Recent Advances in the Application of Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma: A Postprint

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Abstract

Cytoreductive nephrectomy was once recommended for metastatic renal cell carcinoma patients with good performance status during the cytokine therapy era, and it remains an important component of the treatment armamentarium in the targeted therapy era. In recent years, publication of the two prospective studies CARMENA and SURTIME has prompted re-evaluation of the role of cytoreductive nephrectomy in metastatic renal cell carcinoma. This article provides a comprehensive review and discussion of advances in the application of cytoreductive nephrectomy for metastatic renal cell carcinoma, focusing on the results of these two studies and related considerations.

Full Text

Preamble

Recent Advances in the Application of Cytoreductive Nephrectomy in the Treatment of Metastatic Renal Cell Carcinoma

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Abstract

In the interferon era, cytoreductive nephrectomy was recommended for the treatment of patients with good performance status diagnosed with metastatic renal cell carcinoma. After entering the era of targeted therapy, it remains an

important component of the treatment armamentarium for metastatic renal cell carcinoma. With the publication of two prospective studies, CARMENA and SURTIME, the role of cytoreductive nephrectomy in the management of metastatic renal cell carcinoma should be revalued. Based on the results and related considerations of these two studies, we review and discuss the recent progress in the application of cytoreductive nephrectomy in metastatic renal cell carcinoma.

Keywords: renal cell carcinoma; cytoreductive nephrectomy; targeted therapy; prognosis

Renal cell carcinoma (RCC) is a common malignant tumor of the urinary system, with approximately 70% being renal clear cell carcinoma (RCCC) [1], accounting for about 2%-3% of adult malignant tumors [2]. Radical nephrectomy or partial nephrectomy is the preferred treatment for localized renal cancer. However, 25%-40% of patients with localized renal cancer gradually develop recurrence or metastasis after surgery, and approximately 20% of patients have metastatic renal cell carcinoma (mRCC) at initial diagnosis [3]. Cytoreductive nephrectomy (CN) was once recommended for the treatment of mRCC. Although the advent of targeted drugs provided new options for mRCC treatment, cytoreductive nephrectomy still occupies an important position in mRCC management. Recently, with the publication of data from the CARMENA and SURTIME studies, the role of cytoreductive nephrectomy in mRCC treatment has been re-examined. This article focuses on reviewing the recent advances in the application of cytoreductive nephrectomy in mRCC treatment, integrating the results of these two studies.

1. Application of Cytoreductive Nephrectomy in the Cytokine Era

Cytoreductive nephrectomy in mRCC patients can remove the primary tumor, reduce tumor burden, help prolong patient survival, and alleviate tumor-related symptoms and signs. In the cytokine therapy era, studies found that cytoreductive nephrectomy combined with interferon- therapy could improve patient prognosis [4][5], with overall survival (OS) extended by 5.8 months compared to cytokine therapy alone [6]. Consequently, the proportion of mRCC patients undergoing cytoreductive nephrectomy gradually increased from 29% in 1993 to 39% in 2004 [7]. However, complications after cytoreductive nephrectomy can also negatively impact patients.

The SWOG8949 study enrolled 241 patients with metastatic renal cell carcinoma, randomly assigning them to either cytoreductive nephrectomy combined with interferon (IFN) or IFN alone. The results showed that the median OS in the combined therapy group was 11.1 months, compared to 8.1 months in the IFN-alone group. However, the study groups were unbalanced, as patients in the surgery group had better ECOG performance status scores, which may have contributed to the better survival outcomes in the combined therapy group [4]. Another study, EORTC30947, compared 42 patients receiving surgery plus IFN

therapy with 43 patients receiving IFN alone [5]. The results showed OS of 17 months and 7 months, respectively, with a hazard ratio for death of 0.54 (95% CI 0.31-0.94) in the combined therapy group versus the IFN-alone group, suggesting that cytoreductive nephrectomy could improve patient survival. In 2004, Flanigan et al. published a combined analysis of these two studies [6], reporting a median OS of 13.6 months for patients receiving cytoreductive nephrectomy plus IFN therapy versus 7.8 months for those receiving IFN alone (HR 0.69, 95% CI 0.55-0.87). Subgroup analysis by performance status showed that surgery provided survival benefits. Therefore, in the cytokine era, cytoreductive nephrectomy was recommended as the standard treatment for mRCC patients with performance status scores of 0-1.

