Review Article

Partial nephrectomy for metastatic renal cell carcinoma: Where do we stand?

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ABSTRACT

Nephron-sparing surgery (NSS) for renal cell carcinoma (RCC) offers comparable oncologic results, but a lower risk of chronic kidney disease, when compared with radical nephrectomy. However, there are limited data in the literature examining the safety of NSS in the setting of metastatic RCC. To evaluate the feasibility of NSS and impact on cancer-specific survival (CSS) in patients with metastatic disease, we performed a systematic review of the literature. There is ample evidence that NSS is feasible in metastatic RCC, with comparable results in terms of CSS compared with radical cytoreductive nephrectomy.

Key words: Metastatic, partial nephrectomy, renal cell carcinoma

INTRODUCTION

Partial nephrectomy or nephron-sparing surgery (NSS) is considered the treatment of choice for localized small renal masses with oncological outcome in cases of renal cell carcinoma (RCC) comparable to radical nephrectomy (RN).[1] The use of NSS has the advantage of preserving renal function with lower cardiovascular mortality and morbidity.[2-5] Cytoreductive nephrectomy is considered an important component of the treatment algorithm for metastatic renal cell carcinoma (mRCC); however, the role of NSS in this context is not well established. The prognosis of patients with mRCC has markedly improved with the advent of novel targeted therapies. There is increasing interest in the use of an aggressive surgical approach in selected patients, including resection of oligometastatic disease. For patients with small primary tumors amenable to NSS and limited metastatic disease, NSS may be appropriate. Preserving renal function may render patients more tolerant to receive tyrosine kinase inhibitors (TKI).[6] In this review, we sought to evaluate the current available literature on the oncological outcomes of mRCC managed by NSS.

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MATERIALS AND METHODS

We performed a systematic review of the literature based on free-text search in the National Library of Medicine Database MEDLINE using the following keywords: *partial-nephrectomy*, *nephron-sparing surgery*, *cytoreductive-nephrectomy* and *metastatic renal cell carcinoma*. Filtered for human and adult pathologic conditions, articles published in English from 1996 to September 2014 were included in this article. Based on the relevance of the content, our review consisted of five articles. Of note, the reviewed literature had a low level of evidence, constituted by case reports, small case series and reviews. This precluded the ability to conduct statistical analyses.

RESULTS

The findings of our review are listed in Table 1. Five articles reporting the use of NSS in the setting of mRCC have been published between 1996 and 2013. It was noticed that the interest in NSS increased during the targeted therapy era as the majority of patients had their surgery after the introduction of targeted therapy to the treatment algorithm for mRCC. A total of 192 patients have been described by all authors, with a follow-up range between 0 and 212 months. The

Table 1: Overview of all studies reporting survival in patient with mRCC who underwent NSS

Author	Year	Number of patients who underwent NSS	Mean length of follow-up (months)	1-year cancer-specific survival (%)	3-year cancer-specific survival (%)	5-year cancer-specific survival (%)
Krishnamurthi	1996	15	30.4	-	-	-
Krambeck	2006	16	16*	81.3	-	49.2
Hutterer	2007	45	21	86.6	75	-
Capitanio	2008	46	23.5	79.4	-	40.3
Hellenthal	2013	70	6**	49	-	-

*Median follow-up (0-132 months), **Median follow-up (0-212 months), NSS=Nephron-sparing surgery

1-year cancer-specific survival (CSS) of those patients ranged between 49% and 86.6%. Most of the authors concluded that patients who underwent NSS rather than RN for metastatic disease were less likely to succumb from RCC.[7-11]

