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Systematic or Meta-analysis Studies

Prognostic value of biochemical response to neoadjuvant androgen deprivation before external beam radiotherapy for prostate cancer: A systematic review of the literature

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ABSTRACT

External beam radiation therapy (EBRT) in combination with androgen deprivation therapy (ADT) is considered a standard treatment option for patients with aggressive localized and locally-advanced prostate cancer. Randomized phase III trials have provided evidence for combining EBRT to short-term ADT for intermediate-risk disease and to long-term ADT for patients harboring high-risk tumors. Even if several improvements and developments have been made in the last years in terms of radiotherapy delivery techniques, image-guided radiotherapy, and better sparing of the organs at risk the current use of ADT remains still linked to a therapeutic algorithm based on the prostate cancer risk classification as proposed by clinical trials.

Emerging literature has recently shown that the biochemical response to a course of neoadjuvant ADT before EBRT, called the "prostate-specific antigen (PSA) nadir" (lowest value after treatment), may influence the long-term biochemical tumor-control outcomes of prostate cancer patients. An individualized approach adapting the duration of hormonal treatment according to the PSA response during the neoadjuvant phase, as well using new generation hormonal agents, may represent a new therapeutic strategy and a future way to improve the therapeutic ratio for prostate cancer patients.

In this systematic review of the literature we explored the prognostic value of the PSA response to the neoadjuvant ADT phase and the rationale to adjust the use of ADT and EBRT in patients with intermediate- and high-risk prostate cancer based on the biochemical response to the neoadjuvant androgen ablation phase.

Introduction

Based on the results of several randomized phase III trials [1–4], the combination of androgen deprivation therapy (ADT) and external beam radiation therapy (EBRT) has become the current standard of care for men with locally advanced prostate cancer (PCa). Neoadjuvant ADT (nADT) before radiotherapy (RT) and also concomitant and adjuvant ADT for various lengths of time has been used in most of these studies. According to the National Comprehensive Cancer Network (NCCN) guidelines, patients with intermediate-risk PCa may be treated with a combined treatment modality including 4–6 months of ADT [2,5–10], whereas patients with high-risk features benefit at maximum from long-term hormonal therapy (2–3 years) [3,11,12].

Emerging literature has recently shown that the biochemical response to a course of nADT before EBRT, called the "prostate-specific antigen (PSA) nadir" (lowest value after treatment), can influence the long-term biochemical tumor-control outcomes of PCa patients. Moving away from the homogeneous therapeutic algorithm based on the PCa risk classification, a better understanding of the interaction between androgen ablation and RT, together with improvements in RT delivery and development of image-guided RT (IGRT) techniques, may provide a rationale for an individualized approach to improve outcome of PCa patients.

This systematic review will address the prognostic value of the PSA response after the nADT phase and the rationale to adjust the use of ADT and RT in patients with intermediate- and high-risk PCa according to the biochemical response to the neoadjuvant androgen ablation phase.

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Materials and methods

A systematic review of the literature was performed in the PubMed database from January 1995 up to August 2015 according to Preferred reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [13]. Articles reporting on biochemical response to nADT before RT were identified and analyzed. No meta-analysis was carried out. The following keywords were used to identify potential articles: ("PSA level" OR "PSA response" OR "biochemical response" OR "PSA nadir" OR "PSA kinetics") AND ("radiotherapy" OR "radiation") AND ("hormone therapy" or "androgen deprivation"). Relevant articles were also identified using related citations function of PubMed.

Randomized trials and non-randomized trials were included. Only full-text papers published in English were considered. The final reference list was generated on the basis of originality and relevance to the broad scope of this review. The flowchart of the systematic review is represented in Fig. 1.

Results

Retrospective series

Among the firsts to explore the role of the pre-RT PSA nadir response after the nADT phase, Zelefsky et al. reported on an institutional series of 213 patients treated between 1989 and 1995 at the Memorial Sloan-Kettering Cancer Center (MSKCC) [14]. Forty-four percent of the patients were considered as favorable/intermediate risk, while 56% were unfavorable risk. Patients received a 3-months course of nADT followed by a 3D-conformal RT (median dose 75.6 Gy) with concomitant ADT until the last RT day. Monthly PSA measurements were obtained before RT. After 3 months, 162 patients (76%) reached a PSA nadir pre-RT $\leqslant$ 0.5 ng/mL. Using this pre-RT PSA cutoff, patients with a good response (PSA pre-RT $\leqslant$ 0.5 ng/mL) after 3 months of nADT showed a 5-year biochemical relapse-free survival (bRFS) rate of 74%, compared with 40% for patients with higher PSA levels ($p < 0.001$). In a multivariate analysis, the pre-RT PSA nadir level, together with pretreatment PSA and clinical stage, continued to predict independently for PSA relapse-free survival.

In a Japanese series of 46 patients with localized PCa treated between 1987 to 1995 with 3D-CRT to 66 Gy and neoadjuvant, concurrent, and adjuvant ADT with diethylstilbestrol (DES) [15], the 5-years bRFS for patients with a pre-RT PSA < 1 ng/mL was 93.8% ($n = 28$) as compared to 68.2% for patients with a pre-RT PSA $\geqslant$ 1 ng/mL. A pre-RT PSA < 1 ng/mL was significantly associated with bRFS in the multivariate analysis.

