incidence of this cancer in that region (41). In contrast, hepatocellular carcinoma metastatic to the GIT constituted a very rare finding in our dataset (2%) (43).

Similarly, lung cancer metastatic to the GIT has been frequently reported (5, 9, 34, 42); however, lung cancer was responsible for only 5% of secondary gastrointestinal tumors in our series. This is a rather unexpected finding as lung cancer is one of the most common tumors in Austria (10). Reasons for the differences may be due to varying study designs since secondary lesions originating from lung cancer were usually detected in autopsy studies (9, 12, 34, 42). Washington et al. (53) compared secondary tumors from lung cancer detected during autopsy (n=108) to endoscopies (n=73), showing that lung cancer was in first place for autopsies but in fifth place for endoscopy. The varying proportion may be explainable by the aggressive course of metastatic pulmonary disease. Mean reported survival rates were less than half a year for patients suffering from GIT metastases (54), so that patients were spared extensive diagnostic interventions, such as endoscopy, and treatment was limited to best supportive care.

In this series, there was a mean time interval of 30 months between the initial diagnosis of primary cancer and the diagnosis of secondary cancer of the GIT. Interestingly, there were major differences in time intervals among histological entities. Renal cell carcinoma and breast cancer metastasized late to the GIT (mean interval: 62 and 55 months, respectively). The potential for late metastasis is well recognized for renal cell carcinoma (20). Prior to the "era of targeted therapy," the presence of late GIT metastases was usually associated with concomitant metastases to other organs, resulting in poor overall survival (20). Data on renal cancer patients with GIT metastasis undergoing targeted therapy are not available; however, general data on renal cancer patients with metastatic disease suggest dramatically improved survival (55). Secondary tumors originating from malignant melanomas can also be detected very late, up to 20 years following initial diagnosis (22, 43, 56).

4.2.1 Breast cancer as a corresponding primary tumor

Breast cancer is among the most common primary tumors detected in women and has high metastatic potential (9). Accordingly, breast cancer was among the most frequent secondary tumors in this analysis; it was mainly identified in the upper and only rarely in the lower GIT. As expected, the distribution of histological subtypes in our dataset is similar to the literature, which shows that secondary tumors of the invasive carcinoma non-specific subtype (NST) account for 75% of all breast cancers diagnosed, followed by the invasive lobular subtype of breast cancer, which accounts for 5-10% (57). Our series showed no significant differences according to subtypes and anatomical sites or endoscopic presentation.

Differences have been reported when the metastatic patterns of both subtypes are compared. The invasive NST subtype seems to spread to the lungs more frequently than invasive lobular carcinoma, which also tends to metastasize more often to bones or to unusual sites such as the meninges or the GIT (57). In a clinical study, El-Hage et al. (36) analysed 481 patients with diagnosed invasive lobular carcinoma, of whom 6.8 % had a secondary tumour in the stomach and 1.4 % in the colon. Specific molecular factors resulting in this organotropism have not yet been fully elucidated, albeit the "loss of the adhesion molecule E- cadherin in ILC cancer cells as a result of the loss of the CDH1 gene on chromosome 16q22.1" (57) as well as the role of stroma and the extracellular matrix have been discussed (57, 58).

Mathew et al (58) specifically reviewed metastatic patterns of 761 women diagnosed with either invasive NST or lobular breast cancer subtype, detecting increased involvement of the GIT both for the first metastatic event and overall rates in the lobular subtype. Apart from the two studies mentioned, the literature is limited to single case reports or is not reproducible, as data about GIT involvement with breast cancer is summarized under visceral or other metastatic sites (59-62).

Difficulties in obtaining representative biopsy material that may lead to false-negative reports have been described. It was shown that every second metastasis due to invasive lobular breast carcinoma was missed in initial biopsies, as secondary tumors often grew in the submucosa or deep within muscular layers (63). Consequently, a greater number of biopsies, also targeting deeper tissue layers, is recommended (43).

