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Thèse

Pour le

DOCTORAT EN MEDECINE

Diplôme d'État

par

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TITRE

Métastases gastro-intestinales dans le cancer du rein : étude rétrospective multicentrique du Groupe d'Etude des Tumeurs UroGénitales (GETUG)

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Résumé de thèse

Au diagnostic de cancer du rein, 20% des patients sont d'emblée métastatiques. Parmi ceux qui présentent une forme localisée au diagnostic, 20% présenteront une récidive métastatique à distance. Les métastases gastro-intestinales (MGI) sont rares et leur pronostic est peu connu.

Nous avons analysé de manière rétrospective les dossiers de patients traités pour un cancer du rein dans 10 centres français du GETUG et ayant présenté une ou plusieurs MGI entre janvier 2000 et décembre 2021. Nous reportons dans cette étude la présentation clinique de ces métastases, les caractéristiques des patients, les stratégies thérapeutiques utilisées et le pronostic de ces lésions.

74 patients ont été inclus dans l'étude pour avoir présenté un total de 87 MGI, dont 35 lésions gastriques, 26 duodénales, 16 iléo-jéjunales, 9 coliques et 1 œsophagienne. L'histologie du primitif rénal était dans 95% des cas un carcinome rénal à cellules claires. L'âge médian au diagnostic de MGI était de 69 ans. 76% des patients présentaient déjà des métastases extra-digestives au moment de l'apparition de la première MGI. Le délai médian entre le diagnostic du primitif rénal et la première MGI était de 4 ans et 11 mois.

Les MGI ont été symptomatiques chez 52 patients (70%), responsables d'une anémie chez 41 patients (55%) et/ou d'une hémorragie digestive chez 31 patients (42%). Seuls 22 patients asymptomatiques (30%) ont été diagnostiqué de manière fortuite.

Le traitement des MGI a consisté en un traitement systémique seul pour 33% d'entre-elles, un traitement local seul pour 26% d'entre-elles et l'association d'un traitement local et d'un traitement systémique pour 21% d'entre-elles. 20% des MGI n'ont pas entrainé de prise en charge spécifique. Après le diagnostic de MGI, la médiane de survie globale était de 19 mois.

Nous présentons ici le plus large recueil rétrospectif de MGI de cancer du rein. Celles-ci doivent être suspectées devant l'apparition d'une anémie inexpliquée ou d'une hémorragie digestive chez un patient suivi pour un cancer du rein. Leur prise en charge n'étant pas codifiée, reste très hétérogène d'un patient à l'autre. Bien que les MGI semblent être un évènement tardif dans l'histoire naturelle du cancer du rein, leur survenue semble être un facteur de mauvais pronostic, avec seulement 21% de patients encore en vie à 5 ans.

“Gastrointestinal metastases in renal cell carcinoma: a retrospective multicenter GETUG (Groupe d’Étude des Tumeurs Uro-Génitales) study”

Abstract

Background: Among patients with renal cell carcinoma (RCC), 20% have metastases at diagnosis and 20% will later develop metastases. Bone and visceral metastases have a poor prognosis, while endocrine gland metastases have a more favorable prognosis. Gastrointestinal metastases (GIMs) are rare, and their prognosis is still poorly understood.

Objectives: To report clinical presentations, patients' characteristics, therapeutic strategies, and prognosis of GIMs from RCC.

Design, setting and participants: We retrospectively reviewed the records of patients presenting GIMs from RCC, in 10 French GETUG centers, between 2000 and 2021.

Results and limitations: 74 patients with 87 GIMs were identified, most of them were gastric or duodenal. 95% of RCC were clear cell. The median age at GIM diagnosis was 69 years and 76% of the patients already had extra-digestive metastases (EDMs). GIMs occurred after a median of 4.9 years (0-21.5) and 1.9 years (0-17.8) from RCC diagnosis and first EDMs, respectively. GIMs were symptomatic in 52 patients (70%), with anemia in 41 patients (55%) and/or gastrointestinal bleeding in 31 patients (42%). Only 22 asymptomatic patients (30%) were fortuitously diagnosed. The management of GIMs consisted of systemic treatment only in 29 GIMs (33%), local treatment only in 23 GIMs (26%), and both local and systemic treatment in 18 GIMs (21%). For 17 GIMs (20%), there was no therapeutic modification. After diagnosis of GIM, median overall survival was 19 months.

