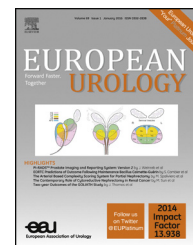




European Association of Urology



EAU Recommendation

The Role of Cytoreductive Nephrectomy: European Association of Urology Recommendations in 2016

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Abstract

Patient summary: After the introduction of systemic targeted therapies, the use of nephrectomy in patients with metastatic renal cell carcinoma has declined. Currently, systemic therapy is offered to more patients first as a means to select those candidates that will likely benefit from removal of their primary tumour. Although studies consistently demonstrate a survival benefit after nephrectomy, most patients with poor risk metastatic disease are unlikely to benefit from surgery. Soon studies will report on the effect of nephrectomy in patients with metastatic disease at diagnosis.

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1. EAU guidelines on cytoreductive nephrectomy

The European Association of Urology (EAU) renal cell carcinoma (RCC) guidelines panel compiles and regularly updates clinical guidelines to provide urologists and oncologists with evidence-based information and recommendations for the management of RCC [1]. The RCC guidelines are based on systematic reviews performed between 2012 and 2015 that are updated using structured literature assessment of studies published since the date of the last search for the systematic reviews. The recommendations are based on the highest available level of evidence, but the current evidence base for cytoreductive nephrectomy (CN) is limited [1]. Tumour nephrectomy is

potentially curative only if all tumour deposits can be excised. For most patients with metastatic disease, CN is palliative and systemic treatments are necessary. In a meta-analysis comparing CN plus immunotherapy versus immunotherapy alone, increased long-term survival was found in patients treated with CN [2]. For CN combined with targeted agents, such as sunitinib or sorafenib, only retrospective confounded data are available, including one systematic review with meta-analysis [3–12] (Table 1). CN is currently recommended in metastatic RCC (mRCC) patients with good performance status (PS), large primary tumours, and low metastatic volume. CN is not recommended in patients with poor PS or International Metastatic Renal-Cell Carcinoma Database Consortium

Table 1 – Retrospective studies comparing cytoreductive nephrectomy versus no nephrectomy including patients treated with vascular endothelial growth factor–targeted therapy

Study (period studied)	Patients, n; CN, no CN	Median OS with CN, mo	Median OS without CN, mo	Statistically significant patient dispositions in favour of CN ($p \leq 0.001$ to $p < 0.05$)
Retrospective, multi-institutional (2004–2008); Choueiri et al., 2011 [3]	314; 201, 113	19.8	9.4	<ul style="list-style-type: none"> • Younger age • Better KPS • One metastatic site • Less calcium
Retrospective, SEER (1993–2010); Conti et al., 2014 [5]	20 104; 6915, 13 189	19	4	<ul style="list-style-type: none"> • Younger age • Male • White • Single
Retrospective, IMDC (2005–2013); Heng et al., 2014 [6]	1658; 982, 676	20.6	9.6	<ul style="list-style-type: none"> • Better IMDC risk • Less non-clear cell RCC • Fewer bone metastases • Fewer liver metastases
Retrospective, multi-institutional (2006–2011); Bamias et al., 2014 [4]	186; 109, 18	23.9	9.0	<ul style="list-style-type: none"> • Younger age • Better PS • Less neutrophilia • Lower LDH • More previous cytokines
Retrospective, SEER (2005–2009); Abern et al., 2014 [9]	2382 [*] ; 1521, 861	20	6	<ul style="list-style-type: none"> • Younger age • Male • White • Single
Retrospective, SEER non-clear cell RCC only (2000–2009); Aizer et al., 2014 [8]	591 ^{**} ; 377, 214	14	6	<ul style="list-style-type: none"> • Younger age • Male • White • Single • Westcoast location
Retrospective, multi-institutional (1999–2009); Mathieu et al., 2015 [11]	351; 298, 53	38.1	16.4	<ul style="list-style-type: none"> • Better MSKCC risk • Better ECOG score
Retrospective population-based registry ^{***} , propensity score matching (2008–2010); De Groot et al, in press [7]	227; 74, 151	17.9	8.8	<ul style="list-style-type: none"> • T stage <T3/T4 • One metastatic site • Fewer bone metastases
Retrospective, National Cancer Data Base, treated with targeted therapy (2006–2013); Hanna et al, in press [12]	15 390; 5374, 10 016	17.1	7.7	<ul style="list-style-type: none"> • Younger age • Privately insured • Academic center • Lower T stage • cN0

CN = cytoreductive nephrectomy; ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal-Cell Carcinoma Database Consortium; KPS = Karnofsky performance status; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; OS = overall survival; PS = performance status; RCC = renal cell carcinoma; SEER = Surveillance, Epidemiology, and End Results registry.

