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Review Article

The role of radiotherapy in metastatic prostate cancer

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Abstract: The current standard of care for patients with metastatic prostate cancer includes ADT with a palliative intent. Recent studies have investigated the role of local therapy in metastatic prostate cancer. While retrospective data has shown some benefit with regard to survival and delay in initiation of ADT, there has been limited prospective Randomized data. To date, there has only been one recent randomized trial revealing a survival benefit with local radiotherapy, largely benefiting patients with the lowest burden of disease. The purpose of this review is to summarize the evidence and ongoing clinical trials regarding the role of radiotherapy in metastatic prostate cancer patients.

Keywords: Prostate cancer, oligometastasis, radiotherapy

Introduction

Prostate Cancer is the second most frequent cancer worldwide and the fifth leading cause of cancer death in men, with an estimated 1.3 million new cases in 2018 [1]. Primary treatment modalities for prostate cancer include radical prostatectomy (RP) or radiation therapy (RT) with or without androgen deprivation therapy (ADT) and one-third of patients select external beam radiation therapy (EBRT) or brachytherapy (BT) for treatment [2]. However, despite improvements in radiation technology and higher radiation dose regimens, biochemical failure may still occur in 30-60% of patients treated with RT [3]. Historically, the treatment intent for metastatic prostate cancer has been palliative, with the current standard of care being ADT to reduce either the synthesis of androgens or interfere with the binding of androgens to the androgen receptor [4, 5]. However, long-term ADT has several known side effects impacting quality of life, such as loss of libido, impotence, osteoporosis, and exacerbation of underlying cardiovascular and metabolic disease [6]. Moreover, the relapse rate on ADT is largely inevitable, with a median time to failure of 11 months [7].

Recently, there have been increasing efforts for aggressive local therapy in patients with metastatic prostate cancer. The rationale for such treatment was originally based on the idea that the primary tumor is a source of metastatic cancer cells and a site for development of resistant clones. More recent studies have shown that there is multidirectional flow between the primary tumor and metastatic sites as well as seeding between metastatic sites, and the primary tumor remains a source for further metastatic potential [8, 9]. Moreover, halting the progression of the primary tumor can prevent the development of symptoms and prevent the need for palliative interventions [10].

Treatment paradigms aggressively targeting primary tumors in the setting of metastatic disease are currently employed for various disease sites, including, lung, breast, ovarian, and renal cell carcinomas. Several retrospective studies have shown surgical debulking to be an effective primary treatment in advanced ovarian cancer [11]. In metastatic breast cancer, multiple retrospective studies have shown the benefit of treating the primary tumor [12], though a recent randomized controlled trial has shown limited benefit [13]. Moreover, while the role of nephrectomy along with immunotherapy in metastatic renal cancer has shown some benefit [14, 15], other trials have not shown this to be superior [16].

While there is a precedent for treating primary tumors in metastatic disease, there is currently

no consensus regarding local radiation therapy in metastatic prostate cancer. There has been an increase in the incidence of metastatic prostate cancer in recent years [17, 18]. Metastatic prostate cancer has been found to be a prognostic factor in overall survival and patients with low-volume metastatic disease may derive the most benefit from aggressive local therapy. The purpose of this review is to summarize the literature regarding the role of local RT in metastatic prostate cancer.

