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Review

WHO SHOULD RECEIVE RADIOTHERAPY IN METASTATIC HORMONE-SENSITIVE PROSTATE CANCER?

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SUMMARY – The standard of treatment of metastatic hormone-sensitive prostate cancer (mHSPC) is androgen deprivation therapy (ADT) with docetaxel or abiraterone. However, numerous retrospective studies suggested outcome benefit of prostate radiotherapy. Small randomized trial (HORRAD) showed no overall survival (OS) benefit of the addition of prostate radiotherapy to ADT but there was a trend toward survival benefit in a low volume disease. Although the results of large randomized study (STAMPEDE) have also not proved improvement of OS in unselected patients, robust improvement of failure-free survival was found. In addition, OS was significantly improved in patients with a low volume disease. In the absence of reliable molecular markers, the extent of metastatic disease has emerged as an important factor for treatment decision making. In this review, we summarize data from non-randomized as well as from randomized studies concerning prostate radiotherapy to contribute to the improvement of treatment tailoring for each individual patient with mHSPC in order to achieve the best possible treatment outcomes.

Key words: *metastatic hormone-sensitive prostate cancer, prostate radiotherapy, low volume disease*

Introduction

Epidemiological data has suggested an increasing incidence of newly diagnosed metastatic hormone–sensitive prostate cancer (mHSPC)[1]. Additionally, 20–40% of patients undergoing radical prostatectomy[2] and 30–50% of patients undergoing primary radiotherapy will experience biochemical recurrence[3] while in one third of them metastatic and/or recurrent disease will be detected within 10 years. The mainstay of treatment of metastatic disease for decades was androgen deprivation therapy (ADT) but with a median time to failure of only 11 months[4]. During 10 years (2004-2014) several new drugs have been approved for the treatment of metastatic castration–resistant prostate cancer (mCRPC) (docetaxel, cabazitaxel, abiraterone, enzalutamide, radium-223)[5-11]. However, since 2015 significant advances have been made in the treatment of mHSPC and ADT with docetaxel or abiraterone has become a new standard of care of mHSPC[12-16].

Recently, there has been increasing interest in local therapy in patients with metastatic prostate cancer. This approach has been derived from the idea that the primary tumor is a source of metastatic cancer cells and a site where resistant clones develop[17]. Moreover, in animal models proliferation of tumor cells at distant metastatic sites has been dependent on compounds secreted by the primary tumor in the circulation[18]. Recent study has shown multidirectional flow between the primary tumor and metastatic sites as well as seeding between metastatic sites in 10 patients with mCRPC[17]. Furthermore, it has been shown that local

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treatment of the primary tumor can prevent development of symptoms[19].

Radical local treatment of the primary tumor has been studied in several randomized trials and retrospective studies in patients with metastatic renal, breast, lung and ovarian cancers. Nephrectomy improved survival of patients with metastatic renal cancer[20,21] but that was not confirmed in a more recent trial[22]. Although retrospective studies showed the benefit of the treatment of primary breast cancer[23], a randomized study showed no improvement of overall survival (OS)[24]. Radiotherapy of the primary tumor did not improve OS of patients with metastatic small-cell lung cancer in small trial[25] while retrospective studies showed effectiveness of cytoreductive surgery in advanced ovarian cancer[26].

The aim of this review is to give an overview of the literature regarding the role of radiotherapy in metastatic prostate cancer.

Methods

We performed a review of literature by searching Medline with the keywords: radiotherapy of metastatic prostate cancer, metastatic hormone-naïve prostate cancer and metastatic hormone-sensitive prostate cancer. All clinical trials and review articles written in English were reviewed. Conference abstracts were also included, and cross-matching references were used to find additional articles.

Randomized data regarding the prostate radiotherapy in hormone-sensitive metastatic prostate cancer

In 2018 two trials, HORRAD and STAMPEDE, reported a potential survival benefit of adding radiotherapy to ADT in patients with newly diagnosed low volume metastatic disease[27,28].

