Locally Advanced/Oligometastatic Prostate Cancer

Subjects: Oncology

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Risk stratification has been conducted by various research groups and guidelines. Cases with a high risk of recurrence are defined as “high-risk PC”; however, because of the heterogeneity in prognosis among these cases, they have been further subdivided into “very high-risk PC”. Oligometastasis is considered as a metastatic carcinoma that lies between locally advanced carcinoma and widely metastatic carcinoma, and it should be treated separately from both in terms of prognosis and treatment.

Keywords: prostate cancer ; locally advanced ; oligometastasis ; very high-risk

1. Introduction

With the introduction of prostate cancer (PC) screening, more men are continuously being diagnosed with clinically nonmetastatic PC. However, 17–31% of them have high-risk localized or locally advanced disease requiring curative treatment [1]. In addition, with the development of new imaging techniques, several types of oligometastatic PC which are between locally advanced cancer and widely metastatic cancer are being discovered [2]. Thus, accurate diagnosis will become more important in the future. Recent advancements have also been made in radiotherapy (RT) for PC due to innovations in medical and physical engineering, and excellent long-term results have been reported [3][4][5][6][7][8][9]. However, the definitions of locally advanced PC and oligometastatic PC are still ambiguous, and there is no standard treatment for these. Furthermore, no studies directly compare local treatment options such as radical prostatectomy (RP) and RT. Thus, the superiority or inferiority of these treatments is unknown. So far, the standard treatment for oligometastatic PC has been systemic therapy, specifically androgen deprivation therapy (ADT). In recent years, however, the significance of combined local treatment has been discussed, and the results of large-scale clinical trials have been reported with and without combined RT [6][10]. In addition, attempts to further enhance disease control by concomitant metastasis-directed therapy (MDT) have been made [11][12][13], and radical curing of oligometastatic PC may be expected in the future.

2. Locally Advanced PC

2.1. Definition

The definitions of very high-risk PC reported so far are shown in **Table 1**.

Table 1. Definition of very high-risk prostate cancer.

Source (Year)	Definition	Reference
Spahn (2010)	2 high-risk features (PSA > 20 ng/mL, GS 8–10, and cT3–4)	[14]
Walz (2011)		[15]
Sundi (2014)	Primary Gleason pattern 5 or 4 cores containing pattern 4	[16]
Joniau (2015)	GS 8–10 in combination with 1 other high-risk factor (PSA > 20 ng/mL and cT3–4)	[17]
NCCN guidelines (2019v2)	cT3b–4 or primary Gleason pattern 5 or >4 cores with Grade Group 4 or 5	[18]
EAU guidelines (2019)	cT3–4 or cN+, any PSA, any GS	[19]

PSA = Prostate specific antigen; GS = Gleason score; NCCN = National Comprehensive Cancer Network; EAU = European Association of Urology.

2.2. Diagnosis

Imaging studies are very important in the diagnosis of locally advanced PC. A cohort study of high-risk PC using multi-parametric magnetic resonance imaging (mpMRI) with a combination of T2-weighted, diffusion-weighted, and dynamic contrast-enhanced images reported an 89% positivity rate of extracapsular invasion and an OR of 10.3 for predicting extracapsular invasion [20]. In addition, a meta-analysis including 17 studies that used mpMRI to detect extracapsular invasion reported a sensitivity of 0.55 (95% confidence interval (CI): 0.43–0.66) and a specificity of 0.87 (95% CI: 0.82–0.91), suggesting the usefulness of mpMRI for diagnosing locally advanced PC [21]. The NCCN, EAU, and American Urological Association guidelines recommend mpMRI for the diagnosis of locally advanced PC [18][19][22], and it is expected to become more widely used in the future.

2.3. Treatment

2.3.1. RP

In most high-risk patients, surgery is performed with the goal of cure. However, for clinical T3b–4 PC, RP can be thought of as “debulking” the primary tumor in order to improve local control. Moltzahn et al. evaluated a multicenter cohort of 266 patients with very high-risk locally advanced PC (cT3b–4) treated surgically. Despite poor pathologic characteristics, the 10-year cancer-specific mortality rate was relatively low (5.6–12.9%) and was influenced by comorbidities and age [23].

