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"Hit the primary": A paradigm shift in the treatment of metastatic prostate cancer?

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ABSTRACT

Patients with metastatic prostate cancer (PC) represent a heterogeneous group with survival rates varying between 13 and 75 months. The current standard treatment in this setting is hormonal therapy, with or without docetaxel-based chemotherapy. In the era of individualized medicine, however, maximizing treatment options, especially in long-term surviving patients with limited disease burden, is of capital importance. Emerging data, mainly from retrospective surgical series, show survival benefits in men diagnosed with metastatic PC following definitive therapy for the prostate. Whether the irradiation of primary tumor in a metastatic disease might improve the therapeutic ratio in association with systemic treatments remains investigational. In this scenario, modern radiation therapy (RT) can play a significant role owing to its intrinsic capability to act as a more general immune response modifier, as well as to the potentially better toxicity profile compared to surgery. Preclinical data, clinical experience, and challenges in local treatment in *de novo* metastatic PC are reviewed and discussed.

1. Introduction

Local control of the primary tumor in the presence of metastatic disease has been associated with improved outcome in several malignancies (Flanigan et al., 2001; Mickisch et al., 2001; Temple et al., 2004). Metastatic renal cell carcinoma could be considered a paradigm in this field: indeed, two phase III trials clearly demonstrated better overall survival (OS) rates in patients treated with radical nephrectomy and interferon-alpha compared to patients receiving systemic treatment alone (Flanigan et al., 2001; Mickisch et al., 2001).

In prostate cancer (PC), evidence from three large prospective randomized phase III trials suggest that, in patients with locally advanced tumors at high risk of occult micrometastatic disease, adding radiotherapy (RT) to androgen deprivation therapy (ADT) significantly improves 10-year outcome (D'Angelillo et al., 2015; Mottet et al., 2012; Warde et al., 2011; Widmark et al., 2009). Reduction in the cancer-specific and overall mortality rates (Warde et al., 2011; Widmark et al., 2009), as well as improvements in loco-regional control and distant metastases-free progression (Mottet

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Nomenclature

ADT	Androgen deprivation therapy
APCs	Antigen-presenting cells
BT	Brachytherapy
CI	Confidence interval
CSM	Cancer-specific mortality
CSS	Cancer-specific survival
CTCs	Circulating tumor cells
CTLA-4	Cytotoxic T-lymphocyte associated antigen 4
DCs	Dendritic cells
DSS	Disease-specific survival
EBRT	External beam radiotherapy
GM-CSF	Ggranulocyte-macrophage colony-stimulating factor
HR	Hazard ratio
IGRT	Image-guided radiotherapy
LH-RH	Luteinizing hormone –relasing hormone
LT	Local treatment of the primary tumor
MCRPC	Metastatic castration resistant prostate cancer
NLT	Non-local treatment of the primary tumor
NSR	No surgery or radiation therapy
OS	Overall survival
PAP	Prostatic acid phosphatase
PC	Prostate cancer
PD-1	Programmed cell death protein-1
PFS	Progression-free survival
PSA	Prostate specific antigen
QoL	Quality of life
RP	Radical prostatectomy
RT	Radiotherapy
SEER	Surveillance epidemiology and end results
SIB	Simultaneous integrated boost
TILs	Tumor-infiltrating lymphocytes

et al., 2012), were observed in the combined modality, starting to emerge early, 3 years after randomization.

On the other hand, in multi-metastatic PC patients (T1-4, N0-1, M1) the role of local control of the primary remains unclear, with ADT using LHRH analogues/antagonists, with or without docetaxel, representing the treatment of choice as recommended by current guidelines (Heidenreich et al., 2014). Although the scientific evidence supporting ADT in metastatic PC patients remains weak, in the case of proven metastatic disease, ADT is considered the up-front standard treatment (Heidenreich et al., 2014). ADT is not curative, but might frequently provide rapid relief of symptoms and a good rate of "temporary" biochemical control.

While the role of local RT as palliative treatment for bleeding or obstruction is well described, the benefit of associating RT to ADT as first-line treatment to improve the therapeutic ratio in metastatic PC patients remains investigational. Such an approach seems to be supported by compelling evidences indicating that patients with a limited number of PC metastases, thus entering the so-called oligometastatic state — an intermediate state of tumor spread with limited metastatic capacity (Weichselbaum and Hellman, 2011) — have a better prognosis compared with those with extensive metastatic disease (Schweizer et al., 2013; Ost et al., 2014).

The aim of the present critical review is to report and discuss available data on the role of prostate irradiation in de novo hormone-naïve metastatic PC patients. Due to the paucity and heterogeneity of data published in the recent literature, our review was not conducted according to a properly performed systematic protocol, but rather represents an overview of the body of knowledge on this topic.

2. Preclinical data

The challenging issue of local irradiation in metastatic PC is whether the natural history of disease progression might be positively influenced, once metastases have developed, by reclaiming the organ of tumor origin.

