

Cytoreductive Nephrectomy in Metastatic Kidney Cancer: Experience of the Urology Department at Aristide Le Dantec University Teaching Hospital

Boris Amougou^{1,*}, Yaya Sow², Arlette Dongmo¹, David Douglas Banga Nkomo¹, Jean Paul Engbang³, Theodore Sala Beyeme³, Joseph Fondop¹, Demba Cisse⁴, Faustin Atemkeng¹, Boubacar Fall⁵, Babacar Diao⁶, Abdoulaye Bobo Diallo⁴, Alain Khassim Ndoeye⁶, Fru Angwafor III⁷, Mamadou Ba⁶

¹Department of Surgery and Surgical Specialties, University of Dschang, Dschang, Cameroon

²Department of Surgery and Surgical Specialties, Gaston Berger University, Saint Louis, Senegal

³Faculty of Medicine and Pharmaceutical Sciences, University of Douala, Douala, Cameroon

⁴Faculty of Medicine and Pharmacy, Gamal Abdel Nasser University, Conakry, Guinea

⁵Faculty of Health Sciences, Ziguinchor Assan Seck University, Ziguinchor, Senegal

⁶Department of Surgery, Cheikh Anta Diop University, Dakar, Senegal

⁷Department of Surgery, University of Yaoundé 1, Yaounde, Cameroon

Email address:

risboamougou@yahoo.fr (B. Amougou)

*Corresponding author

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Abstract: In the management of metastatic kidney cancer, enlarged nephrectomy is part of a multimodal approach with systemic treatment. The lack of data on its place in the management of metastatic kidney cancer in Africa and particularly in Senegal motivated this study. *Aim:* to assess the place of cytoreductive nephrectomy in the management of metastatic kidney cancer in our daily practice. *Patients and methods:* This was a retrospective, descriptive and analytical study from January 2010 to December 2014 on patients aged 18 years and over operated for metastatic kidney cancer. The variables studied were prognostic: Performance Status, tumor stage, sites and number of metastatic sites, prognosis group according to Heng's model, histological type and Furhman grade of the nephrectomy specimen, follow-up postoperative course and overall survival. *Results:* A total of 12 patients were included. The mean size of the largest axis of the tumors was 14.06±5.3 cm with extremes of 8.2 and 23.8 cm and the tumor was graded T3 in 6 cases. The majority of patients had a single metastatic site and the lung was the most common metastatic site in 9 cases. In half of the cases the ECOG-PS score was 1. In 6 cases the patients were classified in the Heng intermediate prognosis group. Lymph node dissection was associated with nephrectomy in 4 cases. Renal adenocarcinoma was the most common histologic type in 8 cases and Furhman's grade was only specified in 6 cases. The mean duration of follow-up was 10.1±13.4 months (range 1 and 39 months), overall survival at 2 years was poor and only 2 patients were alive 3 years and 4 years after their nephrectomy. *Conclusion:* metastatic kidney cancer is uncommon in our context, most of our patients consult with advanced stage tumors. Systemic treatment remains difficult for our populations to access. Nephrectomy remains the main weapon at our disposal.

Keywords: Cytoreductive Nephrectomy, Metastatic Kidney Cancer, Overall Survival

1. Introduction

Kidney cancer represents 3% of all solid cancers in adults and metastatic forms at diagnosis represent 15 to 25% of cases [1]. its incidence varies depending on the geographic region. In Senegal, epidemiological data in 2010 indicated a low incidence [2]. Metastatic kidney cancer has long been considered a cancer with a poor prognosis with only 10-20% of patients having a median overall survival at 2 years [3]. Systemic treatment of kidney cancer has evolved considerably over the past two decades with the advent of targeted therapies [4]. In 2001, two prospective trials had shown that enlarged nephrectomy in metastatic patients treated with interferon-alpha significantly improved overall survival [5, 6]. Since then, numerous studies have attempted to clarify the place of this cyto-reductive nephrectomy in this metastatic situation as well as the ideal sequence of its realization in the era of targeted therapies and immunological treatment. Our study aimed to assess the place of cyto-reductive nephrectomy in the management of metastatic kidney cancer in our daily practice.