2.3.2. Radiation Therapy

Table 2 shows the results of various treatments for high-risk localized and very high-risk PC that have been reported so far.

Table 2. Summary of the treatment of high-risk localized and very high-risk prostate cancer.

Study	No. of Patients	Eligibility Criteria	Treatment	Median Follow-Up	Outcome	Reference
Radical prostatectomy for patients presenting with locally advanced disease						
Moltzahn	**266**	**cT3b–4, N0 or N1, M0**	**RP + PLND ± adjuvant ADT and/or RT**	**9.3 years**	**10-year CSS 87.1–94.4%**	**[23]**
External beam radiotherapy for patients presenting with locally advanced disease						
RTOG 85-31	**977**	**cT3 or N1 or RP + PSM and/or SVI**	**RT vs. RT + ADT (lifelong)**	**11 years**	**10-year OS 39% vs. 49%, p = 0.002; 10-year CSS 78% vs. 84%, p = 0.005; 10-year MFS 61% vs. 76%, p < 0.0001**	**[3][4]**
Intergroup randomized study	**1205**	**cT3–4, N0/Nx, M0 or cT1–2 with either PSA > 40 ng/mL or PSA 20–40 ng/mL and GS 8–10**	**ADT (lifelong) vs. ADT + RT**	**8 years (range, 0–15.2)**	**10-year OS 49% vs. 55% (HR 0.70, 95% CI 0.57–0.85, p < 0.001); CSS higher in combined treatment (HR 0.46, 95% CI 0.34–0.61, p < 0.001); 10-year PFS 46% vs. 74% (HR 0.31, 95% CI 0.25–0.39)**	**[5]**
STAMPEDE	**638/2962**	**Two of the following are met; cT3–4, GS 8–10, PSA > 40 ng/mL**	**SOC vs. SOC + ZA vs. SOC + DOC vs. SOC + ZA + DOC**	**3.6 years (IQR 2.5–5)**	**5-year OS 55% vs. 57% vs. 63% vs. 60%; SOC + DOC (HR 0.78, 95% CI 0.66–0.93, p = 0.006) and SOC + DOC + ZA (HR 0.82, 95% CI 0.69–0.97, p = 0.022) compared to SOC only, respectively**	**[6]**
GETUG 12	**413**	**cT3–4 or GS 8–10 or PSA > 20 ng/mL or pN1**	**ADT (3 years) + local treatment + CT (DOC + EMT) vs. ADT + local treatment**	**8.8 years (IQR 8.1–9.7)**	**8-year RFS 62% vs. 50% (adjusted HR 0.71, 95% CI 0.54–0.94, p = 0.017)**	**[7]**
Rusthoven	**796**	**cT1–4, N1, M0**	**RT vs. no local treatment**	**5.2 years**	**10-year OS 45% vs. 29% (HR 0.58, 95% CI 0.48–0.71, p < 0.001); 10-year CSS 67% vs. 53% (HR 0.61, 95% CI 0.47–0.80, p < 0.001)**	**[8]**

Study	No. of Patients	Eligibility Criteria	Treatment	Median Follow-Up	Outcome	Reference
Lin	3540	cN1, M0 or Mx	ADT + RT vs. ADT alone	5.2 years	5-year OS 71.5% vs. 53.2% (HR 0.50, 95% CI 0.37–0.67, p < 0.001)	[9]
Various modalities of radiotherapy						
Zelefsky	296	cT3, N0, M0	3D-CRT or IMRT+ ADT (3 months)	8 years (range, 2–16)	10-year RFS T3a/T3b: 44%/32%; 10-year CSS T3a/T3b: 88%/79%	[24]
Mizowaki	120	cT3–4, N0, M0	IMRT + ADT (6 months)	97 months (range, 21–120)	8-year RFS 53.2%; 8-year CSS 96.6%; 8-year OS 89.1%	[25]
Goupy	276	cT3b, N0–1, M0	IMRT + ADT (3 years)	26 months (95% CI, 33–39)	5-year RFS 75.2%; 5-year CSS 89.7%; 5-year OS 78.8%	[26]
Yamazaki	249	cT3b–4, N0, M0	HDR + EBRT vs. HDEBRT vs. Conv EBRT	64 months (range, 13–153)	5-year RFS 78.9% vs. 88.1% vs. 66.5% (p = 0.0003)	[27]
Kishan	1809	Gleason score 9–10	RP vs. EBRT vs. EBRT + LDR/HDR	RP, 4.2 years; EBRT 5.1 years; EBRT + LDR/HDR 6.3 years	5-year MFS 76% vs. 76% vs. 92% (p < 0.001); 7.5-year OS 83% vs. 82% vs. 90% (p < 0.05)	[28]