An answer comes from the experimental demonstration of a process called 'tumor self-seeding' (Kim et al., 2009), during which circulating tumor cells (CTCs) — usually seeding distant organs — have the potential to reinfiltrate an established tumor at the primary site. Under these circumstances, tumor growth and progression may be favored if the primary tumor remains locally untreated despite the metastatic disease. Conversely, this reseeding phenomenon could not occur when malignant cells encounter an unfavorable growth environment, such as when the primary tumor is controlled (removed or irradiated).

What really might contribute to a change in the role of RT in the metastatic setting is based on some radiation-induced immunological responses, a phenomenon called "abscopal effect", consisting in the regression of distant disease after a localized treatment of the primary tumor (Demaria et al., 2004). Abscopal effects are most often attributed to the activation of the antitumor immunity, which, unlike site-specific RT, can have broader systemic effects.

Traditionally, RT has been considered a local treatment only. The abscopal effect is proof of the systemic effects of RT (Formenti and Demaria, 2009), and it is triggered by a T cell-mediated and antigen-specific (Demaria et al., 2004, 2005) immune reactions as a consequence of the processing, by macrophages and dendritic cells (DCs), of antigens released during tumor necrosis caused by RT, eliciting tumor-specific CD8+ T cells. The local inflammation induced by RT activates several complex local immunological reactions contributing to better antigen cross-presentation and immune activation, finally leading to CD8+ cytolytic T cell responses (Friedman, 2002; Reits et al., 2006). In other words, danger signals associated with the effects of ionizing radiation could convert the irradiated tumor into an immunogenic hub becoming, in some patients, a very efficient individualized in situ vaccine (Demaria et al., 2004). Once this "vaccination" has taken place, the host's immune response contributes both to the local response to RT and to a systemic rejection of metastases (Formenti and Demaria, 2009).

Intriguingly, a prerequisite for eliciting an antitumor immune response is that tumor-ablative RT doses are delivered by stereotactic body radiation therapy (SBRT), likely because only when RT is applied in this form immunomodulatory effects triggered by inflammation and apoptosis recruit DCs to the irradiated site (Seung et al., 2012; Rubner et al., 2012). A hint of the potential ability of SBRT in evoking the abscopal effect can be found in the favorable results of some series (Ponti et al., 2015; Jereczek-Fossa et al., 2012; Schick et al., 2013) — also confirmed in recent reviews — reporting data on this strategy in the treatment of nodal PC metastases (Ost et al., 2015; De Bari et al., 2014): it may be argued that, despite the very likely presence of micrometastatic disease around the macroscopically involved nodes, higher doses per fraction delivered to the target lesion might result curative on the nearest microscopic disease by the activation of the abscopal effect.

An indirect confirmation of these immune-modulated responses is the role gradually being acquired by modern immunotherapy in defeating the established tolerance toward the cancer and restoring an effective tumor-specific immune response (Quinn et al., 2015; Santoni et al., 2014). At the forefront of this strategy has been the development of Ipilimumab (Hodi et al., 2010), a monoclonal antibody which blocks the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), a checkpoint receptor that inhibits T cell activation. Associated with palliative radiation, this drug has been shown to increase OS in patients with advanced melanoma (Grimaldi et al., 2014; Postow

et al., 2012), thus decreasing PSA concentrations and therefore ameliorating progression-free survival in patients with metastatic castration-resistant PC progressing after docetaxel (Kwon et al., 2014).

A possible hypothesis for such clinical benefits could be that the abscopal effect is less likely to happen after RT alone, which may be insufficient to induce a general systemic and robust antitumor effect. Further evidence in support is provided by the well-known combined modality association in the treatment of PC where the radiation-induced immune response, in conjunction with hormone therapy, can be amplified sufficiently to elicit an abscopal effect, as reflected by the PSA response (Fujimoto et al., 2011).

Androgen-withdrawal hormone therapy is known to shut down gene expression and change the cellular and membrane environment (Utsunomiya and Nakanishi, 1986), which may affect tolerance, enabling cancer cell recognition by the immune system. The combination seems to be even more beneficial when RT can evoke an acute anticancer immune response coupled with "endogenous" vaccine produced by necrotic tumor cell death. This latter mechanism belongs to Sipuleucel-T (Kantoff et al., 2010), a vaccine prepared from autologous antigen-presenting cells (APCs) that are incubated with a recombinant protein composed of PAP linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), which, in some Phase 3 studies, has demonstrated an improvement in the OS of asymptomatic or minimally symptomatic metastatic castration-resistant PC patients (Small et al., 2006), thus representing a new treatment paradigm in castration-resistant PC.

RT-induced anti-tumor immunity however could be restrained by immunoregulatory mechanisms, and preclinical evidences have demonstrated that PD-1 restrains the immune-mediated abscopal effect induced by local radiotherapy in animal models (Park et al., 2015). Indeed, PD-1 blockade or deficiency can synergize with RT to induce tumor-specific CD8+ T-cell immunity and result in a clinical response in the secondary tumors outside of the radiation field. These findings raise a significant clinical interest because they suggest that the combination of anti–PD-1 blockade and local RT can lead to the systemic control of tumors that are refractory to treatment with PD-1 blockade alone.