Conclusions: We report the largest retrospective cohort of GIMs in RCC patients. They should be suspected in case of anemia or gastrointestinal bleeding in any patient with a history of RCC. Their management is very heterogeneous and depends on their location in the digestive tract and whether they are symptomatic. Even if GIMs seem to be a late event in the evolution of RCCs, their occurrence seems to be of poor prognosis.

Patient summary: GIMs from RCC are rare. In this study, we have shown that they occur late in the course of RCC, frequently manifest as anemia or gastrointestinal bleeding, and appear to have a poor prognosis.

Mots clés

Cancer du rein
Métastases gastrointestinales
Hémorragie digestive

Keywords

Renal cell carcinoma
Gastrointestinal metastases
Gastrointestinal bleeding

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En présence des enseignants et enseignantes
de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits aux indigents,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis(e) dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux(euse) et reconnaissant(e) envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs parents.

Que les hommes et les femmes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert(e) d'opprobre
et méprisé(e) de mes confrères et consœurs
si j'y manque.

Table des matières

Liste des abréviations utilisées

AC : Anticoagulant
APD : Antiplatelet Drug
ccRCC : Clear Cell Renal Cell Carcinoma
CNIL : Commission Nationale de l'Informatique et des Libertés
EDM : Extra-Digestive Metastases
EGD : EsophagoGastroDuodenoscopy
GETUG : Groupe d'Etude des Tumeurs Uro-Génitales
GIMs : GastroIntestinal Metastases
IMDC : International mRCC Database Consortium
MD : Missing Data
mRCC : Metastatic Renal Cell Carcinoma
mTOR : Mammalian Target of Rapamycin
OS : Overall Survival
RCC : Renal Cell Carcinoma
ttt : Treatment
VEGFR TKI : Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor

Préambule

Ce travail de thèse est une étude rétrospective, réalisée à l'échelle nationale en collaboration avec le groupe de recherche du GETUG. Il est présenté sous la forme d'un article rédigé en anglais, devant être prochainement soumis pour publication dans le journal European Urology Oncology. L'article a été écrit de manière à respecter les recommandations de ce journal en termes de contenu, de structure, de nombre de mots, de références, de tableaux et de figures.

I. Introduction

With an incidence of 431 288 new cases in 2020 worldwide, renal cell carcinoma (RCC) represents the 16th most diagnosed cancer in the world. Males are the most affected, with a sex ratio of 2.4:1. The lifetime risk for developing RCC is 0.70 in men and 0.36 in women[1]. Its incidence has been rising over years, mainly because of the increasing abdominal imaging use for other medical disorders, leading to incidental renal cancer diagnosis [2]. In 2020, RCC was responsible for 179 368 deaths in the world, making RCC the 16th most lethal cancer[1].

Recent studies showed that approximatively 20% of patients present with metastatic disease at diagnosis[3,4]. Among patients with initially localized cancer, 20% will develop metastases during follow-up[4]. The most frequent metastatic sites are lungs, lymph nodes, bones, liver, adrenal glands, and brain[5]. The prognosis of RCC metastases is very heterogeneous. Liver, brain and pleura metastases are associated with the shortest median overall survival (OS) (< 18 months), whereas metastases to endocrine organs (pancreas, thyroid and adrenal glands) are associated with better prognosis (median OS > 27 months)[5].

Among all cancers, endoluminal metastases to the gastrointestinal tract are rare. They are mostly due to melanoma, lobular breast cancer, and lung cancer [6,7]. Data on gastrointestinal metastases (GIMs) from RCC are scarce, consisting almost exclusively of case-reports (sometimes regrouped in literature reviews[8–11]). To date, the three largest retrospective cohorts are: a Korean cohort of 15 patients [12], a French cohort of 11 patients[13], and an American cohort of 8 patients[14]. Those studies were of limited numbers, mainly due to their single-center design.

Here we present a retrospective multicenter study on GIMs from RCC reported from 10 French oncologic centers, including the French cohort aforementioned. The aim of this study was to describe GIMs characteristics as well as their diagnostic modalities and treatment strategies, and patients' outcome.

