Cytoreductive Surgery in the Management of Renal Tumours: Rationale, Current Evidence and Future Perspectives

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Abstract Renal cell carcinoma accounts for 3% of adult solid malignant tumours. Approximately 25% of the patients present with metastatic disease at presentation. In the era of immunotherapy (interferon alpha-2b and interleukin-2), studies showed significant survival benefit with cytoreductive nephrectomy (CRN) followed by interferon alpha-2b than interferon alpha 2-b alone. Introduction of targeted therapies (vascular endothelial growth factor receptor-tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors) in 2005 generated a great interest in the management of metastatic renal cell carcinoma (mRCC) as these drugs exhibited tumour shrinkage in the primary tumour as well as in the metastatic site/s. Though there is no level 1 evidence, many studies have shown the usefulness of cytoreductive nephrectomy along with targeted therapy as against to targeted therapy alone. This review is aimed at the rationale behind the cytoreductive nephrectomy in mRCC, the current evidence and what is in store for the future. A detailed search on the management of mRCC was carried out on MEDLINE, Embase, CANCERLIT and Cochrane Library databases using the key words “cytoreductive nephrectomy”, “immunotherapy” and “targeted therapy” since 1980 till 2015. Original articles, review articles, monographs, book chapters on metastatic renal cancer and textbooks on urologic oncology, oncology and urology were reviewed. Various international guidelines on this issue were also studied. An identical search was performed using the American Society of Clinical Oncology Abstract database. Trials in the progress or recently completed

that were relevant to this paper were identified through clinicaltrials.gov. The latest information for new articles ahead of publication was last accessed in November 2015. CRN has remained an integral part to the management of metastatic renal cell carcinoma mainly for the patients with good performance status, life expectancy of more than 12 months and in the absence of adverse prognostic factors. It had shown measurable survival benefit in the era of immunotherapy (CRN + immunotherapy vs. immunotherapy alone). In the era of targeted therapy, many studies have shown significant survival benefit with CRN + targeted therapy. However, there is no clear level 1 evidence to support this. The ongoing trials (CARMENA and European Organisation for Research and Treatment of Cancer SURTIME) would perhaps guide us in the way in which we should manage mRCC disease in the future. Maybe we may find some answers on the issues of the effectiveness of targeted therapy, the timing of CRN and sequencing these treatment arms once the results of these ongoing and future trials are through.

Keywords Cytoreductive nephrectomy · Immunotherapy · Targeted therapy · Metastatic RCC

Abbreviations

mRCC	Metastatic RCC
CRN	Cytoreductive nephrectomy
VEGFR	Vascular endothelial growth factor receptor
mTOR	Mammalian target of rapamycin
TT	Targeted therapy
RCC	Renal cell carcinoma
IFN-a2b	Interferon alpha 2-b
IL-2	Interleukin-2

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Introduction

Renal cell carcinoma (RCC) accounts for nearly 3% of adult solid tumours [1]. At first presentation, 45% of patients will have localised disease, 25–30% will have locally advanced disease with lymph node or local organ involvement and around 25% patients have metastatic disease [2, 3].

In the past, nephrectomy was offered mainly as a means of palliation to relieve the pain from local infiltration or haematuria when the conservative measures failed. The survival benefit was never considered as an end point of this treatment strategy as majority of the patients did not survive beyond 2 years. The 2-year survival used to be dismal, around 10–30%. On rare occasions, nephrectomy was performed to relieve severe paraneoplastic manifestations such as hypercalcaemia, but with no improvement in median survival [4]. The phenomenon of spontaneous regression of metastatic disease after nephrectomy caused a great deal of excitement in the past, but it is a rare event. It does occur in 0.4 to 0.8% of the patients [5, 6]. Majority of these historical cases had lung metastasis, and it is important to note that many of them did not have a tissue diagnosis of these so-called “metastasis”. With such a rare and unpredictable event, routine nephrectomy with the hope of spontaneous regression did not make a sense, with no adjuvant therapy in sight.