In summary, some important pre-clinical and clinical evidences are emerging to support the concept that local RT and immunotherapy can successfully synergize and produce a therapeutically effective antitumor immune response, even in metastatic cancer. Whether local therapies may directly impact the progression of existing metastatic disease by regulating the balance between tumor-promoting factors and immunosuppressive cytokines or by decreasing CTCs, rather than by abscopal effect, remains an unanswered question, but it is clear that targeted RT of the primary tumor may act as a systemic disease modifier, thus playing a crucial role in the management of PC at any stage.

Noteworthy, the use of unconventional radiation schedules in one or a few fractions (SBRT), associated with unprecedented biological mechanisms, has the potential to break some old paradigms in radiation oncology, like the fractionation of the dose, and opens the way for the adoption of this emerging option in the clinical management of tumors always considered radioresistant, such as renal cell carcinoma (De Meerleer et al., 2014).

3. Clinical data

Mechanisms underlying the benefit of definitive treatments of the primary in metastatic PC patients are not fully understood. Improvement in the local control and reduction in the need of palliative treatment, removal of a tumor with persistent capability to produce future metastases as well as improved response to ADT might constitute the rationale for definitive treatment of the primary tumor (Ost et al., 2014). As observed by Tzelepi et al. (2011), a persistent network of molecular pathways reportedly linked to disease progression is activated after 1 year of ADT and 3 cycles of docetaxel in men with locally advanced or lymph node-metastatic PC treated by systemic therapy followed by radical prostatectomy (RP). This may suggest that the development or progression of systemic disease may be indirectly controlled or, at least influenced, by the eradication of persistent intraprostatic foci with local therapies.

Arguments in favor of a potential role of definitive local treatment in patients with metastatic PC seem to be supported by a recent retrospective study by Culp et al. (2014), who identified 8185 men with metastatic PC over a 7 year period (2004–2010) from the surveillance epidemiology and end results (SEER) database, comparatively evaluating those who underwent definitive treatment of the primary tumor (RP or brachytherapy [BT]) compared with the rest, who did not receive local treatment. A comparative analysis was performed between patients undergoing RP ($n = 245$) or BT ($n = 129$) and those not receiving surgery or radiation (NSR, $n = 7811$). They found that men with metastatic disease who underwent RP or BT had a significantly better disease-specific survival (DSS) and OS when compared to the NSR group (5-years DSS: 75.8% vs. 61.3% vs. 48.7%, respectively, $p < 0.001$; 5-years OS: 67.4% vs. 52.6% vs. 22.5%, respectively, $p < 0.001$). There was no significant intergroup difference in the death rates of patients dying from non-PC causes, thereby indicating that there was a true beneficial effect in local intervention, and that the observed advantage cannot completely be attributed to selection bias. Although, survival benefits were maintained even in patients with PSA >20 ng/ml or those above 70 years of age, the authors identified certain factors associated with an improved response to local treatment, such as age <70 years, clinical stage $\leq$T3, Gleason score $\leq$ 7, PSA <20 ng/ml and an absence of pelvic lymphadenopathies.

A latest study (Fossati et al., 2015) including 8197 men diagnosed with metastatic PC confirmed this hypothesis, and observed a survival benefit in those managed with local treatment of the primary tumor (LT; either RP plus pelvic lymph node dissection or RT) compared to those who received non-local treatment of the primary tumor (NLT), defined as observation or ADT. Unlike the previous study, the authors also identified optimal candidates for LT of the primary tumor as men with a cancer-specific mortality (CSM) risk <40% (according to the formula available at: http://www.urotecnologie.it/it/research). Namely, they found that LT in patients with predicted CSM risk <30% was associated with a roughly 20% increase in survival after 3 years, which is significantly higher than the survival benefit offered by any of the novel drugs recently approved to treat castration-resistant metastatic PC (Kantoff et al., 2010; de et al., 2011).

Additional evidence concerning the role of cytoreductive RT in multi-metastatic PC comes from a retrospective study published by Zagars et al. (Zagars et al., 2001) on 255 PC patients with lymphadenectomy-proven pelvic nodal metastases treated with early ADT alone ($n = 183$) or with combined ADT and radiation ($n = 72$), indicating that the addition of prostatic RT to ADT significantly improved outcomes in terms of 10-years biochemical-free survival (19% in the ADT group vs 80% in ADT + RT group), distant metastasis free-survival (56% in ADT group vs 85% in the ADT + RT group) and OS (46% in ADT group vs 67% in ADT + RT group) over ADT alone. The superior results of the combined treatment were statistically significant in the univariate and multivariate analyses.

