Review

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Radiotherapy for Oligometastatic Prostate Cancer

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Abstract

The knowledge that disease progression after chemotherapy often occurs in areas affected by the disease at the time of diagnosis has given rise to the concept of oligometastasis. Although it is difficult to define oligometastatic disease clearly, most studies include cases with up to 3-5 metastases in this group. This review aimed to elucidate the role of radiotherapy in oligometastatic prostate cancer, identify appropriate radiotherapy modalities, and establish appropriate dose/fraction schemes. We can discuss radiotherapy for oligometastatic prostate cancer under two main headings: metastasis-directed therapy (MDT) and primary treatment. Most studies on MDT in patients with oligometastatic prostate cancer are retrospective; however, in the results, it is noteworthy that a group of patients benefit from MDT within the classification defined as "oligometastasis". Studies on primary-directed radiotherapy for oligometastatic prostate cancer have revealed the potential benefits of curative treatment. These results should be supported by prospective phase 3 studies. We observed that stereotactic body radiotherapy (SBRT) is a frequently used radiotherapy technique for oligometastatic prostate cancer. The capability of the treatment machine, the location and size of the metastasis, and patient immobilization should be taken into consideration for dose/fraction selection. MDT and primary-directed treatment can slow disease progression in patients with oligometastatic prostate cancer. SBRT is the most commonly preferred treatment modality for this purpose. Prospective studies are needed to clearly define the patient group that will benefit from treatment.

Keywords: Prostate cancer, oligometastatic, radiotherapy

Introduction

Androgen deprivation therapy (ADT), chemotherapy, and palliative radiotherapy constitute the backbone of metastatic prostate cancer treatment (1,2). The knowledge that disease progression after chemotherapy often occurs in areas affected by the disease at the time of diagnosis has given rise to the concept of oligometastasis. The concept of oligometastasis was first introduced by Hellman and Weichselbaum (3). In their 1995 article, the authors defined oligometastatic disease as cancer with limited metastasis burden (3). Although it is not possible to make a clear definition of the term oligometastatic disease, in most studies, cases with a maximum of 3-5 metastases are included in the classification of oligometastatic disease (4-6). The European Organization for Research and Treatment of Cancer and the European Society for Radiation Oncology published a consensus that defined oligometastatic disease as limited metastatic disease (6,7). Presently, discussing curative treatment options for suitable metastatic patients has become part of the daily routine. This review aimed to elucidate the role and efficacy of radiotherapy in oligometastatic prostate cancer, as well as identify appropriate radiotherapy modalities and dose/fraction schemes.

Role of Radiotherapy in Oligometastatic Prostate Cancer

The diagnosis of metastatic prostate cancer may vary depending on the radiological modality used. Radiological techniques, such as choline positron emission tomography/computed tomography (PET/CT), prostate-specific membrane antigen (PSMA) PET/CT, and whole body magnetic resonance imaging (MRI) (8) can now detect metastases that conventional examinations cannot detect (8). When we look at studies on metastatic prostate cancer, there are two main distinctions: diseases with low metastatic burden that benefit from local ablative treatment and diseases with high tumor burden (9-12). In the Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) study, metastatic patients with four or more bone metastases and at least one of them outside the axial skeleton or with visceral metastases were defined as having high tumor burden disease, whereas the remaining metastatic group was considered to have low tumor burden (9). In the LATITUDE study, metastatic patients with three or more bone metastases, visceral metastases, or at least two of the International Society of Urological Pathology-4 disease factors were considered to

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have a high tumor burden, whereas metastatic patients who did not fall into this group were considered to have a low tumor burden (10). The European Association of Urology accepts both definitions (11). We can discuss radiotherapy for oligometastatic prostate cancer under two main headings: metastasis-directed therapy (MDT) and treatment of primary cancer.