In the 1980s, immunotherapy (or cytokine therapy as many would call) in the form of interferon alpha 2-b and interleukin-2 was introduced with a complete response rate of 5–10%, maximum of 20% with the use of interleukin-2 in adjuvant setting. Interferon alpha 2-b was considered safer than interleukin-2; the latter had high toxicity profile, had to be administered in the hospital setting, and was costly. Two major randomised controlled trials (European Organisation for Research and Treatment of Cancer (EORTC) 30947 and Southwest Oncology Group (SWOG) 8949) and their combined analysis showed significant survival benefit when patients with metastatic RCC (mRCC) were treated with cytoreductive nephrectomy and interferon alpha 2-b versus interferon alpha 2-b alone [7–9].

This was the basis of increasing the use of cytoreductive nephrectomy (CRN) after 2001 across the globe [10, 11].

The FDA approved the use of targeted therapy (TT), mainly vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKIs) in 2005. These drugs showed a measurable reduction in the primary as well as metastatic disease, reduced toxicity and improved survival compared with immunotherapy [12]. The use of mammalian target of rapamycin (mTOR) inhibitors and monoclonal antibodies with anti-VEGFR activity was introduced in 2006–2008 with encouraging results as a first-line as well as second-line therapy. Many studies in last 10 years (2005–2015) have shown improved survival with the use of CRN plus targeted therapy; however, we still do not have a clear level 1 evidence to

substantiate this strategy, like the one we had (level 1 evidence) in the immunotherapy era (CRN + interferon alpha 2-b) [13].

This review is aimed at the rationale behind the cytoreductive nephrectomy in mRCC, the current evidence and what is in store for the future.

Material and Methods

A detailed search on the management of mRCC was carried out on MEDLINE, Embase, CANCELIT and Cochrane Library databases using the key words “cytoreductive nephrectomy”, “immunotherapy” and “targeted therapy” since 1980 till 2015. Original articles, review articles, monographs, book chapters on metastatic renal cancer and textbooks on urologic oncology, oncology and urology were reviewed. Various international guidelines on this issue were also studied. An identical search was performed using the American Society of Clinical Oncology Abstract database. Trials in the progress or recently completed that are relevant to this paper were identified through clinicaltrials.gov. The latest information for new articles ahead of publication was last accessed on 15 November 2015.

Discussion and Conclusions

The *rationale* for the use of CRN in mRCC has its roots in the two landmark randomised controlled trials published in 2001. These studies were done in the era of immunotherapy (or cytokine therapy as referred to in some literature) 1990–2001. Interferon alpha 2-b (IFN-a2b) and interleukin-2 (IL-2) were the two main agents used in that era. IFN-a2b, a more commonly used agent, could be given subcutaneously three times a week and had less toxicity profile. IL-2 had a better response rate but had high toxicity profile, was costly and had to be administered intravenously in the institutional set-up with utmost care. Therefore, it is no surprise that the randomised trials we have are with the use of IFN-a2b.

A retrospective analysis in the immunotherapy era had supported the use of CRN in order to achieve a better response rate. However, many people felt that the results were achieved due to selection bias while some felt that CRN could have some biological effect on patient survival. The EORTC in their study—EORTC 30947—and the SWOG in their study—SWOG 8949—studied the issue of CRN with immunotherapy versus immunotherapy alone by using IFN-a2b [7, 8]. Both trials recruited histologically confirmed clear cell mRCC with metastases beyond regional lymphatics, absence of brain metastases, inferior vena cava (IVC) thrombus below hepatic veins, if present. None of these patients had any prior chemotherapy, hormonal therapy, radiotherapy or biological

response-modifying agents. Only patients with good performance status (PS of 0 or 1) were enrolled. The EORTC 30947 study had 83 eligible patients, while the SWOG 8949 study had 241 eligible patients.

The EORTC 30947 study had 42 patients in both arms (CRN + IFN- α 2b vs. IFN- α 2b alone). The median survival was 17 months in the CRN + IFN- α 2b group as against to 7 months in the IFN- α 2b group, with 1-year survival of 59.3 versus 33.7%, respectively, with a hazard ratio (95% CI) of 0.54 (0.31–0.94) [7].