The HORRAD trial randomized 432 patients with newly diagnosed bone metastatic prostate cancer to ADT with or without prostate radiotherapy[27]. Metastatic disease was confirmed by bone-scintigraphy. IMRT was preferable, but 3D-CRT was also allowed. Prescribed doses were 70 Gy in 35 fractions of 2 Gy or 57.76 Gy in 19 fractions of 3.04 Gy, three times a week for 6 weeks. A majority of patients (63%) had high volume disease i.e. more than 5 osseous metastases. Median follow-up was 47 months. The study showed no OS benefit of the addition of prostate radiotherapy. Although not statistically significant, a trend toward survival benefit was seen in a low volume disease (HR 0.68; 95% CI 0.42-1.10). The unadjusted median time to PSA progression was 15 months in the radiotherapy (RT) group versus 12 months in the control group (HR 0.78; 95% CI 0.63-0.97; p = 0.02) but after adjustment the HR was no longer significant.

The STAMPEDE trial[28] was a phase 3 trial conducted in 117 centers in Switzerland and the UK from January 2013 until September 2016. During that period 2061 patients were randomized in 1:1 ratio to receive either ADT (with or without docetaxel which became the new standard of care during the trial) or ADT (with or without docetaxel) plus prostate radiotherapy. Metastatic disease was confirmed by bone-scintigraphy and conventional soft tissue imaging (CT or MRI). Median follow-up was 37 months. Radiotherapy was commenced as practicable after randomization or within 3-4 weeks after the last docetaxel dose. Prescribed dose was 55 Gy in 20 fractions of 2.75 Gy over 4 weeks or 36 Gy in 6 consecutive weekly fractions of 6 Gy. Forty percent of patients had a low metastatic burden defined by CHAARTED trial (four or more bone metastases with one or more outside the vertebral body or pelvis, or visceral metastases, or both). The results showed no improvement of OS in unselected patient group (HR 0.92; 95% CI 0.80-1.06, p = 0.27; median survival 48 months in the RT group vs. 46 months in the control group). However, radiotherapy significantly improved failure-free survival (FFS) (HR 0.76; 95% CI 0.68-0.84, p < 0.0001; 3-year FFS 32% in the RT group vs. 23% in the control group). Pre-specified subgroup analysis based on disease burden was conducted prior to study analysis but not prior to accrual. OS was improved in patients with a low metastatic burden at baseline who had allocated radiotherapy (HR 0.68; 95% CI 0.52-0.90, p = 0.007; 3-year OS 81% in the RT group vs. 73% in the control group). The proportion of patients reporting at least one severe adverse event (Common Terminology Criteria for Adverse Events grade 3 or worse) was similar between the studied groups (38% in the control group vs. 39% in the RT group). According to the authors of the published paper limitations of the study were: 1.) retrospective determination of the metastatic burden, 2.) compliance with allocation to prostate RT was not complete (94%), 3.) median follow-up was shorter than median survival.

Prospectively planned STOPCAP meta-analysis included HORRAD, STAMPED and available results from ongoing PEACE-1 trial[29]. There was an improvement in biochemical progression (HR 0.74; 95% CI 0.67-0.82, p = 0.94 x 10^{-8}) and FFS (HR 0.76; 95% CI 0.69-0.84, p = 0.64 x 10^{-7}), equivalent to ~ 10% benefit at 3 years. The effect of prostate radiotherapy varied by metastatic burden with 7% improvement in 3-year survival in men with fewer than 5 bone metastases.

Therefore, the data suggest a significant survival benefit of prostate radiotherapy in a low-volume mHSPC but the unresolved problem is the lack of exact definition of low-volume as well as of oligometastatic disease. Although oligometastatic disease was first described by Hellman and Weichselbaum[30] in 1995 and the original concept was revised in 2011 to denote disease limited to specific organ or limited number of metastases[31], so far no consensus has been reached regarding the definition of oligometastatic disease. Another issue is the role of more sensitive imaging techniques (eg. ^{68}Ga PSMA PET/CT, whole body diffusion weighted MRI) since conventional bone and CT scan were used in STAMPEDE trial. Further, bone scans demonstrated to be predictive for the benefit of prostate radiotherapy combined with ADT [28].

