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MINI-REVIEW

Oligometastatic prostate cancer: Metastases-directed therapy?



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KEYWORDS

Oligometastatic prostate cancer;
Lymph node dissection;
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ABBREVIATIONS

ADT, androgen-deprivation therapy;
BRFS, biochemical recurrence-free survival;
CPFS, clinical progression-free survival;
CSS, cancer-specific survival;

Abstract Since the introduction of anatomical and functional imaging with multiparametric magnetic resonance imaging and choline or prostate-specific membrane antigen positron emission tomography-computed tomography, we are able to diagnose a previously unknown disease, the oligometastatic prostate cancer after local therapy. Reports on surgical and radiation treatment for low-volume metastatic recurrence have shown promising results, with definitive cure in few but a relevant delay of androgen-deprivation therapy with both treatment methods. Obviously, these results need to be validated with prospective randomised data.

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LND, lymph node dissection;
 PET, positron emission tomography;
 (SB)RT, (stereotactic body) radiotherapy

Introduction

Metastatic prostate cancer is classically treated with hormonal manipulation. Oligometastatic prostate cancer is a relatively new concept. It was originally defined as five or less metastatic sites [1]. It was proposed as a clinically significant state separate from the polymetastatic disease [2] and considered to be less aggressive than other metastatic phenotypes [3]. Importantly, oligometastatic prostate cancer was shown to have a different microRNA profile than polymetastatic disease [4]. Obviously, patients with oligometastatic disease are prone to progress at the initial metastatic foci. The rationale of metastasis-directed treatment comes from the concept that it might delay or avoid the castrate-resistant prostate cancer status by eradicating castration-resistant clones. Indeed, metastasis-directed treatment might postpone the initiation of androgen-deprivation therapy (ADT) and hypothetically may lead to improved survival [5].

Modern anatomical and functional imaging

For metastatic prostate cancer the conventional imaging is CT and bone-scan. It is well documented that these conventional imaging tools have a low sensitivity and limited accuracy. In recent years, new tools have been introduced where anatomical and functional imaging is combined. Multiparametric MRI can indeed provide functional imaging by the use of diffusion-weighted imaging, dynamic contrast-enhanced MRI, and MR spectroscopy imaging, whilst, the use of new tracers in nuclear medicine has continued to improve accuracy, after the use of fluorodeoxyglucose in metastatic prostate cancer was shown to be futile. ^{11}C -choline positron emission tomography (PET)-CT was shown to be much more reliable in cases of fast PSA rise [6] or when a PSA-doubling time of < 6 months was seen [7]. The problem with ^{11}C -choline is its very short half-life, and therefore it needs to be produced on the spot. ^{18}F -choline has also been used, which has a longer half-life, thereby overcoming the problem of on spot fabrication but it has higher urinary excretion that can lead to misinterpretation at the level of the urinary tract.

It is because of the introduction of these new imaging techniques that we have become able to diagnose a previously unknown disease, the oligometastatic disease. Typically prostate cancer metastasises to the bone and these bone metastases are amenable to targeted radio-

therapy (RT). Likewise, metastasis to the lymph nodes could be treated with stereotactic body RT (SBRT) or could be amenable to surgical excision. This way, oligometastatic disease can be managed with a metastasis-directed therapy rather than with the conventional ADT.

Surgical and radiation treatment for low-volume metastatic recurrence

In 2011, Rigatti et al. [8] reported on a single-centre experience of salvage lymph node dissection (LND) for nodal recurrence. At 1 year after salvage LND, 55.2% of the patients had biochemical recurrence-free survival (BRFS), at 3 years 27.5%, and at 5 years 10.3%. The cancer-specific survival (CSS) at 1 year was 98.4%, at 3 years 90.5%, and at 5 years 75%.

Also salvage external beam RT was used in hormone-naïve oligometastatic prostate cancer as reported by Berkovic et al. [9]. They described 24 patients with up to three bone metastases or lymph nodes. RT was given with the dose up to 50 Gy in 10 fractions and the primary endpoint was the ADT-free survival. ADT was initiated when more than three metastases occurred during follow-up or when the PSA level rose to > 50 ng/mL. The median follow-up in their series was 24 months and they showed that ADT was delayed with a median of 38 months (Table 1) [8,12–16].

