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The role of metastasis-directed therapy and local therapy of the primary tumor in the management of oligometastatic prostate cancer

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Oligometastasis has been proposed as an intermediate stage of cancer spread between localized disease and widespread metastasis. Oligometastatic malignancy is now being diagnosed more frequently as the result of improvements in diagnostic modalities such as functional imaging. The importance of oligometastasis in managing metastatic prostate cancer is that it is possible to treat with a curative aim by metastasis-directed or local therapy in selected patients. Many studies have shown that these aggressive treatments lead to improved survival in other oligometastatic malignancies. However, few studies have shown definitive benefits of metastasis-directed or local therapy in oligometastatic prostate cancer. Review of the available studies suggests that stereotactic radiotherapy (RT) of metastatic lesions in oligorecurrent disease is a feasible and safe modality for managing oligometastatic prostate cancer. Also, stereotactic RT can delay the start of androgen deprivation therapy. Many retrospective studies of metastatic prostate cancer have shown that patients undergoing local therapy seem to have superior overall and cancer-specific survival compared with patients not receiving local therapy. Ongoing prospective randomized trials would be helpful to evaluate the role of local therapy in oligometastatic prostate cancer.

Keywords: Neoplasm metastasis; Prostatectomy; Prostatic neoplasms; Radiotherapy

INTRODUCTION

Various modalities such as radical prostatectomy (RP), radiation therapy (RT), and systemic therapy have been used to treat prostate cancer. Conventionally, RP and RT have been offered with the aim of curing localized prostate cancer [1]. Such definitive local therapies are usually not considered in cases of advanced or metastatic disease, for which systemic therapy such as androgen deprivation therapy (ADT) has been used for a palliative aim, even if there is only single lymph node (LN)-positive disease [2]. In advanced or metastatic prostate cancer, ADT is used to delay disease progression and relieve cancer-related or metastasis-related symptoms [3,4].

Since the use of prostate-specific antigen (PSA) measurement in clinical practice, the proportion of advanced prostate cancer at the time of initial diagnosis has decreased. During the early PSA era, Smith et al. [5] reported that the proportion of men with pathologically advanced cancer was reduced from 33% to 27%. Some years later, Ryan et al. [6]

reported that the rate of metastatic prostate cancer at the time of first diagnosis had decreased from 4.2% since 1998 to 1.6%. However, a significant number of patients undergoing local therapy will experience biochemical recurrence. Recently, Mullins et al. [7] observed that 10-, 15-, 20-, and 25-year rates of biochemical recurrence were 18%, 22%, 26%, and 32% in a study that reported 30-year oncological outcomes of 4,478 open RPs performed by a single surgeon between 1982 and 2011.

Among patients with metastatic or recurrent prostate cancer, some patients may have oligometastatic status. Oligometastasis is a minimal metastatic status that is considered an intermediate state between localized disease and widespread metastasis [8]. The importance of oligometastasis is that local therapy for the primary tumor or metastasis-directed therapy could be performed with a curative aim in selected patients with limited metastasis [9]. Actually, many studies have shown that local therapy for the primary tumor is associated with improved survival in other malignancies such as renal cell cancer, colon cancer, and glioblastoma [10-12].

Some studies have inferred that oligometastatic prostate cancer is related to favorable oncologic outcomes. In these studies, a fewer number of metastatic lesions was associated with improved survival in patients with metastatic disease. In addition, metastatic lesions were also important predictors for survival [13-15]. However, few studies of the benefit of metastasis-directed or local therapy in patients with oligometastatic prostate cancer are available. Here we review not only studies about the management of oligometastatic prostate cancer but also studies about "common" metastatic prostate cancer. In addition, we assess the role of metastasis-directed or local therapy for oligometastatic prostate cancer.

TREATMENT OF OLIGOMETASTATIC PROSTATE CANCER

1. Definition of oligometastasis in prostate cancer

It is important to define oligometastatic prostate cancer when carrying out studies. Unfortunately, however, there has been no consensus on the definition of oligometastasis in prostate cancer. But some studies are available that can help to determine the number of metastatic lesions for oligometastasis. For example, Soloway et al. [16] evaluated the relation of extent of metastatic lesions and survival by using a semiquantitative grading system. They found that the 2-year survival rate in patients who had fewer than six bone metastases on a bone scan was 96%. Singh et al. [17] reported that patients with 5 or fewer metastatic lesions

had significantly better survival rates than did patients with more than 5 lesions. Thus, referring to these studies, it might seem reasonable to define oligometastasis as 5 or fewer metastatic lesions. However, most studies related to oligometastasis have used their own definition (Table 1).

