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Real world data of diagnosis, survival, and treatment outcomes in patients with metastatic non clear cell renal cell carcinoma

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Introduction: Metastatic non clear cell renal cell carcinoma (nccRCC) is an heterogenous group, usually excluded from phase 3 trials. We report real life data of prognosis and systemic management of those patients.

Methods: We retrospectively included 102 metastatic nccRCC patients (unspecified papillary, n=10; type 1 and 2 papillary n=10 and n=32; translocation RCC, n=9; chromophobe, n=14; collecting duct, n=14) treated between 2006 and 2020. Objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) were evaluated.

Results: Among patients who underwent pathological review, 40.8% presented a complete histological discordance. First line treatments were mainly tyrosine kinase inhibitor (60.8%), combination including immunotherapy (7.8%) or combination of chemotherapy (13.7%). Median ORR ranged from 0% in unspecified papillary RCC to 42.9% in type 1 papillary RCC. Median PFS ranged from 2.9 months in collecting duct carcinoma to 10.9 months in type 1 papillary RCC. Median OS ranged from 6.8 months in collecting duct carcinoma to 29.1 months in MiT family translocation RCC. Thirty (29.4%) patients were included in a treatment trial during their treatment course.

Conclusion: Metastatic nccRCC patients have variable prognosis due to heterogeneity of histological subtypes. Their diagnosis and access to therapeutic innovation remain suboptimal. Dedicated prospective trials are needed.

Keywords: non clear cell RCC; metastatic; overall survival; systemic treatment; pathological review

Introduction

Renal cell carcinoma (RCC) is one of the most frequent cancers, representing 4% of new diagnoses worldwide ((1), and its incidence has increased in the last few years ((2).

While clear cell type (ccRCC) accounts for 80% of RCCs, almost 20% are non-clear cell type (nccRCC) ((3). This group includes papillary, chromophobe, collecting duct, translocation-associated, medullary and unclassified types. Non-metastatic nccRCC tend to have better survival compared with ccRCC, but survival is much shorter after metastatic occurrence ((4,5). Most published and ongoing trials focused on ccRCC subtypes ((6–8), resulting on progress and leading to new standards of care for both localized and metastatic patients ((9) NccRCC patients however were not eligible in most of these large phase 3 trials. Moreover, this subgroup is usually analyzed as one, while it is composed by several subtypes, with a different carcinogenesis, prognosis or systemic treatment sensitivity ((10,11).

They are two main challenges in the management of these tumors. First, at diagnosis because they are often misclassified, and second treatment options because recommendations for systemic therapy in nccRCC patients do not consider specific histological subtypes and molecular specificities and are based on a low level of evidence. Better knowledge of molecular pathway alterations may open perspectives for new therapeutic options.

We aimed to describe the diagnosis concordance after second reading and the prognosis of each nccRCC subtype in patients from our institution in the era of tyrosine kinase inhibitors (TKI) and immunotherapy (IO).

Material and methods

Study population

We retrospectively collected data of patients with nccRCC treated between January 2006 and January 2021 in the Léon Bérard comprehensive cancer center which is a tertiary center.

Inclusion criteria were: pathologically proven nccRCC patients with synchronous or metachronous metastasis; age 18 years or older. Patients who presented clear cell RCC with sarcomatoid dedifferentiation were excluded. The analysis considered the following histological subtypes: unspecified papillary RCC, type 1 papillary RCC, type 2 papillary RCC, eosinophil carcinoma, chromophobe RCC, collecting duct carcinoma, medullary carcinoma, unclassified RCC and MiT family translocation RCC.

Outcomes

Outcomes were presented according to histological subtype. The primary outcome was overall survival (OS) after systemic treatment initiation. Secondary outcomes were overall survival after surgical resection in case of metachronous metastases, first line progression-free survival (PFS) and objective response rate (ORR) according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1, number of therapeutic lines received, percentage of reading by an expert pathologist and concordance between the two opinions in case of reviewing.

Statistical analyses

Categorical variables were reported as counts and percentages. Continuous variables were reported as mean and range. Survival rates were estimated from introduction of first line treatment using the Kaplan Meier method, and compared by log-rank test. Median follow-up since diagnosis was estimated using the reverse Kaplan Meier method ((12). Statistical analyses were performed using R software version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). The study protocol was reviewed and approved by the institutional ethics committee. Processing of personal data was performed according to MR-004 of the Informatic and Liberties National Commission (CNIL).

Results

Overall population

One hundred and two nccRCC patients were treated between 2006 and 2021 and included in our study. Pure eosinophil and medullary renal cell carcinomas were excluded because they were under-represented (n=2 and n=1, respectively). Patients' characteristics are presented in Table 1. Median age at diagnosis was 61.64 years (IQR, 48.9-71.8). Median follow-up was 102.5 months (IQR 55.8-152.1). Most patients had synchronous metastasis at

diagnosis (56.9 %). Among the 74 patients (72.5%) with evaluable IMDC score, 56.8%, 32.4% and 10.8% were in the intermediate, favorable, and poor prognosis group, respectively (Table 1).

Median OS after initiation of systemic treatment was 15.3 (8.2-29.6), 22 (14.4-35.7) and 3.4 (1.2-Not reached) months for patients in favorable, intermediate, and poor prognosis group, respectively.