The SWOG 8949 study had a more number of eligible patients, i.e. 241 (120 in CRN + IFN- α 2b vs. 121 in IFN- α 2b alone), but it took nearly 7 years to accrue the patients. The median survival was 11.1 months in the CRN + IFN- α 2b group as against to 8.1 months in the IFN- α 2b group, with 1-year survival rate of 49.7% and 36.8 months, respectively [8].

A combined analysis of these two studies by Flanigan et al. in 2004 showed a median survival of 13.6 months in the CRN + IFN- α 2b group versus 7.8 months in the IFN- α 2b alone group. One-year survival was 51.9 versus 37.1 months, respectively, with a hazard ratio (95% CI) of 0.69 (0.55–0.87) [9].

Table 1 illustrates the details of the EORTC study, SWOG study and their combined analysis.

It appears from the combined analysis that there is improved median survival of 5.8 months compared to immunotherapy alone and, at 1 year, survival rate improved from 37.1 to 51.9%, which is significant. It is important to note that patients recruited in this trial had good performance status (PS 0 or 1), clear cell histology and no brain metastasis. At the same time, actual regression of metastatic lesion was rare (around 6%) and not significant in both treatment arms. Majority of the patients could tolerate the CRN procedure

well, had a very low operative death (1.4%) and could start IFN- α 2b treatment within 1 month, with escalating doses up to 5×10^6 IU/m² SC three times a week for 52 weeks or until the disease progression or unacceptable toxicity. Metastectomy (even a solitary) was never a part of this trial; therefore, the issue of CRN with metastectomy followed by immunotherapy was never addressed by these trials.

There is no doubt that there are changes in the immune activity before and after cytoreductive nephrectomy, mainly in the immunosuppressive acidic protein and natural killer (NK) cell activity [14].

With a better understanding of the genetics and molecular basis of the development of RCC and its metastatic spread, newer therapies started emerging after 2002. VEGFR-TKIs, monoclonal antibodies with anti-VEGFR activity and mTOR inhibitors at the later stage were the new entrants on the horizon of treatment of mRCC. These drugs showed a measurable regression in the primary as well as metastatic site/s.

In 2005, for the first time, the FDA approved the drug sunitinib (VEGFR-TKI), and this was the era when TT was started. Many other drugs which could come under the umbrella of targeted therapy were approved in subsequent years (sorafenib, mTOR inhibitors, bevacizumab, pazopanib, axitinib and many others). These drugs showed improvement in the overall survival (OS), progression-free survival (PFS) and response rates as compared to immunotherapy [15–18]. With such a response, even concern has been raised about the delay in the treatment of TT caused by CRN.

Though the rate of CRN improved after 2001 perhaps with the results of the EORTC and SWOG trials [10, 11], it appears that there was a steady decrease in its use which peaked at 39% in 2004 and has decreased every year by 0.6% since then [19]. Tsao et al. also showed a similar pattern in their study in the targeted therapy era, but it is difficult to infer that this was a global phenomenon as both these studies were based on the Surveillance, Epidemiology, and End Results (SEER) data analysis from the USA [20].

Having established the use of CRN in immunotherapy era with level 1 evidence, do we have similar evidence in the targeted therapy era? There are many studies supporting the use of CRN with TT due to the survival benefit, but unfortunately, we do not have randomised controlled trials on this issue in the targeted therapy era.

There are many retrospective studies which have looked into the role of CRN along with the use of TT in mRCC.

A multi-institutional study by Choueiri et al., a retrospective study, examined 314 patients with mRCC (201 patients undergoing CRN vs. 113 patients who did not undergo CRN, and all receiving sunitinib, sorafenib or bevacizumab later). There was a twofold increase in the overall survival of 19.8 months for the CRN group versus 9.4 months for the TT only group (HR 0.44; $p < 0.01$). This survival benefit was persistent on multivariate analysis, but a group of patients

Table 1 EORTC 3089 trial, SWOG 8949 trial and their combined analysis: CRN + IFN- α 2b versus IFN- α 2b alone

Trial (Ref)	Treatment arm	
	Nephrectomy + IFN- α 2b	IFN- α 2b alone
EORTC 30947 [7]		
No. of pts	42	42
Median survival (months)	17	7
1-year survival (%)	59.3	33.7
SWOG 8949 [8]		
No. of pts	120	121
Median survival (months)	11.1	8.1
1-year survival (months)	49.7	36.8
Combined analysis [9]		
No. of pts	161	163
Median survival (months)	13.6	7.8
1-year survival (months)	51.9	37.1

pts patients

with a poor risk or with a KPS score of less than 80% had only marginal survival benefit with CRN [21].

