

Non-Clear Cell Renal Carcinomas: About 23 Cases Experience of the Medical Oncology Department of the Hassan II Hospital in Fez, Morocco

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Abstract

Background: Non-clear cell renal cell carcinomas represent a very rare and heterogeneous variety of kidney cancer. The aim of this study is to describe the main epidemiological, clinical, paraclinical, histological and therapeutic characteristics of these cancers. **Methods:** A descriptive retrospective study was conducted in the Medical Oncology Department of the Hassan II Hospital in Fez, collecting 23 patients with these tumors during the period from January 2008 to January 2020. The statistical analysis is made by the SPSS software version 23. Survival was calculated by the Kaplan-Meier method. **Results:** The average age of the patients was 57.4 years. The sex ratio M/F was 1.3. The main risk factor was smoking (n = 10). The most common symptom was low back pain (n = 23). 17 patients were metastatic, while 6 patients had localized disease. The most common histological type was papillary carcinoma (n = 12). Patients with localized disease have undergone an extended total nephrectomy. After a median follow-up of 145 months, the median of recurrence-free survival was 48 months and that of overall survival was 150 months. In a metastatic situation, 16 patients had received systemic treatment, of which 13 patients had received sunitinib, 2 patients pazopanib and only one patient received everolimus. After a median follow-up of 20 months, the median of progression-free survival was 5 months and that of overall survival was 9 months. **Conclusion:** At the present time, there is no therapeutic standard for the management of patients with these tumors. Surgery for people with localized or locally advanced disease remains the initial and most important approach. For patients with advanced disease, a clinical trial should be considered.

Keywords

Kidney, Non-Clear Cell Carcinoma, Targeted Therapy

1. Background

Kidney cancer is a rare pathology; renal cell carcinoma with clear cells represents the most common histological type with a percentage of 75% [1]. Non-clear cell carcinomas are a heterogeneous group of tumors, accounting for 25% of all kidney cancers [2]. They include papillary carcinomas (10% - 15%), chromophobic carcinomas (5%), unclassified carcinomas (5%), and collecting duct and medullary carcinomas (<5%) [3]. In recent years, the advent of targeted therapies (tyrosine kinase inhibitors and mTOR inhibitors) and immune checkpoint inhibitors has changed the prognosis of kidney cancer; however, these therapies are limited to clear cell histology because the majority of clinical trials conducted to date have excluded patients with non-clear cell histology [4]. There are a limited number of clinical trials treating exclusively nnRCC. Therefore, data on the efficacy of targeted therapies in NCCRC have demonstrated moderate activity in terms of response rate and survival (progression free survival (PFS) and overall survival (OS)). The objective of this study is to determine the main epidemiological, clinical, paraclinical, histological and therapeutic aspects of these tumors in order to compare them with those reported in the literature.

2. Methods

A descriptive retrospective study was conducted at the medical oncology service of the Hassan II University Hospital in Fez, bringing together 23 patients with non-clear cell renal carcinoma during the period from January 2008 to January 2020. We included all patients with the diagnosis of renal cancer with non-clear cell histological evidence, and who were treated in the medical oncology department. The statistical analysis was carried out made by the SPSS version 23 software, the qualitative variables were expressed as frequency and percentage and the quantitative variables were expressed as median, mean and standard deviation. Survival was calculated by the Kaplan-Meier method.

3. Results

3.1. Epidemiological Data

Between January 2008 and January 2020, 23 patients with non-clear cell renal cell carcinoma in the medical oncology department of CHU Hassan II in Fez were included. The mean age of patients at diagnosis was 57.4 years with age ranges ranging from 35 to 88 years. There was a slight male predominance (sex ratio M/F was 1.3). The risk factors for kidney cancer found in our study were smoking in 10 patients and obesity in 6 patients. No history of renal failure, hemodialysis, renal transplant or occupational exposure has been reported, and no

case of familial renal cell carcinoma has been reported.

3.2. Clinical and Paraclinical Data

18 patients were in good general condition at the time of diagnosis (PS at 1). The most common symptom was low back pain reported by all patients, followed by hematuria in 6 patients. Following this clinical symptomatology, all patients had undergone a renal ultrasound followed by a CT scan.

At the end of this assessment, 17 patients were metastatic from the outset, while 6 patients had localized disease. The elective sites of metastases in order of frequency were: lung (n = 17), lymph node (n = 11), bone (n = 11), liver (n = 6) and brain (n = 1).