2. Radiotherapy for oligometastatic prostate cancer

Most studies on the management of oligometastatic prostate cancer have concerned the results of stereotactic RT on metastatic lesions. In the beginning, most studies focused on the safety and feasibility of metastasis-directed RT. Jereczek-Fossa et al. [18] were the first to report the results of treatment with stereotactic RT for metastatic lesions. In that study, 14 patients were treated with CyberKnife image-guided stereotactic RT for isolated LN recurrence. The authors observed that the local control rate was 100% at 18.6 months and that there was no grade 3 toxicity. The same authors reported the results of RT on LN or bone metastasis some years after their first study [19]. They treated 34 patients with 38 lesions and the local control rate was 88% at 16.9 months. The 30-month progression-free survival rate was reported as 42.6%. In another study, Muacevic et al. [20] treated 40 patients with 64 bone metastases with stereotactic body radiation therapy (SBRT). The number of metastatic lesions was less than 2 and the lesions were limited to the spine. The mean follow-up time was 14 months and the estimated local control rate was 95.5% at 6, 12, and 24 months. Some minor adverse effects were reported, including mild nausea in 5 men (12.5%) and a silent rib fracture in 1 patient (2.5%). Ahmed et al. [21] treated one liver lesion and one LN lesion in addition to 19 bone metastases. They observed a 100% local control rate at 4.8 months and that 9 patients (53%) reached an undetectable serum PSA. Six of the 11 patients (55%) with hormone refractory disease achieved either undetectable or declining PSA at the time of analysis. A retrospective multicenter analysis also showed similar results. Ost et al. [22] treated 119 patients with 163 metastatic lesions including LN, bone, and viscera were treated with SBRT. With a median follow-up of 5 years, overall survival (OS) was 88% and distant progression-free survival was 21 months (95% confidence interval [CI], 15–27). The 3- and 5-year distant progression-free survival rates were 31% and 15%, respectively, and the 3- and 5-year local progression-free survival rates were 93% and 92%, respectively.

The studies above allowed ADT before patients received RT because of metastatic or recurrent prostate cancer. Some studies investigated whether repeated SBRT could postpone the initiation of palliative ADT in patients with limited metastatic lesions. Berkovic et al. [23] studied 24 patients

Table 1. Radiotherapy on metastatic lesions of oligometastatic prostate cancer

Study	No. of patients/No. of treated lesions	Maximal number of metastases per patient	Sites of metastasis	Radiation dose/fractions	Local control	Toxicity	Other findings
Jereczek-Fossa et al. [18]	14/14	1	Pelvic LN	30 Gy/3	100% at 18.6 mo	≥Grade 3: 0	
Jereczek-Fossa et al. [19]	34/38	NS	LN, bone	30–36 Gy/3–5	88% at 16.9 mo	≥Grade 3: 5.9%	30-mo PFS: 42.6%
Muacevic et al. [20]	40/64	NS	Bone	Mean dose 20.2 Gy/1	95.5% at 2 y	-	
Ahmed et al. [21]	17/21	≤5	LN, bone, liver	Median dose 20 Gy/1	100% at 4.8 mo	Grade 1: 9.5% Grade 2: 9.5% ≥Grade 3: 0%	12-mo CSS: 100% 12-mo FFDP: 40%
Ost et al. [22]	119/163	≤3	Any	-	93% at 3 y	Grade 1: 14% Grade 2: 3% ≥Grade 3: 0%	Median ADT-FS: 28 mo 5-y OS: 88% 5-y DPFS: 15%
Berkovic et al. [23]	24/29	≤3	LN, bone	50 Gy/10	100% at 2 y	Grade 1 GI: 8% Grade 2 GU: 6% ≥Grade 3: 5.9%	Median ADT-FS: 38 mo 2-y CPFS: 42%
Decaestecker et al. [24]	50/70	≤3	LN, bone	50 Gy/10 or 30 Gy/3	100% at 2 y	Grade 1: 14% Grade 2: 6% Grade 3: 0%	Median ADT-FS: 25 mo 2-y PFS: 35%
Schick et al. [25]	50/-	≤4	NS	Median dose 64 Gy/-	-	≥Grade 3: 0%	3-y bRFS: 54.5% 3-y OS: 92%