DISCUSSION

A combined analysis of both The Southwest Oncology Group (SWOG) 8949 and European Organization for Research and Treatment of Cancer (EORTC) 30,947 trials showed that patients undergoing cytoreductive nephrectomy in the context of mRCC had a longer overall survival (OS) of 13.6 months versus 7.8 months for patients receiving interferon alone, representing a 31% reduction of death in the cytoreductive nephrectomy group.[12] This can be attributed to decreased local tumor complications, tumor burden and improved response to systematic therapy. The same results were found in a population-based survival rate analysis conducted by Zini *et al.* using the Surveillance Epidemiology and End Results Program (SEER) database between 1988 and 2004.[13] This analysis generalized the survival benefit of cytoreductive nephrectomy in mRCC, which was also observed in the selected population of SWOG 8949 and EORTC 30947 trials; moreover, in this analysis, both CSS and OS were higher in the cytoreductive group, regardless of the performance status and baseline characteristics. This may possibly eliminate the selection bias between the surgery and non-surgery groups (the overall mortality rate in the non-surgery group was not increased by non-RCC causes). A report from the International mRCC Database Consortium cited that more than one-third of the patients were not enrolled in clinical trials because they failed to satisfy the eligibility criteria.[14] The introduction of targeted therapy in the management algorithm of metastatic RCC has led to a shift in the standard systemic therapy for mRCC; moreover, it has created a debate about the effectiveness of cytoreductive nephrectomy in the setting of targeted therapy.[15] The ongoing CARMENA trial (NCT 00930033) in Europe, where patients are randomized to upfront cytoreductive nephrectomy followed by treatment with Sunitinib versus treatment with Sunitinib alone, may resolve this debate.

NSS is considered the treatment of choice for localized small renal masses,[1] with oncological outcome comparable to RN, and advantages of preserving renal function and lowering cardiovascular mortality and morbidity.[2-5]

Because chronic kidney disease (CKD, glomerular filtration rate <60 mL/min/1.73 m^2) is more prevalent in a RCC patient,[16,17] the benefit of NSS can be appreciated in this study from Memorial-Sloan Kettering that found the incidence of new-onset CKD in patients with normal serum creatinine and two functioning kidneys, who had underwent NSS and RN for small renal masses, to be 17% and 69%, respectively.[17]

There is mounting evidence in the literature that tumor characteristics rather than surgical approach determine CSS and OS.[18,19] This evidence led to the expansion of the utility of NSS in tumors larger than 4 cm and locally advanced RCC. In a study by Margulis *et al.*, the oncological efficacy of NSS versus RN in patients with locally advanced RCC was compared. In the comparison of 34 patients undergoing NSS and 567 patients undergoing RN, the CSS curves demonstrated comparable outcome.[20]

In a recent analysis of the SEER database of RCC by Hellenthal *et al.*, 15% of patients diagnosed with RCC already have metastatic disease at presentation, 13% of whom have renal tumor ≤4 cm. Only 26% of those patients were candidates for surgery. Interestingly, around 10% of the candidates underwent NSS.[12]

There is a scarcity of data in the literature regarding the role of NSS in the setting of metastatic disease. Marberger *et al.* were the first to report the feasibility of NSS in three patients in 1981.[21] Bazeed *et al.* reported on two patients with metastatic disease who underwent NSS and died of disease progression 3 years postoperatively.[22] Morgan and Zincke described six patients with metastatic disease who underwent NSS, four of whom died after 2 years secondary to disease progression.[23] Long *et a*l. reported on two patients who had metachronous tumors in a solitary kidney after immunotherapy; both of them were tumor free for at least 11 months.[24] In 1996, Krishnamurthi *et al.* retrospectively reviewed 15 patients who underwent NSS for MRCC because of a solitary kidney or CKD secondary to hypertension or diabetes mellitus.[7] The benefit of NSS in mRCC was noted in 93% where the need for hemodialysis was obviated.

The study was limited in its inability to calculate pooled CSS for all the patients due to the heterogeneity of their characteristics, load of metastasis and adjuvant treatment received. Nonetheless, the study concluded that NSS may confer extended survival.