2. Patients and Methods

This was a retrospective, descriptive and analytical study, carried out in the urology department of Aristide Le Dantec hospital from January 2010 to December 2014. She was interested in patients aged 18 and over operated on for metastatic kidney cancer during the study period. We excluded patients under 18 years of age followed for renal tumors, patients with incomplete records and patients in whom surgical exploration did not allow enlarged nephrectomy. We studied the prognostic variables: performance status, tumor stage according to the 2009 TNM classification, sites and number of metastatic sites, the prognosis group according to Heng's model, the histological type of the tumor and the grade of Furhman, postoperative course and overall survival. Data was collected from consultation registers, operative report and individual patient files. The data were recorded and processed on the Epi Info 7 software. The actuarial method was used for the calculation of the overall survival.

Table 1 summarizes the characteristics of the patients in our study.

Table 1. Characteristics of patients.

Patients/sex	Tumor stage	Performance status	Heng criteria	Surgical treatment	Surgical specimen histology	Furhman Grade	Postoperative follow-up
62 years, F	cT3N0M1 (lung)	ECOG 1	0	CN	Clear cell carcinoma	unspecified	Lost of view
67 years, F	cT3N0M1 (liver)	ECOG 2	0	CN	Clear cell carcinoma	unspecified	Alive (4 years)
60 years, F	cT3N2M1 (lung and liver)	ECOG 3	3	CN+ LND	Clear cell carcinoma	unspecified	Lost of view
67 years, M	cT4N1M1 (lung and liver)	ECOG 2	3	CN	Clear cell carcinoma	unspecified	Death (day 1 after surgery)
48 years, M	cT4N2M2 (liver and bone)	ECOG 1	2	CN+ LND	Clear cell carcinoma	unspecified	Death at 1 year
52 years, F	cT3N1M1 (lung)	ECOG 1	2	CN+ LND	Chromophobic cell carcinoma	I	Lost of view
50 years, F	cT2N0M1 (lung)	ECOG 2	2	CN	Renal cystadenocarcinoma	unspecified	Lost of view
30 years, M	cT3N1M1 (liver)	ECOG 1	2	CN+ LND	Clear cell carcinoma	II	Death 6 months postoperatively
62 years, F	cT2N0M1 (lung)	ECOG 2	0	CN	Tubulopapillary renal carcinoma	II	Death 13 months postoperatively
52 years, M	cT2N0M1 (lung)	ECOG 1	2	CN	Oxyphilic cell carcinoma	III	Death 10 months postoperatively
45 years, F	cT2N0M1 (lung)	ECOG 2	3	CN	Clear cell carcinoma	III	Death year of surgery
36 years, F	cT3NOM1 (lung)	ECOG 1	2	CN	Clear cell carcinoma	I	Alive at 3 years

CN: cyto-reductive nephrectomy. LND: lymph node dissection

3. Results

During the study period we collected 34 cases of metastatic kidney cancer. Fourteen cases were operated, and two tumors were inextirpable. A total of 12 cases undergone cyto-reductive nephrectomy.

3.1. Tumor Stage

All patients had urinary tract ultrasound and abdominal and chest CT scans. MRI was not performed in any of our patients. The dimensions of the tumor were evaluated in all our patients. The mean size of the largest axis of the tumors was 14.06 ± 5.3 cm with extremes of 8.2 and 23.8 cm.

The tumor was classified as T2 in 4 cases, T3 in 6 cases and T4 in 2 cases.

The table 2 summarizes the distribution of patients according to the metastatic site.

Table 2. Distribution of patients according to the metastatic site.

Metastatic sites	Number of cases
Lung	9
Liver	5
Bone	1

Eight patients had a single metastatic site while in 4 cases there were 2 metastatic sites. Of the patients with a single metastatic site, 7 had lung metastases and only one patient had the liver as the only metastatic site.