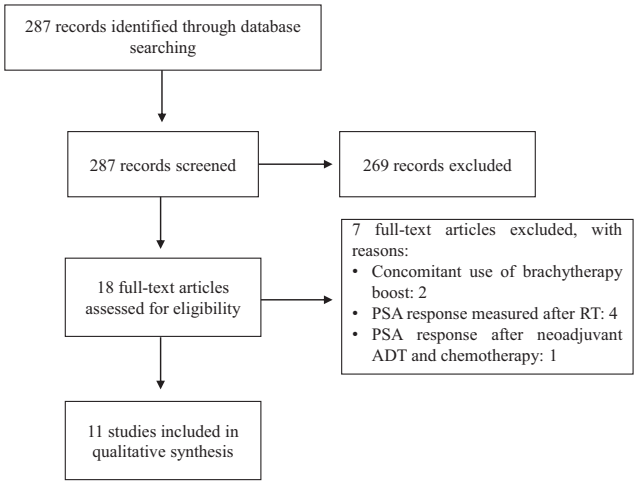

Fig. 1. PRISMA flow diagram of systematic literature review of eligible studies.

In a British Columbia Cancer Agency study, Ludgate et al. analyzed 407 patients treated between 1991 and 2001 with nADT and EBRT for localized high-risk disease [16]. Various combinations of ADT were used, including single-agent or combination hormonal therapies: neoadjuvant only (median duration 3.4 months); neoadjuvant and concurrent (median duration 6.9 months); and neoadjuvant, concurrent, and adjuvant ADT (median duration 13.5 months) were administrated to 63%, 15%, and 21% of the patients, respectively. The median delivered EBRT dose was 66 Gy. With a nADT phase of less than 3 months, the pre-RT PSA was 2.5 ng/mL; between 3 and 8 months, the pre-RT PSA was 0.6 ng/mL; and with nADT longer than 8 months 0.12 ng/mL. The pre-RT PSA level was associated with improved bRFS in both univariate and multivariate analysis. The 5-year bRFS rates were 78%, 59%, 46%, and 36% for patients with pre-RT PSA levels ranging between 0–0.1, 0.11–1.0, 1.01–1.5 and >1.5 ng/mL, respectively. Patients with a pre-RT PSA level $\leqslant$0.1 ng/mL showed also a better prostate cancer-specific survival (CSS) rates. Duration of the nADT, total ADT duration, and RT dose were not associated either with better bRFS, CSS, or overall survival (OS) rates. Nevertheless, analyzing at the same institution a population of 64 patients with high-risk disease (T3/4 disease and/or Gleason score $\geqslant$8 and/or initial PSA levels of >40 ng/mL), Alexander et al. found that the pre-RT PSA nadir, was significantly associated with improved CSS and OS [17]. Duration of ADT, however, was not correlated with survival.

Mitchell et al. retrospectively reviewed 119 patients with intermediate- or high-risk localized PCa treated between 2001 and 2002 with $\geqslant$2 but <9 months of nADT before EBRT, followed by concurrent and optionally adjuvant ADT [18]. Neoadjuvant ADT consisted of luteinizing hormone–releasing hormone (LH–RH) agonists and the median EBRT delivered dose was 64 Gy. According to the PSA level measured during the first EBRT week, the 4-year actuarial bRFS was 84% for patients reaching a PSA nadir of $\leqslant$1 ng/mL ($n = 67$) and 60% for patients with a PSA value >1 ng/mL ($p = 0.0016$). PSA nadir continued to predict for better bRFS in the multivariate model. A benefit in OS and disease-free survival (DFS) was also observed for good responders after nADT (PSA nadir of $\leqslant$1 ng/mL) compared to patients with a PSA nadir >1 ng/mL (94% vs 77.5% and 98.5% vs 82.5%, respectively).

In a larger prospective cohort from Peter MacCallum Cancer Center [19], a total of 502 patients with localized PCa (74% with high-risk disease) treated between 1994 and 2000 with 2–12 months of nADT followed by EBRT (median dose 68 Gy) were retrospectively analyzed to assess the impact of PSA kinetics on bRFS and prostate CSS. PSA halving time, neoadjuvant PSA nadir, and post-therapy PSA nadir were analyzed on their impact to predict for biochemical failure. The median nADT and total ADT durations were 6.9 and 10.8 months, respectively. In univariate and multivariate analyses, only the PSA nadir after the nADT and the post-EBRT PSA (analyzed as continuous or categorical variables) were significantly predictors of biochemical failure and CSS. On the other hand, PSA halving time and the duration of the nADT phase did not predict bRFS and CSS. In some exploratory analyses, pre-RT PSA $\leqslant$ 0.5 ng/mL and a post-RT PSA $\leqslant$ 0.06 ng/mL predicted in high-risk patients for improved bRFS and CSS.

In the more recent radiation therapy era of dose escalation, three published papers addressed the prognostic value of PSA response to nADT. In a series of the MD Anderson Cancer Center, McGuire et al. analyzed 196 patients with high-risk PCa treated with long-term ADT (median, 24 months including LH–RH monotherapy, orchiectomy, or total androgen blockade) and dose-escalated RT (median dose 75.6 Gy)using 3D-conformal RT or intensity-modulated RT (IMRT) techniques [20]. After a median duration of the nADT phase of 2.9 months, 81 (41%) patients