RP = radical prostatectomy; PLND = pelvic lymph node dissection; ADT = androgen deprivation therapy; RT = radiotherapy; SOC = standard of care; ZA = zoledronic acid; DOC = docetaxel; IQR = inter-quartile range; HR = hazard ratio; CI = confidence interval; OS = overall survival; CSS = cancer-specific survival; MFS = metastasis-free survival; PFS = progression-free survival; RFS = recurrence-free survival; CT = chemotherapy; EMT = estramustine; 3D-CRT = three-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; HDR = high-dose-rate; LDR = low-dose-rate; HD = high dose; Conv = conventional; EBRT = external beam radiotherapy.

3. Oligometastatic PC

3.1. Definition

The recently reported definitions of oligometastatic PC are shown in **Table 3**.

Table 3. Definition of oligometastatic prostate cancer.

Source	No. of Patients	Number of Metastases	Number of Metastases	Detection	Reference
Tabata	35	5	Bone only; each site < 50% size of vertebral body	Bone scan	[29]
Ahmed	17	5	NS	^{11}C-choline PET–CT, MRI, biopsy, CT	[30]
Berkovic	24	3	Bone or LN	Bone scan, ^{18}F-FDG PET–CT, ^{11}C-choline PET–CT	[31]
Schick	50	4	NS	Bone scan, ^{18}F-choline PET–CT, ^{11}C-acetate PET–CT	[32]
Decaestecker	50	3	Bone or LN	^{18}F-FDG PET–CT, ^{18}F-choline PET–CT	[33]
Ost	119	3	Any	^{18}F-FDG PET–CT, ^{18}F-choline PET–CT	[34]

CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography; FDG = fluorodeoxyglucose; LN = lymph node; NS = not specified.

3.2. Diagnosis

In addition to conventional imaging methods using CT and bone scintigraphy, many reports have used positron emission tomography-CT (PET-CT) using ^{18}F-fluorodeoxyglucose and ^{11}C-choline, as well as whole-body MRI (WB-MRI) for diagnosis. Shen et al. conducted a meta-analysis of the diagnostic performance of bone metastases and reported that choline PET-CT, MRI, and bone scintigraphy had sensitivities of 87%, 95%, and 79%, respectively, and specificities of 97%, 96%, and 82%, respectively [35]. Recently, PET using prostate-specific membrane antigen (PSMA), a type II transmembrane protein highly expressed in PC, as a tracer has been attracting attention as a promising new imaging modality [36][37].