ADT-FS, androgen deprivation therapy-free survival; bRFS, biochemical relapse-free survival; CPFS, clinical progression-free survival; CSS, cancer-specific survival; DPFS, disease progression-free survival; FFDP, freedom from distant progression; LN, lymph node; NS, not specified; OS, overall survival; PFS, progression-free survival.

with up to 3 metastatic lesions following biochemical recurrence after local curative treatment. None of the patients had been treated with ADT before they received RT. The authors defined ADT-free survival (ADT-FS) as the time interval between the first day of SBRT and the initiation of ADT. With a median follow-up of 24 months, 10 patients started with ADT resulting in a median ADT-FS of 38 months. In another study, Decaestecker et al. [24] treated 50 patients with 70 metastatic lesions and observed a local control rate of 100% at 2 years. The median progression-free survival was 19 months (95% CI, 13–25) and median ADT-FS was 25 months (95% CI, 20–30). On univariate analysis, the authors found that a short PSA doubling time was a significant predictor for both progression-free survival (hazard ratio [HR], 0.90; 95% CI, 0.82–0.99) and ADT-FS (HR, 0.83; 95% CI, 0.71–0.97).

The studies mentioned above concerned the management of metachronous metastatic lesions of prostate cancer. Schick et al. [25] studied 50 prostate cancer patients who were diagnosed with not only metachronous metastasis but also synchronous metastasis. With a median follow-up of 31 months, 4-year biochemical relapse-free survival (bRFS), clinical failure-free survival, and OS rates were 54.5%, 58.6%, and 92%, respectively. The number of metastases and number of radiation doses were related to improved bRFS.

As reviewed, metastasis-directed stereotactic RT is deemed safe and suitable for managing recurrent prostate cancer because it has an acceptable local control rate and relatively low rate of toxicity. However, to evaluate the benefit on oncologic outcomes, more precise randomized controlled trials (RCTs) are needed. Another advantage of SBRT on metastatic lesions is that it seems to delay ADT initiation in patients with recurrent prostate cancer. Long-term ADT induces several significant physical and psychological adverse effects, because of the castration level of testosterone. These side effects include an increased risk of cardiovascular disease, sexual impairment, metabolic syndrome, loss of lean body mass, osteoporosis, fracture, cognitive impairment, fatigue, and anemia. Furthermore, in some patients, ADT may decrease overall life expectancy [26-30]. In this aspect, deferring the start of ADT may help patients live with a better quality of life.

3. Prostatectomy in oligometastatic prostate cancer

Gandaglia et al. [31] assessed perioperative and long-term oncologic outcomes of RP in oligometastatic prostate cancer. Eleven patients who had 5 or fewer metastatic lesions were treated with RP and extended pelvic LN dissection. With a median follow-up of 63 months, the

7-year clinical progression- and cancer-specific mortality-free survival rates were 45% and 82%, respectively. Heidenreich et al. [32] reported a case-control study examining the role of cytoreductive radical prostatectomy (CRP) in selected men with limited metastatic disease. A total of 23 patients diagnosed with prostate cancer with less than three osseous metastases, absence of visceral or extensive LN metastasis, and PSA decrease to <1.0 ng/mL after ADT were included and underwent CRP. The control group consisted of 38 patients with metastatic prostate cancer who received only ADT. Median time to castration-resistant prostate cancer was delayed in the CRP group compared with the control group (40 months vs. 29 months, p=0.04). The CRP group also experienced significantly better clinical progression-free survival (38.6 months vs. 26.5 months, p=0.032) and cancer-specific survival (CSS) (95.6% vs. 84.2%, p=0.043). They also reported complications and functional outcome. Among 38 patients, 3 patients underwent interventions such as percutaneous drainage or laparoscopic marsupialization due to lymphocele and 3 patients experienced DVT. A total of 21 patients were continent, but 2 patients needed two to four pads per day.