There are several ongoing clinical trials which are investigating prostate radiotherapy in mHSPC. The PEACE1 is a phase 3 trial (NCT01957436) which is consisting of four arms: ADT plus docetaxel; ADT plus docetaxel plus abiraterone; ADT plus docetaxel plus prostate radiotherapy; and ADT plus docetaxel plus abiraterone plus prostate radiotherapy. Another phase 3 trial, the SWOG/NCTN trial (NCT03678025) will randomize patients to standard systemic therapy versus standard systemic therapy and either radical prostatectomy or prostate radiotherapy. Similarly, a phase 2 trial (NCT01751438) randomizes patients to best systemic therapy versus best systemic therapy plus either radical prostatectomy or prostate radiotherapy.

The feasibility of prostate surgery in this setting is being investigating in the g-RAMMP trial (NCT02454543) and the TROMBONE trial (ISRCTN15704862).

Non-randomized data regarding prostate radiotherapy in hormone-sensitive metastatic prostate cancer

Non-randomized studies of prostate radiotherapy in metastatic prostate cancer are presented in Table 1. The majority of them indicate that local treatment has been associated with better outcome for patients. Overall survival was improved[32] and prostate cancer specific mortality (PCaSM) was decreased when intensity modulated radiotherapy (IMRT) was applied, which was not the case with conformal radiotherapy (CRT)[33]. It has been reported that the potential benefit of local treatment depended on tumor characteristics whit a higher cancer-specific mortality-free survival rate (CSMFS) in patients with a predicted CSM risk < 40%[34]. In another recent study patients with non-regional metastatic lymph nodes and those with bone metastases and baseline PSA < 60 ng/ml benefited from local treatment (radical prostatectomy or brachytherapy), while no survival benefit was found for patients with other metastatic sites[35].

Although it is well known that retrospective data should be interpreted cautiously, positive results of these studies have encouraged the conduct of randomized studies.

Other treatment options in the setting of hormone-sensitive metastatic prostate cancer

The addition of docetaxel to ADT significantly improved survival compared to ADT alone in the total patient cohort (OS survival benefit of 10.4 months in the CHAARTED and 15 months in the STAMPEDE trial)[12,13]. However, only in the CHAARTED trial[13] was stratification based on disease volume and a survival benefit was absent in the low-volume disease (HR 1.04; 95% CI 0.70-1.55, p = 0.86). The addition of abiraterone and prednisone to ADT also improved survival in the LATITUDE and STAMPEDE trials[14-16]. The LATITUDE trial[14,15] included patients with a high-volume disease defined as two or more of the following risk factors: Gleason score ≥ 8, bone lesions ≥ 3, visceral metastases. The STAMPEDE trial[16] also included patients with a low-volume metastatic disease as well as patients with locally advanced disease. Recently published post-hoc analysis of the STAMPEDE trial according to LATITUDE criteria showed that addition of abiraterone to ADT resulted in a 34% reduction in risk of death in a low-volume disease (HR 0.66; 95% CI 0.44-0.98, p = 0.041) and a 46% reduction in risk of death in a high-volume disease (HR 0.54; 95% CI 0.41-0.70, p < 0.001) compared to the ADT alone group[36]. A retrospective, indi-

rect comparison of two STAMPEDE arms i.e. docetaxel and abiraterone arm, found no difference in OS, prostate cancer-specific survival, metastasis-free survival and symptomatic skeletal-related events[37]. FFS and progression-free survival (PFS) were significantly better in the abiraterone arm. There were more (febrile) neutropenia in the docetaxel arm (13% vs. 1%) and more cardiovascular disorders in the abiraterone arm (9% vs. 3%).

The addition of enzalutamide and apalutamide to ADT also showed survival benefit in comparison to ADT alone[38,39]. Their approval is pending.