Literature review on metastasis-directed therapy

A systematic review of the literature on metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer was published in *European Urology* by Ost et al., 2014 [10]. They looked at the results of metastasis-directed therapy in 450 patients. In all, 299 patients underwent salvage RT: 93 had bone metastasis, 202 had nodal metastasis (of which 128 had pelvic RT and 74 RT to the lymph nodes only), and four had visceral metastasis. In all, 70% of these RT-treated patients had concomitant hormonal treatment. Also, 151 patients had a salvage LND: 78 underwent pelvic LND, 13 retro-peritoneal and 65 pelvic and retro-peritoneal LND. In the surgical series, 58% had hormone treatment and 29% also had RT. Overall, 97% had a primary LND (with 9–11 nodes removed). Between 2.5 and 26 nodes were removed at salvage LND and positive nodes were found in 19% in the internal iliac and obturator fossa, in 15% in the

Table 1 Studies on surgical and radiation treatment for low-volume metastatic recurrence.

Study	N	Mean follow-up, months	ADT before salvage LND, %	ADT after salvage LND, %	Complete response, %	5-year BRFS, %	5-year CPFS, %	5-year CSS, %
Rinnab et al., 2008 [12]	15	13.7	33	73	NA	NA	NA	NA
Rigatti et al., 2011 [8]	72	39.4	56	65	57	19	34	75
Jilg et al., 2012 [13]	47	35.5	79	65	46	9	26	78
Suardi et al., 2013 [14]	162	40	NA	NA	41	40	47	86
Suardi et al., 2014 [15]	59	81.1	63	1-year: 44 5-year: 63	59	29	52	89
Osmonov et al., 2014 [16]	22	NA	NA	41	64	NA	NA	NA

Table 2 Studies on SBRT metastasis-directed therapy.

Reference	Number of patients	Site of metastasis node/bone/visceral	Median follow-up, months
Casamassima et al., 2011 [18]	25	25/0/0	29
Muacevic et al., 2011 [19]	40	0/40/0	14
Ahmed et al., 2012 [20]	17	1/19/1	6
Tabata et al., 2012 [21]	18	0/18/0	NR
Jerezek-Fossa et al., 2012 [22]	19	18/1/0	17
Decaestecker et al., 2014 [23]	52	30/20/2	27
Schick et al., 2013 [24]	50	33/17/0	31
Total	221	110/118/3	22

external iliac, in 21% in the common iliac, and in 46% at the level of the bifurcation or higher. Another literature review was done by De Meerleer and Van Poppel in *Mirrors of Medicine* 2014 [11]. They looked at the results reported by Rinnab et al., 2008 [12]; Rigatti et al., 2011 [8]; Jilg et al., 2012 [13]; Suardi et al., 2013 [14] and 2014 [15]; and by Osmonov et al., 2014 [16]. The longest follow-up was reported in the 59 patients in the Suardi et al., 2014 study [16], with a mean follow-up of 81.1 months. In all, 63% of the patients had ADT before the salvage LND. Moreover, 44% had ADT for 1 year after the LND and 63% had ADT for 5 years after the salvage LND. A complete response was obtained in 59%. The 5-year BRFS was 29%, the 5-year clinical progression-free survival (CPFS) was 52%, and the 5-year CSS was 89%.

A collaborative review published in *European Urology* in 2014 by Abdollah et al. [17] investigated the contemporary role of salvage LND in patients with recurrence after radical prostatectomy. They concluded that the correct patient selection for salvage LND would ideally be the one with a PSA level of <4 ng/mL, a Gleason score of <8, and nodal involvement limited to the pelvic nodes. Actually, whether a template dissection or a resection of PET positive nodes only needs to be done is not clear yet. The authors also reported complications such as prolonged lymphorrhoea, lymphocele, and lymphoedema. After the salvage LND, a complete PSA response, two or less positive lymph

nodes at pathology, and positive lymph nodes limited to the pelvis only, were identified as favourable prognostic factors [13–15].

The literature on SBRT is also summarised (Table 2) [18–24]. In all, seven studies were analysed encompassing 221 patients; 110 patients had nodal, 118 bone and three had visceral metastasis, and the median follow-up was 22 months. Local control was achieved in >90%, CPFS varied between 37% and 71%, and grade 3 toxicity was noted in 0.5% of the patients only.

Conclusion

Salvage LND

For most patients with oligometastatic involvement of the pelvic nodes, a salvage LND will allow postponement of ADT and has limited toxicity. About 50% will achieve a complete PSA response and about one-third will remain free of PSA relapse for 5 years. However, these data need to be validated in prospective randomised trials, whilst the impact on the results of concomitant ADT needs to be analysed further.

Salvage RT

Salvage RT to bone or lymph nodes allows postponement of ADT and is also not very toxic. However, salvage RT will not achieve undetectable PSA levels

unless associated with ADT. It is not known yet how many patients will be free of PSA at 5 years. The only data available today are on CPFS at 3 years, which also need to be validated with prospective randomised data.

In conclusion, metastasis-directed therapy is promising but needs validation in a randomised controlled trial. For the time being, all we can do is optimise selection and individualise the treatment strategies.

Conflicts of interest

None declared.

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