These 2 studies are all of the available research on RP in oligometastatic prostate cancer. Thus, it is hard to evaluate the benefit of local therapy with so few studies. Because an important issue in oligometastasis is the possibility of curing advanced disease with local therapy, it is necessary to try to estimate the effectiveness of local therapy by using review studies that report the benefit of local therapy on advanced or metastatic prostate cancer.

TREATMENT OF LOCALLY ADVANCED OR METASTATIC PROSTATE CANCER

1. Locally advanced or LN-positive prostate cancer

Various combination therapies have been offered to treat locally advanced prostate cancer. Historically, the role of external irradiation in patients with locally advanced disease was controversial because of poor oncologic outcomes as the result of undetectable micrometastasis. Therefore, the combination of RT and ADT was offered. Bolla et al. [33] reported the results of a randomized phase 3 trial assessing the benefit of the addition of ADT to external irradiation in patients with prostate cancer with high metastatic risk. With a median follow-up of 9.1 years, the 10-year OS rate was 39.8% (95% CI, 31.9–47.5) in patients receiving RT alone and 58.1% (95% CI, 49.2–66.0) in those receiving combined treatment (HR, 0.60; 95% CI, 0.45–0.80; p=0.0004). The 10-year clinical disease-free survival was 22.7% (95% CI, 16.3–29.7)

in the RT-alone group and 47.7% (95% CI, 39.0–56.0) in the combined treatment group (HR, 0.42; 95% CI, 0.33–0.55; p<0.0001). Another randomized study showed similar results. At 10 years, the absolute survival rate was greater in the adjuvant ADT group than in the control group (49% vs. 39%, p=0.002) [34].

The results of a population-based study showed that about 33% of patients who underwent RP experienced positive surgical margins [35]. Another study reported that among patients who underwent RP, 9% had seminal vesicle invasion [36]. These unfavorable pathologic results are associated with a higher rate of local failure. To improve local control in patients with undesirable pathologic results, adjuvant RT has been suggested. One RCT reported that metastasis-free survival as well as OS was significantly greater in the RP with adjuvant RT group than in the control group. Another RCT reported that progression-free survival was superior in an RP with adjuvant RT group than in a non-RT group, but that OS and metastasis-free survival were similar between groups [37,38].

As for locally advanced prostate cancer, multimodal therapy has also been examined for LN-positive disease. One matched analysis assessed the impact of combination adjuvant hormonal therapy (HT) and RT on the survival of patients with prostate cancer and pathologically confirmed LN metastasis. Patients treated with adjuvant RT with HT had significantly higher CSS and OS rates than did patients treated with HT alone at 5, 8, and 10 years after surgery (95%, 91%, and 86% vs. 88%, 78%, and 70%, and 90%, 84%, and 74% vs. 82%, 65%, and 55%, respectively; p=0.004 and p<0.001, respectively) [39].

When we look at studies focused on the advantage of definitive local therapy of prostate for local disease control, the Scandinavian Prostate Cancer Group Study 7 and the Swedish Association for Urological Oncology 3 trial reported that cancer-specific mortality (11.9% vs. 23.9%) and overall mortality (29.6% vs. 39.4%) were lower in the RT with ADT group than in the ADT alone group in locally advanced prostate cancer [40]. Warde et al. [41] performed another randomized phase 3 trial involving 1,205 patients who were randomly assigned (602 in the ADT-only group and 603 in the ADT and RT group). With a median follow-up of 6 years, they found that the addition of RT to ADT improved OS at 7 years (74% vs. 66%; HR, 0.77; p=0.033) compared with ADT alone in locally advanced prostate cancer. Another randomized phase 3 trial showed a similar result. Mottet et al. [42] reported that combined therapy was related with higher 5-year progression-free survival (60.9% vs. 8.5%), lower loco-regional progression (9.8% vs. 29.2%), and

lower metastatic progression (3.0% vs. 10.8%) compared with ADT alone. Referring to the RCTs above, it appears that RT for local control may help to reduce the risk of disease progression and improve loco-regional control when it is combined with ADT.

