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Review article

The once and future role of cytoreductive nephrectomy

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Abstract

The role of nephrectomy in the setting of metastatic renal cell carcinoma has long been controversial and has continued to evolve over the last two decades. The practice of cytoreductive nephrectomy has only recently been widely accepted following the publication of 2 large multi-center randomized controlled trials that established a survival benefit for those patients undergoing nephrectomy followed by interferon treatment. Half a decade later, the new paradigm looks set to be questioned with the rapid emergence of tyrosine kinase inhibitors (TKIs). This article reviews the evolution of cytoreductive nephrectomy and speculates on its role in the new frontier of molecular targeting for metastatic renal cell carcinoma.

Keywords: Renal cell carcinoma; Tyrosine kinase inhibitors; Cytoreductive nephrectomy; Metastatectomy; Interfon; Interleukin-2

1. Introduction

For many years it has been "the worst of times" for patient outcomes with the medical treatment of metastatic renal cell carcinoma (RCC). Approximately 20% to 30% of RCC patients present with metastases, and the estimated median survival is 6 to 10 months with a 2-year survival in the order of 10% to 20% [1,2]. More recently, the development of a promising new class of drugs that interfere with the signaling mechanism promoting angiogenesis in tumor progression has offered the opportunity to change this. The impact of molecular targeting agents on the management of metastatic RCC has the potential to be profound and the role of surgical intervention in light of this impact will be subject to review in the coming years.

The concept of cytoreductive nephrectomy has evolved significantly over the last 2 decades. It originated from two observations. First, in isolated cases, spontaneous regression of metastases was observed following nephrectomy for the primary tumor. Second, in early trials of immunotherapy, a history of previous nephrectomy appeared to confer a survival advantage. Single center case series were published throughout the 1990s until 2 randomized controlled trials were reported in 2001. They established cytoreductive nephrectomy followed by interferon as the standard of care in metastatic RCC.

Currently, subsequent to the U.S. Food and Drug Administration's approval of sunitinib (SU11248) and sorafenib (BAY 43–9006) for use in metastatic RCC, targeted tyrosine kinase inhibition appears to be rapidly displacing cytokine therapy as first line treatment for metastatic RCC. Progression free survival benefits with sunitinib over interferon as first line systemic therapy and with sorafenib following cytokine failure have already been demonstrated [3,4]. The purpose of this review is to re-evaluate the role of cytoreductive surgery in light of these developments.

2. Single center series

Table 1 represents a selection of single center series illustrating the historic growth of cytoreductive nephrectomy as a prelude to biological response modification (BRM), usually with interferon-α or interleukin-2, throughout the 1990s. These series were notable for their generally small numbers and significant morbidity and mortality. In addition, there was a high rate of failure to complete the original treatment protocol due either to rapid disease progression or surgery-related morbidity. In those who managed to undergo BRM therapy, a variably defined response

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Table 1
Selected single center series of cytoreductive nephrectomies

Study	Number	Peri-operative morbidity + mortality (%)	Response to interferon (%)	Median survival (months)
SWOG 8949 [8]	120 vs. 121	5 + 0.1	3.3 vs. 3.6	11.1 vs. 8.1
EORTC 30947 [9]	42 vs. 43	14 + 2	19 vs. 12	17 vs. 7
Synthesis [11]	162 vs. 164	5[a] + 1.4	6.9 vs. 5.7	13.6 vs. 7.8

[a]Indicates grade 4 toxicity only.

rate was relatively low. Median survival for patients in each of the studies ranged from 12 to 22 months.

These results must be interpreted in the context from which they were derived. Confounding is a significant potential issue that is likely to have resulted in somewhat optimistic outcomes. Many of the studies did not distinguish between effects of treatment on metachronous as opposed to synchronous metastases and they are likely to have selected patients with good performance status and low disease burden as acceptable candidates for surgery, factors important in patient survival regardless of the treatment received [5–7]. Despite these reservations, the growing amount of generally positive data in a disease in which other options were essentially nonexistent led to the design of well powered randomized controlled trials by the South West Oncology Group (SWOG) and the European Organization for Research and Treatment of Cancer (EORTC) to evaluate the efficacy of cytoreductive nephrectomy in combination with immunotherapy, which were published in 2001 [8,9].

3. Randomized controlled trials

The SWOG and EORTC multi-center trials were created to address several questions in relation to cytoreductive nephrectomy followed by interferon based immunotherapy. They were designed with overall survival as the primary endpoint but were intended to provide information on response to systemic treatment, the morbidity and mortality of the surgery, and the impact of surgery on the timing and completion of systemic treatment. Table 2 summarizes the findings of the respective trials.

The protocol for each trial selected patients with good performance status (WHO or SWOG 0 or 1), adequate hepatic, renal, cardiopulmonary and hematological function, and the absence of brain metastases or recent alternative malignancy (see Table 3). It has been pointed out that these criteria may apply to as little as 7% of the metastatic renal cancer outpatient population and the fact that it took 7 years to recruit the study population for these trials tends to support this assertion [10].

The studies did illustrate that for otherwise healthy patients, the morbidity and mortality of cytoreductive nephrectomy is acceptable and that systemic treatment can be initiated within a median of 19 days. They also clearly demonstrated that measurable response to systemic interferon-α treatment is poor and is not improved following nephrectomy. However, median survival times were increased by 3 months in the SWOG trial, 10 months in the EORTC trial, and 5.8 months overall [11]. Unfortunately information on changes in quality of life throughout the trial as well as the actual causes of death were not reported. These data would have contributed meaningfully to the understanding of the symptomatic consequences of surgery for the patient and the way in which leaving the primary tumor in situ impacts upon survival. Subsequently, despite the toxicity and limited efficacy of interferon, the combination with initial surgery has become the standard of care for patients well enough to receive it, and serves now as a suitable control group for comparative trials.

4. The argument for nephrectomy preceding systemic treatment

There are many theoretical benefits to performing nephrectomy prior to starting systemic treatment for metastatic RCC. Palliation of symptoms due either to local

Table 2
Randomized controlled trials of cytoreductive nephrectomy and interferon-α vs. interferon-α alone

Center	Number	Perioperative morbidity + mortality (%)	Number not receiving BRM (%)	Response (%)	Median survival (months)
Cleveland Clinic 1994 [18]	37	16 + 2	22	8	12
Albert Einstein 1995 [28]	30	50 + 17	77	13	15
UCLA 1996 [29]	63	NR + 0	11	34.5	22
NCI 1997, 1999 [30]	195	13 + 1	38	18	NR
Tufts 1997 [31]	28	NR + 4	7	39	21
MDA 2001 [32]	126	NR + 2	4	NR	12

NR = not reported.