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Systematic or Meta-analysis Studies

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

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ABSTRACT

Background: Brachytherapy boost after external beam radiotherapy for intermediate and high-risk prostate cancer is presented as an attractive technique in numerous retrospective and prospective studies. Currently, three randomized controlled trials comparing brachytherapy versus external beam radiotherapy boost used non-homogenous irradiation features. Therefore, we analyzed the oncological outcomes by a systematic review with meta-analysis of the randomized controlled trials.

Methods: We performed a systematic literature review of MEDLINE and COCHRANE databases up to 30/04/10 and we considered all published randomized controlled trials comparing brachytherapy versus external beam radiotherapy boost 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 using 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 3 RCTs were selected.

Results: There was a significant benefit in 5-year biochemical-progression-free survival in favor of BT versus EBRT boost (HR: 0.49 [95% CI, 0.37–0.66], $p < 0.01$). There was no difference at 5 years in overall survival (HR: 0.92 [95% CI, 0.64–1.33], $p = 0.65$), ≥ grade 3 late genito-urinary (RR: 2.19 [95%CI, 0.76–6.30], $p = 0.15$) and late gastro-intestinal toxicities (RR: 1.85 [95%CI, 1.00–3.41] $p = 0.05$).

Conclusion: This meta-analysis provides further evidence in favor of BT boost for intermediate and high-risk prostate cancer in terms of b-PFS improvement, leading to suggest BT boost as level I and grade A recommendation. However, the risk of grade ≥ 3 late toxicity must be carefully investigated.

Introduction

Surgery and radiotherapy are considered as standard treatments in every risk groups of localized prostate cancer. Regarding radiotherapy, it is well established that dose escalation improves biochemical-progression-free survival (b-PFS) and less likely overall survival (OS) [1–3].

From technical point of view, because brachytherapy (BT) achieves a high conformal dose distribution to the prostate while spearing organs at risk (bladder, urethra, rectum), it is presented as an attractive tool for prostate cancer [4]. BT is proposed either as monotherapy for low and intermediate-risk prostate cancers [5–8] or boost for intermediate- and high-risk prostate cancers [9–11].

Numerous retrospective studies and systematic reviews suggested that BT boost for intermediate- and high-risk prostate cancer could play a key role for b-PFS improvement [12–17]. Currently, three prospective

Abbreviations: A.F, Alexander Falk; ADT, Androgen Deprivation Therapy; AMSTAR, Assessing the Methodological Quality of Systematic Reviews; BED, Biological Effective Dose; b-PFS, Biochemical Progression-Free Survival; BT, Brachytherapy; CI, Confidence Interval; CONSORT, Consolidated Standards of Reporting Trials; D.LCK, Daniel Lam Cham Kee; EBRT, External Beam Radiotherapy; G3, Grade 3; GI, Gastro-intestinal; GU, Genito-urinary; HDR, High-Dose Rate; HR, Hazard ratio; J.D, Jerome Doyen; J.G, Jocelyn Gall; JM.HL, Jean-Michel Hannoun-Levi; LDR, Low-Dose Rate; ME.C, Marie-Eve Chand; NCCN, National Comprehensive Cancer Network; OS, Overall Survival; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis; Qol, Quality of Life; R.S, Renaud Schiappa; RCTs, Randomized Controlled Trials; RR, Relative Risk; TOI, Trial Outcome Index

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randomized controlled trials (RCTs) compared for intermediate- and high-risk prostate cancer, BT boost versus external beam radiotherapy (EBRT) boost [18–20]. However, partly due to the randomization period, all of them used different BT techniques, different total doses and dose per fraction delivered to prostate, different radiotherapy fields and different androgen deprivation therapy duration. All these parameters could influence oncological outcomes and toxicity profiles. In order to provide an objective synthesis of the overall oncological outcome, we performed a systematic review with meta-analysis of these 3 RCTs concerning BT boost for intermediate- and high-risk prostate cancer

Methods and materials

Search strategy

A systematic literature review was performed up to 30 April 2018 using search engines (MEDLINE via PubMed and COCHRANE databases) and we considered all published RCTs comparing BT versus EBRT boost for intermediate- and high-risk prostate cancer. Searches were carried out with the terms “brachytherapy” AND “prostate cancer” AND “randomised/randomized”.

