Author's response to reviews

Title: Androgenic suppression combined with radiotherapy for the treatment of prostate adenocarcinoma: a systematic review

Authors:

Andre D Sasse (sasse@cevon.com.br)
Elisa Sasse (elisahasse@gmail.com)
Albertina M Carvalho (albercinacno@yahoo.com.br)
Ligia T Macedo (ligiamed@gmail.com)

Version: 2 Date: 12 November 2011

Author's response to reviews: see over
Dear Sir,

We appreciated the reviewer’s comments and corrections requested for our manuscript entitled “Androgenic suppression combined with radiotherapy for the treatment of prostate adenocarcinoma: a systematic review”, submitted as Manuscript ID 1264597005588436. They were very important and ensure improvement in the quality and reliability of our study.

We hereby return with the corrections and modifications. Please, see below the specific answers for each of the comments addressed by the reviewers:

Reviewer: Takashige Abe

We updated our search in order to include all relevant trials until current date, and found the 2 randomized trials appointed by the reviewer. One of them was an update of one study already included in our review (Denham 2005). We extracted the data from these new publications and updated the meta-analyses. The results were updated, but did not change our interpretation of data or our conclusions.

Reviewer: Marco De Velasco

1. We included the reasons for excluding trials in figure 1.

2. It was not clear why the reviewer considered that our meta-analysis represents the examination of selected studies. We applied the method for systematic reviews pursued by Cochrane Collaboration aiming to find all published trials and did not find any suggestion of publications bias. Therefore, our conclusions are based in the best available evidence. From our results we don’t recommend the design of further trials comparing radiotherapy versus radiotherapy plus hormone therapy, since we consider there is strong evidence that the benefit in overall survival is both statistical and clinically significant. We agreed with the necessity of evaluate different durations of hormone suppression, focusing specially on toxicity and quality of life and included a paragraph in the discussion: “Our study also suggested that longer androgen suppression results in better DFS and OS. Those observations are in accordance to a previous systematic review focusing the duration of deprivation therapy, and a randomized clinical trial comparing six months versus two years of treatment.”

We consider this systematic review of relevance as it provides recommendations based on the best available evidence, and leads to clinical practice changes.

3. We corrected the number of patients relative to D’Amico’s trial (from 208 to 206), and updated the total number of patients.

Reviewer: Yoshitomo Chihara
The individual results of each trial are exposed in each figure representing the meta-analysis of the relevant endpoints. We added one column in the table 3, specifying the median follow-up of each trial.

Reviewer: Ryuichi Mizuno

1. We added a description of the rationale for combining androgen deprivation with radiotherapy:

   “Since the 1960s, the role of androgen deprivation therapy adjuvant to radiotherapy to treat locally advanced prostate cancer has been investigated. The inhibitory effect of androgen deprivation on the growth and proliferation of androgen-dependent prostate cancer cells is well established. Several studies have shown a rapid regression of prostate cancer after total androgen blockade, leading to hypothesize that the marked regression observed at the prostatic level of both malignant and non-malignant tissue may increase radiation efficacy. In decreasing the tumor size by antiandrogen medication, an optimal dose of radiation could treat adequately prostate cancer with less adverse events.”

2. There are not relevant explanations for the numbers appeared in Figure 2-7 (1.5.1, 1.5.2, ..... , 2.3.2). These numbers are related to the sequence of comparisons made in the statistical program (Review Manager) and are automatically generated with the graphs, and are not of interest of readers.

3. The reviewer is correct, and we repeated the relevant subgroup analysis both on OS and PFS, assuming the Denham’s study as using complete blockade. However, the new results did not change the interpretation of data or the conclusions.

4. There is no justification for exclusion of Lawton’s study from the meta-analysis. This study fulfills all our inclusion criteria and presents relevant data for the review. The stated inclusion criteria are reproduced below:

   “The purpose of this study was to identify all published randomized, controlled clinical trials in English, Spanish or Portuguese, comparing radiotherapy with or without any androgen suppression (orchiectomy, luteinizing hormone-releasing hormone [LHRH] analogues, peripheral anti-androgens or estrogenic therapy) in localized (cT1-2) or locally advanced (T3-4 N0-2 M0) prostate carcinoma. We included studies that evaluated introduction of androgen suppression either before, during or after radiotherapy; and excluded those for which anti-androgenic treatment was performed in both arms.”

Therefore, we decided to maintain the cited manuscript in the meta-analysis.

Thank you for considering our article.

Sincerely,
Andre Deeke Sasse