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REVIEW

The oncologic role of local treatment in primary metastatic prostate cancer

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Abstract
Purpose To determine the oncologic benefit or otherwise of local treatment of the prostate in patients with primary metastatic prostate cancer.
Methods A review of the literature was performed in April 2014 using the Medline/PubMed database. Studies were identified using the search terms "prostate cancer," "metastatic," "metastasis," "high risk," "radiation therapy," "radiotherapy" and "prostatectomy" from 1990 until April, 2014. Articles were also identified through searches of references of these articles.
Results Retrospective series and population-based data suggest that the use of local treatment of the prostate in patients with primary metastatic prostate cancer may improve cancer-specific survival and overall survival compared with treating these patients with androgen deprivation therapy alone. The clinical outcome in metastatic prostate cancer is largely determined by the extent of lymph node involvement and overall metastatic burden. Contemporary data are lacking to recommend one alternative of local therapy (radiotherapy or radical prostatectomy) over

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the other. The primary limitation of this literature review is the lack of published randomized trial assessing the role of local treatment in addition to systemic therapy.
Conclusions Local treatment appears to improve oncologic outcomes in metastatic prostate cancer patients. Nevertheless, due to the lack of high-quality evidence, its role needs to be confirmed in future prospective trials. The selection of ideal candidates and optimal treatment alternative (radiotherapy, radical prostatectomy or other) warrants further investigation.

Keywords Prostate cancer · Metastatic · Metastasis · High risk · Local treatment · Outcomes · Radiation therapy · Radiotherapy · Radical prostatectomy

Introduction

To date, there is no consensus on the role of local therapy in the management of men with metastatic prostate cancer to the lymph nodes (T1-4, N1, M0) [1]. Traditionally, involvement of lymph nodes in prostate cancer was considered as an adverse prognostic factor associated with limited long-term survival regardless of treatment. However, new clinical data are challenging this concept as several studies have suggested an oncologic benefit to local treatment even in a metastatic setting. Thus, a benefit from radical prostatectomy (RP), lymphadenectomy plus androgen deprivation therapy (ADT) may prove advantageous as compared to ADT alone [2, 3]. While the role of radiation therapy (RT) in treating lymph node metastasis is still unclear [4, 5], it appears that the addition of RT to the prostate in men with lymphadenectomy-confirmed pelvic nodal metastases may improve the overall survival when undergoing combined RT of the prostate and ADT as compared to ADT alone [6].

Men with extranodal metastatic prostate cancer (T1-4, N0-1, M1) constitute a heterogeneous group of patients which may be stratified according to various parameters, including the presence of axial versus appendicular bone metastasis, visceral metastasis, performance status and primary tumor characteristics (Gleason score and prostate-specific antigen (PSA) level [7]. These patients usually forgo local treatment of the prostate and generally receive palliative ADT as first-line therapy. Palliative local treatment of the prostate may be performed in the presence of palliative symptoms such as bleeding or obstruction. Because improvements in outcome of metastatic patients after treatment of the primary tumor have been described for other solid cancers such as renal cell carcinoma and colorectal cancer [8–10], the question of whether this can be applied to men with primary metastatic prostate cancer remains imperative.

To date, local treatment has no consensus-based role in metastatic prostate cancer patients. A previous systematic review suggested that addition of adjuvant ADT to local therapy improved outcomes in high-risk or proven lymph node-positive patients [11]. However, the reverse question has not been thoroughly investigated, i.e., local therapy in addition to ADT. We sought to summarize the recent results and clinical implications regarding local treatment of the prostate in patients with primary metastatic prostate cancer.

Methods

References for this Review were identified through searches of PubMed from 1990 until April, 2014. Various algorithms including the following terms were used: "prostate cancer," "metastatic," "metastasis," "high risk," "radiation therapy," "radiotherapy" and "prostatectomy." Articles were also identified through searches of references of these articles. The references lists of the retrieved articles were reviewed to ensure all the key pertinent studies were included. Only papers published in English were reviewed. The final reference list was approved by two authors (PG, GP) on the basis of originality and relevance to the scope of this review article.