Fifty-four patients (52.9%) had a pathological diagnosis or review in an expert center. Among the forty-nine patients who had a central pathological review, 20 (40.8%) presented a complete histological discordance, and 10 of the remaining 22 (45.5%) were up or downgraded (see figure 1).

Thirty (29.4%) patients were included in a clinical trial during their treatment course. Eighty-nine patients (87%) received systemic treatment, and sunitinib was the first line clinician choice for 45 patients (50%). First line ORR, median PFS and OS were 21.7%, 5.4 months (4.6-7.4) and 16.6 months (14.5-23.2), respectively (Figure 2). Five-year OS since first line beginning was 9.6%.

Unspecified papillary RCC

Among the 10 unspecified papillary RCC patients, 9 (90%) experienced tumor resection, with 6 (66%) total nephrectomy. Six (60%) patients did not have metastases at diagnosis. Histopathological review in an expert center was performed in 3 cases (30%).

Among the 7 patients with evaluated IMDC score, 14.3%, 57.1% and 28.6% were in the favorable, intermediate, and poor prognosis group, respectively (Table 1).

Median OS since surgery was 105.8 months (37-Not reached). Eight patients (80%) received systemic treatment, with sunitinib as first line for 5 of them (62.5%). First line ORR, median PFS and OS were 0%, 4.8 months (4-Not reached) and 18.2 months (11.4-Not reached), respectively (see Table 2, Figure 3 and 4). Five-year OS after first line treatment was 0%.

Type 1 papillary RCC

Among the 10 type 1 papillary RCC patients, 7 (70%) underwent primary tumor surgery, all of them had total nephrectomy. IMDC group was available for 8 (80%) patients, with 4 (50%), and 4 (50%) patients in the favorable and intermediate prognosis group, respectively (Table 1). Six (60%) patients did not have synchronous metastases.

Median OS since tumor resection was 34.1 months (27.8-Not reached). Nine (90%) patients received systemic treatment with a mean number of 2 lines (0-5). Sunitinib was the first line in 6 cases (66%). First line ORR, median PFS and OS were 42.9%, 10.8 months (5.7-Not reached) and 17.6 months (14.3-Not reached), respectively (see Table 2, Figure 3 and 4). Five-year OS was 15.6%.

Type 2 papillary RCC

Among the 32 patients group, most patients (n=18, 56.2%) presented metastatic disease at diagnosis. IMDC prognosis was available for 19 (59.1%) of the 32 patients, and well balanced between favorable (50%) and intermediate (50%) groups. Tumor resection was performed for 25 (78.1%) patients, with 80% of total nephrectomy.

Median OS since tumor resection was 55 months (37.2-Not reached). Twenty-six (81%) patients received a systemic treatment, with a mean number of 2.1 lines (0-5). Sunitinib was used as first line in 14 cases (53.8%). First line ORR, median PFS and OS were 17.4%, 5.4 months (4.2-9.4) and 18.9 months (9-29.5), respectively (see Table 2, Figure 3 and 4). Five-year OS was 5.6%.

MiT family translocation RCC (=TFE3)

In this 9 patients sample, 4 (44.4%) had metastases at diagnosis. Among the 7 (78.8%) patients with available IMDC score, 5 (71.4%) and 2 (28.6%) were in the intermediate and favorable prognosis group, respectively (Table 1). Mean age at diagnosis was 39.2 years (21.3-68) and the proportion of women was 44.4%.

Surgery was performed for 7 (77.8%) patients, with partial nephrectomy in 43% cases.

Median OS since tumor resection was 51.7 months (35.3-Not reached), and 29.1 months (21.9-Not reached) after first line introduction. All patients (n=9, 100%) received a first-line systemic treatment, including sunitinib (n=4, 44.4%), and tyrosine kinase inhibitors combined with immunotherapy (TKI-IO) (n=5, 55.6%). Among patients who received immunotherapy as first-line, ORR was 40% (see Table 2, Figure 3 and 4).

First line ORR and median PFS were 22.2% and 7.3 months (2.4-Not reached), respectively. Five-year OS after systemic treatment beginning was 0%.

Chromophobe carcinoma

Among the 14 patients group, most (n=10, 71.8%) did not have metastases at diagnosis, IMDC prognosis was available for 13 patients (78.6%) and all of them had an intermediate prognosis. Surgery was performed for 7 (77.8%) patients, with 91.6% of total nephrectomy.

Median OS since tumor resection was 89.6 months (55.9-Not reached). Among the 12 patients who received a systemic treatment, the only one who received immunotherapy as first line presented a stable disease. First line ORR, median PFS and OS were 16.7%, 6.3 months (3.9-Not reached) and 19.4 months (14.6-Not reached), respectively (see Table 2, Figure 3 and 4). Five-year OS was 25%.

Collecting duct carcinoma

Most of the 14 collecting duct carcinoma patients presented synchronous metastases (n=11, 78.1%) and were in the intermediate or poor prognosis group (n=9, 64.3%). All surgical interventions were total nephrectomy (n=11, 78.6%).

Median OS since tumor resection was 52.3 months (52.3-Not reached). Thirteen patients received a first line systemic treatment, mainly with platinum-based chemotherapy (n=11, 84.6%). First line ORR, median PFS and OS were 38.5%, 2.9 months (1.8-Not reached) and 6.8 months (5.4-Not reached), respectively (see Table 2, Figure 3 and 4). Five-year OS was 9.6%.

