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Urologic Oncology: Seminars and Original Investigations ▮ (2017) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Original article

Adjuvant therapy for locally advanced renal cell carcinoma: A meta-analysis and systematic review

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Received 14 June 2017; received in revised form 15 September 2017; accepted 2 October 2017

Abstract

Objectives: Many adjuvant therapies have been widely used in an attempt to reduce the local recurrence or distant metastasis of locally advanced renal cell carcinoma (RCC) after surgical resection. However, the benefits of adjuvant therapy remain controversial. Thus, we performed this study to analyze the role and safety of adjuvant therapy in renal cancer setting.

Methods and methods: We comprehensively searched PubMed, EMBASE, Web of Science, and the Cochrane Library for published randomized controlled trials comparing adjuvant therapy (chemotherapy, vaccine therapy, immune therapy, and targeted therapy) versus no active treatment after surgery among patients with locoregional RCC. Outcomes of interest were disease-free survival, overall survival, and severe toxicities. Different kinds of adjuvant therapy were evaluated separately.

Results: Twelve studies (5,936 patients) were included in the present analysis. Adjuvant therapy did not contribute to overall survival (HR = 1.04; 95% CI: 0.95–1.15; $P = 0.395$; $I^2 = 0\%$) or disease-free survival (HR = 1.00; 95% CI: 0.92–1.08; $P = 0.971$; $I^2 = 35\%$) when compared to placebo or observation. No survival benefit was observed according to subgroup analyses (targeted therapy, vaccine therapy, and immune therapy). Moreover, adjuvant therapy increased obviously the risk of toxicities.

Conclusions: The addition of adjuvant therapy provided no survival benefit but increased the rates of adverse events for locally advanced RCC patients.

Keywords: Adjuvant therapy; Renal cell carcinoma; Meta-analysis

1. Introduction

Worldwide, about 300,000 new cases of kidney cancer are diagnosed yearly nowadays [1,2], and 70% of patients are presented with locally advanced disease [3], which is potentially curable by radical surgical resection alone [4]. Nevertheless, more than 40% of patients will ultimately develop tumor recurrence or distant metastasis, the majority within 5 years [5].

Historically, many adjuvant therapies have been used in an attempt to improve outcomes for locally advanced renal cell carcinoma (RCC) patients. The effect of postoperative radiation has been studied and, overall, has no impact on disease-free survival (DFS) or overall survival (OS) [6–8]. Trials of adjuvant immunotherapy using interferon-α [9–12] or a variety of tumor cell-based vaccines [13–17] have been disappointing, and no improvement in OS has been reported. Over the past decade, several large, multicenter phase 3 trials have been reported [18,19] or are underway evaluating targeted agents in adjuvant setting.

A recent report [19] suggests that sunitinib, an oral multikinase inhibitor, may be effective as adjuvant therapy. However, it was downgraded because of the lack of mature

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http://dx.doi.org/10.1016/j.urolonc.2017.10.001
1078-1439/

survival data. Thus, it was underpowered to reconcile the conflicting results. In view of this, there is a focus of attention in developing well-tolerated adjuvant therapies for patients at high risk of recurrence following resection of localized RCC.

In the present study, as such, we carried out a systematic review and meta-analysis of randomized trials to clear the efficacy and safety of adjuvant therapy in locally advanced RCC after surgery.

2. Materials and methods

2.1. Search strategy

We comprehensively searched PubMed, EMBASE, Web of Science, and the Cochrane Library for relevant studies before 23 April 2017. The following sensitive terms were used to find eligible trials: "kidney" or "renal" and "cancer" or "tumor" or "carcinoma" or "neoplasm" or "mass" and "adjuvant therapy" or "adjuvant treatment" or "adjuvant." In addition, references of systematic reviews in the background search and references of suitable papers were hand searched.

2.2. Selection criteria

Randomized controlled trials (RCTs), comparing adjuvant therapy (chemotherapy, vaccine therapy, immune therapy, and targeted therapy) versus no active treatment after surgery among patients with loco-regional RCC, appealed to our attention. Furthermore, the restriction of RCTs published or presented in English was applied to the search strategy. Besides, 2 reviewers analyzed the list of references and independently selected the studies. The final decision of which studies to include was achieved by consensus.

The eligibility criteria in this scenario were patients diagnosed as locoregional RCC of any histological type, without any signs of distant metastases after surgical radical resection. When multiple studies were from the same population using overlapping datasets, the most recent or complete trials was included. Trials involving comparison of radiation with placebo were excluded and articles with no key data were also excluded.

Meanwhile, the present study tried to assess the role of adjuvant therapies to high-risk RCC. Herein, high-risk RCC are defined with tumor stage 3 or higher, regional lymph-node metastasis, or both, on the basis of modified the University of California Los Angeles Integrated Staging System (UISS) criteria [20].

2.3. Quality assessments

We evaluated the studies for the level of evidence provided according to Cochrane risk of bias tool. The methodological quality followed on 3 factors: patient selection, comparability of the study groups, and assessment of outcome.

2.4. Data extraction

Two reviewers searched the publications independently and abstracted relevant information according to Cochrane guidelines. A third investigator was consulted to solve disagreements. Information we interested from eligible studies included first author, year of publication, adjuvant treatment, number of patients, patient characteristics, study design (blinded or not), and the outcomes.

The primary study outcome was OS. The other outcomes of interest were DFS and the incidence of Common Toxicity Criteria (CTC) scale grade 3/4 toxicities. When our eligible articles did not provide necessary data to calculate OS or DFS, we contracted authors to full information. The toxicity data were retrieved as far as possible.

The hazard ratios (HRs) of time-to-event data (OS and DFS) were directly extracted from the original study or were estimated indirectly using either the reported number of events and the corresponding P value for the log-rank statistics, or by reading off survival curves, as suggested by Parmar et al. [21]. As for safety, the number of events and number under risk were abstracted.

2.5. Statistical analysis

The meta-analyses were performed using Stata/SE, version 12.0 (Stata Corporation, College Station, TX) with fixed-effects models. HR was used as a summary statistic for survival analysis as described by Parmar et al. [21], while an odd ratio (OR) was used for toxicity evaluation. As the comparison we calculated was adjuvant treatment versus placebo or observation, an HR less than 1 favored active group, yet an HR more than 1 favored placebo or observation. Besides, we estimated respective 95% confidence intervals (95% CI) for each comparison. To safety analyses, an OR less than 1 favored active therapy while an OR greater than 1 favored observation or placebo.

At last, the I^2 statistic [22] was used to examine heterogeneity across studies. An $I^2 > 50\%$ was considered to be a statistically significant difference. To decrease the heterogeneity, we attempted to detect the source of this heterogeneity and perform a separately pooling analysis. We used a funnel plot of Egger test to evaluate publication bias [23]. All kinds of therapies (chemotherapy therapy, vaccine therapy, immune therapy, and targeted therapy) were separately analyzed to calculate their impact in survival and safety.