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Results of Cytoreductive Nephrectomy in Synchronous Metastatic Kidney Cancer and a Review of the Literature

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Abstract: The management of synchronous metastatic renal cell carcinoma (mRCC) continues to be a therapeutic challenge. Surgery is a conceivable therapeutic option in the management of metastatic kidney cancer. The aim of our study is to clarify the interest and place of cytoreductive nephrectomy (NCR) in the treatment of mRCC, in the face of certain African realities where systemic treatment is rare and expensive. It was observational, retrospective, bi-centric study on a series of patients who underwent metastatic nephrectomy regardless of their prognostic group, between 2018 and 2020; monitored and treated jointly at the HIA OBO and at the ICL. Postoperative progression was defined by the appearance of new lesions or by the aggravation of pre-existing metastatic lesions. The primary endpoint of the study was survival without locoregional recurrence (LR), progression-free survival (PFS), the secondary endpoint was overall survival (OS). We collected 14 oligo metastatic patients, ECOG 0-1, the mean age was 50.64 years, with a sex ratio of 1.75. 57% of patients were T3-T4. There was a single metastatic site in 71.5%, 22%, 7.5%, pulmonary, hepatic, adrenal respectively. The patients were distributed according to Heng's prognosis group as follows: 64% patients with good, 22% patients with intermediate, 14% patients with poor prognosis. At 3 years, there was no LR, PFS was 78.57% and OS was 85.71%. 3 patients had received adjuvant treatment with sunitinib. And 5 patients, or 36%, had complete remission (CR). CRN remains a treatment option for metastatic kidney cancer, alone or associated with systemic treatment, in patients in good general condition. This CRN sometimes remains the only therapeutic option available in the absence of adjuvant treatment in our settings, even in the event of a poor prognosis in operable patients.

Keywords: Renal Carcinoma, Metastatic, Nephrectomy

1. Introduction

Kidney cancer is the 6th most common cancer. With the current practice of imaging, especially computed tomography, the diagnosis is increasingly fortuitous. Discovery at a metastatic stage represents 15 to 30% [1]. The treatment of metastatic forms is one that undergoes innovations in the field of systemic therapy [2]. CRN was the standard of treatment in the 2000s in the era of IFN-α and interleukin-2 (IL-2) [1, 3]. Since the mid-2000s, there have been rapid advances in systemic therapies for the treatment of metastatic kidney cancer, beginning with targeted therapies - tyrosine kinase inhibitors - and more recently with the advent of immunotherapeutic agents. However, even before the use of systemic treatment, spontaneous regression of metastases, and improvement in comfort of life after surgery alone had been documented in a small percentage of metastatic patients [3, 4].

The objective of our study was to evaluate survival without recurrence (PFS) or without metastatic progression (mPS), and overall survival (OS), by specifying the place of CRN in our African context, on selected metastatic patients,

where systemic treatment is still not available, sometimes too expensive, and rarely covered or reimbursed by health insurance.

2. Patients and Methods

This is an observational, retrospective, bi-centric study on a consecutive series of patients operated between 2018 and 2020; monitored and treated jointly at the Omar Bongo Ondimba Army Training Hospital (OBO ATH) and at the Libreville Cancer Institute (LCI). Fourteen (14) patients with oligo-metastatic kidney cancer (defined by the existence of a single metastatic site with no more than 3 metastases), had been diagnosed on the data of the CT scan. The diagnosis had been strongly suspected on the data of the renal computed tomography, or in front of a bundle of evocative clinical arguments and confirmed after the anatomopathological analysis of the surgical specimen. The extension assessment mainly included a thoraco-abdomino-pelvic computed tomography (TAP CT). All patients immediately underwent extended total nephrectomy (TN) with open lymph node dissection exclusively, regardless of their prognostic group (Pc) established according to Heng's criteria. Postoperative monitoring was carried out by TAP CT scan every 3 months the first year then every 6 months the second year and once a year the following years. A local or loco-regional recurrence was defined by the presence of tumor elements in the nephrectomy space, or in contact with neighboring structures. Metastatic progression was defined by the increase in diameter (measured according to MASS radiological criteria) of known lesions, or by the appearance of new secondary lesions, on the same site or on another site. Complete remission corresponded to an absence of local recurrence associated with disappearance of the initial secondary lesions. Adjuvant treatment essentially included sunitinib, administered in the event of local recurrence or metastatic progression when this treatment was available. The data was recorded and processed in the Numbers software (updated 2021).

