# Metastatic Tumours: Cytoreductive Nephrectomy


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## Introduction

Cytoreductive nephrectomy(CRN) is a term applied to the surgical removal of a primary renal cell carcinoma in a patient with established metastatic disease with the intention of potentially prolonging patient survival. It needs to be distinguished from palliative nephrectomy which may also be performed in the metastatic setting where the fundamental purpose is to alleviate symptoms—specifically pain and bleeding.

## History

### *CRN Alone*

CRN emerged as a concept based on observational reports of regression of metastatic disease after nephrectomy. These date back as early as 1917 [1] when a patients metastatic pulmonary disease spontaneously resolved following nephrectomy. Subsequent reports of nephrectomy with metastasectomy in the 1930s [2] provided further impetus to support the concept that metastatic disease could be

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managed with surgery with a potential expectation of improving survival [3]. Many subsequent case reports and small institutional series appeared which supported the concept of both CRN and metastasectomy improving survival in patients with metastatic disease. The actual regression of metastatic disease following CRN was a feature in many reports. In some cases metastatic disease was confirmed by biopsy although many relied on the limited radiological investigations available and subjective interpretation of these. Nevertheless enthusiasm was sustained for CRN as an option for patients with metastatic disease in the absence of any other treatment for metastatic RCC [4–6]. Interestingly, 'immunological' factors were hypothesized as a potential mechanism to account for the systemic response to CRN for metastatic disease. Renal cell cancer is a heavily immunological cancer, and studies demonstrate inhibition or down-regulation of immune competence within the primary tumour and systemically, potentially contributing to progression of metastatic disease [7, 8]. Kawashima and colleagues demonstrated that the higher grade the tumour, the greater the consequent immune dysfunction [9]. Thus the effect of cytoreductive nephrectomy may be to remove the immunological 'sump' of the primary tumour, and well as attenuating the burden of proangiogenic factors the primary tumour secretes which may also potentiate the progression of disease [10]. The potential advantage of CRN was however limited to perhaps a subset of patients. It was not universally adopted given the potential morbidity and mortality of surgery in patients with limited life expectancy. A UK audit of national practice of CN in 2012 demonstrated a complication rate of 23% and 30 day mortality rate of 2% [11].

## *Cytoreductive Nephrectomy in Combination with Systemic Therapy*

Systemic treatment of metastatic RCC emerged during the 1960s with utilisation of both chemotherapy and hormonal manipulation. Results were disappointing with both of these modalities [12, 13]. Consequently this sustained some level of support for CRN despite the fact that the metastatic regression described in case reports reflected anecdotal cases.

During the 1980s cytokine therapy, inducing upregulation of immunological response, emerged as a new and novel systemic therapy applicable to kidney cancer and other malignancies such as melanoma that were resistant to cytotoxic drugs. Both interferon-α and interleukin-2 were introduced with some success for patients with metastatic RCC [14, 15]. The toxicity of these agents, and particularly interleukin-2, was a concern which limited their uptake in many countries. CRN thus remained as an intervention of interest both alone and in combination with these cytokine therapies. The combination was supported by observations suggesting that responses at metastatic sites were more profound than with the primary tumour. CRN also appeared most applicable when the metastatic disease was limited and the primary tumour represented the majority of overall disease burden.

Subsequently two key identical randomised control trials, in North America (SWOG) [16] and Europe (EORTC) [17], published in 2001 established an evidence base for CRN in combination with systemic therapy (IFN). Participants in

both studies had measureable metastatic disease, resectable primary tumours and Eastern Co-operative Oncology Group (ECOG) Performance Status 0 or 1. The basis for including performance status in this study was based on concerns that many patients with poorer performance status would not recovery sufficiently to receive systemic treatment following surgery [18].

These trials collectively demonstrated a survival advantage (13.6 months vs. 7.8 months) when CRN was combined with IFNα compared to IFNα alone. In the SWOG trial, when the patients were stratified by performance status, survival advantage was more dramatic in the ECOG 0 vs. the ECOG 1 group (5.7 vs. 2.1 months). This was not seen in the EORTC trial however.