^{*} T3 subset of a total of 7143 patients.

^{**} Subgroup analysis of non-clear cell renal cancer only.

^{***} Only patients receiving sunitinib in first-line treatment.

(IMDC) or Memorial Sloan Kettering Cancer Center (MSKCC) poor-risk disease, with relatively small primary tumours and high metastatic volume, and/or with sarcomatoid tumours.

These guideline recommendations have been based primarily on the paradigm of performing CN in patients with PS 0–1 in the cytokine era. Although systemic therapy has changed profoundly [1,13], CN keeps its place in the treatment algorithm by default until prospective data with higher evidence become available. An argument often expressed to support CN in the targeted therapy era is that 80–90% of patients enrolled in the pivotal trials establishing targeted therapy in first-line treatment underwent a nephrectomy [14–16]; however, most of those patients had a nephrectomy with curative intention for nonmetastatic disease prior to developing metachronous metastases, which might indicate a different tumour biology.

It remains unknown whether CN confers an independent survival benefit or is simply part of a multimodality approach in which the vascular endothelial growth factor (VEGF)–targeting agents are an unknown variable.

2. Ongoing randomised trials

The poor evidence base for CN has been recognised, and randomised trials such as CARMENA (ClinicalTrials.gov identifier NCT00930033) and SURTIME (ClinicalTrials.gov identifier NCT01099423) were opened in 2009 and 2010, respectively, to define the role and the sequence of CN, respectively, in combination with a first-line standard of care: sunitinib, a VEGF receptor (VEGFR) tyrosine kinase inhibitor (TKI) [17,18]. In CARMENA, patients are randomised to upfront nephrectomy followed by sunitinib versus sunitinib alone [17]. SURTIME investigates upfront

nephrectomy followed by sunitinib versus sunitinib followed by nephrectomy in the absence of distant metastatic disease progression [18]. Both trials had difficulties with accrual.

Such difficulties could be partly due to a general decline in incidence of primary metastatic disease observed in Western Europe and North America. The recent literature has consistently reported that approximately 30% of patients diagnosed with a primary renal tumour harbour distant metastasis at diagnosis [19]. However, in a population-based study from the national Swedish RCC registry, the frequency of primary mRCC decreased from 22% in 2005 to 15% in 2010 ($p < 0.001$) [20]. Siegel et al recently reported a 17% rate of primary mRCC in the US cancer statistics in 2014 [21].

In addition, the use of CN has declined since the introduction of targeted therapy, suggesting that more patients will eventually be treated with the primary tumour *in situ*. Using data from the Surveillance, Epidemiology, and End Results (SEER) registry, Conti et al described an increase in the proportion of patients undergoing CN from 29% in 1993 to 39% in 2004 [5]. Since 2005, a modest decrease in the use of CN has become apparent, with a decline to 34% in 2010. One year earlier, Tsao et al published a similar SEER database analysis on stage IV RCC between 2001 and 2008. The use of CN remained stable at 50% between 2001 and 2005 but decreased after the introduction of targeted therapies in 2006 and further declined to 38% in 2008 [22]. A US private insurance database of 610 patients with mRCC from the period 2004–2010 showed a peak in the use of CN of 31.3% in 2005. By 2010, 5 yr later, the CN rate had more than halved to 14.8% ($p = 0.045$) [23]. These data suggest that more patients are currently being treated with targeted therapy with the primary tumour *in situ*.

3. What can we expect from SURTIME and CARMENA?

Of the two randomised trials investigating this issue, SURTIME closed for accrual in April 2015 after it became apparent that the planned number of 458 patients would not be reached. Instead, the trial was terminated after it was postulated that a scientifically valid answer (that could settle the question of the sequence of nephrectomy) might be reached with fewer patients and without amendment of the protocol. The analysis will focus on early postoperative progression in both arms rather than on progression-free survival (PFS), as initially planned. A meta-analysis of two identical phase 2 trials of presurgical sunitinib prior to planned nephrectomy reported a relatively high Response Evaluation Criteria In Solid Tumors progression rate of 37% at the end of the postoperative period in which sunitinib was discontinued [24]. Although most patients had stable disease once sunitinib was reintroduced, it appeared that overall survival (OS) was worse compared with those who did not progress. It remains unclear if this was due to the withdrawal of antiangiogenic therapy before surgery, to the release of growth factors after surgery, or to a combination of both or rather simply to progression due to sunitinib

resistance. Translational research on primary tumour tissue taken from these patients suggests that withdrawal of sunitinib leads to rapid endothelial cell proliferation. This seems to support the hypothesis that a treatment break may trigger progression in some patients, although which ones cannot currently be identified [25,26].