Non-randomized data on RT in metastatic prostate cancer

There are several observational studies analyzing the role of RT to the primary tumor in metastatic prostate cancer and its association to outcome [survival]. For example, a SEER study by Leyh-Bannurah et al examined 13,692 metastatic prostate cancer patients who were treated with either RP or RT or no local therapy. In this study, the authors found that cause-specific mortality was lower in patients who received local therapy in propensity score-matched multivariable competing risk regression analyses, though the difference was more pronounced for RP (65% for RP vs. 52% RT) [19]. In another SEER analysis, Culp et al identified 8,185 patients with metastatic prostate cancer who underwent RP, EBRT, or BT to the primary tumor. They found that patients who underwent RP or BT had improved 5-year overall survival versus those who did not receive any local therapy (67.4% RP, 52.6% BT vs. 22.5% no local therapy) [20]. A similar study by Antwi and Everson found that metastatic prostate cancer patients who underwent RP or BT had lower all-cause mortality and prostate cancer specific mortality than those who did not have local therapy (73% and 72% for RP versus no treatment and 57% and 54% for BT versus no treatment respectively) [21]. Finally, Satkunasivam et al found that patients with metastatic disease who underwent radical prostatectomy and IMRT had a 52% and 62% decrease in prostate cancer specific mortality respectively versus those who did not undergo local treatment. However, conformal radiation therapy was not associated with improved survival [22].

There have also been several observational studies utilizing the NCDB (National Cancer Database) examining the role of local therapy in metastatic prostate cancer. One of the largest studies comparing RP, EBRT, and BT in metastatic prostate cancer patients by Loppenberg et al found that 3-year overall mortality-free survival was higher in patients who received local therapy versus those who did not (69% vs. 54%), though the benefit was affected by baseline characteristics given that those with less aggressive tumors and good health status appeared to benefit the most [23]. Parikh et al also found that patients who received local therapy had improved 5-year overall survival (45.7% versus 17.1%) compared with those not receiving local therapy, with RP and IMRT independently associated with superior overall survival [24]. Similarly, Rusthoven et al examined the benefit of adding ADT to EBRT to the pelvis and prostate versus ADT alone and found that there was improvement in both five year overall survival (49% vs. 33%) and median survival with the addition of radiation to ADT.

There has also been a case-controlled study exploring the role of radiotherapy in metastatic prostate cancer. Yonsei et al examined a cohort of 140 patients and compared patients who received RT and those who did not. They found that overall survival and biochemical failure-free survival were improved in patients who received RT (69% vs. 43% and 52% vs. 16% respectively) [25]. Overall, while the aforementioned non-randomized studies indicate that there may be a survival benefit associated with local RT in metastatic prostate cancer, retrospective data must be interpreted cautiously and further prospective randomized studies should be conducted in order to clarify the impact that local therapy may have on outcomes in this patient cohort.

Randomized data on local RT in hormone-sensitive metastatic prostate cancer

The STAMPEDE Trial is one of the largest randomized controlled trials investigating the role of radiotherapy in metastatic prostate cancer. In this trial, 2,061 patients were randomized in a 1:1 ratio to standard of care with lifelong ADT and upfront docetaxel or radiotherapy in a regimen of 55 Gy in 20 fractions over 4 weeks or weekly 36 Gy in six fractions over 6 weeks [26]. About half of the patients had a high metastatic burden, defined as four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both. In pre-specified analysis by metastatic burden,

overall survival was improved in patients with low metastatic burden who received radiotherapy at 3 years (81% vs. 73%) and failure-free survival increased from 33% to 50%. However, overall survival was not improved in the overall cohort with radiotherapy, despite improved failure free survival (32% vs. 23%). Moreover, there was no improvement in failure-free survival or overall survival in patients with high metastatic burden [26].

The HORRAD Trial was a smaller trial which randomized 432 patients to ADT alone versus ADT and EBRT (70 Gy in 35 fractions of 2 Gy or 57.76 Gy in 19 fractions of 3.04 Gy). A majority of these patients had more than five osseous metastasis and the median PSA value was 145 ng/dL. There was no difference in overall survival between both groups. While the unadjusted median time to progression was 15 months versus 12 months for those who received RT, this association did not remain significant after adjustment. However, the radiation doses used in this trial are not reflective of current practice [not dose-escalated] [27].