3.3. Histological Data

The most common histologic type was papillary carcinoma (n = 12), followed by renal carcinoma (n = 6), then chromophobic carcinoma (n = 4) and finally sarcomatoid carcinoma observed in a single patient.

3.4. Therapeutic Data

An enlarged total nephrectomy was performed in all patients with localized disease.

After a median follow-up of 145 months, the median recurrence-free survival was 48 months and that of overall survival was 150 months.

In a metastatic situation, whether onset or relapse after curative surgical treatment, 16 patients had received systemic treatment, of which 13 patients had received sunitinib, 2 patients received pazopanib and only one patient had everolimus (**Table 1**).

Table 1. Patient characteristics.

Characteristics	Number (%)	
Gender	Male	13 (57)
	Female	10 (43)
Risk factors	Smoking	10 (43)
	Obesity	6 (26)
	Renal failure, hemodialysis	0 (0)
	Kidney transplant	0 (0)
	Professional exposure	0 (0)
	Family cases	0 (0)
Circumstances of discovery	Back pain	23 (100)
	Haematuria	6 (2)
	Lucky find	0 (0)
Performance status (PS)	1 - 2	18 (78)
	3	5 (22)

Continued

Stage	Localized	6 (26)
	Metastatic	17 (74)
Metastatic sites	Lung	17 (74)
	Lymph nodes	11 (48)
	Bone	11 (48)
	Liver	6 (26)
	Brain	1 (4)
Histological type	Papillary carcinoma	12 (52)
	Renal adenocarcinoma	6 (26)
	Chromophobic carcinoma	4 (18)
	Sarcomatoid carcinoma	1 (4)
First line treatment	Enlarged nephrectomy	6 (26)
	Systemic treatment	12 (52)
	Palliative care	5 (22)
Systemic treatment 1st line	SUNITINIB	13 (81)
	PAZOPANIB	2 (13)
	EVEROLIMUS	1 (6)

The main undesirable effects that were induced by the targeted therapies: haematological toxicity (n = 9), fatigue (n = 8), mucositis (n = 5), hand-foot syndrome (n = 3). Vomiting and nausea occurred in 2 patients. Diarrhea has been reported in patients receiving pazopanib. High blood pressure was observed in 4 patients who were on sunitinib.

After a median follow-up of 20 months, the median progression-free survival was 5 months and that of overall survival was 9 months.

4. Discussion

In our study, renal non-clear cell carcinomas were more common in males. The main risk factors were smoking and obesity. The clinical symptomatology was non-specific, dominated by low back pain. Most of the patients were in good general performance status at the time of diagnosis. The majority of cases diagnosed were metastatic to begin with. The most common metastatic sites were the lung, bone and lymph nodes. The non-clear cell carcinomas found in our study were papillary carcinoma, adenocarcinoma, chromophobic carcinoma and sarcomatoid carcinoma. Sunitinib was the most widely used first-line therapy. The main side effects observed with targeted therapies were fatigue, mucositis and haematological complications. The median overall survival was 9 months after a median follow-up of 20 months in metastatic patients and it was 150 months in those with localized disease.

Non-clear cell renal carcinomas (NCCRC) are heterogeneous histologic types

of tumors; they represent 25% of all renal cancers [2]. In our series, NCCRCs represented 26% of all renal cancers diagnosed during the study period. NCCRCs most commonly occur in men with a sex ratio of 2 men to 1 woman [5]. This rate is close to that found in our series (sex ratio M/F of 1.4). The clinical signs are nonspecific and renal carcinomas, in particular NCCRCs, are increasingly revealed by chance thanks to improved imaging techniques. In our study, no cases were incidentally discovered because the majority of cases had metastatic disease at the time of diagnosis.