4.2.2 Malignant melanoma as corresponding primary tumor

The incidence of primary malignant melanoma has increased by 700% over the last four decades (64). Malignant melanoma was the most frequent underlying primary tumor in this series, which is consistent with previous reports pointing out the propensity of melanomas to spread to the GIT (22, 40). An affinity for the duodenum has been reported (40), in contrast to our series in which the stomach was most frequently affected. The difference can likely be explained by study design as instead of endoscopic data, autopsy studies were evaluated and only one-fourth of patients seem to have been diagnosed with a tumor secondary to melanoma while still alive (40). Despite the known propensity of melanoma to metastasize into the GIT, there are no current studies on secondary melanomas of the GIT, or studies focus on other anatomical sites such as the brain, lymph nodes or bone (65). As seen in our study, over 50% of patients with secondary tumors in the GIT have further metastatic disease and therefore advanced cancer stages (66). Survival rates for patients with tumors of the GIT secondary to melanoma have been reported to be less than 10% at 5 years (66). However, this has to be interpreted with caution as data were retrieved from a time well before the introduction of targeted therapy, i.e. BRAF inhibitors or immunotherapy. While a few decades ago, the prognosis of metastatic melanoma patients was miserable, targeted therapy has led to prolonged survival even for advanced tumor stages (67). In this regard, it is important for metastatic sites to be biopsied so that tissue samples can be screened for prognostically relevant mutations (67). In order to obtain enough and representative biopsy material, samples also have to be collected from deeper layers. This is particularly important for malignant melanoma as it is often difficult to distinguish between primary and secondary lesions within the GIT (66).

4.3 Routes of cancer dissemination

This study revealed that distinct routes of cancer spread were mostly predetermined by the histology of the underlying corresponding primary tumor as well as anatomical localization (43). In particular, prostate, gastric and ovarian cancer almost exclusively invaded the lower parts of the GIT directly, often through peritoneal carcinomatosis. In contrast, breast cancer and malignant melanoma metastases preferred invasion of the GIT via vascular spread. Rarely, there can also be direct invasion, as has been described for isolated cases of breast cancer (36). It should be noted that this study did not include perineural invasion as a route

of cancer dissemination. It was already described in the 19th century and is defined as the presence of tumor cells within either the endo-, peri- or epineurium of the nerve. With a retrospective study design, however, histological evaluation of perineural invasion is not feasible. Perineural invasion is best investigated in prostate, head and neck and pancreatic cancer and is independent of vascular or lymphatic spread of tumor cells. In detail, PNI was detected in 3 out of four prostate cancer resection specimens and is regarded as a significant prognostic factor. For other histological entities than the ones described above, both clinical and basic research is very limited (68).

4.3.1 Routes of cancer dissemination for malignant melanoma

Malignant melanoma was most frequently detected as the corresponding primary in this series and was disseminated exclusively via vascular spread (43). Generally, melanomas tend to show a high propensity for systemic dissemination (69). In a large, registry-based study of approx. 3000 melanoma patients, 16% developed secondary tumors, 4% of which were distant metastases (70). Currently, three sub-categories of tumor dissemination are discussed for melanomas: satellite lesions, lymph node metastases and distant metastases with a predilection for visceral (including the GIT) sites (69). In this regard, the chronological and spatial modalities have been discussed controversially and include three models of explanation. First, a "stepwise spread model" (69), which sees distant melanoma metastases as the result of lymphatic tumor cell dissemination via lymph nodes, which ultimately leads to systemic dissemination. Second, a "simultaneously spread model" (69), proposing simultaneous lymphatic and hematogenous spread. Third, a model of "differential spread" (69), suggesting that some melanoma cells have no potential for metastatic spread, while others are capable of either hematogenous or lymphatic spread or both.

The time interval until the occurrence of distant metastases depends on the route of cancer dissemination, with longer intervals for distant (70) than local or regional metastases (69). Interestingly, the time intervals until distant metastases seemed not be influenced by prior local or regional recurrences (69). Risk factors that affect the development of distant metastases are anatomical location in the upper extremity and trunk region as well as primary tumor thickness and male gender (69, 71).

4.4 Anatomical distribution of secondary tumors

In this series secondary tumors were mainly localized in the stomach – the anatomical site best investigated in the literature to date (5, 13, 34, 42) – followed by the duodenum and the rectum (43). In a study of 389 patients with secondary gastric tumors who were mainly investigated postmortem, malignant melanoma was the most common corresponding primary tumor in about one-third of cases, followed by esophageal, and breast cancer in 12% of lesions, respectively (13). Other groups draw our attention to the fact that invasive lobular breast carcinoma spreads to the GIT, even though this subtype comprises only 5-10% of all invasive breast tumors (36, 63). El-Hage et al. (36) investigated 481 patients with invasive lobular breast carcinoma and found only five (1%) patients with gastric metastases and one with metastasis to the colon. This shows that despite a propensity of invasive lobular breast cancer to generate high numbers of metastases (9) and a propensity to metastasize to uncommon sites such as the GIT, this is still a very rare event compared to other anatomical sites.
The most common primaries metastaszing via direct invasion to the rectum were prostate cancer and ovarian cancer, followed by primaries in the genitourinary tract (43). Often these patients present at very advanced tumor stages and their prognosis is poor (72, 73) . In the rectum, Li et al. (74) have addressed the problem of false negative biopsies of both primary and secondary tumors during colonoscopy when neoplastic disease resembled solitary rectal ulcer syndrome. Endoscopically, these lesions present as polypoid masses or ulcers and may simulate a benign condition; as superficial biopsies may reveal only histologically unspecific reactive changes, their study emphasized the need for deep, extensive sampling and careful histological workup.
Apart from the aforementioned studies, data are scarce and to our knowledge there is no systematic analysis of secondary tumors of the GIT and their relation to anatomical sites to which our results could be compared.