Unclassified RCC

Among the 13 patients, 9 (75%) had metastases at diagnosis. IMDC group was available for 11 (84.6%) patients, with 54.5%, 27.3% and 15.4% of favorable, intermediate, and poor prognosis, respectively (Table 1). Only 3 (25%) underwent tumor resection by total nephrectomy.

Median OS since tumor resection was 17 months (5.3-Not reached). Among the 11 patient who received a systemic treatment, sunitinib was the used TKI in 75% of cases. First line ORR, median PFS and OS were 16.7%, 4.1 months (1.8-Not reached), and 13.7 months (4.8-Not reached) respectively (see Table 2, Figure 3 and 4). Five-year OS was 0%.

Central pathological review

All initial diagnosis of type 1 papillary RCC, chromophobe RCC, and collecting duct carcinoma were confirmed. In contrast, most unspecified papillary (n=4, 80%), MiT family translocation (n=3, 37.5%) and unclassified RCC (n=2, 40%) were misclassified at diagnosis.

The reclassification led to meaningful standard of care modifications for 10 (20.4%) patients (see appendix). Reclassified patients did not present poorer prognosis when compared to initially well classified patients (p=0.99).

Discussion

Although nccRCC represent almost 25% of RCC ((13) and have poorer prognosis than metastatic ccRCC ((5,14), they are usually not included in phase 3 (6–8) but mostly in phase 2 trials with small sample size ((10,11,15). Our work was conducted in a national comprehensive cancer center where most patients have access to clinical trials. Nevertheless, only a third of our metastatic nccRCC patients were included in a trial despite the lack of data and therapeutic options. Thus, most of those patients do not benefit from an adapted and specific treatment strategy. This seems to be confirmed in the current TKI-IO associations which changed the metastatic ccRCC prognosis ((6,8) whereas sunitinib and cabozantinib are still standards of care of metastatic nccRCC ((16).

First line IO-IO or IO-TKI associations improve PFS and OS in metastatic ccRCC ((6–8) and thus became new standards of care ((9). Nevertheless, the place of IO is still debated for metastatic nccRCC patients. Keynote427B is a single arm, prospective, multicentric study showing promising results of first line pembrolizumab in this indication ((17), with an ORR, median PFS and OS of 28.8%, 5.5 and 31.5 months, respectively.

Koshkin et al. ((18) also reported clinical activity of nivolumab, as well as Chahoud et al. in a retrospective study ((19). Tykodi et al. ((20) showed results from the nccRCC cohort of the CheckMate 920 trial with encouraging antitumor activity of ipilimumab and nivolumab association in first line for metastatic nccRCC patients. In this trial, histological subtypes were papillary, chromophobe, translocation associated, collecting duct, medullary or unclassified. ORR, median PFS and OS were 19.6%, 3.7 months and 21.2 months, respectively. In a retrospective study, Graham and al. reported better OS in advanced nccRCC patients treated with IO based therapy, when compared to TKI or mTOR (28.6 months, 16.4 months, and 12.2 months, respectively)(21).

However, IO sensitivity seems to vary between subtypes. For instance, while overall response rate is around 25% in papillary RCC ((17) chromophobes tumors do not seem to respond to IO (17,22). More recently in a phase 2 study, Lee and al. evaluated the efficacy of IO-TKI association (nivolumab plus cabozantinib), regarding histological subtype. The results were promising in the papillary, unclassified and translocation associated RCC (ORR and PFS of 47.5% and 12.5 months, respectively), but no responses were observed in the chromophobe group(23).

Main phase 2 trials focusing on metastatic nccRCC reported heterogenous median PFS and OS of 3-12 months and 12-31 months (Table 3). Our results are consistent with literature data, with a median PFS and OS of 5.4 months (95% CI 4.6-7.4) and 16.6 months (95% CI 14.5-23.2), respectively.

Non clear cell RCC challenges begin at diagnosis because this group is composed by many subtypes. CARARE is a French national multidisciplinary network that has been created in 2013. It aims to identify rare kidney tumors and promote their best management nationwide. Every rare kidney cancer cases, are supposed to be reviewed by a CARARE pathological expert and cases are discussed in a specialized multidisciplinary board.

In our study, 20 (40.8%) patients had a complete histological discordance. Prognosis did not seem to be impaired by initial misclassification. Nevertheless, these data only involved patients that underwent histological review. Moreover, since all patients were reclassified before systemic treatment, the impact of such changes remains unknown. To the best of our knowledge, our study is the first describing pathological discordance after expert review in nccRCC.

A parallel could be drawn with sarcomas. In those rare heterogeneous tumors, Ray-Coquard et al. showed that 40% of first histological diagnoses were modified at second reading, which potentially changes the disease management (24). This highlights the importance of an expert pathological review. Moreover, the 2016-WHO (World Health Organization) classification of RCC was recently updated by the Genitourinary Pathology Society (GUPS) ((25), leading to a new classification of nccRCC. For instance, papillary RCC subtype 1 or 2 is no longer recommended and should be divided into variants that consider ISUP grade and tumor architecture.

