available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Opinion

Oligometastatic Prostate Cancer: Is it Only a Matter of Perspective?

Giuseppe Di Lorenzo [a,*], *Carlo Buonerba* [a,b]

[a] *Department of Clinical Medicine and Surgery, University Federico II of Naples, Naples, Italy;* [b] *Zoo-prophylactic Institute of Southern Italy, Portici, Italy*

Multiple recent breakthroughs in recurrent and metastatic prostate cancer have not involved the discovery of a novel agent but have been rather obtained by expanding the indication for approved treatments in different clinical scenarios, mainly defined by the extent of tumor dissemination. In this regard, the "oligometastatic" state of prostate cancer has increased in clinical importance because of its implications for surgery, radiotherapy, and systemic therapy. In a retrospective analysis of 654 prostate cancer patients who were treated with salvage lymph node dissection after nodal-only recurrence diagnosed on positron emission tomography (PET) after radical prostatectomy, only 25% experienced clinical recurrence within 1 yr. Importantly, 91% of patients had fewer than four positive spots on their PET scans, which shows that lymph node dissection can be an effective therapeutic strategy for managing oligometastatic lymph node-only recurrent disease [1]. In the CHAARTED trial [2], docetaxel provided a survival advantage in men with high-volume castration-sensitive prostate cancer (CSPC), but not in patients with low-volume disease, while abiraterone was associated with a survival advantage both in low- and high-volume CSPC patients in the abiraterone substudy of the STAMPEDE trial [3]. In another STAMPEDE substudy [4], radiotherapy was associated with a survival benefit if administered to the primary tumor in low-volume CSPC [2]. Although no survival advantage was reported in the overall study population of 2061 randomized patients, a statistically significant 32% reduction in the risk of death was seen in low-burden patients receiving radiotherapy, with 3-yr survival of 81% versus 73% among controls. Notably, only 18% of the patients also received docetaxel, so the interaction between docetaxel and radiotherapy to the primary tumor could not be adequately assessed in this trial, but is being explored in the ongoing PEACE-1 trial [5]. Furthermore, no local palliative effect was associated with radiotherapy to the primary tumor, which implies that a true antineoplastic effect was exerted at a systemic level by local therapy. One proof-of-concept randomized phase 2 study on choline PET [6] was conducted among 62 noncastrate, asymptomatic patients with oligometastatic prostate cancer who were randomly assigned to either surveillance or surgery/stereotactic body radiotherapy of all lesions detected. Metastases-directed therapies included stereotactic body radiotherapy in 25 patients and surgery in six patients. The median time to androgen deprivation therapy (ADT), which was started at the time of progression, was longer in the interventional than in the observational arm (21 vs 13 mo). This difference did not reach statistical significance, possibly because of the limited sample size. Consistent results were obtained in the POPSTAR trial, in which patients presenting not more than three bone or lymph-node lesions were treated with stereotactic ablative body radiotherapy. At 2 yr, there was no significant decrease in quality of life, and 39% of patients were free of distant progression [7]. These results show that an even larger effect could have been achieved for patients with a low disease burden treated in the STAMPEDE trial [4] if radiotherapy had been delivered to all detectable metastatic lesions. In addition, radiotherapy was administered according to a plan consisting of 20 fractions of 2.75 Gy over 4 wk (55 Gy) or of six weekly fractions of 6 Gy (36 Gy), with no emerging signal of a difference in effectiveness between the two radiotherapy schedules. Further studies are required to investigate if the magnitude of the survival advantage associated with radiotherapy to the primary tumor can be improved by administering the standard radiotherapy doses used for curative treatment

* Corresponding author. Medical Oncology, Genitourinary Cancer Section, University Federico II of Naples, Via Pansini 5, 80131 Naples, Italy.
E-mail address: dilorengiuseppe@gmail.com (G. Di Lorenzo).