In SURTIME, both arms investigate the status of disease compared with baseline 4 wk after surgery. The trial provides a unique opportunity to investigate the potential rapid progression rate in both arms. Given the magnitude of the observed postoperative progression after presurgical TKI, a statistically significant difference could be demonstrated with the sample size of 98 patients included in SURTIME. In comparison, historical data of postoperative progression after treatment-naïve CN were reported in 2–12% [27,28].

While the final analysis of SURTIME is pending, CARMENA continues to include patients. Retrospective data have shown that patients with IMDC [6] and MSKCC [11] poor risk are unlikely to derive a benefit from CN; therefore, it will be essential to document and explicitly report the prognostic risk score of patients that were included in CARMENA. In 2014, the IMDC released the largest retrospective data set on 1658 patients with synchronous mRCC in whom CN status was adjusted to the number of IMDC prognostic factors in the targeted therapy era [6]. Median OS of patients who underwent CN was 20.6 mo versus 9.5 mo for those who did not ($p < 0.0001$). Admittedly, patients who had CN had better IMDC prognostic risk; however, after adjusting for IMDC risk groups, the hazard ratio of death remained 0.60 (95% confidence interval [CI], 0.52–0.69; $p < 0.001$) in favour of CN. The study is retrospective and must be interpreted with caution, but the results strongly suggest that OS after CN is dependent on prognostic factors.

4. Where to go from here?

The decision to perform CN is not difficult in patients with solitary or oligometastasis because they can potentially be induced into long-term remission by CN and complete resection of metastatic sites or may benefit from a substantial delay of systemic therapy, and associated adverse events, before further progression requires medication [29]. For patients with primary metastatic disease that cannot be completely resected but who present with low-volume disease, surveillance after CN instead of immediate systemic therapy may be an option. A recent retrospective analysis, presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium, showed that the median time to targeted therapy in this population was 14 mo (range: 3–43 mo), with a median OS of 21.5 mo (range: 4–75 mo) [30].

It should be pointed out that these patients with low metastatic burden were not even eligible for CARMENA or SURTIME because there was no urgent or immediate need for systemic therapy. In contrast, retrospective series consistently demonstrated that patients with Eastern Cooperative Oncology Group or World Health Organisation

PS ≥ 2 or Karnofsky PS $< 80\%$ have short OS and poor outcomes after CN [3]. Again, these patients are not eligible for CARMENA and SURTIME based on PS. It is essential to be aware of the exclusion of both groups when the results of both studies will become available. Many mRCC patients, however, have good PS but unresectable asymptomatic metastases at more than one site. Retrospective studies identified potential risk factors that may be used to select patients for CN [31]. A nomogram has been developed to predict the 6- and 12-mo probability of death after CN [32]. Although these surgical risk factors and nomograms discriminate between long- and short-term survivors, one should take into account that they were generated from single-institution databases including patients from the cytokine era and that none of these nomograms have been externally validated.

While the final results of both randomised trials are awaited, a clinically appropriate approach for patients with documented progressive disease requiring immediate VEGFR-targeted therapy may be upfront systemic therapy followed by CN in the absence of distant disease progression. It became evident that targeted agents do not cure mRCC but rather temporarily control both the primary tumour and metastatic sites. Primary tumours respond to VEGF-targeted therapy in $>70\%$ of cases, with a mean reduction in diameter of 9–28% depending on the agents studied [33–36]. A retrospective series of patients with low-risk disease treated without CN demonstrated median OS of up to 30.3 mo [37]. Taken together, these data raise questions about the need to perform CN in an essentially palliative setting. Moreover, mRCC is a clinically and biologically heterogeneous disease; therefore, selecting patients for CN is paramount [38]. In the absence of biomarkers, initiating systemic therapy with the primary tumour *in situ* may be a feature for selection for surgery. After previous single-arm prospective studies with sunitinib, a more recent phase 2 study of 12 wk of pazopanib prior to nephrectomy in patients with metastatic clear cell RCC was reported [39]. Patients were continued on pazopanib after surgery. Overall, 84 of 100 (84%) gained control of disease before planned CN, which was ultimately done in only 61% of patients. The median reduction in the size of the primary tumour was 14% (range: 33–41%). Fourteen patients (22%) had surgical complications. There was one postoperative surgical death. For the whole cohort, the median PFS was 7.4 mo (95% CI, 5.9–9.4) and the median OS was 22.7 mo (95% CI, 14.3 to not evaluable). Patients with MSKCC poor-risk disease or progressive disease prior to surgery had particularly poor outcomes. The authors concluded that this approach was safe and can be considered for patients who need to start systemic therapy quickly. This was particularly true for patients with MSKCC intermediate-risk disease.