Most entities are enriched by the knowledge of molecular pathway alterations that can either be prognostic or predict metastatic pattern or therapeutic sensitivity. Carlo et al. recently reported new data regarding patients with a metastatic type 1 papillary carcinoma ((26). Those tumors tend to have a high proportion of MET alterations and chromosomal aberrations such

as gain on chromosome 7 (26,27). In this study, patients with MET alterations who received cabozantinib seemed to benefit from the treatment. In another trial, Pal et al. also reported the interest of cabozantinib for patients with a type 1 papillary carcinoma ((28). As an example, a phase II trial is currently evaluating a MET inhibitor in type 1 papillary RCC (NCT02019693; source: clinicaltrials.gov).

Another interesting molecular alteration is NF2 mutations in unclassified RCC, which could be associated with poorer prognosis ((29), but also mTOR inhibitors sensitivity ((30). Further prospective multicentric trials are needed to evaluate those hypotheses.

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is a rare autosomal dominant disorder caused by genetic alterations of the fumarate hydratase gene (FH). It was previously classified as type 2 papillary renal cell carcinoma, but now recognized by the WHO classification as a unique entity called fumarate hydratase deficient renal cell carcinoma. FH inactivation causes HIF upregulation, leading to VEGF and EGFR inhibitors sensitivity, with promising clinical results. In the phase 2 trial AVATAR (31), patients with FH deficient tumors treated with Bevacizumab plus erlotinib had an ORR and median PFS of 64% and 21.1 months, respectively.

MiTF family translocation RCC involves the translocation of the TFE3 gene on the X chromosome, and is more frequent in pediatric population. The exact mechanism leading to kidney cancer remains to be cleared and could involve lysosomal biogenesis, autophagy and mTOR pathway ((32). Currently, there is no standard of care for this histological subtype.

The International Metastatic RCC Database Consortium (IMDC) is a worldwide used prognostic tool for metastatic ccRCC ((33). Kroeger et al. ((5) validated this model for nccRCC metastatic patients. However, they did not evaluate or stratify the results by subtype. Although most trials concern all nccRCC subtypes ((10,34,35), it is known to be an heterogenous group composed by multiple subtypes with various prognosis and standard of care ((14,36). In this era of molecular biology and personalized medicine, place and validity of IMDC remain uncertain. Our study was underpowered to evaluate the prognostic value of IMDC because our sample sizes were not large enough. As the confidence intervals for OS in favorable and intermediate groups cross, we cannot conclude on these results for the IMDC. However, it appears that the unfavorable group has a significantly lower OS than the other two groups.

The present work has some limitations. First, it is a retrospective study, and our results must be interpreted with caution because they can be biased by known or unknown confounders. Second, all patients come from a unique institution and our results should be

confirmed by a prospective multicentric trial. Even if our institution is a national expert center, we can hypothesize that some patients may have not been addressed by local hospitals. However, since the data of patients with metastatic nccRCC are limited, this study is a way to enrich our knowledge about the prognosis and treatment response. In addition, and in contrast with most previous studies, our results were analyzed for each subtype specifically ((10,11,15).

Conclusion

Non clear cell RCC is an heterogeneous group including many subtypes, with various molecular alterations and prognosis. Sensitivity to current therapies such as IO remains uncertain regarding histological subtypes and despite the better knowledge of molecular pathways, there is still few therapeutic impacts for those patients. Large prospective randomized trials are needed to improve standard of care and survival.

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AUTHOR CONTRIBUTIONS

Conceptualization: FI, AF

Methodology, software, formal analyses and visualisation: BA

Investigation, data curation: FI, BA, RG

Writing - Original Draft: FI

Writing - Review & Editing: all authors

Supervision: SN, AF

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was reviewed and approved by the Institutional Review Board of the Centre Léon Bérard comprehensive cancer center, and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The requirement for written consent was waived and processing of personal data was performed according to French reference methodology n°004 of the Informatic and Liberties National Commission.

CONSENT FOR PUBLICATIONS: Not applicable.

DATA AVAILABILITY :

Deidentified patient-level data can be made available upon request with appropriate approval by the investigator team and research administrative offices. Data sharing will be subject to appropriate data transfer agreements. Data requests can be made to the corresponding author after manuscript publication.

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The authors have no conflict of interest to declare.

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Table 1. Patients' characteristics