Results

Rationale

The first association between metastatic progression and primary tumor was observed by Stephen Paget back in 1889. Illustrating this concept by the "seed and soil" theory, he was the first to point out the influence of the primary tumor on subsequent anatomical distribution of metastases. Recently, the concept of a "premetastatic niche" was described by Kaplan et al. [12]. These authors highlighted the fundamental role of nonmalignant bone marrow-derived cells in sensitizing the target tissue to be able to accept circulating malignant cells. In other words, the primary tumor is able to prime the microenvironment where metastatic deposits will develop. In addition to the delivery of malignant cells into the circulation, the primary tumors may also control the metastatic burden and distribution of metastasis by reciprocating with nonmalignant cells and endocrine

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factors. In a large cohort of 384 patients with prostate cancer undergoing bone marrow aspiration, the risk of developing clinical metastases has been associated with the presence of tumor cells in bone marrow only when the primary tumor was present. The risk of metastasis was negligible when the primary tumor had been removed, even when circulating tumor cells were still detected [13]. Cytokine-based influence via the primary tumor was hypothesized as a plausible explanation to this observed difference.

Contrary, several series have shown the opposite, where in fact surgical removal of the primary tumors was associated with distant angiogenesis and increased growth of metastases [14].

Role of radical prostatectomy in men with metastatic prostate cancer

The vast majority of RP series reporting on the oncologic outcomes in metastatic prostate cancer patients have focused on patients with pathologically confirmed lymph node metastasis. Overall, the 10-year cancer-specific survival after RP for pathologically proven positive lymph node cancer ranged from 70 to 85 % [3, 15, 16]. Conversely, the biochemical recurrence-free rates were poor from 20 to 35 % 5 years after surgery. These discrepancies may be explained by the use of multimodal adjuvant or salvage strategies (RT of the prostate and pelvic lymph nodes, ADT) leading to promising cancer-specific survival outcomes [16]. Thus, Abdollah et al. [16] recently suggested that adjuvant RT combined with ADT did better than ADT alone reinforcing the oncologic role of local therapy.

Such good results after RP, even in lymph node-positive prostate cancer patients, encouraged urologists to complete RP and led them to give up intraoperative frozen section of pelvic node during RP. Retrospective series from Germany confirmed the potential benefit of RP in lymph node-positive patients. The first series published by Frohmüller and colleagues assessed the oncologic outcomes in 139 patients with histologically proven node metastases [17]. In 87 patients, only lymphadenectomy plus ADT was performed. The remaining 52 patients who also underwent RP had significantly better survival rates as compared with their nonoperated counterparts (10-year cancer-specific survival rates 70 vs. 32 %, respectively). Nevertheless, the possible selection bias inherent in any retrospective analysis reflected in subgroups imbalances limited a meaningful comparison between both groups.

More recently, 1,413 prostate cancer patients with lymph node metastasis were retrospectively identified in the Munich Cancer Registry [3]. Among this cohort, RP was aborted in 456 patients at the surgeon's discretion. Patients in whom RP was completed had improved survival compared with those in whom RP was aborted. While this study is, again, limited by its retrospective nature, a multivariate model controlling for possible confounders (such as age, stage, Gleason score, PSA level and number of positive nodes) found RP to be an independent predictor of survival (hazard ratio 2).

Steuber et al. [18] also investigated the oncologic impact of RP in a retrospective series of prostate cancer patients with lymph node metastasis. The series included 158 patients as follows: 50 patients undergoing lymph node dissection and ADT alone, and 108 patients treated by RP, lymphadenectomy and adjuvant ADT. Type of treatment (aborted or completed RP) and number of positive lymph nodes were independent predictors of cancer-specific and clinical progression-free survival.