Similar survival benefit was reported by a systematic review (Verhagen et al., 2010) of randomized studies, including patients with proven systemic disease (node-positive patients after RP). Data herein presented showed an only limited benefit for OS (hazard ratio [HR]: 0.90; 95% confidence interval [CI], 0.83–0.97) and cancer-specific survival (CSS) (HR: 0.79; 95% CI, 0.71–0.89) when immediate ADT is compared to deferred ADT without local treat-

ment, but a clinically important survival benefit (HR for OS: 0.69; 95% CI, 0.61–0.79) when ADT was used as adjuvant treatment to RT in patients with high-risk localized or locally advanced disease, thereby confirming a better outcome whenever a local treatment is applied to the primary tumor. Likewise, another study (Lin et al., 2015) addressed the important oncologic issue of whether local therapy along with systemic therapy improves survival over systemic therapy alone in the setting of clinically lymph node-positive (cN+) PC. The authors evaluated the comparative effectiveness of ADT alone and ADT + RT in the management of men with nodal involvement in absence of distant metastatic disease, using data from the National Cancer Data Base on 3540 patients: after adjustment for multiple confounding factors, the addition of RT to ADT was associated with a 50% decreased risk of five-year all-cause mortality (HR = 0.50, 95% CI = 0.37–0.67, two-sided $P < 0.001$; crude OS rate: 71.5% vs 53.2%), thus suggesting that, if properly validated by randomized trials, a substantial proportion of patients at high risk for PC death may be undertreated, warranting a reevaluation of current practice guidelines.

The positive impact of a local therapy (RP ± RT) in patients with locally advanced disease and metastatic lymph node involvement was confirmed in two recent retrospective studies (Briganti et al., 2011; Abdollah et al., 2014), performed at the same institution. The last published one (Abdollah et al., 2014) reported on 1107 patients with pN1 PC treated with RP and anatomically extended pelvic lymph node dissection between 1988 and 2010, followed or not by adjuvant pelvic irradiation. Overall, adding RT to RP resulted significantly associated with more favorable outcome (HR for CSS: 0.37; $P < 0.001$). The authors determined that this beneficial impact was highly influenced by tumor characteristics and concluded that patients presenting a low-volume nodal disease (≤2 positive nodes) in the presence of intermediate- to high-grade pT3-4 disease or with positive margins (HR: 0.30; P = .002), and those with 3–4 positive nodes (HR: 0.21; P = .02) derived substantial benefits from the combined strategy.

In a recent analysis of patients from the Munich cancer registry, Engel et al. (2010) demonstrated a survival advantage for patients who underwent RP in spite of the intraoperative detection of positive lymph nodes compared to those in whom the procedure had been abandoned. In this study, recruiting 938 lymph node positive patients, those who proceeded with RP ($n = 688$) had a significantly better 5- and 10-year OS (84% and 64%) compared to those in whom RP was aborted (60% and 28%). The estimated 5- and 10-years DSS was also better in the former group (95% and 85%) as compared to the latter (70% and 40%). Despite some biases in the population enrolled in this study, in the multivariate model, RP was a strong independent predictor of survival (hazard ratio: 2.04 [95% confidence interval, 1.59–2.63; $p < 0.0001$]). Data of retrospective studies providing analysis of survival of patients with locally advanced or metastatic PC according to the treatment received are summarized in Table 1. Although many of these studies included a substantial proportion of many N+, but M0 patients, who are likely to have a better prognosis and might act as a separate entity, all of them consistently showed a long lasting survival benefit in favor of those who received a local treatment to the primary tumor.

Metastatic PC patients, however, constitute a heterogeneous group of patients with survival rates varying between 13 and 75 months, as a function of the type of metastases (bone versus visceral), bone metastases location (appendicular versus axial), performance status, Gleason score and prostate-specific antigen (PSA) levels (Hussain et al., 2006). In this scenario, the optimal treatment can best be done when the burden of metastatic disease is minimal because of having small and few lesions, which portends by itself a better prognosis. In addition, the prognosis of metastatic disease may vary according to the distribution of disease, as the presence of visceral metastases alone or with concomitant bone involvement confers a worse survival compared to bone metastases alone (Gandaglia et al., 2015).

A recent study (Halabi et al., 2014) combined individual patient data from 3993 chemotherapy-naive metastatic castration resistant prostate cancer (MCRPC) patients randomized to receive docetaxel (D) based therapy on 5 phase III trials: CALGB 90,401 (D +/− Bevacizumab): SWOG 0421(D +/− atrasentan), ENTHUSE 33 (D +/− zibotentan), TAX327 (D 3 wks, D weekly) and SWOG 9916 (D + estramustine). The authors found that liver metastases had the worst OS (12.1 m), while patients with lung metastases had better OS (16.5 months) compared to those with liver metastases, but still significantly worse compared to patients with non-visceral bone metastases (20 months).

Unexpectedely, metastatic site even within the same organ, such in the case of the skeleton, may play an important role in predicting the ultimate prognosis. Yamashita et al. (1993) found that the presence of bone metastasis outside the pelvis and lumbar spine was predictive of a short survival. Conversely, another study (Singh et al., 2004) showed different patterns of survival since patients with disease confined to the pelvis had diffuse involvement of the pelvic bones compared to those with less diffuse disease confined to the lumbar spine, thus confirming that the extent of disease, rather than the site of recurrence, is the most powerful prognostic indicator of the outcome in metastatic disease.