These trials established initial CRN as the standard of care for appropriate patients with good performance status during the 'Interferon era'. They also influenced trial design and clinical practice for patients presenting with metastatic disease as newer and more effective therapeutic agents were introduced.

## *Tyrosine Kinase Inhibitor (TKI's) ERA*

Shortly after the publication of the CRN trials, a new class of drugs—tyrosine kinase inhibitors (TKI's) emerged. These drugs targeted mediators of angiogenesis including vascular endothelial growth factor (VEGF)—many of which are regulated by the VHL gene which is mutated in clear cell renal cell carcinoma. Clinical trials showed these resulted in improved progression free survival, safety and quality of life compared to cytokine therapy [19]. Cytoreductive nephrectomy continued but TKI's replaced interferon as standard systemic therapy. Initial trials evaluating TKI's had included CRN as a preliminary to systemic therapy as this was viewed as standard practice. This retained CRN within the 'TKI era' management paradigm: In a large retrospective collaborative series, Choueiri and colleagues [20] demonstrated a 10 month survival advantage for those that had upfront surgery. Interestingly a sub-analysis with stratification by Karnofsky performance status (KPS) showed no appreciable benefit if the KPS was <80. The results were widely reproducible and reinforced with a systematic review published in 2016 [21].

The data was retrospective and soiled by selection basis, even though adjustments were made for prognostic factors. This led to two RCTs to evaluate CRN and its impact on patients presenting with metastatic disease treated with TKI's.

## *The CARMENA Trial*

This trial comprised 450 patients enrolled over an 8 year period with a median follow-up of 51 months [22]. It compared the overall survival for patients receiving initial CRN followed by sunitinib (a TKI) to patients receiving sunitinib alone. Eligibility criteria was ECOG performance status 0 and 1, and a metastatic disease burden requiring systemic therapy. It was a non-inferiority study, and reported on an intention-to-treat basis.

The results were surprising: overall survival in the sunitinib only arm was 18 months compared to 13.9 months in the CRN arm, which reached statistical significance. This contrasted to the more favourable outcomes for initial CRN in systematic reviews of large volume retrospective series. A potential flaw of this study was the inclusion of poor risk stratified patients, previously shown not to benefit from CRN with IFN in the earlier RCT's. These patients comprised a significant proportion of the overall number.

Nevertheless the results have challenged the role of CRN in combination with TKI's with the lead author of this trial concluding that "cytoreductive nephrectomy is no longer the standard of care" [23].

This study and its conclusions remains a topic of debate. It has been suggested that several factors have meant that the results can not be generalised to the type of patient that would typically be selected for a CRN [24, 25]

1. Patient selection: a large proportion of these patients (>40%) had poor risk stratification on MSKCC criteria for survival [26]
2. Disease selection: the median number of metastatic sites was 2, with an estimated metastatic proportion of total disease of 40% (based on linear tumour measurements)
3. Completeness of reporting: TNM staging was only reported in 30% of the patients
4. Poor accrual of patients: 450 patients over 8 years amounts to 0.7 patients per centre per year. In the UK in 2012, there were c. 300 cytoreductive nephrectomies; France has a slightly larger population—at the authors own admission, many patients were excluded from the trial as 'too good for CARMENA'
5. Protocol violations: in the surgical arm, 7% did not undergo surgery whilst 18% did not receive sunitinib; whilst in the sunitinib only arm, 17% underwent subsequent nephrectomy, the majority of which were because of excellent systemic treatment response. As a result of this, the analysis of 'per protocol' outcomes in the supplementary data, in contrast to 'intention to treat', showed no difference in median survival

Despite criticism, the trial clearly indicates that for poor risk patients systemic treatment of their metastatic disease is the management priority and CRN is not indicated. The introduction of TKI's as an effective systemic treatment for metastatic RCC may have influenced practice independent of the CARMENA study which has only been recently reported. Poor risk patients may have proceeded to systemic therapy without CRN. This is a potential explanation for the apparent benefit of CRN seen in the large retrospective systematic reviews of outcomes with TKI treatment of metastatic RCC.