There are currently additional ongoing prospective trials which are investigating local RT in the context of metastatic prostate cancer. For example, MD Anderson has an ongoing Phase II trial (NCT01751438) which looks at best systemic therapy versus best systemic therapy and either RT or RP with results expected in March 2019. Additionally, the PEACE1 trial (NCT01957436) is a phase III study to compare the clinical benefit of ADT (+docetaxel) with or without local RT with or without abiraterone acetate and prednisone in patients with metastatic hormone-naïve prostate cancer with results expected in 2030. Similarly, there is a recent SWOG/NCTN study (NCT03678025) which plans to randomize patients to standard systemic therapy versus standard systemic therapy and either RP or RT to the primary site with results expected in 2031. Overall, only one randomized trial to date has found some survival benefit with the use of local RT in metastatic prostate cancer, though this benefit seems more prominent in those with a low burden of metastatic disease. Randomized trials are ongoing and will help to elucidate the role of such treatment and perhaps be practice-changing, but many of these trials have just opened and will not have results for several years.

Local RT in oligometastatic disease

As aforementioned, there are indications that the benefit of local RT may be dependent on the burden of metastatic disease. As a result, several studies have explored the role of RT in oligometastatic disease, albeit with no general consensus regarding the definition of oligometastatic disease. An early study defined it as an intermediate state between purely localized lesions and widely metastatic disease [28]. Subsequent studies have found better survival in patients who had less than five and six bone metastases respectively, lending further credence to the idea of oligometastases [29, 30].

The currently available trials of ablative radiotherapy in oligometastatic disease are of limited sample size, but do provide some evidence of benefit. For example, Habl et al found that stereotactic body radiation therapy (SBRT) had high local control rates and an increase in time to initiation or intensification of ADT from 9.3 to 12.3 months, though the PSA progression-free survival was limited due to a rather high distant failure rate [31]. Multiple Italian trials have also shown some benefit for patients with oligometastatic disease. Triggiani et al showed improvement in distant progression-free survival in patients who received SBRT, while Ingrosso et al found an improvement in biochemical progression-free survival with a median of 24 months and mean ADT-free survival of 13.58 months [32, 33]. Furthermore, Jereczek et al found a 30 month progression-free survival rate of 42.6% after SBRT to a lymph node recurrence, and Casamassima et al found overall survival, disease-free survival and local control rates were 92%, 17% and 90%, respectively [34, 35]. Another trial from Belgium discovered that patients who underwent SBRT had a median ADT-free survival of 38 months [36]. In the United States, a study by Muldermans et al found that biochemical progression-free survival was 54% at 16 months and Ahmed et al found a 100% local control rate and a freedom from distant progression of 40% at one year [37, 38].

While these studies demonstrate the benefit of SBRT in men with oligometastatic prostate cancer, there may still be a need to validate these findings in larger prospective trials. There are two large Phase II/III Canadian trials that are actively accruing to evaluate the role of SBRT in

oligometastatic disease. In GROUQ's PCS IX (NCT02685397), castrate-resistant prostate cancer patients with an oligometastatic recurrence are being randomized in 1:1 ratio to either enzalutamide alone or enzalutamide and SBRT to five or less metastatic lesions with a primary endpoint of time to radiological progression. NCIC-CCTG PR20 is another prospective Phase III randomized trial of hormone sensitive prostate cancer patients in which patients will be randomized to standard systemic therapy or standard systemic therapy with SBRT to the oligometastatic lesions. The results of these trials will help to establish the role of SBRT in oligometastatic disease.

Conclusion

The role of radiation in metastatic prostate is evolving, with recent studies attempting to clarify the benefit of local therapy in metastatic disease. While retrospective studies have been encouraging and demonstrated benefit of local RT in patients with metastatic prostate cancer, there are ongoing prospective trials to further validate these findings. Thus far, the STAMPEDE trial is the only randomized dataset to demonstrate a survival benefit, though this was limited to those who had a relatively low metastatic burden [26]. Current ongoing and future studies will continue to inform the treatment paradigm in patients with metastatic prostate cancer.

Disclosure of conflict of interest

None.

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