Zini et al., using the SEER database, studied more than 5000 patients in a population-based retrospective study. The study included 2447 patients with CRN versus no surgery out of 2925 patients with mRCC and showed a 2.5-fold greater risk of death without CRN. Use of CRN, tumour size and age of the patient were the predicting factors for survival on multivariate analysis [22].

Heng et al. have also analysed the role of CRN in patients with synchronous metastasis from RCC on behalf of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). This is the largest study of 1658 patients in a pooled analysis from 20 countries. Of 1658 patients, 982 underwent CRN, while 676 did not. All patients received TT with most receiving sunitinib as a first-line treatment (72%). Patients undergoing CRN had better prognostic variables than those who did not undergo CRN. The median OS for CRN patients was 20.6 versus 9.6 months for patients not receiving a CRN ($p < 0.001$). CRN was also associated with an increase in PFS of 7.6 versus 4.5 months. The authors also concluded that patients estimated to survive <12 months may receive marginal benefit from CRN and patients who have four or more IMDC prognostic criteria did not benefit from CRN [23].

A large study using the SEER database examined CRN and survival in the era of immunotherapy as well as TT and found an overall survival of 19 months for TT with CRN versus only 4 months of TT [19]. This study also inferred that the median OS amongst the patients receiving CRN improved from 13 to 19 months between the era of immunotherapy (1993–2004) and the era of targeted therapy (2005–2010) and there was no significant difference in OS in these two eras in patients who did not undergo CRN. Using the SEER data, improved overall survival with cytoreductive nephrectomy has also been confirmed by Abern et al. and Nelson et al. [24, 25]. Pal et al. have also looked into the disease-specific survival in the 2392 patients of cytokine (immunotherapy) era and 2784 patients of targeted therapy era using the SEER database analysis. The authors noted an improvement of disease-free survival from 13 months (cytokine era) to 16 months (targeted therapy era) [26].

Xiao et al. have studied the factors related to the choice of CRN in mRCC and survival rate with or without CRN in the targeted therapy era. This was the SEER database analysis based on data from the USA. From 2006 to 2009, 1505 patients with mRCC were identified from the SEER database, 1045 had undergone nephrectomy, while 460 patients had not. After the match based upon propensity scores, the 1-, 2- and 3-year cancer-specific survival rate estimates were 45.1, 27.9 and 21.7% for the no surgery group versus 70.6, 52.2 and 41.7% for the surgery group, respectively (HR 0.42, 95% CI 0.35–0.52, long rank $p < 0.001$). The authors noted that the effect of performing CRN was related to a 2.5-fold increase in cancer-specific survival rate ($p < 0.001$) [27].

In terms of the *extent of CRN*, ideally, one should aim for complete clearance of the disease in the retroperitoneum (R0) as much as possible. Removal of ipsilateral adrenal in upper polar tumours, T3 disease, LN-positive disease and renal vein/IVC thrombus has been debated in many studies, as well as lymph node dissection and its extent at the time of nephrectomy. But, it makes a sense to achieve the R0 status as much as possible, in order to reduce the tumour burden and have effective targeted therapy. However, one should not risk the life of the patient in performing heroic resection of the involved organs or attempting to remove the fixed lymph nodes or major vascular resection. CRN, though safe, can have higher complication rates and increased morbidity and mortality [28].