3. Results

Table 1. *Demographic variables.*

Age, median (IQR), year **Baselines features n (%)**	**50 (31 – 65)** **Effective (n)**	**%**
HTA	8	57
type 2 diabete	3	21
Tabagism	9	64
low back pain	3	21
gross hematuria	2	14
low back pain and hématurie	2	14
lucky find	9	64
ECOG perfomance status		
0	11	79
1	3	21
Stage TNM		
T2aN1M1	2	14
T2bN1M1	4	28,5
T3aN2M1	4	28,5
T3bN2M1	2	14
T4N1M1	2	14
Stage T		
T2	6	43
T3	6	43
T4	2	14
Stage N		
N1	8	57
N2	6	43
Metastatic site (M1)		
Lung	10	71,5
Hépatic	3	22
Adrenal	1	7,5
Heng risk group n (%)		
Good pronostic	9	64
intermédiair Pronostic	3	22
bad pronostic	2	14
Topography		
superor	7	50
inferor	4	28,5
median	2	14
Side of tumor		
right	11	79
left	3	21
Histological findings	10	71,5
Clear cell carcinoma	3	22
Papillary carcinoma	1	7,5
Chromophobe carcinoma		
Perioperatives complications		
Splenectomy	1	7,5
liver injury	1	7,5
duodenum wound	1	7,5
Post opératives complications		
Surgical site infection	4	28,5
Deep vein thrombosis	1	7,5
Metastatic progression (mPS) at 3 years		
Pulmonary metastatic progression	1	7,5
Hepatic metastatic progression	2	14
Death	2	14
Sunitinib adjuvant therapy	3	22
Results at 3 years		
PFS	/	78,57
OS	/	85,71
Complete remission (CR)	5	36%

4. Discussion

Renal cell carcinoma (RCC) accounts for about 3% of malignant tumors in adults and 90-95% of kidney tumors. Metastatic renal cell carcinoma (mRCC) is one of the most treatment-resistant malignancies and its prognosis is generally poor and its median survival after diagnosis is very short [1, 4]. Cytoreductive nephrectomy (CRN) has been established as a treatment that may improve antitumor immune system response in the era of immunotherapy, based on the results of two randomized trials (EORTC and SWOG) demonstrating an overall survival benefit (OS) of 5.8 months in a combined analysis study [2, 3]. However, targeted therapies have emerged and demonstrated superiority over immunotherapy, becoming the standard of systemic treatment in mRCC. The role of CRN in mRCC has been questioned because some patients are unable to receive targeted therapy

after CRN due to disease progression or perioperative complications [5, 6]. All our patients had been operated after discussion in MCM and this whatever their prognosis group. Our sample was largely young, with an average age of 50 years, which is the most published age range in many series of nephrectomy, however some authors believe that a CRN on cancer T4 N1 should be prohibited regardless of the general condition of the patient beyond the age of 76 [6-8]. The fortuitous mode was the most frequent mode of discovery, on patients with a history of smoking and hypertension in 64% and 57% respectively. The diagnosis was confirmed on analysis of the surgical specimen. The patients had been classified into a prognosis group according to Heng's criteria, with 64% good prognosis, 22% intermediate prognosis and 14% poor prognosis. The analysis of our series shows that these are oligo-metastatic patients with large tumor volumes (67% T3-T4), significant lymph node involvement (57% N1, 43% N2), with metastatic involvement remotely, predominantly pulmonary in 71% of cases. The decision at moment of MCM was a nephrectomy from the outset as initial treatment, was based on current recommendations (AUA, EAU, NCCN guidelines) [6, 9], specifying the role of surgery for the good and intermediate prognosis group in patients with a general state preserved [9-11]. For patients with a poor but operable prognosis, surgery was the only possible option before simple monitoring, in the absence of systemic treatment [5, 12].

The surgery was complete, and no partial surgery was possible in a metastatic situation, even though 50% and 28.5% of the tumors were superior and inferior polar respectively. We do not have any validated guidelines for this indication. Surgery was the only therapeutic option in all oligometastatic patients regardless of the prognosis group with a preserved general condition. This surgery, as shown by several publications [10, 11], is a complex surgery associating significant morbidity and mortality [10, 12, 13]. This complication rate is 10.9% intraoperatively, the most frequent of which are blood loss (36%), splenic laceration (19%), and vascular lesions (16%) [12]. Intraoperative complications represented 22.5% in our study, but there were 3 complications, a splenectomy for a wound in the splenic artery, a wound in the liver and duodenum for a right kidney tumor classified as T4N1 for a tumor of the upper pole of the left kidney. Post-operative complications are 29.5% in many series, headed by surgical site infection and thromboembolic complications, which in our series accounted for 4 (28.5%) and 1 (7, 5%) respectively. Another study retrospectively evaluating 294 patients who suffered CN between 1990 and 2009 showed an overall early complication rate of 12%, including an early major complication rate of 5% (Clavien Dindo ≥3) [12]. NCR brings a gain in terms of recurrence-free survival and overall survival, but it is rarely enough on its own to control metastatic disease, especially in patients belonging to the poor prognosis group [1, 15]. This surgery is a source of delay in adjuvant systemic treatment. Nearly 61% of patients who are candidates for systemic treatment will not have received it within 60 days of surgery [10, 12]. The treatment of these forms is rarely surgical from the outset, and the place of surgery is debated at length [7, 14, 16]. So, what alternative to the proposed treatment, in the absence of systemic treatment? in our country, there is a real difficulty in obtaining it and even that its price is often out of insurance coverage. Early treatment in an adjuvant sequence is often impossible. The patients are monitored postoperatively on the biological and radiological clinical level by TAP CT, and in the event of progression, either they are simply treated symptomatically or sometimes some can obtain systemic treatment. Three of our patients, or 22% (hepatic and pulmonary) had metastatic progression of their initial lesions and had been put on sunitinib after surgery. As supported by the CARMENA trial, should CRN be abandoned despite PFS (78.57%) and OS 85.71%? Systemic treatment is not within the reach of all budgets and its availability is questionable. Several recent studies further support this indication for surgery in this M1 [13, 17]. Indication the place of CRN on OS and specific survival is well known and published in several guidelines [7, 8, 18].