4.4.1 Ampulla Vateri

The anatomical region consisting of the duodenum, the terminal tract of the pancreatic duct and the final portion of the common bile duct was first described by Abraham Vater in 1720 and named after him (75). In contrast to primary ampullary cancer, mainly the pancreatobilary and the intestinal type, secondary tumors are very rare in this anatomical region (76). So far only 31 cases of secondary tumors metastatic to the ampulla of Vater have been

reported in the literature (46). Sarocchi et al. (46) conducted a systematic literature review of the clinical and endoscopic presentation, corresponding primary tumors as well as treatment and outcome of secondary tumors of the papilla of Vater. In summary, patients are usually affected in their sixth decade of life, albeit the youngest patient in this collective was 27 years old. As corresponding primary tumors, renal cell carcinoma (about 1/3 of patients), malignant melanoma (another 1/3 of patients) and breast cancer were among the most frequent primaries with similar frequencies compared to the dataset for the entire GIT. Interestingly, for renal cell carcinoma, the mean time interval between primary diagnosis and the detection of a secondary tumor of the ampulla of Vater was approx. 9 years. There was no specific morphological finding of secondary tumors in this region upon endoscopy. Sarocchi et al. (46) also investigated treatment and clinical outcome of patients with tumors metastatic to the ampulla of Vater. In general, in the palliative setting, drainage or stenting should be considered to relieve symptoms like jaundice, bleeding or pruritus. Despite the risk of perioperative complications and death from surgery, patients with secondary renal cell carcinoma seemed to benefit most from wide surgical resections with better survival by several years than with other histological entities.

4.5 Strengths and limitations

This study represents the largest series of secondary GIT tumors to date. All lesions were diagnosed endoscopically (in the upper or lower GIT) in multiple endoscopy units and confirmed by biopsy diagnosis at one institute of pathology, resulting in a large study cohort, whereas previous studies focused on autopsies, case reports or single-center experiences. Our study provides a detailed overview of secondary tumors of the GIT with respect to anatomical site and histological entities, while other analyses were limited to one histological entity or a single anatomical location (43).

Although the numbers of patients investigated in our series is high, absolute numbers for some corresponding primaries, such as uterus, urinary bladder or lungs are low due to the rarity of the respective disease, so that results must be interpreted with caution. Furthermore, endoscopic evaluation of tumors was limited as imaging was not available or incomplete for a substantial portion of lesions dating from an era when there were no electronic data files. In these cases, classification was not possible or was based on written reports from twelve different endoscopy units and with several endoscopists at each unit. This might introduce

information bias and should be considered when interpreting the results. In addition, patients with asymptomatic secondary tumors of the GIT are missed as they never undergo endoscopy and consequently, the distribution of corresponding primary tumors within the GIT might be other than in this endoscopy-derived analysis. When the distinct routes of cancer dissemination were classified on the basis of clinical records, patients with advanced cancer may have had a limited diagnostic workup and peritoneal carcinomatosis, though present, remained undiagnosed.

5. Conclusions

In summary, malignant melanoma, breast cancer and pancreatic cancer are the most common underlying primary tumors that metastasize to the GIT. Secondary tumors disseminate predominantly to the stomach via vascular spread, to the rectum, colon and esophagus via direct invasion, and via both pathways to the duodenum. Mean time intervals between diagnoses of primary and secondary tumors are highly variable, with intervals less than one month for pancreatic cancer and up to 67 months for renal cell carcinomas. About one-fourth of corresponding primary tumors are unknown until detection of a secondary lesion within the GIT. As clinical presentation and endoscopic findings are highly unspecific, every suspicious lesion within the GIT should be subject to biopsy and histological workup, especially since clinicians assessed about one-half of secondary lesions endoscopically as primary tumors.

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