3.2. Performance Status

The general condition of our patients was assessed by the

Eastern Cooperative Oncology Group (ECOG-PS) score. Half of our patients had an ECOG-PS score of 1 or 6 cases, followed by those with an ECOG-PS score of 2 in 5 cases. Only one patient had an ECOG-PS score of 3.

3.3. The Prognosis Group

The patients were classified according to Heng's prognosis groups. Half of the patients were classified in the intermediate prognosis group, ie 6 cases. Three patients had a poor prognosis as well as 3 cases in the good prognosis group.

3.4. The Surgical Procedure

All our patients had a nephrectomy, ie 12 cases. Four patients had a lymph node dissection as an associated procedure, the site of which was not specified. A patient with lymph node involvement on CT did not have lymph node dissection because of the close relationship between the lymph node bundle and the abdominal aorta. No patient has had surgery for metastases.

3.5. The Anatomicopathological Results

Renal carcinoma was present in 8 cases. There was one case of chromophobic cell renal adenocarcinoma, renal cystadenoma, tubulopapillary renal adenocarcinoma and oxyphilic cell adenocarcinoma, respectively. Fuhrman's rank had only been specified in 6 cases. It was grade 1 in 2 cases, grade 2 in 2 cases and grade 3 in 2 cases.

3.6. Nephrectomy Survival and Morbidity

Postoperative follow-up was carried out in 7 patients. The mean duration of follow-up was 10.1 ± 13.4 months (range 1 and 39 months). Four patients were lost to follow-up and it was not possible for us to assess the carcinologic results as well as the specific mortality in these patients.

One case of perioperative death by pulmonary embolism was noted (postoperative day 1) and 5 cases of death from kidney cancer, ie a specific mortality of 57.1%.

Overall survival at 6 months, 12 months and 24 months was 84%, 47% and 32%, respectively.

Two patients were alive at 3 and 4 years after their nephrectomy.

4. Discussion

4.1. Number of Cases and Incidence

Over a period of 5 years, from 2010 to 2014, the number of metastatic kidney cancer recorded was 34 out of 88 cases of kidney cancer recorded over this same period while the number of metastatic kidney cancer operated on was 14. Therefore, an average annual incidence of 6.8 cases. Epidemiological data on metastatic kidney cancer are poor [7] nevertheless it is generally accepted that if the annual incidence of kidney cancer represents 3.9% of the incidence of new cancers 25% will be diagnosed at a metastatic stage [1]. In Africa, there are no studies to our knowledge that have

evaluated metastatic kidney cancer. Like the African series on the subject [2, 8], this low incidence of kidney cancer in the African context contrasts with the data from the Western series [9, 10-13]. This low incidence in Africa would probably be underestimated if we considered the increasing frequency of risk factors for kidney cancer, including tobacco, obesity and hypertension due to changes in eating habits which tend to increase. westernize. Keeping and updating cancer registries could approach a true estimate of most cancers in Africa, especially kidney cancer.

4.2. Tumor Stage

In our study we used the TNM 2009 classification of the UICC. Thus, half of the patients in our sample were of clinical stage T3 (n = 6), only 2 cases had a tumor classified as T4. Our results are like those of Fall et al. [2] and Tengue et al. [8] which had mainly found T2 stages. Most of our patients had an advanced tumor stage (n = 8 cases) and probably underestimated by the lack of an optimal extension workup, especially MRI, which could explain the high mortality in our study. The tumor stage being a major prognostic factor in metastatic kidney cancer associated with a decrease in overall survival after nephrectomy, especially since it is associated with other criteria such as the presence of symptoms related to the disease, lymph node invasion and visceral invasion [14]. Eight patients in our study had a single metastatic site and lung metastasis was the most common (n = 7) while only one had the liver as the only metastatic site. Liver metastases were frequent in our study (n = 5), in all cases they were synchronous metastases. Our results are consistent with those in the literature which find the lung as the most frequent metastatic site (50 to 80%), followed by bone and liver (10 to 35%) whatever the histological type and whatever the mode of revelation (synchronous or not) [15-17]. The presence of distant extension is an independent prognostic factor associated with decreased specific survival. In addition, hepatic invasion is a poor prognostic factor associated with a decrease in overall survival after nephrectomy [14]. Thus, in our study, among the cases who died within one year of surgery, one case had the only metastatic site in the liver with a cT3N1 tumor stage and 2 cases had two metastatic sites including the liver (cT4N1 and cT4N2). If the presence of a distant extension is already a factor of poor prognosis for overall survival, the number of metastatic sites is also a major prognostic factor for the prediction of the response to immunotherapy in the prognostic model of the French Group of Immunotherapy with a median survival of 5.5 months [18] and in the UCLA study [19]. From the analysis of these studies, it appears that patients with multiple metastatic sites do not have a considerable survival rate and that cytoreductive nephrectomy, in them, would work more to improve local symptoms related to the tumor than to improve the survival.