## *SURTIME*

The SURTIME trial, another RCT published in 2018 [27] evaluated the timing of CRN in the patient with metastatic disease considered to require systemic therapy at presentation. Patients undergoing initial CRN followed by sunitinib were

compared to those receiving sunitinib for 4 months who then underwent CRN if there was no progression of disease. Patients who underwent CRN in this group comprised those with either stable disease or regression on radiological parameters. Unfortunately only 100 patients were recruited compared to the 458 required for the aim of a superiority analysis. Patients with T3 or higher primary tumours, metastatic disease requiring systemic treatment, and no poor risk disease by Culp criteria were enrolled [28].

On analysis of enrolled patients there was no statistical difference in the primary endpoint (progression free status at 28 weeks). The trial did not have the power to demonstrate an overall superiority of survival on an intention-to-treat basis, although this was evident in the deferred nephrectomy group. This benefit was quite profound, with a median survival of 32.4 months compared to 15 months in those undergoing initial CRN. Caution is required in interpreting the results, as this endpoint was not part of the trial design, and that this benefit was not demonstrated in the per protocol analysis. A further point is that none of the patients in this trial had a metastatic disease burden that would be considered appropriate for initial surveillance, and therefore not typical of patients currently selected for cytoreductive nephrectomy.

This trial remains under significant discussion in reviews and other forums. A common conclusion has been that the results, which have limitations as a consequence of its termination, raise the suggestion that a trial of systemic therapy may serve as a 'litmus test' to select the appropriate patient who may benefit from CRN. Similarly the study suggests that patients who experience rapid progression with systemic therapy may avoid the morbidity of CRN as their outcome will remain poor.

## *Active Surveillance of Metastatic Kidney Cancer*

Active surveillance of low volume asymptomatic metastatic disease as recurrence following initial radical nephrectomy has been adopted by many clinicians following the introduction of TKI's [29]. This is based on the observation that whilst metastatic disease can progress rapidly, it can also behave indolently with extended periods of stability or slow progression. Prospective studies have demonstrated no detriment to survival in patients with oligometastatic disease burdens who have TKI therapy until significant disease progression occurs [30, 31]. This is supported by the point that patients undergoing nephrectomy with initial curative intent but subsequently exhibit metastatic recurrence have effectively had a CRN. Clearly these patients have had sub-clinical metastases at diagnosis—with then slow progression before radiological detection. It logically follows that if a patient presents with low volume metastatic disease a CRN may be an appropriate initial intervention when the clinician is comfortable with surveillance and deferred systemic treatment.

With this approach, patients may avoid exposure to the toxicity of systemic treatment, from which a curative response is exceedingly rare, for significant periods of time. This management paradigm with CRN and deferred treatment should be considered for patients presenting with minimal metastatic burden as an option that is

unlikely to impact on overall survival and reduce treatment related morbidity. This approach has been reported with a median time to progression of 12 months and time to systemic therapy of 14 months following CRN [32].

## Impact of the Immuno-Oncology (IO) Era

The introduction IO drugs for metastatic kidney cancer has created further uncertainty with respect to the role of CRN. CRN clearly conferred a survival advantage, albeit modest, for good performance status patients for patients treated with IFN—a cytokine immune stimulant. Current IO agents are more specific in the effect and clearly rather more effective. It remains to be determined whether CRN will amplify the effects of these drugs in appropriate patients as it did with IFN—a rather crude and perhaps somewhat ineffective immunotherapy agent.

Currently nivolumab, ipilimumab and pembrolizumab are the most widely utilised of the many drugs available. These can be used alone, in combination with another IO drug or a TKI. As with the previous TKI trials, IO studies have included significant numbers of patients with prior nephrectomy. In CHECKMATE 214 [33], one of the initial studies demonstrating superiority of IO over TKI's—80% of patients had previous nephrectomy. Whilst TKI's appear to fundamentally be life prolonging—IO may result in profound responses and quite possibly complete responses in some patients.