3.3. Treatment

In the past, treatment of oligometastatic PC was discussed only in terms of ADT, which is the cornerstone of systemic treatment. However, in recent years, the significance of combined local treatment has been widely discussed; MDT may be useful in some cases and should be considered as part of multimodal therapy. The following mechanisms have been postulated: suppression of growth factors and immunosuppressive cytokines by eradicating the primary tumor site [38], reduction of circulating tumor cells [39], and promotion of the anticancer immune response by the abscopal effect (i.e., regression of metastases after therapeutic irradiation of the primary tumor site) [40]. However, there is no standardized treatment for the choice of local treatment because the superiority of RT over surgery is unknown due to the lack of direct comparative studies. Although there is no standardized treatment, there have been a few recent reports suggesting the efficacy of local RT. In 2018, a randomized controlled trial, the HORRAD trial, compared ADT with local radiation versus ADT alone for PC complicated by bone metastases [10]. Although the two groups had no significant difference in OS (HR: 0.90; 95% CI: 0.70–1.14; p = 0.4), a subanalysis suggested that RT to the prostate improved OS in patients with low tumor volume (<5 bone lesions). In 2018, the STAMPEDE trial investigated ADT ± docetaxel with local irradiation [6]; this was a phase 3 randomized controlled trial in which patients with newly metastatic PC were randomized 1:1 to receive ADT ± docetaxel as standard therapy with or without concomitant RT to the prostate. RT consisted of either daily irradiation (55 Gy/20 doses) for four weeks or weekly irradiation (36 Gy/6 doses) for six weeks. Although survival was significantly prolonged in the standard treatment plus RT group (HR: 0.76, 95% CI: 0.68–0.84; p < 0.0001), OS was not prolonged in the standard treatment plus RT group (HR: 0.92, 95% CI: 0.80–1.06; p = 0.266). Notably, in the subanalysis by tumor volume, there was a significant difference in OS at three years in the low metastatic volume group (73% in the standard treatment group vs. 81% in the standard treatment plus radiation group; HR: 0.68, 95% CI: 0.52–0.90; p = 0.007), whereas combined radiation treatment had no prognostic effect in the high metastatic volume group. In fact, the results of the HORRAD and STAMPEDE trials suggest the usefulness of local irradiation, since the combination of hormonal therapies with local RT was found to prolong prognosis in low metastatic burden [6][10]. However, the options for RT are diversifying, and it is currently unclear which irradiation method is optimal. Radiobiologically, the α/β value of PC is as low as 1.5 Gy, therefore RT for PC is considered to be more effective with higher doses in smaller fractions [41][42]. In summary, the efficacy of HDR brachytherapy, which delivers a high dose per instance of irradiation, has been recognized for the control of the primary disease; however, there are no reports of HDR brachytherapy against PC with oligometastasis.

These results suggest that the combined local irradiation is effective for patients with low metastatic volume. The CHAARTED study defines high metastatic volume as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis [43], whereas low metastatic volume is often defined as having <3 bone metastases, which is exactly in line with the definition of oligometastasis. Furthermore, a few randomized controlled trials are currently underway to test the efficacy of local treatment for metastatic PC [44]. The SWOG 1802 trial (NCT01751438) is evaluating the effect of local treatment (external beam radiation or surgery) in addition to systemic treatment for M1 PC, while the g-RAMPP trial (NCT02454543) is evaluating the effect of RP plus extended lymph node dissection in addition to systemic treatment for M1b PC (≤5 bone metastases). These studies are expected to evaluate the efficacy of local treatment, and future results will be interesting.

As for systemic treatment, ADT is the basic treatment for locally advanced PC. Docetaxel and abiraterone, which is a new anti-androgenic agent, are both currently being used upfront, and the choice of these agents is also noteworthy. However, considering that the CHAARTED study, which demonstrated the benefit of early docetaxel administration in patients with untreated metastatic PC, was unable to show the survival benefit of docetaxel uptake in patients with low metastatic volume [43], the use of early chemotherapy or novel ADT for oligometastatic PC should be further investigated.

Treatment of metastases consists of surgical resection or SBRT. The goals may be to control the cancer, slow down further metastasis, and avoid or delay systemic therapy-related toxicity. A systematic review has given an overview of the

current evidence for MDT in oligometastatic PC [11]. Local control rates at two years ranged between 76–100%. Progression free survival (PFS), its definition was inconsistent, was reported from 38–100% at one year and 22–83% at two years. The ORIOLE Trial, a randomized phase 2 study comparing observation and MDT, showed a significantly better PFS of MDT than observation (median, not reached vs. 5.8 months; HR: 0.30; 95% CI: 0.11–0.81; p = 0.002) [12]. Moreover, an interim analysis of a large prospective trial involving SBRT in oligometastatic PC patients with up to five metastatic sites was reported [13]. The proportion of patients who did not require treatment escalation (e.g., modification of ADT, introduction of chemotherapy, or palliative RT) was 51.7% (95% CI: 44.1–59.3%) at two years after SBRT, and the median survival without treatment escalation over the entire follow-up period was 27.1 months (95% CI: 21.8–29.4 months). In addition, PSA reduction was observed in 75% of patients. Therefore, the SBRT shows very promising potential for the long-term suppression of oligometastatic PC.

4. Conclusions

Although there is still no standard treatment for very high-risk locally advanced or oligometastatic PC, a major shift in treatment strategy is underway, with reports on the benefits of combined local RT with ADT as a cornerstone. On the other hand, RT delivery methods and protocols vary from study to study, which is an issue that remains unresolved. It will be interesting to see the results of currently ongoing large-scale studies in this field which will be reported in the future.

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