The *role of nephron-sparing surgery (NSS) in metastatic RCC* has also been studied by few centres. NSS has shown equivalent efficacy to radical nephrectomy in non-metastatic setting, so it is interesting to see whether we can apply the same logic in the presence of metastatic disease. The situation of mRCC in a solitary kidney certainly would make one think about the possibility of NSS. Krambeck et al. have studied the possibility of NSS in metastatic pM1 RCC in 16 patients and found that cancer-specific survival in patients undergoing NSS was equivalent to that in those who underwent cytoreductive nephrectomy. This study demonstrated that NSS could achieve adequate cytoreductive therapy while preserving renal function, with postoperative complication rates similar to those of pM0 nephron-sparing surgery cases [29].

In the light of improved OS with CRN and TT, *can we better select patients for CRN?* I think the answer is perhaps yes, based on the studies in the immunotherapy era and TT era. In the era of immunotherapy, the EORTC and SWOG trial patients with PS of 0 or 1, clear cell histology and no brain metastases did very well. The study by Heng et al., based on the IMDC data, showed that patients with four or more prognostic criteria did poorly and did not benefit from CRN and patients who are expected to live more than 12 months did well, while patients with shorter life expectancy are not the candidates for CRN [23]. There are many poor prognostic factors and laboratory parameters indicating the aggressiveness of the disease. These parameters should be taken into consideration before embarking on CRN [30]. A study conducted by the MD Anderson group has also examined who will benefit from CRN and concluded that survival differences between CRN and non-CRN patients did not begin to diverge until 8.5 months [31]. There are statistical models available in predicting the OS in patients with mRCC treated with TT, and maybe, one can make use of these models while selecting patients for CRN [32]. There is no surprise that the ongoing CARMENA and EORTC SURTIME prospective trials have recruited patients with good performance status.

A study by Kader et al. has shown that the prognosis in elderly patients is comparable to that in younger patients if they survive the surgery, questioning an increasing age as an adverse risk factor while dealing with mRCC [33].

In terms of what holds in the future, we are waiting for the results of two ongoing prospective trials: CARMENA and EORTC SURTIME. The French-led CARMENA trial is looking into the utility of CRN. In this study, 576 patients will be randomised to receive either sunitinib alone or cytoreductive nephrectomy [34]. The primary end point of the trial is OS, and the secondary end points are postoperative morbidity and non-compliance with sunitinib therapy. In the EORTC 30073 (SURTIME) trial, 458 patients was randomised to receive either sunitinib followed by cytoreductive nephrectomy or cytoreductive nephrectomy followed by sunitinib, aiming on progression-free survival as the primary end point and looking at the timing of CRN [35]. One of the major concerns about these two trials is the use of sunitinib as the only agent out of the many targeted therapy agents which have shown promising results. Concerns have been raised on the background of many other new therapies (current and upcoming), and the results of these two trials may be antiquated by the time they are available [36].

If some of these agents prove effective in the adjuvant setting in the future, then the next step would be transition to its use in the neoadjuvant setting. It will be interesting then to see if we could convert the poor-risk group of patients into the better-risk group by downsizing the primary lesion as well as metastatic burden, use CRN in between and then continue TT as adjuvant therapy. As of today, we are far away from that scenario.

Many trials are ongoing with the use of vaccines, immune checkpoint inhibitors (a resurgence in immunotherapy once again) and novel targeted agents as a first-line therapy in mRCC in adjuvant setting and poor-risk groups. The coming years will witness the utility of these drugs in mRCC which would also tell us where we stand on the issue of CRN.

We know that CRN is not for everyone in mRCC, and the question still remains unanswered as to what best we can offer to the poor-risk, poor-performance patients of mRCC.

In conclusion, CRN has remained an integral part to the management of metastatic renal cell carcinoma mainly for the patients with good performance status, life expectancy of more than 12 months and in the absence of adverse prognostic factors. It had shown measurable survival benefit in the era of immunotherapy (CRN + immunotherapy vs. immunotherapy alone). In the era of targeted therapy, many studies have shown significant survival benefit with CRN plus targeted therapy. However, there is no clear level 1 evidence to support this. The ongoing trials (CARMENA and EORTC SURTIME) would perhaps guide us in the way in which we should manage mRCC disease in the future. Maybe we may find some answers on the issues of the effectiveness of

targeted therapy, the timing of CRN and sequencing these treatment arms once the results of these ongoing and future trials are through.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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