Adjuvant therapy for locally advanced renal cell cancer: a systematic review with meta-analysis

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CRD summary
The authors concluded that available data provided no support for the hypothesis that the agents studied provided any clinical benefit for renal cancer patients and they increased the risk of toxic effects. The conclusions appear reliable, although likely language bias and incomplete reporting of study details suggest a need for some caution.

Authors’ objectives
To assess the efficacy of adjuvant therapy in patients who undergo surgical resection for renal cell cancer.

Searching
PubMed, EMBASE, LILACS, ClinicalTrials.gov and The Cochrane Library were searched (from database inception until June 2010). Search terms were reported. Only trials published or presented in English were considered. American Society of Clinical Oncology, American Urological Association, European Cancer Organisation and European Society for Medical Oncology meetings were searched. Reference lists of relevant reviews and articles were handsearched.

Study selection
Randomised controlled trials (RCTs) that compared post-surgical therapy versus no further active therapy (placebo or observation) in patients who underwent surgery for renal cell cancer (any histological type) with no sign of metastases and rendered disease free after radical surgery were eligible for inclusion. Trials that enrolled patients with metastatic and nonmetastatic disease were considered only where separate data on non-metastatic patients was provided. Trials that used radiation as adjuvant therapy were excluded. Outcome measures were overall survival, disease-free survival and severe toxicities.

Six trials were conducted in Europe, three in USA and one in Japan. Trials enrolled high-risk patients: about 60% were diagnosed with lymph node disease; 86% were diagnosed with pT2 or more advanced disease; and none had previously received systemic therapy. Treatments evaluated included: vaccine therapy (three trials), interleukin/interferon therapy without high dose therapy (three trials), biochemotherapy (one trial), thalidomide (one trial) and chemotherapy alone (one trial).

Two reviewers independently assessed studies for inclusion; differences were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed study quality by considering generation and concealment of sequence of randomisation, blinding, use of intention-to-treat analysis, use of placebo and sources of funding.

Data extraction
Two reviewers independently extracted data to enable calculation of risk ratios (RRs), hazard ratios (HRs), odds ratios (ORs) and their 95% confidence intervals (CIs). Disagreements were resolved by involvement of a third reviewer. Authors of primary studies were contacted for further information where necessary.

Methods of synthesis
Pooled risk ratios, hazard ratios, odds ratios and corresponding 95% CIs were calculated using fixed-effects meta-analysis. Heterogeneity was assessed using $X^2$ and $I^2$. Effects of different strategies of adjuvant treatment were assessed separately. Risk of toxicity was compared using the number needed to harm (NNH). Sensitivity analysis was performed to assess effects of dimensions of study quality on results. Subgroup analysis was conducted to assess the effects of different therapies (hormonal, biochemotherapy, chemotherapy, vaccine and immunotherapy) on survival and safety. Publication bias was assessed using Egger’s test.

Results of the review
Ten RCTs (2,609 participants) were included. None of the trials were placebo-controlled double-blind trials.

No significant difference was found between adjuvant therapy compared to no treatment on overall survival (HR 1.07, 95% CI 0.89 to 1.28, I²=0%; six RCTs) and disease-free survival (HR 1.03, 95% CI 0.87 to 1.21, I²=26%; nine RCTs) outcomes. Subgroup analysis of different adjuvant therapies (immunotherapy, vaccines, biochemotherapy and hormone therapy) revealed no significant effects on survival outcomes.

Vaccine and immunotherapy were reported to cause mild but frequent skin induration, injection site pain and flu-like symptoms. In one trial, vaccine therapy when compared to no treatment was associated with a significantly higher risk of grade 3/4 neutropenia (RR 62.33, p=0.004) but no effect was found on anaemia.

No evidence of publication bias was found.

**Authors' conclusions**
Available data provided no support for the hypothesis that the agents studied provided any clinical benefit for renal cancer patients and they increased the risk of toxic effects. Until on-going trials yielded results, no adjuvant therapy could be recommended for patients who underwent surgical resection for renal cell cancer.

**CRD commentary**
The review addressed a clearly stated question. Several electronic databases and sources of grey literature were searched, which minimised potential publication bias. Only published papers in English were considered and this raised the possibility of language bias. Study selection, data extraction and validity assessment were performed in duplicate, which minimised likely biases and errors.

Risk of bias was assessed using appropriate quality domains, but results were not fully reported. Statistical combination of results was appropriate given an absence of evidence of heterogeneity. Details of included studies and results of study quality assessment could not be confirmed as summary tables were not accessible.

The authors’ conclusions appear reliable, although likely language bias and incomplete reporting of study details suggest a need for some caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that until on-going RCTs on targeted therapies yielded results, no adjuvant therapy could be recommended for patients who underwent surgical resection for renal cell cancer.

**Research:** The authors stated that RCTs to investigate targeted adjuvant therapies were on-going (S-TRAC: sunitinib treatment of renal adjuvant cancer; SORCE: sorafenib in treating patients at risk of relapse after undergoing surgery to remove kidney cancer and ASSURE: adjuvant sorafenib or sunitinib for unfavourable renal carcinoma).

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