II. Material and methods

II. 1. Study design

This is a retrospective multicenter study conducted in 10 French centers of the "Groupe d'Étude des Tumeurs Uro-Génitales" (GETUG). Eligibility criteria were: patients over 18 years old, an RCC histologically confirmed, diagnosed with at least one GIM between January 2000 and December 2021. We only considered endoluminal metastases located to the gastrointestinal tract (esophagus, stomach, duodenum, small bowel, colon, or rectum). Pancreatic, hepatic, and biliary tract metastases were not included. Neither were locoregional gastrointestinal extensions by peritoneal carcinomatosis or renal tumor, or local recurrence in the surgical site.

II. 2. Outcomes

The primary endpoint was to describe RCC GIMs clinical and biological presentations. Secondary endpoints were to discuss diagnosis procedures, therapeutic strategies, and to estimate median OS for patients with RCC GIMs.

II. 3. Ethics

The study was conducted in accordance with the authorization of the French Data Protection Agency, the National Commission for Computing and Liberties (CNIL). All living patients received an information letter, and none expressed objection to be included in the study. It was approved by an independent local ethics review board from Tours University Hospital.

II. 4. Statistical analysis

Continuous variables were expressed as medians with their minimum and maximum values. As a few patients presented with metastases in different gastrointestinal organs, they were then analyzed as patients for the primary endpoint, and then each metastatic site was considered for the analyses conducted for the secondary endpoints. Two metastatic locations were considered synchronous if they occurred within a period of less than 3 months.

OS from the date of first GIM diagnosis was estimated with the Kaplan Meier method and analysis was performed using R software version 4.3.0.

III. Results

III. 1. Patients' characteristics

A total of 74 patients who presented with RCC GIMs between January 2000 and December 2021 were included. Their characteristics are reported in Table 1. They were mostly men (sex ratio of 4.7:1) with a good general condition (median Karnofsky score of 80%) and a median age of 69 years at time of GIM diagnosis. 18% of patients were active or former smokers. 30% of the patients were on long-term treatment with antithrombotic agents (antiplatelet agents and/or anticoagulants). Primary tumors were predominantly clear cell renal cell carcinomas (ccRCC) (95%).

56 patients (76%) already had at least one extra-digestive metastasis (EDM) at the time of GIM, and 14 patients (19%) presented with synchronous gastrointestinal and extra-digestive metastatic disease. EDM were mostly in lungs (61%). For 7% of the patients, GIMs were synchronous with RCC diagnosis. Overall, GIMs occurred after a median of 4.9 years (range: 0-21.5 years) from initial RCC diagnosis, and after a median of 1.9 years (range: 0-17.8 years) from first EDM. At the onset of GIM, among the 56 patients already metastatic, most of them had previously been exposed to systemic antineoplastic treatment (37 patients = 66%). Details on number and type of treatments received are provided in Table 2.

Table 1: Characteristics of patients with GIM

	All patients (N=74)
Age at GIM (in years): Median (min – max)	69 (37-85)
Sex: N (%)	
- Male	61 (82)
- Female	13 (18)
Smokers: N (%)	
- Active or Former	13 (18)
- MD	21 (28)
Comorbidities*: N (%)	
- Arterial hypertension	21 (28)
- Diabetes	9 (12)
- Dyslipidemia	10 (14)
- MD	14 (19)
Antithrombotic use (AC and/or APD): N (%)	
- Yes	22 (30)
- MD	2 (3)
RCC histological subtypes: N (%)	
- Clear cell RCC	70 (95)
- Papillary RCC	2 (3)
- Chromophobe RCC	1 (1)
- MD	1 (1)
Führman grade: N (%)	
- Grades 1 – 2	20 (27)
- Grades 3 – 4	32 (43)
- MD	22 (30)
TNM: N (%)	
- Tx	3 (4)
- T1 – T2	19 (26)
- T3 – T4	37 (50)
- Nx	17 (23)
- N0	36 (49)
- N1 – 2	6 (8)
- Mx	10 (14)
- M0	36 (49)
- M1	13 (18)
- MD	15 (20)
Temporality of GIM: N (%)	
- GIM after EDM	56 (76)
- GIM synchronous to EDM	14 (19)
- GIM without EDM	4 (5)
EDM sites at time of GIM: N (%)	
- None	4 (5)
- Lung	45 (61)
- Metastatic lymph nodes	29 (39)
- Liver	28 (38)
- Bones	17 (23)
- Pancreas	17 (23)
- Adrenal glands	15 (20)
- Peritoneal carcinomatosis	8 (11)
- Central nervous system	5 (7)
- Others	20 (27)