Kamberk *et al*. reviewed the Mayo Clinic Nephrectomy Registry between 1970 and 2002.[8] Sixteen patients who underwent NSS for MRCC with a median follow-up of 18 months (0–132 months) were compared with 404 patients who underwent RN for MRCC, and demonstrated that survival of patients undergoing NSS is not inferior to those undergoing RN with 1-, 3- and 5-year CSS for the NSS group of 81%, 49% and 49%, respectively, versus 51%, 21% and 13%, respectively, for the RN group. One major drawback of this study is that 87.5% of the patients in the NSS group underwent complete resection of all metastatic disease compared with 22.5% from the RN group; hence, comparing disease-specific survival of both groups may be confounded.

In a multi-institutional trans-Atlantic study, Hutterer *et al*. reviewed the nephrectomy database of 17 institutions between 1984 and 2001.[9] Of 796 patients with MRCC undergoing surgery, 14 patients were excluded for missing data. Only 5.7% of the remaining patients underwent NSS. With a mean follow-up of 21.6 months, the 1-, 2- and 3-year RCC-specific survival in the NSS group was 86.6%, 86.6% and 75% versus 73.3%, 60.2% and 52.7% for the RN group, respectively. In both the matched analysis and the unmatched analysis, it was concluded that RN predisposed to a higher cancer-specific mortality. Multiple limitations were encountered in this study: Inter-institutional differences in surgical techniques and adjuvant treatments as well as lack of central pathology. Moreover, patients from different ethnicities were pooled together despite the mounting evidence in the literature that there is CSS disparity among the different races, as African American patients have worse RCC CSS.

Capitanio *et al*. re-examined the effect of NSS on RCC-specific survival relative to RN using the SEER cancer registries from specific areas and states in an attempt to simulate the total population of the United States.[10] From 1988 to 2004, a total of 2043 patients with metastatic disease underwent cytoreductive nephrectomy, with a mean follow-up of 23.5 months (1–202 months). NSS was performed in 2.2% of the patients. It was concluded that NSS was not associated with worse RCC-specific survival compared with RN.

Hellenthal *et al*. identified 56,011 patients with RCC who were also registered in the SEER database between 1988 and 2005.[11] 15% of the patients had metastatic disease at presentation. Of these patients, 0.8% underwent NSS and 33.8% underwent RN. On multivariate analysis, patients undergoing RN were at a two-time higher risk of dying from mRCC than those undergoing NSS.

While there are no prospective studies examining the efficacy and safety of tyrosine kinase inhibitors in patients with metastatic RCC and CKD, patients with preserved nephron volume may tolerate tyrosine kinase inhibitors with less complications. Parasa *et al*. reported that Grade I and II adverse effects of sorafenib were more frequent in CKD patients. Serious adverse effects of TKI in CKD patients, such as subarchanoid hemorrhage, cerebellar hemorrhage, myocardial infarction, congestive heart failure and pancreatitis, were reported.[6,25-27]

Nonetheless, several case series reported that the median progression-free survival and median OS in patients with CKD, including patients receiving hemodialysis, were comparable to patients with normal renal function; despite this, dose reduction and interruption was higher in CKD patients.[25,27,28]

There are multiple limitations in this review. All the studies were retrospective and relied on a small number of highly selected patients. This significant selection bias may be attributed to the fact that NSSs were performed for imperative indications, such as solitary kidney, bilateral disease or CKD. The presence of previous systematic treatment, performance status, hemoglobin, serum calcium and LDH, which are part of the Motzer criteria, were unavailable. The number and site of metastasis and fractional percentage of tumor removed at the time of nephrectomy were not reported by any of the available studies.

CONCLUSION

Given the above-mentioned limitations, NSS, when feasible, may be a viable option for surgical debulking in metastatic RCC. For patients with primary tumors amenable to NSS, established prognostic factors can be used for patient selection. Patients most likely to benefit from a nephron-sparing approach are those for whom RN is not feasible due to preexisting renal impairment and patients with limited metastatic disease expected to enjoy prolonged survival with a combination surgical intervention and systemic therapy.

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