Direct Treatment for Metastasis in Patients with Oligometastatic Prostate Cancer

Since the concept of oligometastasis was introduced, studies have been conducted on whether direct treatments for metastases in oligometastatic prostate cancer prolong the duration of clinical progression and delay the time to start ADT (13,14). When we look at the literature, it is evident that the majority of the information on this subject is based on retrospective data (15). In the phase 2 study conducted by Ost et al. (14), prostate cancer patients who relapsed with a maximum of 3 extracranial lesions after receiving curative treatment were divided into 2 groups: observation or MDT for all metastatic foci. The number of lesions was determined using choline PET/CT. Surgery or stereotactic body radiotherapy (SBRT) was the preferred MDT modality. The study included 62 patients, and the primary endpoint was ADT-free survival. At 3-year follow-up, ADT-free survival was 21 months in the MDT arm and 13 months in the observation arm. Furthermore, the MDT arm had a significantly longer time to prostate-specific antigen (PSA) progression (6-10 months). Both groups showed similar quality of life, and none experienced treatment-related grade 2-5 side effects. Although not starting ADT in patients with metastatic prostate cancer is a controversial issue, delaying the start of ADT as much as possible by applying treatment modalities, such as SBRT, in this patient group is on the agenda due to side effects.

Similar to Ost et al.'s (14) study, the ORIOLE phase 2 study (16) included patients with metastatic prostate cancer who relapsed after definitive treatment. The study included patients with 1-3 asymptomatic metastases with a metastasis size of 5 cm. The number of metastases was determined by CT, MRI, and/or radionuclide bone scan. The study divided the patients into two main groups: the SBRT and observation arms, with the primary endpoint being the rate of progression within 6 months. The SBRT regimens applied were 19.5-48 Gy/3-5 fractions. Patients were considered to have progressed if one or more of the following factors occurred: PSA progression (≥2 ng/dL), radiological progression, symptomatic progression, the need to initiate ADT, or death. The study analyzed 80 patients and found that the rate of patients experiencing progression at 6 months was 19% in the SBRT arm and 61% in the observation arm, significantly favoring the SBRT arm. The proportion of patients experiencing PSA progression was also significantly lower in the SBRT arm (11% vs. 50%). In the SBRT arm, the median progression-free survival (PFS) was significantly longer. In addition to these findings, the fact that no grade 3 or higher side effects were observed in any of the evaluated patients indicated the treatment's tolerability. In both of the studies mentioned above, MDT was found to be a safe treatment with a low incidence of side effects.

In the The Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) phase 2 study (17), 99 patients with oligometastatic cancer from various tumor groups, including lung, colorectal, breast, and prostate cancer, were assigned to receive either palliative standard of care treatment alone or standard of care plus SABR for all metastatic lesions. Patients with a maximum of 5 metasteses were included. Diagnostic imaging methods included MRI or CT for cranial scanning, PET/CT or whole-body CT and bone scan for the entire body, and MRI imaging for the vertebrae. SABR regimens of 30-60 Gy/3-8 fractions were applied. The primary endpoint was overall survival, which was higher in the SABR arm (41 vs. 28 months). One of the striking findings of the study was that the rate of grade 2 and higher side effects was significantly more frequent in the SABR arm than in the BR arm (29% vs. 9%). Additionally, 3 patients (4.5%) in the SABR arm died from treatment. Although the study demonstrated that SABR was an effective treatment in patients with oligometastatic tumors, it was emphasized that attention should be paid to toxicity.

Decaestecker et al. (18) conducted a prospective study on patients with prostate cancer who relapsed after receiving local curative treatment. The study included patients with a maximum of three metastases, and PET/CT was used to detect metastases. Patients were treated with SBRT regimens of 30 Gy/3 fractions or 50 Gy/5 fractions. In total, 70 lesions in 50 patients were treated. The primary endpoint of the study was ADT-free survival, with 1- and 2-year ADT-free survival rates of 82% and 60%, respectively. The 2-year local control rate was 100%, and the median PFS was 19 months. In addition to the efficacy of the treatment, no grade 3 or higher side effects were observed, indicating low toxicity. This prospective study with a low toxicity profile highlighted the positive impact of SBRT against the progression of oligometastatic prostate cancer, which is extremely valuable.