*Patients may have more than one comorbidity

Abbreviations: MD, missing data; AC, anticoagulant; APD, antiplatelet drug; RCC, renal cell carcinoma; GIM, gastrointestinal metastases; EDM, extradigestive metastases; RCC, renal cell carcinoma

Table 2: Systemic treatments received before and at the onset of GIM

	mRCC at GIM diagnosis (N=56)
Number of anticancer regimens before GIM: N (%)	
- 0	10 (18)
- 1	14 (25)
- 2	12 (21)
- ≥ 3	9 (16)
- MD	11 (20)
Ongoing treatment at GIM diagnosis: N (%)	
- None	24 (43)
- Anti-VEGFR TKI	22 (39)
- Immune checkpoint inhibitors	7 (13)
- mTOR inhibitors	1 (2)
- Others	2 (4)

Abbreviations: MD, missing data; GIM, gastrointestinal metastases; mRCC, metastatic renal cell carcinoma; VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; mTOR, mammalian target of rapamycin

III. 2. GIM localization

63 patients (85%) presented with metastatic progression in only one location of the digestive tract, 9 patients (12%) in two different locations, and 2 patients (3%) in three different locations, resulting in a total of 87 GIMs identified. Among them, 35 (40%) were gastric, 26 (30%) were in the duodenum, 16 (18%) were ileo-jejunal, 9 (10%) were colonic, and 1 (1%) was in the esophagus.

Gastric lesions were in the body (29%), fundus (26%), cardia (11%) or antrum (9%). One patient had bifocal gastric progression in the body and antrum. Duodenal metastases were in the first portion (23%), second portion (50%) or third portion (4%). Among the 16 ileo-jejunal metastases, 6 (38%) were in the jejunum and 3 (19%) in the ileum. Colonic mets were located in the right colon (33%), left colon (33%) and caecum (11%).

A portion of the digestive tract could be the site of multiple lesions: 12 out of 87 (14%) were bi or tri-focal, and 4 (5%) had at least 4 lesions, but the majority (67/87, 77%) were unifocal.

III. 3. Clinical and biological presentation

GIMs were symptomatic in 52 patients (70%): 41 (55%) had anemia, 31 (42%) presented gastrointestinal bleeding. The 22 asymptomatic patients (30%) were diagnosed fortuitously by imaging or endoscopic examination conducted during follow-up or for another medical disorder. Median hemoglobin level at diagnosis was 9.1 g/dL (range: 4.4-16.9 g/dL). For comparison, in patients with EDMs anterior to GIM, median hemoglobin was 13.7 g/dL (range: 8.8-16.8 g/dL) at the time of the first EDM. Detailed clinical and biological presentation of GIM by location is presented in Table 3. The patient presenting with esophagus metastasis was symptomatic (dysphagia).

Table 3: Clinical and biological presentation of GIMs by location

	Stomach (N=35)	**Duodenum (N=26)**	**Ileojejunum (N=16)**	**Colon (N=9)**
Symptoms leading to GIM diagnosis: N (%)				
Fortuitously:				
- On radiologic imagery	13 (37)	2 (8)	2 (13)	3 (33)
- On endoscopy	3 (9)	0 (0)	0 (0)	0 (0)
Anemia	14 (40)	21 (81)	10 (63)	4 (44)
Digestive bleeding:	12 (34)	13 (50)	8 (50)	5 (56)
- Melena	10 (29)	10 (38)	7 (44)	2 (22)
- Rectal bleeding	2 (6)	2 (8)	3 (19)	3 (33)
- Hematemesis	4 (11)	3 (12)	0 (0)	0 (0)
Intestinal obstruction	0 (0)	1 (4)	4 (25)	0 (0)
Abdominal pain	3 (9)	2 (8)	2 (13)	0 (0)
Dyspepsia	0 (0)	2 (8)	0 (0)	0 (0)
Jaundice	0 (0)	1 (4)	0 (0)	0 (0)
Hemoglobin level at GIM diagnosis:				
Median	10.8	8.8	7.6	8.8
(min – max)	(4.4 – 16.9)	(5.5 – 12.6)	(5.6 – 13.6)	(6.8 – 16.2)
MD : N (%)	11 (31)	12 (46)	9 (56)	5 (56)