Given both the efficacy and the mechanistic differences of IO agents with previous systemic treatments the role of CRN remains to be determined. Currently recent retrospective studies [34, 35] support the continued use of initial CRN although more trials are clearly needed and planned. Theoretically if 'priming' the immune system with the original tumour was important for a favourable response to IO treatment, an inferior response would be anticipated in patients undergoing initial CRN (prior to IO treatment) compared to CRN and TKI group. This has not been reported to date. The morbidity of IO may be substantial and overall it appears rather more toxic than TKIs. Thus management strategies that defer systemic therapy as long as possible may need to be considered. CRN is thus likely to continue as an initial step in patients with low volume metastatic disease as well as specific subsets of patients who require systemic therapy. Clinical trials will clearly be required to precisely define suitable patients.

## Selecting the Candidate for Cytoreductive Nephrectomy

Metastatic RCC has a varied clinical course encompassing a spectrum from rapid progression to slow attenuated or intermittent progression. Evidence suggests that surgery has a limited role with the former but is likely to benefit the latter. Local management of tumour sites, including the primary disease, may prevent or delay the need for systemic treatments. CRN will thus remain as a treatment modality in patients with low volume metastatic disease likely to experience slow progression

and patients who exhibit significant responses to systemic therapies. Case selection will be critical—which will require effective objective criteria to predict the pattern of progression and/or treatment response in individual patients.

Various tools have been developed including the MSKCC and the more recent IMDC risk stratification models [26, 36] to select patients for surgery. The parameters for IMDC are shown in Table 1

These models have been based on oncology tools developed to predict survival in patients who developed metastatic recurrence after initial nephrectomy who were treated with TKI's. These models include a number of parameters in patient selection for surgery including:

1. Good performance status
2. Expectation of slow progression of metastatic disease
3. Paraneoplastic syndrome indicating poor outcome (haematology disruption)

Several other major cancer centres have published more surgically orientated stratification models, including factors such as number of metastatic sites, specific metastatic sites (liver, bone, brain, lymph nodes), constitutional symptoms, degree of local progression, grade and necrosis within the tumour [28, 37–39]. In a pragmatic investigation [40] an external validation of ten prognostic models, including those previously mentioned was performed. Whilst the performance of all models was similar, none of these are particularly robust or provide tangible advantage in selecting patients for cytoreductive nephrectomy.

Plasma and genomic markers have also been studied to predict survival and systemic treatment response more generally in the metastatic patient. To date none have proven particularly effective although current research suggests that objective criteria are likely to be established through analysis of the genetic phenotypes of individual patients tumours which is discussed in a later section.

## *Other Indications for Cytoreductive Nephrectomy*

There are specific clinical scenarios where nephrectomy, outside the criteria for a cytoreductive or palliative procedure, may be considered. RCC may be associated with intracaval tumour extension and attendant risks of caval obstruction, cardiac failure, hepatic congestion and Budd-Chiari syndrome, and recurrent pulmonary emboli. These factors can preclude patients from systemic treatment. Selected

**Table 1** IMDC risk stratification criteria

| IMDC risk factors | Risk stratification |
|---|---|
| 1. Time from diagnosis to systemic therapy < 1 year<br>2. Karnofsky performance status < 80<br>3. Haemoglobin < low limit normal<br>4. Neutrophils > upper limit normal<br>5. Corrected calcium > upper limit normal<br>6. Platelets > upper limit normal | Favourable—0 risk factors<br>Intermediate—1 or 2 risk factors<br>Poor—3 or more risk factors |

patients who are suitable candidates for surgery may be considered for CRN to facilitate their opportunities of receiving systemic therapy.

Bleeding and pain are future potential complications that may be avoided with initial surgery before systemic therapy has commenced. In the CARMENA study, only 3% of patients who commenced sunitinib without CRN subsequently required emergency nephrectomy for these reasons.

In contrast initial CRN may be beneficial for patients experiencing symptoms—although this would be regarded as a palliative procedure. A study investigating symptom control in metastatic RCC reported symptom resolution or improvement for local and systemic symptoms 43% and 71% respectively with CRN [41, 42]. For local symptoms, resolution was seen in 91%. The risk of surgery must of course be weighed against the control of symptoms which may possibly be achieved by other means. Major complications and mortality with palliative nephrectomy has been reported to be 10% and 3% respectively. There is also a concern that the morbidity of surgery or the delay and subsequent progression may obviate patients from receiving systemic therapy: this has been reported as 12% in some series, but up to 40% in others [43].

