



# 1 The value of cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy.

You D, Jeong IG, Ahn JH, Lee DH, Lee JL, Hong JH, Ahn H, Kim CS.  
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The article of Dalsan You et al. is interesting because it addresses and discusses the important controversial question of the necessity for cytoreductive nephrectomy in the era of targeted therapy. Obviously, the article does not provide an answer with the retrospective matched analysis but fuels the ongoing controversy. Currently, two international phase III trials are ongoing of which the Clinical Trial to Assess the Importance of Nephrectomy (CARMENA) focuses on the role of cytoreductive nephrectomy {1} and the European Organization for Research and Treatment of Cancer (EORTC) 30073 on its sequence in combination with targeted agents {2}. Collectively, both trials should be able to answer these important questions.

The authors reviewed the records of 78 patients treated with targeted therapy between 2006 and 2009 of whom 81-88% received sunitinib. They then compared 45 patients who were treated with upfront therapy to 33 patients who received targeted therapy only. They tried to match the two groups and estimated progression-free and overall survival using Kaplan-Meier curves. Finally, a univariate Cox proportional hazard regression model was used to estimate the prognostic significance for each variable, which was followed by a multivariate analysis. Not surprisingly, prognostic factors were Karnofsky performance status and sarcomatoid features. Median progression-free survival was 11.7 months and 9.0 months in the nephrectomy and no-nephrectomy groups ( $p=0.270$ ) and 21.6 months versus 13.9 months for median overall survival ( $p=0.128$ ), respectively.

The authors concluded that they found no significant differences between the two groups. However, at close scrutiny, it is obvious that this analysis suffers from the well-known inherent biases of retrospective patient evaluations. In the surgery group, the percentage of patients with more than one metastatic site was 42% while it was 55% in the drug treatment-only group. A total of 91% presented with symptoms in the drug treatment-only group versus 86% in the surgery group. Most importantly, 36% of the no-nephrectomy group had a Karnofsky of  $<80$  versus only 23% in the surgery group. As expected, sarcomatoid features were more frequent (13% versus 3%) in the nephrectomy group, which is a result of better histopathological evaluation carried out on the entire specimen. Most strikingly, however, we may observe that there is a survival difference that does not reach significance in the small groups that were compared. The smaller the numbers, the larger the confidence intervals and  $p$  values. It is tempting to believe that this difference could have been significant with higher numbers involved as has been demonstrated recently by another landmark retrospective evaluation on cytoreductive nephrectomy by Choueiri et al. {3}.

Collectively and scientifically, these data cannot replace the need for a phase III trial formally comparing nephrectomy followed by targeted agents versus targeted agents alone. However, they suggest that the future question on cytoreductive nephrectomy will most likely circle around its sequence in a multimodality concept, trying to identify 'in whom' and 'when' to perform surgery rather than its overall necessity.

### References

1. "Clinical Trial to Assess the Importance of Nephrectomy (CARMENA)." (Estimated study completion date: May 2013). Clinical trial details can be found [here](#) (Accessed 27 April 2011).
2. "Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer." (estimated primary completion date: October 2014). Clinical trial details can be found [here](#) (Accessed 27 April 2011).
3. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy.  
Choueiri TK, Xie W, Kollmannsberger C, North S, ..., Lampard JG, McDermott DF, Rini BI, Heng DY. J Urol 2011 Jan; 1(185):60-6  
PMID: 21074201

### Disclosures

None declared

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### Abstract:

We evaluated the value of cytoreductive nephrectomy in patients with metastatic renal cell carcinoma in the targeted therapy era. We reviewed the records of 78 patients treated with targeted therapy for metastatic renal cell carcinoma between 2006 and 2009. A total of 45 patients underwent cytoreductive nephrectomy followed by targeted therapy (cytoreductive nephrectomy group) and 33 were treated with targeted therapy alone (nontoreductive nephrectomy group). We estimated progression-free and overall survival using Kaplan-Meier curves. The prognostic significance of each variable was estimated with a Cox proportional hazards regression model. Clinicopathological variables did not differ in the 2 groups except for Karnofsky performance status and sarcomatoid feature. The treatment response rate did not differ in the 2 groups (23.1% vs 30.3%,  $p = 0.488$ ). Median progression-free survival was 11.7 and 9.0 months in the cytoreductive and nontoreductive nephrectomy groups ( $p = 0.270$ ), and median overall survival was 21.6 and 13.9 months, respectively ( $p = 0.128$ ). On multivariate analysis Karnofsky performance status (HR 2.9, 95% CI 1.4-5.7,  $p = 0.003$ ) and sarcomatoid features (HR 2.9, 95% CI 1.3-6.7,  $p = 0.013$ ) were independent predictors of progression-free survival. Karnofsky performance status (HR 3.3, 95% CI 1.7-6.5,  $p = 0.001$ ), sarcomatoid features (HR 2.7, 95% CI 1.2-6.2,  $p = 0.021$ ) and liver metastasis (HR 2.7, 95%

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