Another prospective study (19) evaluated prostate cancer patients who relapsed after definitive treatment, with a maximum of 5 metastases. In cases before 2014, MRI, bone scan, and choline PET/CT were used to detect metastases; while PSMA PET/CT was used for cases after 2014. In this study, which included 199 patients, an SBRT regimen of 50 Gy/10 fractions was administered to the lesions. The primary endpoint was the proportion of patients who did not require treatment escalation within 2 years of SBRT. The rate of patients who did not require treatment escalation within 2 years was 51.7%, and there was no significant difference in this rate between patients with 1-3 metastases and those with 4-5 metastases. PSA decreased in 75% of patients. No patient showed toxicity above grade 2. The finding that SBRT delayed treatment escalation with a low side effect profile in patients with oligometastatic prostate cancer attracted attention as evidence supporting Decaestecker et al.'s (18) prospective study.

In a systematic review of 56 studies on radiotherapy for oligometastatic prostate cancer (15), local control rates were found to be high following the application of MDT for oligometastatic disease. However, since the majority of studies were retrospective, it was stated that prospective phase 3 studies were needed. The diverse patient groups included in the studies made it difficult to provide a clear definition of the concept of oligometastasis. However, in most studies, patients with up to 3-5 metastases were included in this definition.

The review by Lancia et al. (20) stated that MDT delays the initiation of ADT and prolongs PFS, but the studies did not demonstrate its effect on overall survival. In a phase 2 study of patients with oligometastatic castration-resistant prostate cancer (21), patients who received abiraterone plus SBRT for all metastatic foci had an increased PFS compared with those who received abiraterone alone. In this study, patients with 3 or fewer non-visceral metastases were considered oligometastatic. A systematic review by Lim et al. (22) revealed an increase in PFS with MDT in patients with 3 or fewer non-visceral metastases. A systematic review by Le Guevelou et al. (23) found an increase in PFS with SBRT in patients with oligometastatic castration-resistant disease. Important studies on MDT in prostate cancer and their results are shown in Table 1.

Based on these encouraging studies, it becomes clear that there is a group that benefits from MDT within the group defined as "oligometastasis". It is obvious that these results should be supported by prospective phase 3 studies, and a clearer definition of oligometastasis is needed.

Radiotherapy for Primary Oligometastatic Prostate Cancer

In addition to MDT, the approach to the primary area of oligometastatic prostate cancer remains controversial. One of the most important studies addressing this issue is the multicenter randomized controlled HORRAD study (24). In this study, ADT and ADT + primary-directed RT were compared among patients with prostate cancer and primary bone metastases. Radiotherapy regimens of 70 Gy/35 or 57.76 Gy/19 fractions were applied. The study evaluated 432 patients and found that although combined treatment did not increase overall survival at a median follow-up of 47 months, it could be beneficial for patients with low tumor burden.

In the retrospective analysis conducted by Rusthoven et al. (25), ADT vs. The ADT + RT or radical prostatectomy (RP) arms were compared among patients with newly diagnosed metastatic prostate cancer. A total of 6382 patients were included, and it was observed that the RT + ADT arm exhibited increased overall survival compared with the ADT alone arm at 5-year follow-up. In another analysis, no difference in survival was found between the ADT + RT and ADT + RP arms, and both treatment modalities were found to be superior in terms of survival compared with ADT alone.

The randomized controlled phase 3 STAMPEDE (26) study evaluated newly diagnosed metastatic prostate cancer. Patients were divided into standard treatment (ADT ± docetaxel) and standard treatment + radiotherapy groups to the primary arms. Radiotherapy dose schedules of 55 Gy/20 or 36 Gy/6 fractions (1 fraction per week) were applied. This study analyzed 2061 patients and found that although radiotherapy increased recurrence-free survival, it did not increase overall survival. Subgroup analysis revealed that radiotherapy improved overall survival in patients with low tumor burden disease. The distinction between low and high tumor burden was made according to CHAARTED criteria. Considering these findings, it is clear that curative radiotherapy for primary oligometastatic prostate cancer may be beneficial.