Characteristics	Overall	PX	P1	P2	TFE3	Chromophobe	Bellini	Unclassified
Number	102	10	10	32	9	14	14	13
Sex								
Male	74 (72.5%)	9 (90%)	8 (80%)	27 (84.4%)	5 (55.6%)	7 (50%)	7 (50%)	11 (84.6%)
Female	28 (27.5%)	1 (10%)	2 (20%)	5 (15.6%)	4 (44.4%)	7 (50%)	7 (50%)	2 (15.4%)
Age								
	59.4 (21.3-86.5)	68.3 (53.7-85.5)	68.5 (52.5-78.4)	60.7 (26.7-86.5)	39.2 (21.3-68)	60.8 (25.7-77.5)	57.6 (22.2-78.1)	55.2 (39.6-77.8)
Karnofsky index (%)								
	86.8 (30-100)	87.8 (50-100)	89 (60-100)	84.4 (40-100)	94.4 (80-100)	93.6 (80-100)	80.8 (50-100)	82.5 (30-100)
BMI (kg/m2)								
	24.5 (17.6-35.8)	26.3 (21.5-32.3)	25.3 (21-31.1)	24.1 (18-32.7)	24.9 (19.5-31.5)	24.8 (17.6-31.2)	23 (19.4-27.7)	25.9 (19.9-35.8)
Tobacco use								
	36 (35.3%)	2 (20%)	2 (20%)	11 (34.4%)	6 (66.7%)	3 (21.4%)	4 (28.6%)	8 (61.5%)
Hypertension								
	31 (30.4%)	3 (30%)	4 (40%)	10 (31.2%)	0 (0%)	3 (21.4%)	5 (35.7%)	6 (46.2%)
Chronic kidney failure								
	10 (9.8%)	3 (30%)	3 (30%)	2 (6.2%)	0 (0%)	1 (7.1%)	0 (0%)	1 (7.7%)
Genetic syndrome								
	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)	0 (0%)
IMDC group								
Favorable	24 (23.5%)	1 (10%)	4 (40%)	9 (28.1%)	2 (22.2%)	0 (0%)	2 (14.3%)	6 (46.2%)

Characteristics	Overall	PX	P1	P2	TFE3	Chromophobe	Bellini	Unclassified
Intermediate	42 (41.2%)	4 (40%)	4 (40%)	9 (28.1%)	5 (55.6%)	11 (78.6%)	6 (42.9%)	3 (23.1%)
Unfavorable	8 (7.8%)	2 (20%)	NA (NA%)	1 (3.1%)	NA (NA%)	0 (0%)	3 (21.4%)	2 (15.4%)
Non available	28 (27.5%)	3 (30%)	2 (20%)	13 (40.6%)	2 (22.2%)	3 (21.4%)	3 (21.4%)	2 (15.4%)
Initial T stage								
T1	17 (16.7%)	2 (20%)	2 (20%)	2 (6.2%)	3 (33.3%)	2 (14.3%)	4 (28.6%)	2 (15.4%)
T2	18 (17.6%)	1 (10%)	2 (20%)	7 (21.9%)	3 (33.3%)	3 (21.4%)	1 (7.1%)	1 (7.7%)
T3	41 (40.2%)	4 (40%)	3 (30%)	18 (56.2%)	2 (22.2%)	6 (42.9%)	4 (28.6%)	4 (30.8%)
T4	8 (7.8%)	1 (10%)	1 (10%)	1 (3.1%)	0 (0%)	1 (7.1%)	3 (21.4%)	1 (7.7%)
Tx	18 (17.6%)	2 (20%)	2 (20%)	4 (12.5%)	1 (11.1%)	2 (14.3%)	2 (14.3%)	5 (38.5%)
Initial N stage								
N0	38 (37.3%)	4 (40%)	6 (60%)	10 (31.2%)	5 (55.6%)	7 (50%)	3 (21.4%)	3 (23.1%)
N1	16 (15.7%)	2 (20%)	1 (10%)	7 (21.9%)	2 (22.2%)	2 (14.3%)	2 (14.3%)	NA (NA%)
N2	28 (27.5%)	1 (10%)	1 (10%)	9 (28.1%)	2 (22.2%)	3 (21.4%)	8 (57.1%)	4 (30.8%)
Nx	20 (19.6%)	3 (30%)	2 (20%)	6 (18.8%)	NA (NA%)	2 (14.3%)	1 (7.1%)	6 (46.2%)
Initial M staging								
M0	44 (43.1%)	6 (60%)	6 (60%)	12 (37.5%)	4 (44.4%)	10 (71.4%)	3 (21.4%)	3 (23.1%)
M1	55 (53.9%)	4 (40%)	4 (40%)	18 (56.2%)	4 (44.4%)	4 (28.6%)	11 (78.6%)	10 (76.9%)
Mx	0 (0%)	0 (0%)	0 (0%)	2 (6.2%)	1 (11.1%)	0 (0%)	0 (0%)	0 (0%)

Characteristics	Overall	PX	P1	P2	TFE3	Chromophobe	Bellini	Unclassified
Tumor resection	74 (72.5%)	9 (90%)	7 (70%)	25 (78.1%)	7 (77.8%)	12 (85.7%)	11 (78.6%)	3 (23.1%)
Biopathology in expert center	54 (52.9%)	3 (30%)	5 (50%)	15 (46.9%)	8 (88.9%)	7 (50%)	11 (78.6%)	5 (38.5%)
Number of systemic lines	2.2 (0-10)	2.3 (0-10)	2 (0-5)	2.1 (0-5)	4 (2-8)	2.3 (0-6)	1.6 (0-3)	1.8 (0-4)

Note:

Continuous variables : mean
(range)

Categorical variables : n (%)

Abbreviations :

CT, P1, type 1 papillary RCC; P2, type 2 papillary RCC; PX, unspecified papillary RCC