https://doi.org/10.1016/j.eururo.2018.12.010

(eg, 60 Gy delivered in 3-Gy fractions or 72–80 Gy delivered in 2-Gy fractions). While radiation therapy to the primary tumor was associated with better outcomes for patients with low-burden mCSPC, docetaxel [2] in the castration-sensitive setting and radium-223 [8] in the castration-resistant setting have been beneficial for patients with high-volume disease. In such a scenario, there is increasing clinical utility of nuclear imaging based on tracers such as ^{18}F-sodium fluoride, ^{68}Ga-labeled prostate-specific membrane antigen (PSMA) ligands, and ^{11}C-choline, as well as magnetic resonance imaging (MRI) using diffusion-weighted and other sequences [9], as these imaging techniques may better assess systemic tumor burden. As an example, ^{68}Ga-PSMA PET/computed tomography (CT) has specificity close to 100% and is overall more accurate than bone and CT scans for both bone and visceral disease [9]. The potential added value of nuclear or MRI imaging lies not only in the better diagnostic accuracy for oligometastatic disease but also in more precise detection of all the metastatic sites involved, which is required for planning of metastases-directed interventions. An important question on oligometastatic prostate cancer revolves around the existence of an underlying biological background. In fact, since the number of metastases invariably increases over time, oligometastatic disease may simply represent a transient state of the natural course of the disease, that is, the result of a temporal perspective. In this regard, apart from testing patients with oligometastatic disease for different biomarkers that might reflect systemic tumor burden, such as circulating tumor cells and circulating DNA, it might be wise to confirm the diagnosis of oligometastatic disease during a short period of observation (eg, 6 wk), which would also allow measurement of the pace of radiological progression. In fact, one patient may progress from a few to multiple metastatic sites in a few weeks, especially in cases with a short prostate-specific antigen doubling time. In this regard, some microRNAs, such as mi-RNA 200, may be useful for discriminating patients who are likely to respond to metastasis-directed local therapies from those who are not [10].

Improving the definition of oligometastatic disease in prostate cancer offers a unique opportunity to discover whether disease burden is a clinically meaningful variable per se, for example, because of the risk of missing the window of therapeutic opportunity for a certain treatment before the disease progresses or because a greater metastatic burden means that local therapies are directed against an insignificant fraction of the entire neoplastic population. As an alternative hypothesis, oligometastatic disease may represent a distinctive state of the disease with a largely unexplored biological background that is associated with different sensitivity to treatment and may offer novel therapeutic targets against this deadly disease.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Fossati N, Suardi N, Gandaglia G, et al. Identifying the optimal candidate for salvage lymph node dissection for nodal recurrence of prostate cancer: results from a large, multi-institutional analysis. Eur Urol 2019;75:176–83. http://dx.doi.org/10.1016/j.eururo.2018.09.009.

[2] Gravis G, Boher JM, Chen YH, et al. Burden of metastatic castrate naive prostate cancer patients, to identify men more likely to benefit from early docetaxel: further analyses of CHAARTED and GETUG-AFU15 studies. Eur Urol 2018;73:847–55.

[3] Hoyle AP, Ali SA, James ND, et al. Effects of abiraterone acetate plus prednisone/prednisolone in high and low risk metastatic hormone sensitive prostate cancer. Ann Oncol 2018;29(8 Suppl), mdy424.033.

[4] Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018;392:2353–66. http://dx.doi.org/10.1016/S0140-6736(18)32486-3.

[5] Fizazi K, Abrahamsson PA, Ahlgren G, et al. Achievements and perspectives in prostate cancer phase 3 trials from genitourinary research groups in Europe: introducing the Prostate Cancer Consortium in Europe. Eur Urol 2015;67:904–12.

[6] Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol 2018;36:446–53.

[7] Siva S, Bressel M, Murphy DG, et al. Stereotactic ablative body radiotherapy (SABR) for oligometastatic prostate cancer: a prospective clinical trial. Eur Urol 2018;74:455–62.

[8] Smith MR, Parker CC, Saad F, et al. ERA 223 a phase III trial of radium-223 (Ra-223) in combination with abiraterone acetate and prednisone/prednisolone for the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve patients (pts) with bone-predominant metastatic castration-resistant prostate cancer (mCRPC). Ann Oncol 2018;29(Suppl 8), mdy424.035.

[9] Lecouvet FE, Oprea-Lager DE, Liu Y, et al. Use of modern imaging methods to facilitate trials of metastasis-directed therapy for oligometastatic disease in prostate cancer: a consensus recommendation from the EORTC Imaging Group. Lancet Oncol. In press. https://doi.org/10.1016/S1470-2045(18)30571-0.

[10] Lussier YA, Xing HR, Salama JK, et al. MicroRNA expression characterizes oligometastasis(es). PLoS One 2011;6:e28650.