At the moment, since we have no proven molecular biomarkers Belderbos[40] et al. suggest clinical factors such as metastatic extent and comorbidities to help us individualize treatment of patients with mHSPC. In the low-volume disease they suggest novel androgen receptor (AR) targeted therapies or prostate radiotherapy while in the high-volume disease they suggest docetaxel or abiraterone combined with ADT. In patients with increased risk of cardiovascular morbidity they suggest docetaxel or prostate radiotherapy depending on the metastatic extent of the disease. However, results of sub-group analysis by metastatic burden from long-term follow-up of metastatic patients in the STAMPEDE trial that will be announced shortly could possibly have impact on treatment decision.

Metastasis-directed therapy (MDT) of oligometastatic disease

Prostate cancer mainly spreads to bones and lymph nodes, while visceral metastases are rare. Local treatment options are surgery, external beam radiotherapy (EBRT) and stereotactic body radiation (SBRT). There are three scenarios of oligometasatic disease: synchronous to the newly diagnosed primary tumor (hormone sensitive), oligorecurrence (hormone sensitive) and oligoprogression (castration resistant)[41]. As a local treatment SBRT has been studied little in the first scenario, but there are numerous studies in other two scenarios with a predominance of retrospective studies[41]. The studies were very heterogeneous in terms of patient population, treatment schemes and primary endpoints. Toxicity was low and local control excellent but the impact of such approach upon OS is not known. The STOMP trial, a phase 2 trial, was the first randomized study exploring the role of MDT compared to standard of care in oligorecurrent patients[42]. ADT-free survival and biochemical relapse-free survival were longer than in the control group. The ORIOLE study is the first randomized study to evaluate the efficacy of SBRT as measured by quantification of circulating tumor cells in hormone sensitive oligometastatic disease. The preliminary results are promising[43]. Other clinical trials exploring MDT are ongoing: PLATON (NCT03784755), CORE (NCT02759783), PEACE V (STORM, NCT03569241), PCS IX (NCT685397).

Conclusion

Prostate radiotherapy has emerged as a novel treatment option for newly diagnosed low-volume metastatic prostate cancer. Although numerous retrospective studies suggested substantial survival benefit, until now only one randomized study has shown significant survival benefit of prostate radiotherapy in mHSPC and that effect was limited only to the group of patients with the low-volume disease. Therefore, results of ongoing studies are eagerly expected to help to better elucidate patients who will benefit the most from the treatment, the optimal radiation dose and possibly the optimal systemic therapy to be combined with the local treatment.

Conflicts of interest

The author has no funding or conflicts of interest to disclose.

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Sažetak

U KOJIH BOLESNIKA PRIMIJENITI RADIOTERAPIJU U METASTATSKOM HORMONALNO OSJETLJIVOM KARCINOMU PROSTATE?

V. Bišof

Standard liječenja metastatskog hormonski osjetljivog karcinoma prostate (mHSKP) je androgen deprivirajuća terapija (ADT) s docetakselom ili abirateronom. Međutim, brojne retrospektivne studije su ukazale na korist od radioterapije prostate. Rezultati male randomizirane studije (HORRAD) nisu pokazali poboljšanje ukupnog preživljenja kod primjene radioterapije prostate uz ADT, no uočen je trend ka poboljšanju preživljenja kod bolesnika s malim volumenom metastatske bolesti. Iako rezultati velike randomizirane studije (STAMPEDE) također nisu pokazali poboljšanje preživljenja u ukupnoj populaciji bolesnika, preživljenje bez neuspjeha liječenja bilo je značajno poboljšano. Pored toga, ukupno preživljenje je bilo značajno poboljšano u bolesnika s malim volumenom metastatske bolesti. U nedostatku pouzdanih molekularnih markera, opseg metastatske bolesti pojavio se kao važan čimbenik kod odlučivanja o liječenju. U ovom preglednom radu iznosimo rezultate ne-randomiziranih i randomiziranih studija o radioterapiji prostate kako bi doprinijeli poboljšanju izbora liječenja za svakog pojedinog bolesnika oboljelog od mHSKP s ciljem postignuća najboljeg mogućeg ishoda liječenja.

Ključne riječi: *metastatski hormonski osjetljivi karcinom prostate, radioterapija prostate, bolest malog volumena*