Table 1. Important studies on MDT in prostate cancer and their results

Studies	Study design/ phase	Definition of oligometastasis	Number of patients	Arms	MDT regimens	SBRT regimens	Primary endpoint	Conclusion
Decaestecker et al. (13)	Phase 2	≤3 bone or lymph node lesions		Active surveillance vs. MDT	SBRT or surgery	30 Gy/3 fractions	ADT-free survival	
Ost et al. (14)	Phase 2	≤3 extracranial lesions	62	Observation or MDT	SBRT or surgery	30 Gy/3 fractions	ADT-free survival	13-21 months
Phillips et al. (16)	Phase 2	≤3 asymptomatic lesions, size <5 cm	54	Observation or MDT	SBRT	19.5-48 Gy/3-5 fractions	Rate of patients progressed within 6 months	61-19%
Palma et al. (17)	Phase 2	≤5 lesions	99	Standard of care or MDT	SBRT	30-60 Gy/3-8 fractions	Overall survival	28-41 months
Decaestecker et al. (18)	Phase 2	≤3 lesions	50	MDT	SBRT	30 Gy/3 fractions or 50 Gy/5 fractions	1 and 2 year ADT-free survival	82-60%
Bowden et al. (19)	Phase 2	≤5 lesions	199	MDT	SBRT	50 Gy/10 fractions	The proportion of patients did not require treatment escalation within 2 years of SBRT	51.70%
Francolini et al. (21)	Phase 2	≤3 non-visceral lesions	157	Abiraterone vs Abiraterone + MDT	SBRT	Rate of biochemical response	Rate of biochemical response	68.3-92%

MDT: Metastasis-directed therapy, SBRT: Stereotactic body radiotherapy, ADT: Androgen deprivation therapy

Radiotherapy Techniques and Dose/Fraction Regimes for Oligometastatic Prostate Cancer

While SBRT is often preferred for MDT in patients with oligometastatic prostate cancer, moderately hypofractionated or normofractionated regimens can also be preferred (14-16). Studies have shown that many different dose/fraction regimens are used for MDT. Dose schedules of 15-24 Gy/1 fraction, 24-36 Gy/3 fractions, 30-50 Gy/5 fractions stand out as SBRT regimens that can be preferred for MDT. Among these regimens, the most preferred regimen is the 30 Gy/3-fraction regimen. If we look at the MDT doses applied to lymph nodes, we see that after 45-50 Gy elective nodal irradiation with conventional fractionation, 63-74 Gy with boost to the affected area or 24-50 Gy/3-10 fractions with SBRT are preferred (15).

Ost et al.'s (14) study found that PFS increased when the biological effective dose was >100 Gy (27). Schick et al.'s (28) study concluded that the biochemical recurrence-free survival rate increased when the applied dose was EQD2 >64 Gy (alpha/beta: 2 Gy). Muldermans et al.'s (29) study found that the local control rate was higher in the group administered the 18 Gy/1 fraction regimen compared with the 16 Gy/1 fraction group.

Although existing studies provide us with clues about the regimen that should be selected, it is obvious that more studies are needed to determine the ideal dose/fraction regimen. Regarding the dose/fraction regimen to choose, factors such as the capability of the treatment machine, experience of the treatment team, the location and size of the area to be treated, and patient immobilization should be taken into account. Although the risk of serious toxicity with SBRT is extremely low, clinicians should not ignore the risk of treatment-related toxicity.

Conclusion

Although there is currently no definitive definition of the concept of "oligometastasis", MDT and primary-directed treatment can help slow down disease progression and contribute to the treatment process in prostate cancer, which is considered oligometastatic. SBRT is the most preferred treatment modality for this purpose. Various dose/fraction regimens are available in the literature. Treatment machine use, clinical, and patient-related factors should be considered when selecting the most appropriate regimen. More prospective studies are needed to clearly define the patient group that will benefit from treatment and to determine the ideal treatment for this group.

Footnote

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Short Quiz

1. According to Ost et al.'s study, above which value does BED increase PFS?

A. 70
B. 80
C. 90
D. 100

2. Which regimen is the most frequently used dose-fraction scheme for oligometastatic prostate cancer?

A. 50 Gy/5 fraction
B. 30 Gy/3 fraction
C. 15 Gy/1 fraction
D. Gy/3 fraction