The definitive diagnosis remains the histological examination; it is made either on a biopsy sample or on an excisional piece. On the anatomopathological level, several histological varieties are distinguished: the first variety is represented by papillary carcinomas (PC); it is the most common form of NCCRC, it accounts for 10% to 15% of renal cancers [3], this type of tumor starts from the proximal convoluted tube of the nephron [6]. There are 2 histological subtypes, PC type 1 and type 2 based on distinct morphological and molecular characteristics defined by alterations in the *c-Met* oncogene (type 1) or the fumarate hydratase gene (type 2) [7] [8]. PC type 2 represents the most aggressive form with a significant risk of relapse and death compared to that of type 1. The second histological type is represented by chromophobic carcinomas. These tumors are rarer, they represent 5% of renal cancer cases [3], and they originate from intercalary cells of the distal nephron [6]. They preferentially affect the female sex at a young age [9]. It has been shown through studies that obesity and tobacco consumption promotes the occurrence of this type of cancer [10]. One of the peculiarities of these carcinomas is the rarity of metastatic forms [11]. Their prognosis is generally favorable because they are generally mild tumors, of limited stage and of low grade. Collector duct carcinomas and medullary carcinomas are extremely rare and very aggressive tumors, characterized by a fatal and poor prognosis because they often present early metastases, they represent 1% to 2% of all renal cancers [3], these tumors originate from the distal tubule [6] and share similarities with urothelial carcinomas of the upper urinary tract, which implies the use of platinating agents in their therapeutic approach [12]. Another rare histological type of NCCRC is the unclassified carcinoma, the latter represents approximately 5% of renal cancers [3], this type will be evoked when the carcinoma does not correspond to the macroscopic and histological criteria of the other carcinomas and it is of pejorative prognosis. There is another type of carcinoma associated with the translocation [13], these carcinomas are secondary to chromosomal translocations of the transcription factor genes in particular the transcription factor E3 (TFE3), the transcription factor EB (TFEB) and MITF [14]. They most often occur in children and young adults. Finally, the sarcomatoid variant is often included in NCCRCs; however, it is not considered a distinct histologic type and can be found with any histologic type [15] [16], its presence is generally associated with an appalling prognosis [17]. In our study, the results were almost similar to those reported in the literature in terms of incidence; the most common histological type was papillary carcinoma (52%),

Table 2. Randomized controlled studies conducted in the treatment of patients with NCCRC.

Study	Protocol	Number	Line	Median progression-free survival (months)	Hazard ratio (95% confidence interval)	Median overall survival (months)	Hazard ratio (95% confidence interval)
ASPEN [19]	Everolimus vs Sunitinib	57	1	5.6	1.41 (1.03 - 1.92)	13.2	1.12 (0.7 - 2.1)
		51	1	8.3		31.5	
RECORD [20]	Everolimus vs Sunitinib	31	1	7.9	1.4 (1.2- 1.8)	-	-
		35	1	10.7			
ESPN [21]	Everolimus vs Sunitinib	35	1	4.1	-	14.9	-
		33	1	6.1		16.2	
ARCC [22]	Interferon- α vs Temsirolimus	36	1	1.8	0.38 (0.23 - 0.62)	4.3	0.49 (0.29 - 0.85)
		37	1	7.0		11.6	
SWOG [23]	Tivantinib vs Tivantinib + erlotinib	25	1 et 2	2	-	10.3	-
		25	1 et 2	3.9		11.3	

followed by renal carcinoma (26%), then chromophobic carcinoma (18%) and finally sarcomatoid carcinoma in 4% of cases.

Therapeutically; for metastatic forms, there is no consensus on the best treatment to use as a first-line treatment due to the rarity of these tumors, the recommendations of learned societies require the inclusion of patients with these tumors in clinical trials [18]. Several studies evaluated the effectiveness of tyrosine kinase inhibitors (TKIs) and mTOR pathway inhibitors in the treatment of patients with locally advanced or metastatic CRNCC, these trials included 5 randomized controlled studies [19] [20] [21] [22] [23] (Table 2) 21 phase II single-arm trials and 4 prospective meta-analyzes testing 22 systemic treatments for a total of 2134 patients. Overall, the treatment results were modest and were inferior to those found in clear cell renal cancers. In our study, 16 patients received systemic treatment, of which 13 patients received sunitinib, 2 patients received pazaopanib and only one patient received everolimus.

In the absence of effective systemic treatment, cytoreductive nephrectomy (CN) plays an important role in the management of NCCRCs. Although the majority of studies, have been performed in patients with clear cell carcinoma [24] [25]. Aizer and his colleagues studied the role of cytoreductive nephrectomy in NCCRCs and found a survival benefit of CN in patients with these tumors [26].

5. Conclusion

At present, there is no therapeutic standard for the treatment of patients with NCCRC. Although inhibition of the mTOR and VEGF signaling pathways may have a clinical benefit, it is often marginal and the prognosis remains poor. Sur-

gery for people with localized or locally advanced disease remains the initial and most important approach. For patients with advanced disease, a clinical trial should be considered.

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Conflicts of Interest

The authors declare that they have no competing interests.

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