Table 2. ORR according to histological subtype and systemic treatment

Systemic treatment	Overall	PX	P1	P2	TFE3	Chromophobe	Bellini	Unclassified
Chemotherapy	6/14 (42.9%)	-	0/1 (0%)	-	-	-	5/11 (45.5%)	1/2 (50%)
Double IO	0/5 (0%)	-		-	0/2 (0%)	0/1 (0%)	0/2 (0%)	-
IO-TKI	2/3 (66.7%)	-		-	2/3 (66.7%)	-	-	-
mTOR	0/4 (0%)	-		0/4 (0%)	-	-	-	-
TKI alone	9/56 (16.1%)	0/7 (0%)	3/6 (50%)	4/19 (21.1%)	0/4 (0%)	1/10 (10%)	-	1/10 (10%)
TKI-mTOR	1/1 (100%)	-	-	-	-	1/1 (100%)	-	-
Overall	18/83 (21.7%)	0/7 (0%)	3/7 (42.9%)	4/23 (17.4%)	2/9 (22.2%)	2/12 (16.7%)	5/13 (38.5%)	2/12 (16.7%)

Table 3. Main published prospective trials in metastatic nccRCC

Systemic therapy	Trial name	Number of patients	ORR (%)	Median PFS (months)	Median OS (months)
Axitinib	AXIPAP(37)	13 (type 1)	7.7 %	6.7	Not reached
	Papillary tumors	30 (type 2)	35.7 %	6.2	17.4
Sunitinib	SUPAP(38)	15 (type 1)	Overall:	6.6	17.8
	Papillary tumors	46 (type 2)	12%	5.5	12.4
Everolimus	RAPTOR(39)	8 (type 1)	Overall:	5	17.8
	Papillary tumors	30 (type 2)	1%	4	20.5
Sunitinib vs Everolimus	ASPEN ((10)	70 (all papillary types)	24% vs	8.1 vs 5.5	Overall: 31.5 vs 13.2
		10 (chromophobe)	5%	5.5	
		8 (unclassified)	10%	11.5	
			0%		
Sunitinib vs Everolimus	ESPN ((11)	27 (all papillary types)	Overall:	5.7 vs 4.1	16.6 vs 14.9
		12 (chromophobe)	9% vs 3%	NA	31.6 vs 25.1
		10 (unclassified)		9.4 vs 4.7	15.4 vs NA for everolimus
Sunitinib vs cabozantinib	SAVOIR(40)	41 (type 1)	Overall:	Overall: 5.6 vs 9	Overall: 16.4 vs 20
		63 (type 2)	4% vs		
		35 (mixed)	23%		

Pembrolizumab	KEYNOTE 427B(17)	118 (all papillary types)	28.8%	5.5	31.5
		21 (chromophobe)	9.5%	3.9	23.5
		26 (unclassified)	30.8%	2.8	17.6
Atezolizumab + Bevacizumab	(41)	18 (ccRCC with sarcomatoid differentiation)	50%	Overall 8.3	Not reached
		42 (all nccRCC)	26%		
Cabozantinib vs sunitinib	PAPMET	152 (all papillary types)	23%	vs 9 vs 5.6	20 vs 16
	Papillary tumors		4%		
Cabozantinib + Nivolumab	(23)	40 (papillary, unclassified, translocation-associated RCC)	47.5%	12.5	28
		7 (chromophobe)	0%	NA	NA

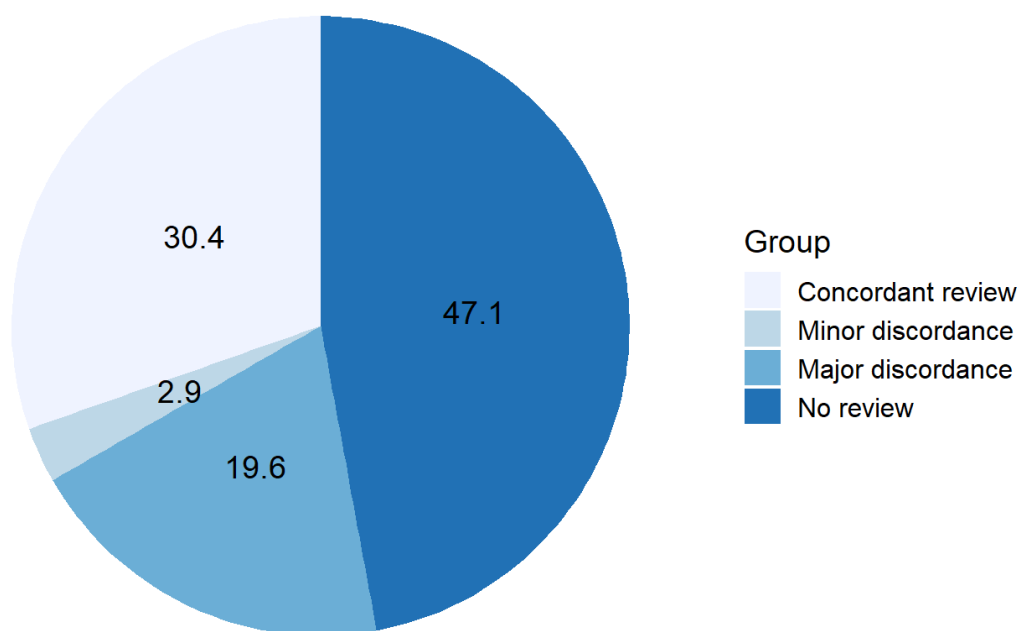
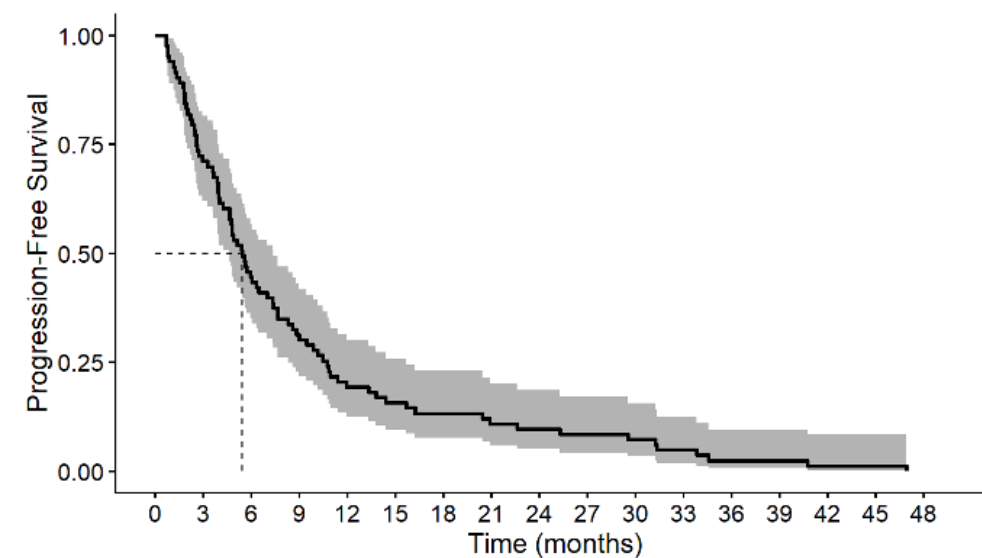