Ultimately, patients with pelvic lymph nodes involvement alone may experience a better prognosis compared with their counterparts with skeletal and visceral metastases. As a matter of fact, Nini et al. (2015) tested the association between the site of recurrence and cancer-specific mortality (CSM) in 1003 patients with node-positive PC patients treated with RP and extended pelvic lymph node dissection, and found that not all patients with pN + PC who develop clinical recurrence (CR) harbor distant metastatic disease, since roughly 60% of them were free from CSM at 5-yr follow-up.

Taken together these arguments underline as in the era of individualized maximizing treatment options in patients with primary metastatic PC is of capital importance, especially in long-term survivors with limited disease burden that can still be rendered free of disease through the use of aggressive therapies, such as surgery and radiation therapy.

4. Treatment options

Despite the inherent biases due to their retrospective nature of many of the studies acknowledged in the previous paragraph, which lay the groundwork for a role of definitive treatment of the primary tumor in the context of metastatic PC, a confirmation in a prospective fashion is warranted. The choice of local therapy, either RP or RT, in this setting remains challenging.

Potential benefits of RP consist in the removal of the malignant prostate, thus avoiding the complications of local tumor growth, including hematuria, urinary tract infections, outflow obstruction, hydro-ureteronephrosis and their consequent morbidity, as demonstrated in some series of castration-resistant PC (Steinberg et al., 1990; Won et al., 2013). Additionally, the physical removal of the prostate allows to obtain detailed histopathology as well as the discharge of the seeding tumor/organ, which on turn, might be reseeded by distant metastases, thus breaking the vicious circle off (Kim et al., 2009). Nevertheless, the surgical removal of a fibrotic prostate previously treated with ADT may be associated with a high risk of serious complications, and few surgeons are willing to perform the operation. Moreover, surgical removal of an untreated prostate in the setting of metastatic disease does not usually allow radical resection with clean margins, since the majority of patients present with locally advanced tumors. As a consequence, the combination of RP and adjuvant RT could then be considered an

Table 1
Summary of retrospective studies providing analysis of survival of patients with locally advanced or metastatic prostate cancer according to the treatment received.

Study	Patients	Local treatment (RP or RT)		No local treatment	Median follow up (months)	Outcome remarks
Culp (Culp et al., 2014)	8185	129 (BT)	245 (RP)	7811	16	5y-OS: 52.6%–67.4% vs 22.5%
Fossati (Fossati et al., 2015)	8197	628		7569	36	20% 3y-OS benefit in favor of LT[a]
Zagars (Zagars et al., 2001)	255	72		183	112.8	10y-OS: 67% vs 46%
Verhagen[b] (Verhagen et al., 2010)	7751	4980		2771	–	31% OS benefit in favor of LT
Lin[c] (Lin et al., 2015)	3540	318 (RT)		318	60.2	5y-OS: 71.5% vs 53.2%
Engel (Engel et al., 2010)	938	688		250	67.2	10y-OS: 64% vs 28%

(RP = radical prostatectomy; RT = radiation therapy; BT = brachytherapy, ADT = androgen deprivation therapy; LT = local treatment; cN+ = clinically lymph node-positive; CSM = cancer-specific mortality; OS = overall survival).

[a] Only in a subset of patients with CSM <30%.
[b] Only data from randomized trials in N1 and/or M1 patients have been included.
[c] Only patients with cN+ disease.

option to achieve maximal local control in this situation. However, whether the additional morbidity associated with the use of combined treatment improves overall outcome is less certain, given the highly selected nature of patients who underwent this multimodal therapy, as demonstrated in the aforementioned studies (Briganti et al., 2011; Abdollah et al., 2014).

On the other hand, modern RT allows the delivery of high doses of radiation with steep gradients that decrease the treatment related toxicity (Alongi et al., 2009; Bauman et al., 2012; De Bari et al., 2014; Zelefsky et al., 2000; Staffurth, 2010). In addition, image-guided on-board imaging systems within RT (IGRT) platforms permit consideration of setup errors and organ motion, resulting in more precise radiation delivery (Zelefsky et al., 2012). A further capability of intensity-modulated RT techniques is to deliver various doses to different volumes in the same number of fractions through the simultaneous integrated boost (SIB) technique, which requires shorter treatment time compared to the sequential boost. Radiobiologically, such an acceleration of the overall treatment time could impact on the repopulation of cancer cells leading to theoretical advantages in local control (Withers and Thames, 1988). Furthermore, the SIB approach could be useful to irradiate concomitantly prostate and distant disease, especially when metastatic foci are found in the pelvic region (Engels et al., 2009; Kiljunen et al., 2014). Moreover, the delivery of extreme hypofractionated RT schedules may potentially further improve the therapeutic ratio in these patients, simultaneously reducing waiting lists, health costs and improving overall patient compliance.