4.3. The Prognosis Group

We used Heng's prognostic group classification in our study.

This model, validated in the era of targeted therapies, has become the standard model in the literature on metastatic kidney cancer [20, 21]. Thus, in our study 6 patients were classified in the intermediate prognostic group, 3 patients in the poor prognosis group and 3 in the good prognosis group. The fact that almost all the patients in our study consulted with symptomatic disease would likely explain our results, highlighting the long duration of their disease hence the presence of several prognostic criteria in most of them. In addition, among the 2 patients still alive, one was classified as having a good prognosis (at 4 years after the nephrectomy) and the other as an intermediate prognosis (at 3 years after the nephrectomy) with only one prognostic criterion present (anemia), one tumor stage cT3N0M1 and a Furhman grade of 1 on the nephrectomy specimen. This leads us to think that even in the intermediate risk groups there would be a “favorable” subgroup which would have better overall survival.

4.4. The Performance Status

Half of the patients in our study had an ECOG-PS score of 1 ($n = 6$), five patients had an ECOG-PS score of 2, and only one patient had an ECOG-PS score of 3. The older our patients were higher the higher the PS thus the mean age of the patients who had an ECOG-PS score of 1 was 46.6 years, that of those who had a score of 2 was 58.2 years and the only one patient with an ECOG-PS score of 3 was 60 years old but had multiple lymph node involvement (N2) and 3 prognostic criteria present according to Heng's classification. Patients who had an ECOG-PS score of 2 had more factors associated with decreased survival. Our results differ from Brian Such *et al.* [22] which found higher ECOG-PS score in young subjects. He concluded that the beneficial effect of surgery in these patients was more evident in those who had local symptoms due to the tumor and that most of these patients, due to their poor general condition, could not benefit from it. systemic treatment. A larger sample would probably have allowed us to better define the importance of this parameter when tumor cytoreduction surgery is considered in metastatic patients.

4.5. Anatomical Pathology

Clear cell adenocarcinoma was the most common histologic type in our patients in 8 cases. High Furhman grades were present in deceased patients in 4 cases. Prognostic factors such as histological type, Furhman grade, invasion or not of the surgical margins, the presence of tumor necrosis within the tumor and of a sarcomatoid component are associated with a decrease in overall survival after nephrectomy. They also make it possible to assess the need for adjuvant treatment but also to adapt the postoperative follow-up according to the risk of cancer progression [14].

4.6. Nephrectomy

All the patients of the study had open tumor cytoreductive nephrectomy with a lymph node dissection, the site of which had not been specified in 4 of the 5 patients who had lymph node involvement. Lymph node dissection was not possible