An important consideration is that not all lymph node-positive patients appear to benefit from RP. The overall metastatic burden may determine the postoperative disease course and may help identify patients at high risk of progression who may not be considered ideal candidates for aggressive local treatment. Data from RP series indicated that disease-free survival decreased with increasing number of positive lymph nodes, thus supporting the relationship between size and number of involved lymph nodes and disease prognosis [3, 19].

Given that no randomized controlled trial has compared ADT alone versus ADT plus RP in patients with lymph node metastasis, some cautious conclusions can be inferred by comparing outcomes of different phase III trials. In 2006, Messing and colleagues published results from a phase III trial comparing immediate versus deferred androgen deprivation therapy after RP in men with lymph node involvement [2]. Three years later, Schröder et al. [20] reported outcomes in lymph node-positive patients treated by immediate of deferred ADT without local treatment of the primary tumor. Both trials excluded patients with bone or visceral metastases and have achieved at least a 10-year median follow-up. The main difference between studies was the presence (Messing trial) or absence (Schröder trial) of primary tumor treatment. The 10-year overall survival rates in the immediate ADT arms were >70 % when a RP was performed compared with 30 % in the absence of local treatment. In patients receiving deferred ADT, survival rates were about 55 % and 25 %, respectively. Even if one considers the comparison of outcomes from two studies involving different cohorts as fundamentally flawed, the question of whether targeting the primary tumor may have had a role in dramatically improving patients' survival in the setting of limited lymph node metastasis cannot be overlooked.

Published reports also suggested that in lymph node-positive patients, RP offered better oncologic results when incorporated into a multimodal strategy using adjuvant RT as well as adjuvant ADT [2, 16]. Recent updated report

from Abdollah and colleagues also suggested that addition of RT to RP plus ADT in lymph node-positive patients was independently associated with improved cancer-specific survival [16]. However, while adjuvant combined treatments appeared promising in the postoperative management of these patients, there is no convincing evidence supporting the use of neoadjuvant treatment before RP. The timing and duration of adjuvant ADT also remain debatable [1, 2, 16].

Role of radiation therapy in men with metastatic prostate cancer

Few RT series have assessed the benefit of adding RT to ADT alone in metastatic prostate cancer. Two large randomized controlled trials including high-risk prostate cancer patients at high risk of micrometastatic disease, who were classified as cM0 patients at inclusion [21, 22], have compared ADT alone versus ADT and RT of the prostate. A significant overall survival advantage of almost 10 % at 10 years or 8 % at 7 years in favor of the combined treatment was observed, respectively. While applying these findings to patients with overt metastatic disease is limited, the data imply that treatment of the primary tumor may inhibit pathophysiological pathways promoting cancer dissemination and metastatic growth in prostate cancer [12, 23].

Evidence also suggests that in lymph node-positive patients, RT should not be given alone. Poor long-term survival rates ranging from 20 to 30 % at 10 years have been reported in small series of pathologically proven lymph node-positive patients treated by RT alone. The superiority of RT plus ADT as compared with RT alone has been definitely proven by one phase III trial (protocol RTOG 8531) in terms of overall survival and freedom from metastases [24].

To date, no randomized controlled trial comparing ADT alone versus ADT combined with RT to the primary tumor in the proven metastatic setting has been completed. One retrospective series reported oncologic outcomes of 183 lymph node-positive patients treated by RT plus ADT or ADT alone between 1984 and 1998 [6]. The radiotherapy volume did not include pelvic nodes. Addition of RT to ADT was associated with better outcomes in terms of biochemical-free, metastasis-free and overall survivals. Confounders between treatment groups were controlled by a multivariate analysis confirming RT as an independent predictor of outcome.