In 2005, the FDA approved sorafenib for the treatment of advanced metastatic renal cancer, ushering in the era of targeted therapy for renal cancer. Currently, FDA-approved targeted drugs for advanced renal cancer mainly include: vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs), such as sorafenib, sunitinib, pazopanib, axitinib, and cabozantinib; VEGF pathway monoclonal antibodies like bevacizumab; and mammalian target of rapamycin (mTOR) pathway inhibitors (everolimus, temsirolimus, etc.). In the era when targeted therapy is recommended as first-line treatment for advanced renal cancer, cytoreductive nephrectomy still occupies an important position and was once recommended for advanced renal cancer patients with good performance status, low risk, and oligometastatic disease.

Some retrospective studies have shown that cytoreductive nephrectomy combined with VEGFR-TKI therapy provides better survival benefits than targeted therapy alone for advanced renal cancer [8]-[10]. Hanna et al. analyzed data from the National Cancer Database from 2006 to 2013 [10], finding that approximately 35% of mRCC patients underwent cytoreductive nephrectomy. These patients were younger, had lower tumor stage, and better physical condition than non-surgical patients. The analysis showed that cytoreductive nephrectomy could reduce the risk of death in mRCC patients receiving targeted therapy. Heng et al. retrospectively analyzed data from 1,658 mRCC patients receiving targeted therapy [11], of whom 982 underwent cytoreductive nephrectomy. These patients had better performance status and IMDC prognostic scores than the 676 non-surgical patients. After adjustment, the analysis showed that surgical patients had lower mortality risk and better median OS than non-surgical patients. Although these retrospective studies suggest that cytoreductive nephrectomy improves survival in mRCC patients, they lack support from level I evidence. Moreover, patients undergoing cytoreductive nephrectomy often have better performance status, fewer metastatic lesions, and better prognostic risk profiles than non-surgical patients, creating selection bias. Additionally, postoperative complications may delay the initiation of targeted therapy [12], leaving the role of cytoreductive surgery in advanced renal cancer treatment still controversial.

Prognostic models for advanced renal cancer are widely used to evaluate prog-

nosis in targeted therapy for advanced renal cancer and can guide treatment strategy selection through different risk stratifications. The 2002 MSKCC classification system includes five risk factors: Karnofsky performance status score <80%, serum lactate dehydrogenase level >1.5 times the upper limit of normal, hemoglobin below the lower limit of normal, serum calcium >2.5 mmol/L, and time from diagnosis to systemic therapy <1 year. It classifies mRCC patients with 0, 1-2, and 3-5 risk factors into low-, intermediate-, and high-risk groups. Higher MSKCC risk stratification correlates with worse survival outcomes in mRCC patients receiving targeted therapy [13]. The IMDC scoring system is similar to the MSKCC classification system, retaining four risk factors from MSKCC (Karnofsky performance status, hemoglobin, serum calcium, and time from diagnosis to treatment) and adding neutrophil count >upper limit and platelet count >upper limit, comprising six risk factors for risk stratification. It classifies mRCC patients with 0, 1-2, and 3 or more risk factors into low-, intermediate-, and high-risk groups, with higher risk correlating with worse patient survival outcomes [14].

3. Overview of CARMENA and SURTIME Studies

The recently published CARMENA study is a prospective, multicenter, open-label, non-inferiority, randomized controlled trial comparing cytoreductive nephrectomy combined with targeted therapy versus targeted therapy alone for metastatic renal cell carcinoma [15]. The study enrolled 450 mRCC patients eligible for cytoreductive nephrectomy or targeted therapy, without brain metastases, with ECOG scores of 0-1, and no prior systemic therapy. Patients were randomized into two groups: 226 were scheduled to receive sunitinib 3-6 weeks after cytoreductive nephrectomy (though ultimately 16 did not undergo surgery and 40 did not receive medication), and 224 received sunitinib alone (though ultimately 11 did not receive medication and 38 underwent cytoreductive nephrectomy after starting medication). Sunitinib was administered at 50 mg daily for 4 weeks followed by a 2-week break. In the surgery group, 55.6% and 44.4% of patients were MSKCC intermediate- and high-risk, respectively, compared to 58.5% and 41.5% in the non-surgery group. Median tumor size was 8.6 cm and 8.8 cm, respectively, and the number of metastatic lesions was 2 (range 1-5) in both groups.