5. Conclusions

Since the introduction of targeted therapy, the use of CN has declined. More patients are now likely treated with the primary tumour *in situ*, using systemic therapy to eventually

better select those candidates before surgery. North America and Western Europe observed obvious declines in incidence of synchronous mRCC. Although large retrospective studies have consistently demonstrated a survival benefit after CN, confounding factors preclude definite conclusions except for patients with solitary or oligometastatic disease. However, patients with a short life expectancy or IMDC/MSKCC poor-risk disease are unlikely to benefit from CN. While prospective data are pending, prognostic models and life expectancy estimates help define the role of CN for the individual patient. SURTIME and CARMENA will report soon, and it will be essential to analyse patient characteristics when interpreting the results of these studies for patients with synchronous mRCC to enable us to properly select the best candidates for CN.

Conflicts of interest: A. Bex has received company speaker honoraria from Pfizer; has participated in trials for Pfizer Europe; has participated on advisory boards for GSK and Novartis; is a company consultant for Pfizer and Novartis; and has received grants/research support from Pfizer. B. Ljungberg has received company speaker honoraria from GlaxoSmithKline, Roche, Pfizer, and Novartis; has participated in trials for GlaxoSmithKline, Medivation, Pfizer, and Janssen R&D, Inc.; and is an advisory board member for Pfizer and GSK. T. Powles is a company consultant for and has received grants/research support from Novartis, Pfizer, and GSK; has received company speaker honoraria from Novartis, Pfizer, GSK, and Genentech; and has participated in trials for GSK, Pfizer, BMS, Genentech, and Genentech. H. Van Poppel has nothing to disclose.

References

- [1] Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol* 2015;67:913–24.
- [2] Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol* 2004;171:1071–6.
- [3] Choueiri TK, Xie W, Kollmannsberger C, et al. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. *J Urol* 2011;185:60–6.
- [4] Bamias A, Tzannis K, Papatsoris A, et al. Prognostic significance of cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma treated with first-line sunitinib: a European multiinstitutional study. *Clin Genitourin Cancer* 2014;12:373–83.
- [5] Conti SL, Thomas IC, Hagedorn JC, et al. Utilization of cytoreductive nephrectomy and patient survival in the targeted therapy era. *Int J Cancer* 2014;134:2245–52.
- [6] Heng DY, Wells JC, Rini BI, et al. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol* 2014;66:704–10.
- [7] de Groot S, Redekop WK, Sleijfer S, et al. Survival in patients with primary metastatic renal cell carcinoma treated with sunitinib with or without previous cytoreductive nephrectomy: results from a population-based registry. *Urology* 2016;95:121–7.
- [8] Aizer AA, Urun Y, McKay RR, Kibel AS, Nguyen PL, Choueiri TK. Cytoreductive nephrectomy in patients with metastatic non-clear-cell renal cell carcinoma (RCC). *BJU Int* 2014;113:E67–74.
- [9] Abern MR, Scosyrev E, Tsivian M, Messing EM, Polascik TJ, Dudek AZ. Survival of patients undergoing cytoreductive surgery for metastatic renal cell carcinoma in the targeted-therapy era. *Anticancer Res* 2014;34:2405–11.