Population-based data

Culp et al. [25] analyzed the outcomes of all patients with metastatic prostate cancer at diagnosis from the Surveillance Epidemiology and End Results (SEER) database, treated between 2004 and 2010 by either brachytherapy, RP or no local treatment. Patients who were coded as treated by external beam RT were excluded, because the target volume (prostate or, e.g., bone lesion) could not be verified in the database. A total of 8185 patients were identified and the majority ($n = 7811$) received no local treatment, while RP was performed in 245 patients and brachytherapy in the remaining 129 patients. The median follow-up was 16 months. A total of 3,115 patients (38.1 %) died of prostate cancer. The 5-year overall survival and cancer-specific survival were significantly higher in patients undergoing radical prostatectomy (67.4 and 75.8 %) or brachytherapy (52.6 and 61.3 %) as compared to patients without local treatment of the prostate (22.5 and 48.7 %; $p < 0.001$). In a multivariate analysis, the application of local therapy was independently associated with decreased cancer-specific mortality ($p < 0.01$). To account for patients who might not benefit from local therapy, a subset analysis was performed excluding patients who died $\leq$12 months from diagnosis ($n = 1,813$) or with additional known malignancy ($n = 618$). At a median follow-up of 27 months, the 5-year overall survival rates remained higher in patients undergoing local treatment (RP 76.5 %; brachytherapy 58.2 %) as compared with those without local treatment of the prostate (30.6 %; $p < 0.001$). Additionally, use of radical prostatectomy or brachytherapy remained independently associated with decreased cancer-specific mortality compared with patients who did not undergo local treatment, with 5-year disease-specific survival probabilities of 75.1, 64.5 and 46.9 %, respectively. Factors associated with increased cancer-specific mortality in patients undergoing local treatment of the prostate included T-classification T4, high-grade disease, prostate-specific antigen $\geq$20 ng/ml, age $\geq$70 year and positive pelvic lymph nodes, suggesting that these patients may less likely benefit from local treatment.

Based on the Swedish national prostate cancer registry, Sooriakumaran et al. [26] performed an observational study on 34,515 men primarily treated for prostate cancer with radical prostatectomy ($n = 21,533$) or RT ($n = 12,982$). The primary objective was death from prostate cancer. Competing risks regression hazard ratios for RT versus surgery were computed without adjustment and after propensity score and traditional (multivariable) adjustments, as well as after propensity score matching. The median follow-up time was 5.37 years. Among patients with non-metastatic prostate cancer ($n = 32846$), the HR for prostate cancer mortality appeared to favor RP (HR 1.76, 95 % confidence interval 1.49–2.08, for RT vs. prostatectomy), whereas there was no such difference observed in treatment effect among men with primary metastatic disease (T4 or N+ or M+ or PSA > 50 ng/mL) ($n = 1,206$).

Discussion

Today, high-quality data on local treatment versus no local treatment in metastatic (N+ or M+) are not available.

Local treatment of the prostate in men with metastatic prostate cancer might prove beneficial in several manners: It undoubtedly may improve local tumor control thereby decreasing the need for subsequent palliative therapies, such as transurethral resection or urinary diversion. Moreover, it may alter the natural course of disease by slowing down progression of metastasis, as others have described that the untreated primary prostate cancer may act as a potential source for tumor spread and metastasis [12, 23]. Furthermore, in patients with locally advanced or nodal positive prostate cancer, it may also improve the response to ADT [11]. These potential benefits must be weighted against potential treatment-related toxicities and other consideration points such as general surgery risk (major complications after radical prostatectomy) or significant time commitment for RT.

A recent SEER population-based analysis suggested that the use of local treatment of the prostate in patients with primary metastatic prostate cancer may improve cancer-specific survival and overall survival as compared to patients without local treatment [25]. Based, on the Swedish national prostate cancer registry, in the setting of primary metastatic prostate cancer, radical prostatectomy and RT appear to be equally effective as local treatment modalities [26].

These data, however, must be regarded as hypothesis generating at best and warrant confirmation in future prospective clinical trials before it can be recommended in routine clinical practice. The SEER database analysis has important limitations including proper stage assignments through tumor registries, detailed patient information (e.g., number of metastases) and detailed treatment information (e.g., use of ADT or description of RT target volumes). If this novel approach is confirmed by further research, it may change the current standard of care in metastatic prostate cancer, which consists of palliative ADT as monotherapy. The SEER analysis [25] further suggested that local treatment in primary metastatic patients with prostate cancer might be less effective in the presence of certain risk factors including T-classification T4, high-grade disease, prostate-specific antigen $\geq$20 ng/ml, age $\geq$ 70 year and pelvic lymphadenopathy. This information might help to better select patients who may benefit mostly from local treatment, despite the presence of distant metastasis.