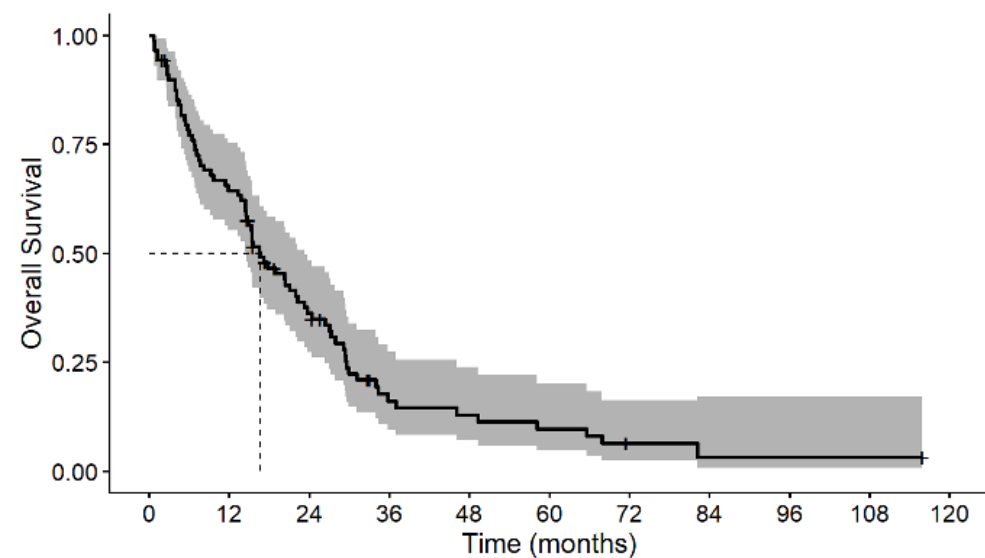
Figure 1. Histological concordance after review



Number at risk

A.

All	83	59	37	26	16	13	11	9	8	7	6	4	2	2	1	1	0
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48



Number at risk

B.

All	89	56	28	10	8	6	2	1	1	1	0
	0	12	24	36	48	60	72	84	96	108	120

Figure 2. Progression free survival (A) and Overall survival (B) in overall population