It is also uncertain whether nephrectomy will ameliorate paraneoplastic syndromes. Extremely limited evidence is available in the literature regarding improvement in paraneoplastic syndromes after CRN: 81% of patients normalised their calcium after surgery, but in this series of just 11 patients [44]. Anecdotally it has suggested that patients most likely to experience resolution or improvement of a paraneoplastic symptoms are those with a very large primary tumour burden and minimal volume metastatic disease.

## Future Work

Defining patients who will benefit from CRN will remain an ongoing challenge as systemic therapies continue to evolve. Case selection currently is dependent on clinical features and patient performance status. These largely reflect the burden of disease and the physiological reserve of the patient in undergoing treatment both surgical and systemic. Objective information predicting the behaviour of an individual's tumour is likely to be far more useful.

Within the last 10 years, genomic analysis of RCC has made significant strides in understanding of key genetic mutations in RCC [41, 45]. Preliminary steps have been made in adding genomics parameters to existing risk stratification systems [46].

This work has been extended defining the protracted evolution of RCC which actually spans decades [47]. Progression encompasses sequences of mutations which define different patterns of tumour behaviour. Individual patients' primary disease consequently contains multiple discrete tumour clones—with metastatic disease evolving from a limited number of these [48].

Ultimately detailed genomic analysis of metastatic disease sites may define patients who will benefit clinically from a CRN as well as whether this should be

prior to or after commencement of systemic therapy. Preliminary CRN may also be considered to allow a detailed genomic analysis of the clones within the primary to select the most appropriate systemic therapy for an individual patient, which might not be apparent from a biopsy.

Thus selection of patients for CRN may be driven by tumour specific genomic parameters rather than patient clinical features.

## Conclusion

Whereas further trials are underway to produce high quality evidence for the use of cytoreductive nephrectomy in the IO era [49, 50], the same problems as those encountered with CARMENA and SURTIME may persist if inclusion criteria does not reflect current selection practice; the data may not be accepted as generalizable. Molecular profiling of metastatic vs primary tumours will allow us to appropriately classify the metastatic RCC patient at presentation and improve the accuracy of existing risk stratification models; we can then decide which deposit of cancer, for which treatment, and when we need to do it.

Currently, we must rely on good clinical judgement for patient selection for CRN with consideration of the following principles:

1. Decisions to be made on a patient by patient basis, with the help of a multidisciplinary team, in particular a consensus opinion between the medical oncologist and urologist
2. Consider which aspect of the disease forms the management priority for the patient, the primary, the individual metastasis or the systemic metastases, and treat those first
3. Heed the lessons of CARMENA—upfront surgery for multi-site metastases on poor risk patients does not improve outcomes
4. Surgery for symptoms and potential complications of the primary tumour remains apposite in maintaining quality of life for many patients

**Key Points**

1. Cytoreductive nephrectomy (CRN) is the surgical removal of a primary renal cell carcinoma in a patient with established metastatic disease with the intention of prolonging patient survival.
2. It was originally adopted after observation that removal of the primary tumour induced regression of metastatic disease, however this is a rare occurrence.
3. In some patients, CRN affords the patient potentially long periods of safe observation, sparing them systemic therapy until their indolent metastatic disease progresses.

4. Randomised controlled trials at the turn of the century demonstrated a survival advantage when given with immunotherapy drugs, such as interferon, compared to using interferon alone.
5. More recent randomised controlled trials have challenged this benefit with more effective targeted therapies available, however there have been problems generalising these findings to clinical practice.
6. As new systemic therapies emerge, the role of CRN may need to be repeatedly re-evaluated.
7. Choosing the appropriate candidate for CRN remains a key challenge. Scoring systems that use clinical factors and patient performance status to predict good outcome remain unreliable and good clinical judgement is still required.
8. Genetic understanding of renal cell carcinoma is developing rapidly and a more objective means of predicting appropriate candidates for cytoreductive nephrectomy will be available.

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