Inclusion criteria, study eligibility, and data extraction

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria were used for article selection (Fig. 1), which were performed independently by three investigators (D.LCK, J.G and JM.HL). Furthermore, the study was also reviewed using Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool evaluation as suggested recently by Weed [21]. Only full text articles published in English language with RCTs comparing BT versus EBRT boost for intermediate- and high-risk prostate cancer (defined by NCCN: National Comprehensive Cancer Network risk stratification) were considered. Data were extracted from the trial results and not from the individual patient data collection due to lack of availability. Any differences in extracted data were resolved via within-pair consensus. If a consensus could not be reached within study pairs, the entire group was consulted to achieve consensus on the most accurate results. Extracted data included details on study design, inclusion and exclusion criteria, randomization, participant demographic and oncologic characteristics, interventions, measured outcomes and results (number of events, hazard ratios (HR), relative risks (RR), 95% confidence interval (CIs), and p values).

Statistical analysis

Meta-analysis was performed using R 3.2.2 software on Windows® and metafor R package. Heterogeneity between studies was measured by visual inspection of plots and the I^2 statistic [22]: a higher I^2 value indicates higher heterogeneity. Both random-effects models and fixed-effects models were used for calculation in forest plots. If heterogeneity was measured, random-effects models were preferred. Otherwise fixed-effects models were used. For time to event data, HR and 95% CI obtained directly from studies were used to compare results, using the inverse variance technique. For dichotomous data, Mantel-Haenszel method was used and expressed as risk ratio with 95% CI. In both cases, $p < 0.05$ was considered significant.

Assessment of risk of bias and trial quality

Identified reports were reviewed according to Consolidated Standards of Reporting Trials (CONSORT) [23] and the risk of bias in individual studies was assessed using a tool recommended by meta-analysis guidelines that evaluate aspects of RCT design and execution [24,25]. The general quality of this review article was done using AMSTAR tool evaluation [26,27].

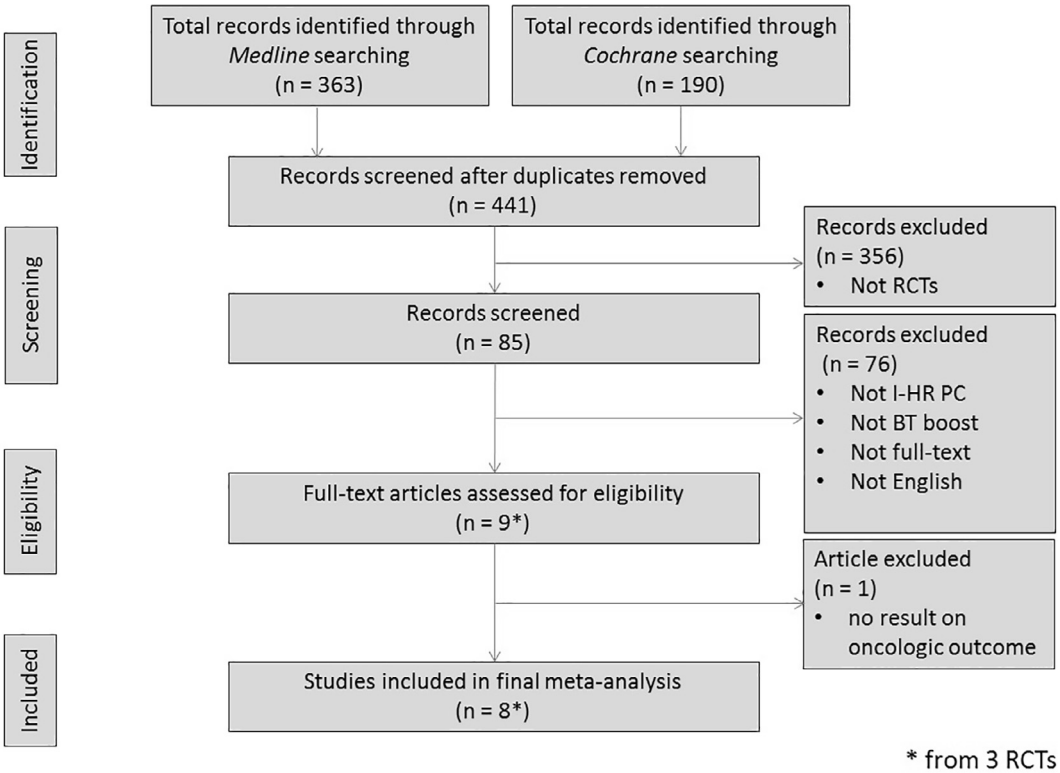

Fig. 1. PRISMA flow diagram detailing the search strategy and identification of studies used in data synthesis. RCTs: Randomized controlled trials; INTERMEDIATE AND HIGH-RISK PROSTATE CANCER: Intermediate and High-risk prostate cancer; BT: Brachytherapy.