Abbreviations: GIM, gastrointestinal metastasis; MD, missing data

Among the 52 symptomatic patients, 19 (37%) were pretreated with anti-VEGFR TKI, and 15 (29%) were undergoing such treatment at the time of GIM. Among the 22 asymptomatic patients, 12 (55%) had received at least one anti-VEGFR TKI, and 7 (32%) were still undergoing such treatment. 16 symptomatic patients (31%) and 6 asymptomatic patients (27%) were on long term treatment with antithrombotic agents. 4 symptomatic (8%) and 2 asymptomatic patients (9%) were undergoing both anti-VEGFR TKI and antithrombotic treatment at time of GIM.

III. 4. Endoscopic features

Diagnosis was endoscopic for 53 (61%) of the 87 GIMs: 46 (53%) through esophagogastroduodenoscopy (EGD) and 7 (8%) through colonoscopy. 3 GIMs (3%) required videocapsule endoscopy. Among the 53 GIMs explored by endoscopy, 26 were described as polypoid, 12 were ulcerated, and 2 were flat. The median size of the lesions was 30 mm (range: 7-100 mm). The detailed endoscopic description of the lesions by location is presented in Table 4. The only esophageal metastasis reported in our study was diagnosed during an EGD performed in a context of dysphagia, the lesion caused an esophageal stricture.

Table 4: Detail of endoscopic features by location

	Stomach (N=35)	Duodenum (N=26)	Ileojejunum (N=16)	Colon (N=9)
Endoscopy use: N (%)				
None	11 (31)	4 (15)	12 (75)	1 (11)
Esophagogastroduodenoscopy	23 (66)	22 (85)	0 (0)	0 (0)
Colonoscopy	0 (0)	0 (0)	0 (0)	7 (78)
Videocapsule endoscopy	1 (3)	0 (0)	2 (13)	0 (0)
MD	0 (0)	0 (0)	2 (13)	1 (11)
Endoscopic aspect: N (%)*				
Polypoid	11 (48)	10 (45)		4 (57)
Ulcerated	8 (35)	4 (18)	-	0 (0)
Flat	1 (4)	1 (5)		0 (0)
MD	3 (13)	7 (32)		3 (43)
Size of main lesion (mm):				
Median (min-max)	30 (10 – 50)	30 (7 – 70)	-	35 (20 – 100)

Abbreviations: MD, missing data

*% is expressed as the proportion of metastases that underwent endoscopy

III. 5. Treatment

GIMs management consisted of exclusive systemic treatment in 29 GIMs (33%), local treatment alone in 23 GIMs (26%), and both local and systemic treatment in 18 GIMs (21%). For 17 GIMs (20%), there was no therapeutic modification. Among the 47 patients who underwent a change in treatment line, 26 (55%) were treated with anti-VEGFR TKI, 13 (28%) with immunotherapy, 6 (13%) with mTOR inhibitor, and 3 (6%) with another treatment (bevacizumab, interferon, and combination of erlotinib + bevacizumab).

The details of GIMs treatment by location are provided in Table 5. The esophageal metastasis was treated with bevacizumab, without local treatment.