Some retrospective studies are available to evaluate the effectiveness of local therapy of the primary tumor for patients with LN-positive prostate cancer. Lin et al. [43] assessed the effect of the addition of RT to ADT on survival with clinically node-positive prostate cancer using the National Cancer Data Base. Of 3,540 patients, 1,141 patients (32.2%) were treated with ADT alone and 1,818 (51.4%) received ADT with RT. Compared with ADT alone, the addition of ADT to RT was associated with a 50% decreased risk of 5-year overall mortality. Engel et al. [44] reported the effectiveness of RP in LN-positive prostate cancer. In that study, a total of 938 LN-positive patients from the Munich Cancer Registry were studied: 688 patients had received RP and 250 patients had not. With 5.6 years of median follow-up, 10-year OS and 10-year estimated CSS were 64% and 86% with RP and 28% and 40% with aborted RP, respectively. Another study based on the Surveillance, Epidemiology, and End Results (SEER) database showed similar results. Rusthoven et al. [45] divided 3,787 patients into clinical (cN+) and pathologically confirmed (pN+) LN-positive cohorts. Among cN+ patients, 340 patients underwent external beam radiation therapy (EBRT) and 456 had no local therapy. Outcomes for cN+ patients demonstrated that the EBRT group had a greater 10-year OS rate (45% vs. 29%, p<0.001) and CSS rate (67% vs. 53%, p<0.001) than did the no local therapy group. Among 2,991 pN+ patients, 2,334 patients underwent local therapy (RP, 1,709; EBRT, 293; both, 332) and 657 patients had no local therapy. Outcomes for pN+ showed favorable results in the local therapy group, with 10-year OS rates of 65% vs. 42% (p<0.001) and CSS rates of 78% vs. 56% (p<0.001). Among pN+ patients, there was no significant difference in survival between RP versus EBRT and RP with or without adjuvant EBRT.

2. Metastatic prostate cancer

The early studies related to local therapy in metastatic prostate cancer evaluated RP or RT as a factor influencing ADT for recurrent prostate cancer. Swanson et al. [46] followed until death 94 patients in whom primary RT failed and 67 in whom RP failed. All patients received ADT. This study showed that more patients in the RT group (78%) died of prostate cancer than in the RP group (63%, p=0.04). Thompson et al. [47] used data from the Southwest Oncology Group Study 8894, which was a randomized double-blind prospective phase III trial comparing orchiectomy plus the antiandrogen flutamide with orchiectomy plus placebo in men with metastatic prostate cancer [48]. The authors evaluated the impact of RP and RT on outcomes in patients with metastatic prostate cancer. They reported that previous RP in patients with metastatic prostate cancer was associated with a decreased risk of death (HR, 0.77; 95% CI, 0.53–0.89) relative to those who had not received RP. However, previous RT was associated with a greater risk of death in those who had previously undergone RP and in those who received no definitive earlier therapy.

Table 2 shows the studies related to local therapy of the prostate in metastatic prostate cancer. First, Culp et al. [49] used data from the SEER database and showed that definitive treatment of prostate cancer was related to a survival benefit in patients diagnosed with metastatic prostate cancer. For a total of 8,185 patients, the 5-year OS rate and predicted disease-specific survival rate were higher in patients undergoing RP (67.4% and 75.8%) or brachytherapy (52.6% and 61.3%) than in patients who underwent no surgery or RT (22.5% and 48.7%, respectively; p<0.001). In the multivariable competing risk regression analysis, patients treated with RP had a 62% lower risk of cancer-specific mortality (subhazard ratio [SHR], 0.38; 95% CI, 0.27–0.53; p<0.001) and patients who underwent brachytherapy had a 32% lower risk (SHR, 0.68; 95% CI, 0.49–0.93; p=0.018). Data from the Munich Cancer Registry showed a survival benefit of RP in metastatic prostate cancer. In a study of 1,538 patients newly diagnosed with metastatic prostate cancer, the RP group showed a 5-year OS rate of 55% compared with 21% in the non-RP group (p<0.01) [50]. Antwi and Everson [51] used data from the SEER database and showed similar results. Interestingly, the authors used propensity score analysis in addition to the conventional multivariable survival model. In the propensity score analysis, those receiving RP or BT had a lower risk of all-cause death regardless of extent of metastasis (M1a, M1b, M1c). Adjusted HR associated with RP was 0.18 (95% CI, 0.07–0.50; p=0.0008), 0.22 (95% CI, 0.16–0.30; p<0.0001), and 0.23 (95% CI, 0.16–0.35; p<0.0001) relative to no local therapy for metastatic disease, respectively.