From a biological perspective, the rationale for the advocacy of RT in the control of the primary tumor in a metastatic disease is that, once irradiated, the prostate is largely atrophied and poorly vascularized, and it might not be hospitable for tumor growth. Additionally, as previously discussed, RT potentially allows the induction of some immunological reactions which are not possible after surgery. Therefore, modern RT techniques have the potential to play an important role in this setting, significantly lessening the care burden and further improving the compliance and QoL of such patients.

5. Ongoing trials

Despite the promising results of retrospective and cohort studies published so far, the real benefit of definitive local treatment in de novo metastatic PC remains unknown at this writing. Hopefully, many open questions concerning the potential role of local RT in the management of these patients will be probably answered in the coming years by three phase III trials.

Results obtained through a phase II ongoing multidisciplinary clinical trial intended to assess the role of systemic therapy versus systemic therapy plus definitive treatment of the primary (RT or RP based on a multidisciplinary evaluation by the treating team or according to patient preference) in men with metastatic PC (available at: www.clinicaltrials.gov, trial number: NCT01751438), will probably provide answers to several questions now open as to the best treatment option for these patients.

The HORRAD randomized phase III trial (Netherlands trial Register NTR271) is a Dutch study opened on 2004 allocating approximately 500 patients with primary metastatic (bone) PC to receive hormonal treatment alone versus hormonal treatment plus local RT (70 Gy to the prostate). The primary endpoint is OS, with secondary endpoints biochemical progression and QoL (24 months). End of the study is incoming and while preliminary data are awaited, doubtful expectations are legitimated from the use of suboptimal RT doses.

More recently, the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial (ClinicalTrials.gov, NCT00268476), an ongoing multi-stage and multi-arm randomized study, opened a new study arm exploring the benefit of local RT directed on the prostate tumor when combined with ADT over ADT alone in men with newly diagnosed M1 disease. Two RT dose-fractionation schedules are allowed, namely 36 Gy in 6 fractions of 6 Gy, administered weekly over 6 consecutive weeks or 55 Gy in 20 fractions of 2.75 Gy, administered daily, five days per week, over 4 consecutive weeks.

Finally, although recruiting has not yet begun, the Prostate Cancer Consortium in Europe (PEACE I) phase III trial is testing the addition of abiraterone and RT directed at the primary cancer in patients with de novo metastatic hormone-naïve PC treated with ADT. Primary endpoints are OS and progression-free survival (PFS) with events defined as the onset of castration-resistant PC or death.

6. Conclusions

The potential and beneficial impact of local treatment of the primary tumor in men with *de novo* metastatic PC is supported by a strong rationale, but requires further validation in future studies. In this emerging scenario, modern RT can play a significant role owing to its intrinsic capability to act as a more general immune response modifier, as well as to the potentially better toxicity profile compared to the surgery. Accurate selection of the optimal candidates is mandatory in maximizing the benefits from local treatments, through exposure to potential toxicities only those patients who would benefit most from them. Results from ongoing prospective trials are eagerly awaited to establish the role of local approaches in metastatic PC patients over the next few years.

Conflicts of interest

All authors declare no financial and personal relationships with other people or organisations that could inappropriately influence their work.

References

Abdollah, F., Karnes, R.J., Suardi, N., et al., 2014. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. J. Clin. Oncol. 32 (December (35)), 3939–3947.

Alongi, F., Di Muzio, N., 2009. Image-guided radiation therapy: a new era for the radiation oncologist? Int. J. Clin. Oncol. 14, 568–569.

Bauman, G., Rumble, R.B., Chen, J., et al., 2012. Members of the IIEP. Intensity-modulated radiotherapy in the treatment of prostate cancer. Clin. Oncol. (R. Coll. Radiol.) 24, 461–473.

Briganti, A., Karnes, R.J., Da Pozzo, L.F., et al., 2011. Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2–4 pN+ prostate cancer: results of a matched analysis. Eur. Urol. 59, 832–840.

Culp, S.H., Schellhammer, P.F., Williams, M.B., 2014. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. Eur. Urol. 65, 1058–1066.

D'Angelillo, R.M., Franco, P., De Bari, B., et al., 2015. Combination of androgen deprivation therapy and radiotherapy for localized prostate cancer in the contemporary era. Crit. Rev. Oncol. Hematol. 93, 136–148.

De Bari, B., Fiorentino, A., Arcangeli, S., et al., 2014. From radiobiology to technology: what is changing in radiotherapy for prostate cancer. Exp. Rev. Anticancer Ther. 14, 553–564.

De Meerleer, G., Khoo, V., Escudier, B., et al., 2014. Radiotherapy for renal-cell carcinoma. Lancet Oncol. 15, e170–e177.

Demaria, S., Ng, B., Devitt, M.L., et al., 2004. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. Int. J. Radiat. Oncol. Biol. Phys. 58, 862–870.

Demaria, S., Kawashima, N., Yang, A.M., et al., 2005. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. Clin. Cancer Res. 11, 728–734.