Table 5: Details of GIMs treatment by location

	Stomach (N=35)	Duodenum (N=26)	Ileojejunum (N=16)	Colon (N=9)
Management strategy of GIM: N (%)				
Local ttt only	11 (31)	6 (23)	3 (19)	3 (33)
Introduction/change of systemic ttt only	12 (34)	7 (27)	7 (44)	2 (22)
Local ttt and introduction/change of systemic ttt	4 (11)	7 (27)	3 (19)	4 (44)
No therapeutic modification	8 (23)	6 (23)	3 (19)	0 (0)
Local ttt: N (%)				
Total local ttts*	17 (49)	15 (58)	6 (38)	10 (111)
Endoscopic:	6 (17)	5 (19)	0 (0)	2 (22)
Endoscopic resection	3 (9)	0 (0)	0 (0)	1 (11)
Hemostasis	2 (6)	3 (12)	0 (0)	1 (11)
Cryotherapy	1 (3)	0 (0)	0 (0)	0 (0)
Endoscopic prothesis	0 (0)	2 (8)	0 (0)	0 (0)
Surgical resection	6 (17)	5 (19)	6 (38)	5 (56)
Radiotherapy	3 (9)	4 (15)	0 (0)	2 (22)
Vascular embolization	2 (6)	1 (4)	0 (0)	1 (11)
Introduction/change of systemic ttt: N (%)	**			
Total	16 (46)	14 (54)	10 (63)	6 (67)
Anti-VEGFR TKI	8 (23)	11 (42)	4 (25)	3 (33)
Immune checkpoint inhibitor	7 (20)	1 (4)	4 (25)	1 (11)
mTOR inhibitor	2 (6)	1 (4)	2 (13)	1 (11)
Other systemic treatment	0 (0)	1 (4)	0 (0)	1 (11)

Abbreviations: GIM, gastrointestinal metastasis; ttt, treatment; VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; mTOR, mammalian target of rapamycin

*1 colonic metastasis required 3 different local treatments. 2 gastric metastases, 2 duodenal metastases and 1 colonic metastasis required 2 different local treatments.

**1 gastric metastasis was treated with combined immune checkpoint inhibitor and anti-VEGFR TKI.

For each patient, the treatment of the first GIM was analyzed based on its symptomatic or asymptomatic nature. Among 52 patients presenting symptomatic GIMs, 17 (33%) were treated exclusively locally, 13 (25%) with systemic treatment alone and 11 (21%) with both local and systemic treatments. Anti-VEGFR TKIs were used for 33% of symptomatic GIMs vs 6% for immunotherapy.
Out of the 22 patients presenting asymptomatic GIMs, 10 (45%) were treated with systemic treatment alone, 5 (23%) with local treatment alone and 3 (14%) with both local and systemic treatments. Immunotherapy was the most frequently used systemic therapy in asymptomatic GIMs (32% vs 18% for anti-VEGFR TKIs). For 21% of symptomatic GIMs and 18% of asymptomatic GIMs there was no therapeutic modification.

III. 6. Prognosis

After presenting GIMs from RCC, median OS was 19 months (Figure 1). OS rate was 65% at 1 year, 39% at 3 years, and 21% at 5 years.

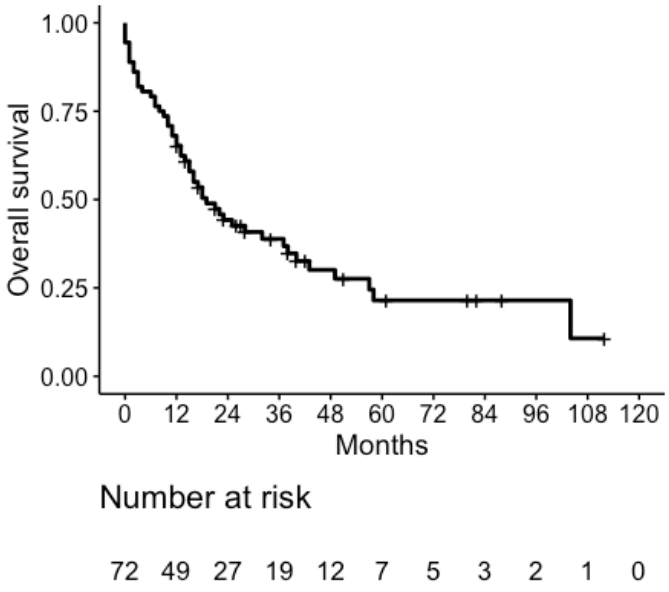

Figure 1 : Kaplan-Meier estimates of overall survival.

Tick marks represent data censored at the last time the patient was known to be alive.

At first GIM, median OS was 21 months for patients presenting with gastric metastases, 37 months for duodenal metastases, 17 months for ileo-jejunal metastases and 19 months for colonic metastases. The only patient presenting with esophageal metastasis died 43 days after diagnosis.

IV. Discussion

With 74 patients and 87 GIMs, this article is, to our knowledge, the largest reported retrospective cohort of GIMs from RCC. These metastases are extremely rare: the proportion of patients developing GIMs is estimated at 1.6% of patients with metastatic RCC (mRCC)[13], and 0.04% of all patients with RCC (metastatic or not)[12].