Another population-based study also used the SEER database. Unlike the previous studies that used SEER, Satkunasivam et al. [52] divided the RT group into an intensity-modulated radiation therapy (IMRT) group and a conformal radiation therapy (CRT) group. They excluded patients with 15 or fewer treatment claims because such treatment likely represented palliative radiation. In addition, they also excluded patients who had received ADT by using

Table 2. Result of local therapy of the primary tumor in metastatic prostate cancer

Study	No. of patients/study design	Treatment	Overall survival	Cancer-specific survival	Multivariable analysis
Culp et al. [49]	8,185/population-based (data from SEER)	RP (n=245) BT (n=129) NLT (n=7,811)	5-Year 67.4% 52.6% 22.5% p<0.001	5-Year 75.8% 61.3% 48.7% p<0.001	SHR (CSM) 0.38 (0.27–0.53, p<0.001) 0.68 (0.49–0.93, p=0.018) 1.00 (reference)
Gratzke et al. [50]	1,538/population-based (data from MCR)	RP (n=74) RT (n=389) ADT (n=635) Other (n=440)	5-Year 55% (RP) 21% (No RP)	-	-
Antwi and Everson [51]	7,858/population-based (data from SEER)	RP (n=222) BT (n=120) NLT (n=7,516)	5-Year 82.0% 66.7% 43.6% p<0.0001	5-Year 84.7% 71.7% 54.6% p<0.0001	aHR (CSM) 0.28 (0.20–0.39) 0.46 (0.33–0.64) 1.00 (reference)
Satkunasivam et al. [52]	4,069/population-based (data from SEER)	RP (n=47) IMRT (n=88) CRT (n=107) NLT (n=3,827)	3-Year 73% 72% 37% 34% p<0.0001	3-Year 79% 82% 49% 46%	aHR (CSM) 0.48 (0.27–0.85, p=0.01) 0.38 (0.24–0.61, p<0.001) 0.85 (0.64–1.14, p=0.3) 1.00 (reference)
Parikh et al. [53]	6,051/population-based (data from NCDB)	RP (n=622) IMRT (n=52) CRT (n=153) NLT (n=5,224)	2-Year 72.5% 80.6% 47.6% 48.9%	-	HR (OS) 0.51 (0.45–0.59, p<0.01) 0.47 (0.31–0.72, p<0.01) 1.04 (0.86–1.27, p=0.67) 1.00 (reference)
Cho et al. [54]	140/case-control study	RT (n=38) No RT (n=102)	-	-	HR (OM) 0.43 (p=0.015)

ADT, androgen deprivation therapy; aHR, adjusted hazard ratio; BT, brachytherapy; CRT, conformal radiation therapy; CSM, cancer-specific mortality; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; MCR, Munich Cancer Registry; NCDB, National Cancer Database; NLT, no local therapy; OM, overall mortality; OS, overall survival; RP, radical prostatectomy; RT, radiotherapy; SEER, Surveillance Epidemiology and End Results; SHR, subhazard ratio.

billing-derived patient comorbidity and underwent early (less than 6 months) bone radiation because such early treatment might be a marker of advanced disease. With propensity score analysis, they observed that RP and IMRT were related to a lower risk of cancer-specific mortality with HRs of 0.48 (95% CI, 0.27–0.85; p=0.01) and 0.38 (95% CI, 0.24–0.61; p<0.001), respectively. However, CRT was not associated with a survival benefit relative to no local therapy (HR, 0.85; 95% CI, 0.64–1.14; p=0.3). Parikh et al. [53] showed consistent results in a study that used the National Cancer Database. They also reported that the use of RP and IMRT but not CRT to treat the primary disease was associated with improvements in OS for patients with metastatic prostate cancer.

