# Cytoreductive nephrectomy in the tyrosine kinase inhibitor era: a question that may never be answered

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**Key words:** renal cell cancer; clinical trials; cytoreductive; nephrectomy; tyrosine kinase inhibitors; sunitinib; immunotherapy

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**Word count**: 1013 words

Renal cancer surgeons are acutely aware of the pre-eminent data from the immunotherapy era demonstrating a significant survival advantage for patients with metastatic renal cell cancer (mRCC) having cytoreductive nephrectomy (CNx) prior to IFN-alpha treatment [1,2]. However, oncological treatments given to patients with mRCC have radically changed in the current era where pan-tyrosine kinase inhibitors (TKIs) and those specifically targeting VEGF or mTOR are used. In 2009/2010 the urological surgery community widely supported the launch of two randomised controlled trials that aimed to assess the place of CNx in mRCC patients treated with TKIs, as well as assessing the timing of the CNx in relation to TKI administration. In the French CARMENA trial (NCT00930033), patients were to be randomised to CNx and sunitinib *vs* sunitinib alone without CNx (supplemental figure 1). In the EORTC sponsored SURTIME trial (EORTC 30073; NCT01099423), the sequencing of drug and surgical therapies was to be assessed. Patients were randomised to sunitinib followed by CNx and subsequent sunitinib *vs* CNx followed by sunitinib (supplemental figure 2). However, recruitment to these two studies has proven to be hugely challenging.

After initial robust recruitment in France, CARMENA was opened to recruitment in the UK in May 2011. A total of 26 sites around the UK were opened for CARMENA recruitment. However, in 2014 CARMENA was closed to recruitment in the UK, as over four years only 14 patients were recruited. However, the CARMENA study does continue to recruit slowly in France (411 of 576 patients recruited) and it is likely to complete recruitment in September 2017; the study is estimated to end 6 years later than originally planned. In an attempt to try and determine why this study failed to recruit in a nation with robust trials infrastructure an investigator questionnaire was

sent to the UK investigators. Responses indicated that there was a lack of patient and clinician equipoise and inability of the clinical team to convince patients to be randomised (see box 1). Within the investigator questionnaire, 34 varied mRCC clinical scenarios were described, with investigators asked if they would recommend surgery, drug treatment, best supportive care or entry into CARMENA. Of the 17 respondents (65% response rate), the 5 urologists gave a median of 20 of the scenarios (range=11-22) where their preferred management strategy would be CARMENA and the 12 oncologists gave a median of 8.5 CARMENA scenarios (range=6-19). Thus urologists appeared to have greater levels of equipoise for the study. However, if there is one key individual within the clinical team who lacks equipoise this is usually transferred to the patient making recruitment more challenging.

The SURTIME study has also been hugely challenging with poor recruitment in many centres. Efforts were made by the EORTC to improve accrual by online education tools and regular updates. Accrual was strongest in the Netherlands and Canada and best in centres with a main focus on RCC management, where study eligibility was discussed at multidisciplinary tumour boards with urologists and oncologists together. However, SURTIME eligibility criteria were complex and were considered among the main reasons for the poor accrual. This was especially true for smaller centres, where small numbers of patients precluded experience with the entry criteria from being gained. In addition, despite surgery and therapy being offered in both arms, it proved difficult to convince patients to be randomised. The study closed early in 2016 and is likely underpowered to show differences in the primary and secondary endpoints of PFS and OS but may answer the question of rapid progression after pretreatment and interruption for surgery.

As such, the main hope for level 1 evidence regarding the place of CNx in metastatic kidney cancer in the TKI era comes from recruitment to CARMENA study by the French team. However, there are some concerns that this study will only answer the question of whether both arms are “equivalent”; 1134 patients would need to be recruited to be able to determine if either arm was deleterious. As such, it maybe that lower levels of evidence, which suggest CNx is beneficial in selected situation such as those patients predicted to have greater than 1 year life expectancy, are the best we will have to answer this common clinical dilemma [3]. Concerningly, there is evidence that CNx utilisation is now underutilised, especially in non-academic centres, Black or uninsured patients. This underutilisation of CNx was associated with a 10 month worse survival from mRCC [4].

However, recruitment issues with surgical trials are not a urology specific phenomenon. It has been recognised for a number of years that randomised controlled trials in surgery are exceedingly challenging for a number of reasons [5,6]: surgeon and patient equipoise, perceived threat to surgeon’s personal interests, lack of funding, infrastructure and experience in data collection, operative learning curves, and blinding. Indeed, a recent study revealed that 1 in 5 surgical randomised controlled trials was stopped early and 1 in 3 completed trials did not publish after a median of 4.9 years [7]. The commonest reason for discontinuation was, as in the example of SURTIME, poor recruitment. Numerous initiatives have been tried to improve recruitment to surgical RCTs and are currently ongoing to improve renal cancer surgery related trials but it is clear that there is not one solution that will improve the situation (box 2). As such, in addition to the multiple sensible measures to improve recruitment once the trial has opened it is now recommended that in any renal cancer surgery related RCT a feasibility or pilot study in a limited number of patients and

centres be instigated prior to launching the main trial. The results of successful feasibility/pilot studies will allow the launch of a fully powered study, may influence the power calculation for the full study and provide a cadre of engaged urologists to deliver future clinical trials.

There are signs that in surgery in general the tide is changing in terms of delivery of successful RCTs [8]. Despite this, as we move into RCC immunotherapy era v2, it is likely that we will never answer the question of the place of CNx in patients treated with TKIs.

## Acknowledgements

CARMENA is sponsored by Assistance Publique-Hôpitaux de Paris (APHP). CARMENA-UK was funded by Cancer Research UK and administered by CRUK Clinical Trials Unit, The Beatson West of Scotland Cancer Centre, Glasgow. SURTIME was sponsored by EORTC.

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**Box 1.** Selection of quotes from investigator questionnaire, illustrating lack of clinician and patient equipoise.

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| ‘Randomisation is difficult and if offered surgery as a possible treatment, most patients decided to have it off trial’ |
| ‘Relatively few patients with clinical equipoise’ |
| ‘Patient choice was our main failure’ |
| ‘Patients unwilling to be randomised between surgical and non-surgical option. Patients often have strong views as to whether they would want to undergo surgery or not in a palliative setting.’ |
| ‘There was rarely equipoise at MDT discussion’ |
| ‘Unwillingness to recruit due to surgeon/oncology bias.’ |
| ‘Many patients I saw either "obviously" needed a nephrectomy or "obviously" needed oncology. I did not want to delay their treatment.’ |

**Box 2.** Recommendations for future surgery related RCTs

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| Canvassing of the speciality regarding key questions for clinical trials e.g. using Delphi process |
| Iterative process of discussion with NCRI Clinical Studies Group during development |
| Initial pilot or feasibility study (refine recruitment procedures and inform recruiter training by: piloting recruitment materials, determine reason for screening failures) |
| Consideration of clinical nurse specialist providing information in unbiased manner with enough time for full discussion |
| Confirm commitment and explicitly make the case for equipoise with potential investigators at each site by interview process |
| Education and training programme for recruiters |
| Ensure clear ‘reward’ process (i.e. authorship rights, research nurse funding) for high recruiters |