- [10] Petrelli F, Coiu A, Vavassori I, et al. Cytoreductive nephrectomy in metastatic renal cell carcinoma treated with targeted therapies: a systematic review with a meta-analysis. *Clin Genitourin Cancer*. In press. <http://dx.doi.org/10.1016/j.clgc.2016.04.001>.
- [11] Mathieu R, Pignot G, Ingles A, et al. Nephrectomy improves overall survival in patients with metastatic renal cell carcinoma in cases of favorable MSKCC or ECOG prognostic features. *Urol Oncol* 2015;33:339.e9–15.
- [12] Hanna N, Sun M, Meyer CP, et al. Survival analyses of metastatic renal cancer patients treated with targeted therapy with or without cytoreductive nephrectomy: a National Cancer Data Base study [abstract]. *J Clin Oncol*. In press. <http://dx.doi.org/10.1200/JCO.2016.66.7931>.
- [13] Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25(Suppl 3):iii49–56.
- [14] Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *J Clin Oncol* 2010;28:2144–50.
- [15] Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356:125–34.
- [16] Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356:115–24.
- [17] Clinical trial to assess the importance of nephrectomy (CARMENA). *ClinicalTrials.gov* Web site. <http://clinicaltrials.gov/ct2/show/NCT00930033>. Accessed July 28, 2010.
- [18] Immediate surgery or surgery after sunitinib malate in treating patients with metastatic kidney cancer (SURTIME). *ClinicalTrials.gov* Web site. <http://clinicaltrials.gov/ct2/show/NCT01099423>. Accessed May 5, 2010.
- [19] Flanigan RC. Debulking nephrectomy in metastatic renal cancer. *Clin Cancer Res* 2004;10:6335s–41s.
- [20] Thorstenson A, Bergman M, Scherman-Plogell AH, et al. Tumour characteristics and surgical treatment of renal cell carcinoma in Sweden 2005–2010: a population-based study from the national Swedish kidney cancer register. *Scand J Urol* 2014;48:231–8.
- [21] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9–29.
- [22] Tsao CK, Small AC, Kates M, et al. Cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy in the United States: a SEER analysis. *World J Urol* 2013;31:1535–9.
- [23] Psutka SP, Kim SP, Gross CP, et al. The impact of targeted therapy on management of metastatic renal cell carcinoma: trends in systemic therapy and cytoreductive nephrectomy utilization. *Urology* 2015;85:442–50.
- [24] Powles T, Kayani I, Sharpe K, et al. A prospective evaluation of VEGF-targeted treatment cessation in metastatic clear cell renal cancer. *Ann Oncol* 2013;24:2098–103.
- [25] Griffioen AW, Mans LA, de Graaf AM, et al. Rapid angiogenesis onset after discontinuation of sunitinib treatment of renal cell carcinoma patients. *Clin Cancer Res* 2012;18:3961–71.
- [26] Sharpe K, Stewart GD, Mackay A, et al. The effect of VEGF-targeted therapy on biomarker expression in sequential tissue from patients with metastatic clear cell renal cancer. *Clin Cancer Res* 2013;19:6924–34.
- [27] Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001;345:1655–9.
- [28] Kutikov A, Uzzo RG, Caraway A, et al. Use of systemic therapy and factors affecting survival for patients undergoing cytoreductive nephrectomy. *BJU Int* 2010;106:218–23.
- [29] Albiges L, Oudard S, Negrier S, et al. Complete remission with tyrosine kinase inhibitors in renal cell carcinoma. *J Clin Oncol* 2012;30:482–7.
- [30] Bex A, de Bruijn R, Noe A, Blank CU, Horenblas S, Haanen JB. Time to targeted therapy after cytoreductive nephrectomy (CN) and surveillance in patients with synchronous unresectable metastases of renal cell carcinoma (RCC). *J Clin Oncol* 2016;34(Suppl 2S), abstract 604.
- [31] Culp SH, Tannir NM, Abel EJ, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? *Cancer* 2010;116:3378–88.
- [32] Margulis V, Shariat SF, Rapoport Y, et al. Development of accurate models for individualized prediction of survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. *Eur Urol* 2013;63:947–52.
- [33] Abel EJ, Culp SH, Tannir NM, et al. Primary tumor response to targeted agents in patients with metastatic renal cell carcinoma. *Eur Urol* 2011;59:10–5.
- [34] Cowey CL, Amin C, Pruthi RS, et al. Neoadjuvant clinical trial with sorafenib for patients with stage II or higher renal cell carcinoma. *J Clin Oncol* 2010;28:1502–7.
- [35] van der Veldt AA, Meijerink MR, van den Eertwegh AJ, et al. Sunitinib for treatment of advanced renal cell cancer: primary tumor response. *Clin Cancer Res* 2008;14:2431–6.
- [36] Karam JA, Devine CE, Urbauer DL, et al. Phase 2 trial of neoadjuvant axitinib in patients with locally advanced nonmetastatic clear cell renal cell carcinoma. *Eur Urol* 2014;66:874–80.
- [37] Richey SL, Culp SH, Jonasch E, et al. Outcome of patients with metastatic renal cell carcinoma treated with targeted therapy without cytoreductive nephrectomy. *Ann Oncol* 2011;22:1048–53.
- [38] Bex A, Powles T. Selecting patients for cytoreductive nephrectomy in advanced renal cell carcinoma: who and when. *Expert Rev Anticancer Ther* 2012;12:787–97.
- [39] Powles T, Sarwar N, Stockdale A, et al. Safety and efficacy of pazopanib therapy prior to planned nephrectomy in metastatic clear cell renal cancer. *JAMA Oncol*. In press. <http://dx.doi.org/10.1001/jamaoncol.2016.1197>.