Intention-to-treat (ITT) analysis showed that the median OS was 18.9 months in the non-surgery group and 13.9 months in the surgery group, with a hazard ratio (HR) for death of 0.89 (95% confidence interval [CI] 0.71-1.10), establishing non-inferiority—meaning sunitinib alone was non-inferior to cytoreductive nephrectomy combined with sunitinib. Per-protocol (PP) analysis also showed that sunitinib alone was non-inferior to the combination. For MSKCC intermediate-risk patients, median OS was 23.4 months in the non-surgery group versus 19.0 months in the surgery group (HR=0.92, 95% CI 0.60-1.24). For MSKCC high-risk patients, median OS was 13.3 months and 10.2 months, respectively (HR=0.86, 95% CI 0.62-1.17). The clinical benefit rate and duration of targeted

therapy tolerance were better with sunitinib alone than with surgery plus sunitinib (47.9% vs 36.6%, P=0.02; 8.5 vs 6.7 months, P=0.04), though objective response rate (ORR) and median progression-free survival (PFS) showed no statistically significant differences. In terms of safety, the sunitinib-alone group had slightly higher rates than the combination group (42.7% vs 32.8%).

The SURTIME study is a prospective, multicenter, open-label, randomized controlled trial investigating the timing of cytoreductive nephrectomy [16]. It enrolled 99 treatment-naive mRCC patients with WHO performance status 0-1, randomly assigned to deferred surgery (49 patients) or immediate surgery (50 patients). The deferred surgery group received sunitinib for 3 cycles before cytoreductive nephrectomy, then resumed targeted therapy 4 weeks postoperatively. The immediate surgery group started sunitinib 4 weeks after cytoreductive nephrectomy. Sunitinib was administered at 50 mg daily for 4 weeks followed by a 2-week break per cycle. Baseline clinical characteristics were similar between groups.

In the deferred surgery group, 40 of 49 patients completed 3 preoperative cycles of sunitinib, with 34 patients experiencing varying degrees of tumor volume reduction (median 13.8%). Eleven patients achieved partial response after targeted therapy, while 14 experienced disease progression. Ultimately, 34 patients underwent cytoreductive nephrectomy, with 26 resuming sunitinib postoperatively; 1 died after surgery, and 7 were no longer suitable for targeted therapy. In the immediate surgery group, 46 of 50 patients underwent cytoreductive nephrectomy, with 40 receiving sunitinib postoperatively; 2 died after surgery, and 4 were no longer suitable for targeted therapy.

ITT analysis showed that the 28-week progression-free survival rates were 43% and 42% in the deferred and immediate surgery groups, respectively, with no statistically significant difference in disease progression risk (HR 0.88, 95% CI 0.56-1.37, P=0.57). Median OS was 32.4 months in the deferred surgery group versus 15.0 months in the immediate surgery group, with a death hazard ratio of 0.57 (95% CI 0.34-0.95, P=0.03). In PP analysis, median OS in the deferred surgery group remained superior to the immediate surgery group, though the difference was not statistically significant. Analysis also showed that patients with disease progression before surgery in the deferred group and those with disease progression within 16 weeks after surgery in the immediate group had poor survival outcomes. The incidence of surgical complications was 53% and 52% in the two groups, respectively.

4. Discussion and Considerations on CARMENA and SURTIME Studies

Both studies are prospective randomized controlled trials that have re-examined the role of cytoreductive nephrectomy in mRCC patient management, with high evidence level and reference value, but they require objective and comprehensive discussion and evaluation. The CARMENA study had a relatively large

sample size and, contrary to previous retrospective studies suggesting that cytoreductive nephrectomy improves outcomes in mRCC patients, concluded that sunitinib alone was non-inferior to cytoreductive nephrectomy combined with sunitinib for MSKCC intermediate- and high-risk patients. The reason may be that retrospective studies have inevitable patient selection bias, with surgical patients having more favorable prognostic factors than non-surgical patients, leading to better survival outcomes in the surgery group [11]. The CARMENA study also noted that the MSKCC high-risk mRCC patients included were those who could tolerate surgery and were in relatively good condition. For MSKCC high-risk patients with poorer performance status, more metastatic lesions, and greater tumor burden, the non-inferiority conclusion of this study may be underestimated, and targeted therapy alone might be superior to surgery plus targeted therapy in this population. Cytoreductive nephrectomy may even have negative effects, as surgical treatment and postoperative complications inevitably delay the initiation of targeted therapy, with some postoperative patients dying before starting targeted therapy, thus missing the opportunity for survival benefits from targeted therapy [17].