In our article, GIMs appear to be a late event in the natural course of RCC, as they were diagnosed in median 5 years after initial diagnosis of RCC. This result is consistent with the studies conducted by Rony[13] and Grosser[14], who respectively found a median of 4.3 years and 6 years between nephrectomy and the first GIM. In Park's study[12], GIMs were diagnosed after a median interval of only 2.6 years.

Moreover, 95% of patients had concomitant EDM (prior or synchronous) with GIM. This finding is consistent with the study by Park, which found a 93.3% rate of concomitant EDM, with an average number of 3.1 metastatic sites per patient[12]. In our study, EDM were predominantly found in lungs, lymph nodes, and liver, and 38% of patients also had glandular metastases (adrenal glands, pancreas, thyroid, or parotid gland). Noteworthy 11% of patients had peritoneal carcinomatosis, although it is usually a rare metastatic site in RCC (2% of metastatic ccRCC [5]).

We found a majority of gastric and duodenal metastases. Gastric lesions appear to predominate in the body of the stomach, and duodenal lesions seem to predominate in the peri-ampullary region, as previously described [8,9]. Other portions of the gastrointestinal tract seem to be less frequently involved, particularly the colon and esophagus. Indeed, the most recently published literature review on colonic metastases from RCC found only 12 cases[11]. In our study, we chose to select only endoluminal lesions of hematogenous dissemination, thereby excluding many colonic lesions caused by parietal invasion from local recurrences in the surgical nephrectomy site. To our knowledge, there is no literature review on esophageal metastases from RCC, and only 7 case-reports have been published so far[15–21].

RCC metastases are known to be hypervascular[22] and so to be at high risk for hemorrhagic complications[23,24]. Indeed, in our study, GIMs were often diagnosed due to gastrointestinal bleeding and/or anemia in part resulting from bleeding (gastrointestinal bleeding or occult bleeding). Anemia in RCC may occur for various other reasons (paraneoplastic, inflammatory, iatrogenic), but GIMs should be investigated in cases of unexplained anemia or anemia associated with iron deficiency. It should be noted that 30% of patients were undergoing treatment with anti-VEGFR TKI at the time of GIM diagnosis, and 30% were undergoing antithrombotic medications (among whom 8% were receiving both treatments), which could have contributed to the symptomatic presentation of GIMs. However, we observed similar proportions of patients undergoing anti-VEGFR TKIs and/or antithrombotic treatments among symptomatic and asymptomatic patients. In our study, few patients had received immunotherapy. This could be partly explained as we collected records that were sometimes anterior to the widespread use of immunotherapy in mRCC. For comparison, in Rony's study, where patients were enrolled from 2007 whereas we enrolled from 2000, 46.1% of patients were treated with anti-VEGFR TKI and 30.8% with immunotherapy at the time of GIM occurrence[13].

The management of GIMs from RCC is not standardized, and patients in our study received in very similar proportions, exclusive local treatment (26% of GIMs), exclusive systemic treatment (33%), combination of local and systemic treatment (21%), or no therapeutic modification (20%). It is worth noting that ileo-jejunal metastases received fewer local treatments, likely due to a more difficult access to the metastasis because of its location. On the other hand, 78% of colonic metastases underwent local treatment, probably due to their easiest access for surgery as well as for endoscopy.

It is interesting to study how the symptomatic presentation of the GIMs may have influenced the treatment. Accordingly, symptomatic metastases logically received more local treatments than asymptomatic ones, while asymptomatic GIMs were more likely treated with systemic therapy. The most chosen systemic treatment was anti-VEGFR TKI for symptomatic metastases, which may be surprising considering the hemorrhagic risk associated with such treatment, estimated around 15% for any bleeding, with a 3% risk of major bleeding event[25,26]. In our study, asymptomatic GIMs were more likely to be treated with immunotherapy, probably mostly because they had already received an anti-VEGFR TKI (55%), when less symptomatic patients had (37%).

With an estimated median OS of 19 months, GIMs from RCC are among the metastatic sites with the worst prognosis in RCC, approaching the median OS of hepatic and bone metastases reported by Dudani et al [5].