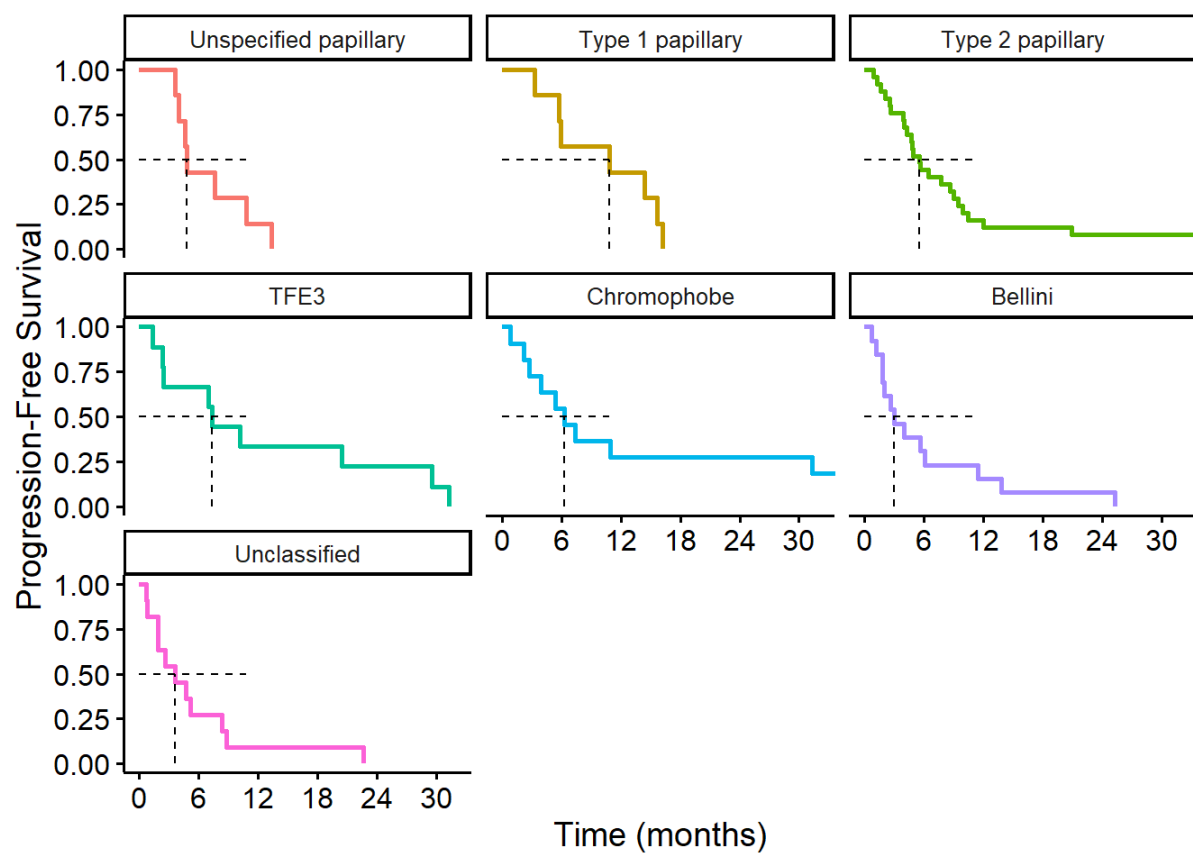


Figure 3. Progression free survival according to histological subtype

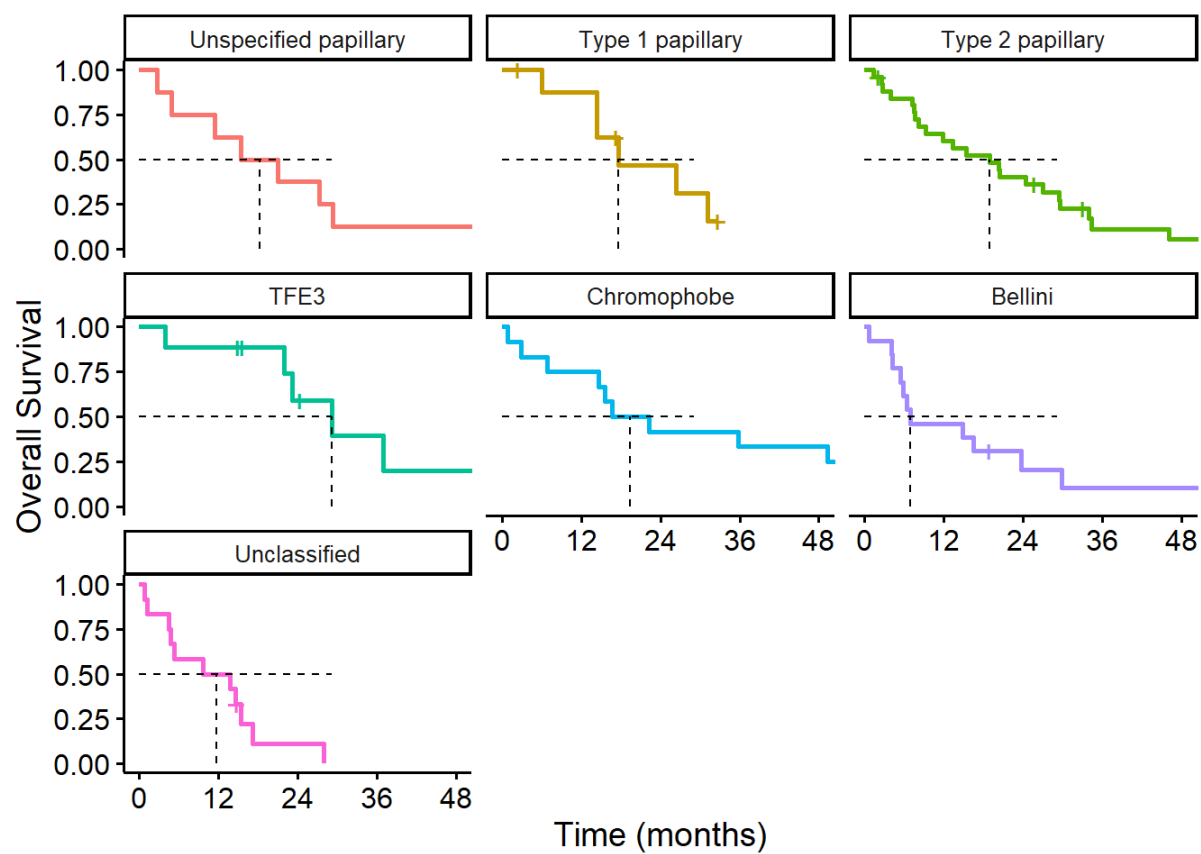


Figure 4. Overall survival according to histological subtype