Engel, J., Bastian, P.J., Baur, H., et al., 2010. Survival benefit of radical prostatectomy in lymph node-positive patients with prostate cancer. Eur. Urol. 57, 754–761.

Engels, B., Soete, G., Tournel, K., et al., 2009. Helical tomotherapy with simultaneous integrated boost for high-risk and lymph node-positive prostate cancer: early report on acute and late toxicity. Technol. Cancer Res. Treat. 8, 353–359.

Flanigan, R.C., Salmon, S.E., Blumenstein, B.A., et al., 2001. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N. Engl. J. Med. 345, 1655–1659.

Formenti, S.C., Demaria, S., 2009. Systemic effects of local radiotherapy. Lancet Oncol. 10, 718–726.

Fossati, N., Trinh, Q.D., Sammon, J., et al., 2015. Identifying optimal candidates for local treatment of the primary tumor among patients diagnosed with metastatic prostate cancer: a SEER-based study. Eur. Urol. 67, 3–6.

Friedman, E.J., 2002. Immune modulation by ionizing radiation and its implications for cancer immunotherapy. Curr. Pharm. Des. 8, 1765–1780.

Fujimoto, N., Kubo, T., Shinsaka, H., et al., 2011. Duration of androgen deprivation therapy with maximum androgen blockade for localized prostate cancer. BMC Urol 11, 7.

Gandaglia, G., Karakiewicz, P.I., Briganti, A., et al., 2015. Impact of the site of metastases on survival in patients with metastatic prostate cancer. Eur. Urol. 68, 325–334.

Grimaldi, A.M., Simeone, E., Giannarelli, D., et al., 2014. Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. Oncoimmunology 3, e28780.

Halabi, S., Kelly, W.K., Zhou, H., et al., 2014. The site of visceral metastases to predict overall survival (OS) in castration-resistant prostate cancer (CRPC) patients: a meta-analysis of five phase III trials. J. Clin. Oncol. 32 (5s), suppl; abstr 5002.

Heidenreich, A., Bastian, P.J., Bellmunt, J., et al., 2014. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur. Urol. 65, 124–137.

Hodi, F.S., O'Day, S.J., McDermott, D.F., Weber, R.W., Sosman, J.A., Haanen, J.B., et al., 2010. Improved survival with ipilimumab in patients with metastatic melanoma. N. Engl. J. Med. 363, 711–723.

Hussain, M., Tangen, C.M., Higano, C., et al., 2006. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from southwest oncology group trial 9346 (INT-0162). J. Clin. Oncol. 24, 3984–3990.

Jereczek-Fossa, B.A., Beltramo, G., Fariselli, L., et al., 2012. Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. Int. J. Radiat. Oncol. Biol. Phys. 82 (February (2)), 889–897.

Kantoff, P.W., Higano, C.S., Shore, N.D., et al., 2010. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N. Engl. J. Med. 363, 411–422.

Kiljunen, T., Kangasmaki, A., Aaltonen, A., et al., 2014. VMAT technique enables concomitant radiotherapy of prostate cancer and pelvic bone metastases. Acta Oncol., 1–7.

Kim, M.Y., Oskarsson, T., Acharyya, S., et al., 2009. Tumor self-seeding by circulating cancer cells. Cell 139, 1315–1326.

Kwon, E.D., Drake, C.G., Scher, H.I., et al., 2014. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 15, 700–712.

Lin, C.C., Gray, P.J., Jemal, A., et al., 2015. Androgen deprivation with or without radiation therapy for clinically node-positive prostate cancer. J. Natl. Cancer Inst. 107 (July (7)), djv119.

Mickisch, G.H., Garin, A., van Poppel, H., et al., 2001. European Organisation for R, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 358, 966–970.

Mottet, N., Peneau, M., Mazeron, J.J., et al., 2012. Addition of radiotherapy to long-term androgen deprivation in locally advanced prostate cancer: an open randomised phase 3 trial. Eur. Urol. 62, 213–219.

Nini, A., Gandaglia, G., Fossati, N., et al., 2015. Patterns of clinical recurrence of node-positive prostate cancer and impact on long-term survival. Eur. Urol., http://dx.doi.org/10.1016/j.eururo.2015.04.035.

Ost, P., Decaestecker, K., Lambert, B., et al., 2014. Prognostic factors influencing prostate cancer-specific survival in non-castrate patients with metastatic prostate cancer. Prostate 74, 297–305.

Ost, P., Bossi, A., Decaestecker, K., et al., 2015. Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: a systematic review of the literature. Eur Urol 67 (May (5)), 852–863.

Park, S., Dong, H., Liu, X., et al., 2015. PD-1 Restrains radiotherapy-induced abscopal effect. Cancer Immunol. Res. 3 (June (6)).

Ponti, E., Ingrosso, G., Carosi, A., et al., 2015. Salvage stereotactic body radiotherapy for patients with prostate with isolated lymph node metastasis: a single-center experience. Clin. Genitourin. Cancer 13 (August (4)), e279–e284.