The ideal local therapy in a metastatic setting likewise remains unknown as there is no head-to-head comparison between local modalities in a randomized design. Resilient retrospective comparisons would need to consider only studies in the modern RT era with adequate follow-up time to allow meaningful analysis of hard clinical endpoints such as cancer-specific survival. While several large retrospective studies suggested an advantage to radical prostatectomy over RT [26–32], these comparisons remain largely limited by the profound selection bias as patients undergoing RT are significantly older, have more comorbidities and more advanced and aggressive disease compared with patients undergoing radical prostatectomy. Use of propensity scores or other statistical approaches cannot reliably compensate for these inherent confounders. Retrospective comparisons are further biased by the common application of further treatments, e.g., use of salvage RT in patients with biochemical recurrence after radical prostatectomy would need to be considered, as this procedure by itself improves overall survival [33].

The clinical outcome in lymph node-positive patients is largely determined by the lymph node characteristics. Thus, data regarding the outcome of patients with varying pathologic or clinico-biologic features may help to identify patients who will benefit most from local treatment. When the decision for a certain local treatment of the prostate was made in a primary metastatic prostate cancer patient, another question would be, whether the metastatic sites, if safely possible, should also be treated. Recent data suggest that patients with metastatic prostate cancer who received metastasis-directed therapy (metastasectomy or RT) after primary treatment with radical prostatectomy or RT of the prostate might have a benefit in terms of cancer-specific survival compared with those treated with ADT alone [34]. This must also be further clarified in future prospective trials. It is important to note that imaging methods for the detection of distant metastasis have significantly improved over the recent years as ^{18}F-fluoride PET/CT [1] and more recently PET imaging with a [68 Ga] gallium-labeled PSMA ligand [35] are highly sensitive and specific imaging modalities and identify a relatively high number of distant metastasis in patients who would else have been staged and treated as "nonmetastatic."

A recent report from the Munich Cancer Registry described the overall survival in metastatic prostate cancer patients who underwent or not a RP. From the 4.8 % of patients ($n = 74$) who underwent a RP, the overall survival was significantly higher as patients who underwent RT ($n = 389$) or ADT alone ($n = 635$) [36]. It is, however, obvious that a selection bias, at least in part, contributed to these results as patients with metastatic disease who underwent RP had most probably more limited metastatic burden as patients who underwent RT or ADT alone.

Several trials are ongoing to further elucidate the local treatment in the primary metastatic setting. The HORRAD randomized trial (Netherlands Trial Register [trialregister.nl], NTR271) and STAMPEDE as a multistage, multiarm randomized trial (ClinicalTrials.gov,

NCT00268476) both explore whether ADT combined with RT is superior to ADT alone in patients with metastatic prostate cancer. Moreover, a phase II randomized trial of systemic therapy versus systemic therapy plus definitive treatment of the prostate (RT or RP) in men with metastatic prostate cancer is recruiting patients in the USA (ClinicalTrials.gov, NCT01751438). A similar trial is being planned in Europe.

Conclusion

Low quality evidence suggests that local treatment of the primary tumor may improve survival in patients with primary metastatic prostate cancer, particularly in cases of limited metastatic burden. The use of lymph node status to propose or not a curative intent treatment does not appear appropriate. This finding, supported by recent population-based data and retrospective series, awaits confirmation by ongoing prospective randomized trials and has the potential to significantly change the clinical management of patients with metastatic prostate cancer. Published reports also highlight the need for more aggressive treatments which should be based on multimodality strategies including both local and systemic therapies. To date, the literature does not allow meaningful comparison between the available different local treatments (radiotherapy, surgery).

Conflict of interest There is no conflict of interest to disclose.

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