Brachytherapy versus external beam radiotherapy boost for prostate cancer: Systematic review with meta-analysis of randomized trials

Lam Cham Kee D, Gal J, Falk AT, Schiappa R, Chand ME, Gautier M, Doyen J, Hannoun-Levi JM. Cancer Treat Rev. 2018;70:265-271.

What was your motivation for initiating this study?

While the 2000-2010 decade was marked by a level "1" of evidence after the publication of the results of dose-escalation randomised trials in prostate cancer, the current decade has highlighted the impact of this dose-escalation technique through comparisons of external-beam and interstitial brachytherapy.
In France, as in many European countries, the use of brachytherapy is directly correlated with its cost. In order to promote the use of brachytherapy boost in prostate cancer, it is crucial to obtain reimbursement. The French rules to obtain specific reimbursement for a new treatment procedure require extensively documented evidence in which this procedure is presented as a new approach with a higher therapeutic value than the standard treatment. In 2016, on behalf of the French Society of Radiation Oncology (FSRO), we submitted to the ad hoc administration (the French Health Authority, the Haute Autorité de la Santé, HAS) this evidence, which included the results of three randomised trials [1;4;6]. Our demand was rejected. One of the reasons was that no meta-analysis of randomised trials had been published yet. After several months of the same observation, we decided to tackle this issue ourselves.

What were the main challenges during the work?

The meta-analysis results were derived from these randomised trials, and therefore the final result did not vary from the results in terms of biochemical control. Indeed, all phase III trials concluded that, whatever the brachytherapy technique used (low dose rate, high dose rate or permanent implants), a significantly higher rate of biochemical control was systematically observed in the brachy-boost arm. Nevertheless, it was important to be able to confirm this idea with strict methodology. A systematic literature review of MEDLINE and COCHRANE databases was performed for publications up to 30 April 2010 by considering all published randomised-controlled trials (RCTs) that compared the boosts offered by brachytherapy with those offered by external-beam radiotherapy for intermediate and high-risk prostate cancer, according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. The review was assessed through use of the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool and the identified reports were reviewed according to the Consolidated Standards of Reporting Trials (CONSORT). Eight publications from three RCTs were finally selected [1-8].
Besides the oncological outcome, it was also crucial to investigate the impact of brachy-boost on late genito-urinary (GU) and gastro-intestinal (GI) cancers ≥ G3 toxicities. Indeed, the excellent results of the ASCENDE-RT trial (an analysis of treatment-related morbidity for a randomised trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external-beam boost for high- and intermediate-risk prostate cancer) in terms of biochemical outcome were tempered by a significantly higher risk of GU toxicities. However, we wanted to find out whether these GU toxicities would be observed if we pooled the results of these three randomised trials in a meta-analysis.

What were the most important findings of your study?

The published meta-analysis confirmed that, using strict methodology, brachy-boost for intermediate and high-risk prostate cancers provided a highly significant advantage in terms of biochemical relapse compared with external-beam boost ($p < 0.001$), with no impact on overall survival (Fig. 1) [9].

Moreover, even though the boost from permanent implants was found to induce a higher risk of GU toxicity in the ASCENDE-RT trial, the late GU toxicity ≥ G3 in the pooled analysis was not significantly increased by the brachy-boost ($p = 0.15$ - heterogeneity < 0.01; random effect). Interestingly, the rate of late GI toxicity ≥ G3 was significantly higher in the brachy-boost ($p = 0.05$ – heterogeneity 0.5; fixed effect).

What are the implications of this research?

Currently, what can we really do with this meta-analysis? First, these results raised the technical brachy-boost question: is permanent implant better or not (toxicity/efficacy) compared with HDR brachy-boost? This question can seem both relevant and dangerous, because one of our first goals is to promote brachy-boost for intermediate and high-risk prostate cancers and certainly not to open a deleterious debate between two brachy groups. However, retrospective studies based on a sufficient number of patients might give us some interesting information on this technical issue.
Some radiation oncologist colleagues have highlighted the fact that brachy-boost was only able to increase biochemical control with no impact on overall survival, making it difficult to promote this boost technique and consider it as the new gold standard. There is currently no impact on overall survival, but did the numerous phase-III randomised trials of dose escalation with external-beam radiation therapy provide any advantages in terms of overall survival? As far as we are concerned, the answer is no and yet dose escalation has become the gold standard with 'only' a biochemical advantage. Our radiation oncology community should not use two different yardsticks but the same rules for the interpretation of scientific reports.
In 2018, on behalf of the FSRO, with the results of this meta-analysis, we resubmitted our reimbursement demand for brachy-boost, hoping that the HAS would acknowledge that brachy-boost was a cost-effective boost technique and should receive specific reimbursement.

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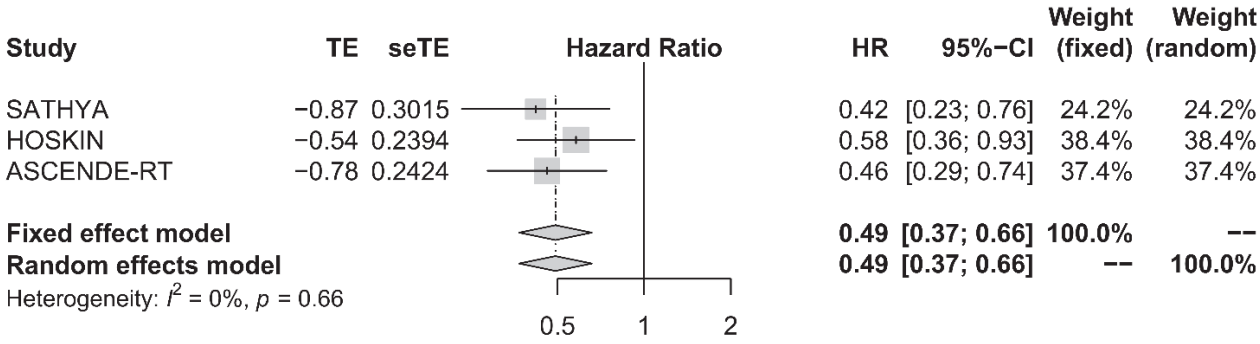

Figure 1: Forest plots of five-year biochemical progression-free survival for brachytherapy boost versus external-beam boost in intermediate and high-risk prostate cancer.

Jean-Michel Hannoun-Levi
Department of Radiotherapy
Centre Antoine Lacassagne
University of Cote d'Azur
Nice, France.

Daniel L.C. Kee
Department of Radiotherapy
Centre Antoine Lacassagne
University of Cote d'Azur
Nice, France