However, the CARMENA study does not completely negate the value of cytoreductive nephrectomy. The study population was limited to MSKCC intermediate- and high-risk patients, with nearly half being high-risk—a group that was not originally the best candidate for cytoreductive nephrectomy, which may have limited the impact of cytoreductive nephrectomy on survival outcomes. The CARMENA study itself also noted that some enrolled mRCC patients had very small primary tumors, and the benefits of cytoreductive nephrectomy may not be realized in this patient type, thereby underestimating the value of surgery. Since MSKCC low-risk patients were not included as study subjects, the CARMENA conclusions may not be applicable to this group. Based on previous retrospective studies, cytoreductive nephrectomy may still provide survival benefits for low-risk mRCC patients. Notably, some patients in the sunitinib-alone group of the CARMENA study ultimately underwent cytoreductive nephrectomy, demonstrating that cytoreductive nephrectomy remains an important component of treatment strategies for mRCC patients.

The SURTIME study enrolled mostly MSKCC intermediate-risk patients and had a small sample size with suboptimal completion, limiting the reliability of its conclusions. The results suggest that deferred cytoreductive nephrectomy after sunitinib therapy is safe and may provide better survival benefits than immediate surgery, though this remains to be confirmed. Some studies suggest that preoperative sunitinib therapy creates favorable conditions for surgery, can shrink the primary tumor, enables more complete tumor resection, and may improve surgical resectability, allowing some patients originally considered unresectable to obtain surgical cytoreduction opportunities [18][19]. The SURTIME study proposed that the response to preoperative sunitinib therapy could serve as a prognostic indicator, as patients with progressive disease often have poor prognosis.

The 2019 EAU guidelines incorporated these two prospective studies as references, guiding treatment through risk stratification of mRCC patients: cytoreductive nephrectomy is not recommended for MSKCC high-risk patients; it is not recommended for asymptomatic MSKCC intermediate-risk patients who can receive targeted therapy; deferred cytoreductive nephrectomy may be considered for MSKCC intermediate-risk patients with stable disease or minimal metastases after sunitinib therapy; immediate cytoreductive nephrectomy may be recommended for patients in good physical condition who cannot receive targeted therapy; and for patients with oligometastatic disease, immediate cytoreductive nephrectomy may be performed when metastases are resectable.

Additionally, the EAU guidelines have made new recommendations regarding the role of immunotherapy in mRCC treatment. Since 2010, multiple studies have preliminarily shown that immune checkpoint inhibitors, particularly PD-1/PD-L1 inhibitors, demonstrate encouraging efficacy in mRCC treatment [20]. Motzer et al. published a phase III clinical trial in the New England Journal of Medicine in 2015 comparing nivolumab versus everolimus in mRCC patients with progressive disease after prior therapy [21]. The results showed that the nivolumab group had a median OS of 25 months, with superior survival benefits compared to 19.6 months in the everolimus group (death hazard ratio 0.73), and nivolumab also had better toxicity and safety profiles than everolimus. At the 2017 ESMO conference, the CheckMate214 study was presented, comparing nivolumab plus ipilimumab versus sunitinib as first-line therapy for mRCC. The results showed that for treatment-naive IMDC intermediate- and high-risk mRCC patients, nivolumab plus ipilimumab provided superior survival benefits compared to sunitinib [24]. The 2018 EAU guidelines recommended it as first-line treatment for mRCC, further maturing the immunotherapy era and elevating its status in mRCC treatment. The value of cytoreductive nephrectomy in the immunotherapy era remains to be further explored.

5. Conclusion

In the post-CARMENA era of mRCC treatment, patients should undergo risk stratification. Cytoreductive nephrectomy is not recommended for MSKCC high-risk patients or MSKCC intermediate-risk patients who can receive targeted therapy; these patients should receive targeted therapy alone. Cytoreductive nephrectomy is recommended for patients in good physical condition with oligometastatic disease who cannot receive targeted therapy. We believe that for MSKCC low-risk patients, cytoreductive nephrectomy remains an important treatment strategy. In the current era where targeted therapy has matured and immunotherapy has taken the front stage, there is no one-size-fits-all solution for mRCC treatment. We should avoid a "one-size-fits-all" approach of complete affirmation or negation, and instead pursue individualized and precision treatment based on each patient' s actual condition.

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Note: Figure translations are in progress. See original paper for figures.