in one patient due to the intimate relationship between the lymph node bundle and the great vessels. Fall *et al* [2] in a previous study had reported low rates of nephrectomy in metastatic patients due to the high frequency of patients with low Performance Status, liver metastases and inextirpable tumors. Tengue *et al* [8] in their series had performed the nephrectomy when the general condition of the patient permitted. Since the work of Flanigan *et al.* [5] and Mickisch *et al* [6] tumor cytoreductive nephrectomy occupies an important place in the management of metastatic forms by being integrated into a multimodal approach. Its interest is twofold: to reduce the tumor volume and to improve the local symptoms due to the presence of the tumor or the symptoms linked to paraneoplastic syndromes. This considerably improves the quality of life of the patients and makes them fit to receive systemic treatment. Leibovich *et al* [23] also reported in a series of 173 patients who had cytoreductive nephrectomy followed by systemic treatment with Interleukin 2 (IL-2) that the worst overall survival after cytoreductive nephrectomy was associated with lymph node invasion with local symptoms, involvement of multiple metastatic sites or at a single site other than the lung and bone and the presence of a sarcomatoid component. The mean overall survival was 47 months, 19 months and 5 months respectively in the low, intermediate and high-risk groups. Some authors have also been interested in the metastatic distribution and the survival of patients after cytoreductive nephrectomy, thus Han *et al* [19] had noted that the rate of response to immunotherapy differed according to the metastatic site with a rate of overall response of 44% for single lung metastatic disease, 22% for single bone disease and 14% for multiple metastatic disease. Similarly, overall median survivals differed according to metastatic sites with an overall survival of 31 months for single lung disease, 31 months for single bone disease and 13 months for multiple metastatic disease. All our patients had open surgery which would probably have the effect of increasing the convalescence time and delaying the initiation of any systemic treatment even if no serious complications were noted in all of patients of our study except severe clinical anemia and one case of immediate postoperative death.

We have no experience with laparoscopy for this indication although it would allow a shorter recovery time and allow early initiation of systemic treatment after nephrectomy [24]. Its high cost would not be accessible to our populations under our operating conditions. However, some studies have compared the laparoscopic route to open surgery. These studies have shown comparable results in terms of operating time, frequency of complications and time to start systemic treatment [25-29].

4.7. Systemic Treatment

No patient in our study received systemic treatment (immunotherapy or antiangiogenic therapy) although scientific data suggests that systemic treatment is a standard in the management of metastatic kidney cancer [30-32]. Fall *et al.* in a previous study had no patients who received systemic

treatment [2] while Tengue et al. had only 3 patients started on Sunitinib [8]. The high cost of these treatments as well as their unavailability makes them inaccessible to our patients who, moreover, must bear it out of their pockets. Their use in our patients would however be of great hope since they would allow a significant reduction in the size of a primary tumor allowing the resection of an initially inextirpable tumor, thereby improving the prognosis of these patients.

4.8. Overall Survival and Morbidity of Nephrectomy

A significant mortality was noted in our study with 57.14% specific death from kidney cancer. The morbidity related to nephrectomy was low in our study with only one case of perioperative mortality noted by pulmonary embolism in a patient with ECOG-PS DE 2, a stage cT4 tumor and moreover classified as having a poor prognosis. The most common surgical complication was anemia. Flanigan et al [5], Mickisch et al [6] and the combined analysis of their two studies had noted results comparable to ours [33]. This reveals that despite the small sample size of our study, we are probably making a better selection of patients who are candidates for this therapeutic option in a multidisciplinary consultation meeting and the fact that this surgery remains reserved for surgeons who have good experience of the latter. In our study the overall survival at 6 months, 12 months and 24 months was 84%, 47% and 32%. Our results confirm the heavy mortality that characterizes metastatic kidney cancer in our context. Especially because our patients consult at a stage when the general condition is already very deteriorated and when local symptoms (hematuria, lower back pain) or even general occur. In addition, surgery, the only option we have, in these patients is often a gamble and weighed against the option of monitoring since systemic treatment is not available to our patients.

5. Conclusion

Kidney cancer in adults varies depending on the geographic region. In Senegal, the incidence is low, and the metastatic forms, which count for a third of all kidney cancers during the study period, have a poor prognosis with overall survival hardly reaching 24 months. The high cost of drugs and their unavailability constitute as many limits in the optimal management of these cases in our population. Since abstention from therapy is not a reasonable option in the face of the patient's anxiety about his illness and the rush, often out of despair, from patients to traditional healers, the only therapeutic weapon is surgery, which despite everything retains its place in our context.

This study is also a plea for the attention of the administrative authorities of Senegal so that health policies are put in place to make available and accessible the current therapeutic weapons for metastatic kidney cancers.

Author Contribution

All authors have read and approved the final version of the manuscript before submission.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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