Postow, M.A., Callahan, M.K., Barker, C.A., et al., 2012. Immunologic correlates of the abscopal effect in a patient with melanoma. N. Engl. J. Med. 366, 925–931.

Quinn, D.I., Shore, N.D., Egawa, S., et al., 2015. Immunotherapy for castration-resistant prostate cancer: progress and new paradigms. Urol. Oncol.

Reits, E.A., Hodge, J.W., Herberts, C.A., et al., 2006. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J. Exp. Med. 203, 1259–1271.

Rubner, Y., Wunderlich, R., Rühle, P.F., et al., 2012. How does ionizing irradiation contribute to the induction of anti-tumor immunity? Front. Oncol. 2, 75.

Santoni, M., Scarpelli, M., Mazzucchelli, R., et al., 2014. Targeting prostate-specific membrane antigen for personalized therapies in prostate cancer: morphologic and molecular backgrounds and future promises. J. Biol. Regul. Homeost. Agents 28, 555–563.

Schick, U., Jorcano, S., Nouet, P., et al., 2013. Androgen deprivation and high-dose radiotherapy for oligometastatic prostate cancer patients with less than five regional and/or distant metastases. Acta Oncol. 52, 1622–1628.

Schweizer, M.T., Zhou, X.C., Wang, H., et al., 2013. Metastasis-free survival isassociated with overall survival in men with PSA-recurrent pros- tate cancer treated with deferred androgen deprivation therapy. Ann. Oncol. 24, 2881–2886.

Seung, S.K., Curti, B.D., Crittenden, M., et al., 2012. Phase 1 study of stereotactic body radiotherapy and interleukin-2-tumor and immunological responses. Sci. Transl. Med. 4, 137, ra74.

Singh, D., Yi, W.S., Brasacchio, R.A., et al., 2004. Is there a favorable subset of patients with prostate cancer who develop oligometastases? Int. J. Radiat. Oncol. Biol. Phys. vol. 58 (1), 3–10.

Small, E.J., Schellhammer, P.F., Higano, C.S., et al., 2006. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J. Clin. Oncol. 24, 3089–3094.

Staffurth, J., 2010. Radiotherapy Development Board. A review of the clinical for intensity-modulated radiotherapy. Clin. Oncol. (R. Coll. Radiol.) 22, 643–657.

Steinberg, G.D., Epstein, J.I., Piantadosi, S., et al., 1990. Management of stage D1 adenocarcinoma of the prostate: the Johns Hopkins experience 1974–1987. J. Urol. 144, 1425–1432.

Temple, L.K., Hsieh, L., Wong, W.D., et al., 2004. Use of surgery among elderly patients with stage IV colorectal cancer. J. Clin. Oncol. 22, 3475–3484.

Tzelepi, V., Efstathiou, E., Wen, S., et al., 2011. Persistent, biologically meaningful prostate cancer after 1 year of androgen ablation and docetaxel treatment. J. Clin. Oncol. 29, 2574–2581.

Utsunomiya, N., Nakanishi, M., 1986. A serine protease triggers the initial step of transmembrane signalling in cytotoxic T cells. J. Biol. Chem. 261, 16514–16517.

Verhagen, P.C., Schroder, F.H., Collette, L., et al., 2010. Does local treatment of the prostate in advanced and/or lymph node metastatic disease improve efficacy of androgen-deprivation therapy? A systematic review. Eur. Urol. 58, 261–269.

Warde, P., Mason, M., Ding, K., et al., 2011. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet 378, 2104–2111.

Weichselbaum, R.R., Hellman, S., 2011. Oligometastases revisited. Nat Rev Clin Oncol 8, 378–382.

Widmark, A., Klepp, O., Solberg, A., et al., 2009. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet 373, 301–308.

Withers, H.R., Thames, H.D., 1988. Dose fractionation and volume effects in normal tissues and tumors. Am. J. Clin. Oncol. 11, 313–329.

Won, A.C., Gurney, H., Marx, G., et al., 2013. Primary treatment of the prostate improves local palliation in men who ultimately develop castrate-resistant prostate cancer. BJU Int. 112, E250–E255.

Yamashita, K., Denno, K., Ueda, T., et al., 1993. Prognostic significance of bone metastasis in patient with metastatic prostate cancer. Cancer 71, 1297–1302.

Zagars, G.K., Pollack, A., von Eschenbach, A.C., 2001. Addition of radiation therapy to androgen ablation improves outcome for subclinically node-positive prostate cancer. Urology 58, 233–239.
Zelefsky, M.J., Fuks, Z., Happersett, L., et al., 2000. Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. Radiother. Oncol. 55, 241–249.
Zelefsky, M.J., Kollmeier, M., Cox, B., et al., 2012. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. Int. J. Oncol. Biol. Phys. 84, 125–129.
de Bono, J.S., Logothetis, C.J., Molina, A., et al., 2011. A biraterone and increased survival in metastatic prostate cancer. N. Engl. J. Med. 364, 1995–2005.

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