In comparison with other primary tumors known to develop GIMs, RCC appears to more frequently result in unifocal lesions (77% of unifocal lesions in our study, compared to 66% and 45% for breast and melanoma GIMs, respectively), and occurs later in the natural course of the neoplastic disease[7]. The prognosis of GIMs from other primary tumors is highly variable, with a median OS of 33 months in lobular breast cancer[27] and approximately 3 months in lung cancer[28,29].

This study has certain limitations. Firstly, the retrospective nature of the study inevitably led to missing data. As a result, some analyses such as patient's IMDC prognostic groups or proportion of sarcomatoid component in primary tumors were not possible. Lastly, this study only included patients with confirmed GIMs from RCC, so we were unable to estimate the prevalence of such metastases. In any case, it may be tricky not to underestimate prevalence of GIMs from RCC as only the largest ones would be identified on radiologic imagery, and only symptomatic cases would undergo endoscopy. Hence the prognosis of these metastases may be biased by selection of the most severe lesions in our study.

V. Conclusion

We report here the largest retrospective cohort of GIMs in RCC patients. Considering our observations, we believe that GIMs should be suspected in case of anemia or gastrointestinal bleeding in any patient with a history of RCC. Their management is very heterogeneous, depending on their location in the digestive tract and whether they are symptomatic. Even if GIMs seem to be a late event in the evolution of RCCs, their occurrence seems to be of poor prognosis.

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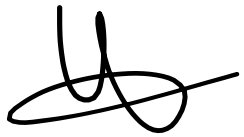

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CARNEIRO Florian

32 pages, 5 tableaux, 1 figure

Résumé :
Au diagnostic de cancer du rein, 20% des patients sont d'emblée métastatiques. Parmi ceux qui présentent une forme localisée au diagnostic, 20% présenteront une récidive métastatique à distance. Les métastases gastro-intestinales (MGI) sont rares et leur pronostic est peu connu.
Nous avons analysé de manière rétrospective les dossiers de patients traités pour un cancer du rein dans 10 centres français du GETUG et ayant présenté une ou plusieurs MGI entre janvier 2000 et décembre 2021. Nous reportons dans cette étude la présentation clinique de ces métastases, les caractéristiques des patients, les stratégies thérapeutiques utilisées et le pronostic de ces lésions.
74 patients ont été inclus dans l'étude pour avoir présenté un total de 87 MGI, dont 35 lésions gastriques, 26 duodénales, 16 iléo-jéjunales, 9 coliques et 1 œsophagienne. L'histologie du primitif rénal était dans 95% des cas un carcinome rénal à cellules claires. L'âge médian au diagnostic de MGI était de 69 ans. 76% des patients présentaient déjà des métastases extra-digestives au moment de l'apparition de la première MGI. Le délai médian entre le diagnostic du primitif rénal et la première MGI était de 4 ans et 11 mois.
Les MGI ont été symptomatiques chez 52 patients (70%), responsables d'une anémie chez 41 patients (55%) et/ou d'une hémorragie digestive chez 31 patients (42%). Seuls 22 patients asymptomatiques (30%) ont été diagnostiqué de manière fortuite.
Le traitement des MGI a consisté en un traitement systémique seul pour 33% d'entre-elles, un traitement local seul pour 26% d'entre-elles et l'association d'un traitement local et d'un traitement systémique pour 21% d'entre-elles. 20% des MGI n'ont pas entrainé de prise en charge spécifique. Après le diagnostic de MGI, la médiane de survie globale était de 19 mois.
Nous présentons ici le plus large recueil rétrospectif de MGI de cancer du rein. Celles-ci doivent être suspectées devant l'apparition d'une anémie inexpliquée ou d'une hémorragie digestive chez un patient suivi pour un cancer du rein. Leur prise en charge n'étant pas codifiée, reste très hétérogène d'un patient à l'autre. Bien que les MGI semblent être un évènement tardif dans l'histoire naturelle du cancer du rein, leur survenue semble être un facteur de mauvais pronostic, avec seulement 21% de patients encore en vie à 5 ans.

Mots clés : Cancer du rein, Métastases gastrointestinales, Hémorragie digestive

Jury :

Président du Jury :	Professeur Claude LINASSIER
Directeur de thèse :	Docteur Mathilde CANCEL
Membres du Jury :	Professeur Thierry LECOMTE
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