A similar cohort study based on the International Metastatic Renal Carcinoma Database found that patients who received CRN had better OS than those who did not had [9, 11, 17]. Therefore, the CRN, although it is an equally traumatic therapeutic method, is still accepted by many urologists and patients [11, 12, 18]. The potential advantages of CRN are the tendency of spontaneous regression of metastases, the reduction in the incidence of de novo metastases or the relief of clinical symptoms especially haematuria [12]. Ablation of large tumor volumes, or even of the entire renal tumor mass, can reduce the potential for development and growth of new aggressive biological clones [12, 13, 15]. Cyto-reductive surgery could provide enough samples for the most accurate pathological assessment, which could guide further drug selection or even new experimental treatments [12, 13]. The study conducted by Li C et al. Shows huge difference between CRN and no surgery groups (19 vs 4 months) [13]. Many other similar studies were published in the era of targeted treatments, the survival data from these studies was almost in line with previous results, showing that the outcome did not improve much over time despite huge research and test in progress. In Roussel's work, the patients most likely to benefit from CRN had oligometastatic disease and had only lung metastases, with identical overall survivals [12, 14, 18].

We note that in the USA, many patients continue to benefit from treatment with TKIs contrary to current recommendations based on the use of targeted therapy (VEGF). The use of TKIs should still be relevant in our countries for economic and social reasons. And even more so since there are still non-clear cell carcinomas in our series (29.5% in our study) which would be less sensitive to targeted therapies.

Is there an active monitoring place after the CRN?

In a series of retrospective NCDB reviews, Woldu et al. had examined patients with mRCC who underwent delayed treatment with targeted therapy after CRN. The

median treatment delay time was 2.1 months, and many patients started adjuvant systemic treatment (targeted therapy) within 4 months of CRN. Time delay to treatment was not a predictor independent of OS [14]. More recently, Iacovelli et al. reported data from 16 Italian hospitals on 635 patients with mRCC who had been deemed eligible for adjuvant systemic therapy but had opted for active surveillance post-surgery. Of those who were metastatic at diagnosis, 68.7% had undergone CRN. The median OS was 27.7 months (95% CI: 24.8-30.5), and the median progression-free survival (PFS) was 11.1 months (95% CI: 9.9-12,3) in all patients. The delay time to treatment was 8 weeks for patients with CRN versus 5.3 weeks for those who underwent nephrectomy for initially localized disease (P=0.001). However, time delay to treatment after CRN did not affect OS. Together, these studies provide evidence that active surveillance may be a safe initial treatment strategy in some carefully selected mRCC patients and does not require a trade-off between survival and postoperative quality of life [15]. This surveillance consists of clinical and biological examinations and especially computed tomography imaging every three months.

In sum, these recent data, together with the findings of our study and the overall finding, again underscore the importance of surgery for patients with mRCC. The optimal choice is to find the most appropriate candidate for the initial CRN, such as those with a good general condition and a limited metastatic tumor burden, regardless of the prognostic group [16, 18]. CRN should be considered for significant clinical signs such as hematuria in all operable patients. The choice to combine TKIs according to the old recommendations is an alternative to new drugs in a country where these therapies are rare and expensive.

CRM in our countries in a metastatic situation should be a real treatment option in the absence of systemic treatment. prospective studies should be necessary to really show the contribution in terms of overall survival, on much larger cohorts.

5. Conclusion

The role of CRN has evolved as the landscape of systemic mRCC therapy has changed, CRN remains an important treatment option in carefully selected patients with good or intermediate risk mRCC. But in the absence of systemic therapy, the indication can be extended to all selected symptomatic oligo-metastatic patients regardless of the Pc group.

Abbreviations

MASS: Mass Attenuation Size and Structure
L'IFN-α: interféron alpha
IL-2: l'interleukine-2
NCDB: The National Cancer Database
MCM: Multidisciplinary Consultation Meeting
AUA: American Urological Association
EAU: European Association of Urology
NCCN: National Comprehensive Cancer Network
TKI: Tyrosine Kinase Inhibitors
VEGF: Vascular Endothelial Growth Factor

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contribution

All authors contributed to the design and implementation of this study.

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