Cho et al. [54] performed a case-control comparison evaluating the efficacy and toxicity of RT for the primary tumor in prostate cancer with metastasis. Among 140 men who were involved in the study, 38 patients underwent prostate RT, 39 patients underwent palliative RT, and the remaining 63 men did not receive any RT. They found that 3-year OS (69% vs. 43%, p=0.004) and 3-year biochemical failure-free survival (52% vs. 16%, p=0.002) were improved in prostate RT patients relative to the group who did not receive any RT. In the multivariate analysis, prostate RT was a significant predictor of OS (HR, 0.43; p=0.015). There was no grade 3 or greater toxicity among the patients who received prostate RT.

RATIONALE FOR LOCAL TREATMENT IN METASTATIC PROSTATE CANCER

Although most studies that have evaluated the benefit of local therapy on LN-positive and metastatic prostate cancer have been retrospective, the results suggest that local therapy may improve survival. However, the mechanism of the survival benefit of local therapy or cytoreductive surgery in metastatic prostate cancer is unclear. The "seeding and soil" theory is an important and widely accepted theory in cancer biology. It explains metastasis as being determined by interactions between the "seed" and the "soil." The "seed" has been renamed the progenitor cell, initiating cell, cancer stem cell, or metastatic cell, and the "soil" as host factors, stroma, or the organ microenvironment [55]. Haffner et al. [56] traced the evolution of a lethal cell clone from the primary cancer to metastasis through samples collected during disease progression and at the time of death. The authors used whole-genome sequencing and molecular pathological analyses to characterize the lethal cell clone. They found that the lethal clone arose from a small, relatively low-grade cancer focus in the primary tumor and not from the bulk, higher-grade primary cancer or from a LN metastasis resected during RP. Lindberg et al. [57] tried to identify the area in the prostate that gave rise to metastasis by searching for metastatic-specific DNA alterations in multiple regions of the prostate. They found that the clone most closely related to the metastasis was found in an intraductal carcinoma of the prostate. Traditionally, it has been thought that seeding of tumor cells is a unidirectional process. However, Kim et al. [58] showed that circulating tumor cells can also colonize their tumors of origin in a process they called "tumor self-seeding." Thus, the primary tumor can act as a self-seeding site for circulating tumor cells primed and deposited from established metastatic sites. Local therapy of the primary tumor or a metastatic site may alter the tumor biology and result in depressed growth or may limit the establishment of new metastatic sites.

Some preclinical studies support the role of cytoreductive surgery. Predina et al. [59] injected TC1 or LKR tumor cells into mice for induction of metastatic lung cancer and then performed cytoreductive surgery. They found that cytoreductive surgery helps to restore anti-tumor potency in immunotherapy for advanced cancer. The immune mechanisms that explained this restoration of anti-tumor immune responses included increased CD8 T-cell trafficking and reduced myeloid-derived suppressor cell populations.

We have also reviewed many retrospective studies on local therapy of the prostate in metastatic prostate cancer in the clinical setting. Most studies showed a consistent survival benefit of local therapy compared with nonlocal therapy. Retrospective studies have some limitations, however, such as treatment selection bias and the effect of unmeasured factors. Therefore, prospective randomized controlled studies are needed. There are currently many ongoing prospective randomized trials evaluating the role of primary tumor treatment in metastatic prostate cancer. Many of these are limited to oligometastatic prostate cancer. With data from these trials, we could understand the role of local therapy of the prostate and change the treatment paradigm of metastatic prostate cancer.

CONCLUSIONS

Oligometastasis is a metastatic status with limited metastatic lesions. It is thought of as an intermediate status between localized disease and widely metastatic disease, and it is possible to treat this stage with a curative aim in selected patients. However, no consensus exists on the definition of oligometastasis in prostate cancer. Thus, a

definition of oligometastasis is needed that is based not only on the number of metastatic lesions but also on the sites of metastasis, because the affected sites are also related to survival in metastatic disease. Stereotactic RT of metastatic lesions in limited recurrent prostate cancer is a suitable and safe modality for managing oligometastatic prostate cancer; it has a good local control rate and a low rate of severe toxicity. In addition, stereotactic RT can help to improve the quality of life by delaying the initiation of ADT. Although only a few retrospective studies are available, the data suggest that patients with metastatic prostate cancer undergoing local therapy might have superior survival compared with patients not undergoing local therapy. There are many ongoing prospective RCTs related to local therapy in oligometastatic prostate cancer. These ongoing studies will help us to better understand the role of local therapy in oligometastatic prostate cancer.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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