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Special Article

Management of de novo Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) and the role of Radiation Therapy: A Consensus by the Italian Association of Radiotherapy and Clinical Oncology (AIRO)

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Purpose: Prostate cancer treatments paradigms are in continuous evolution, especially in the metastatic setting. In this context, the Genito-Urinary Group of Italian Association of Radiotherapy and Clinical Oncology aimed to create a consensus on radiation therapy indication in de novo metastatic hormone-sensitive prostate cancer both on primary tumor and metastatic sites.

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Methods: A panel of experts, involved in clinical management of prostate cancer, through the estimate-talk-estimate method, developed a list of items and correspondent statements on the identified topic.

Results: Seven conclusive items were identified with 12 statements about the chosen topic, radiation therapy in metastatic hormone-sensitive prostate cancer on primary tumor and metastatic sites.

Conclusions: This consensus might help clinicians in prostate cancer managing in daily clinical practice.

Introduction

During recent decades, the treatment of prostate cancer (PCa) patients has considerably changed. Combination of different treatments strategies, either systemic and locally, has improved the outcomes and helped to shape the landscape of PCa care[1]; more specifically, in the setting of metastatic hormone-sensitive prostate cancer (mHSPC), the prognosis has been progressively improved by docetaxel and/or second generation androgen receptor signaling inhibitors (ARSIs) associated with androgen deprivation therapy (ADT).[2-6] Furthermore, radiation therapy (RT) to the primary tumor has been incorporated in the standard-of-care (SOC) treatment paradigm for low-volume metastatic patients,[7-9] whereas recent findings have also shown advantages for its use in high-volume disease.[10]

Metastasis-directed therapy (MDT) plays a crucial role in the setting of oligometastatic prostate cancer (OMPC), because it could reduce further disease spread and defer systemic treatment shift, as demonstrated in some phase 2 randomized clinical trials.[11-15] Generally, treatment intensification appears to be associated with better prognosis.[16]

Furthermore, PCa genomic profiling is increasing in importance and relevance for routine clinical practice in the scenario of metastatic PCa. Defects in DNA damage response genes and the subsequent approval and use of poly (ADP-ribose) polymerase inhibitors (PARP inhibitors) had a profound impact on the biological and therapeutic landscape of PCa.[17] Many trials are investigating targeted treatments in different setting of PCa disease, even in the earlier phases.[18]

Despite recent experts' consensus and even published guidelines,[19-22] many aspects still represent topics of debate. Disease volume, number of metastatic lesions to define the oligometastatic state, the role of imaging in disease characterization, timing and optimal treatments' sequence, the most appropriate schedules of RT to be adopted for both primary and metastatic sites, the integration of systemic and local therapies—all these represent issues which need to be addressed.

In this controversial scenario, the Genito-Urinary Group of the Italian Association of Radiotherapy and Clinical Oncology assembled a panel of experts involved in clinical management of PCa, with the aim of developing a consensus on the use of RT both to the primary and to the metastatic sites in de novo metastatic hormone-sensitive prostate cancer (mHSPC).

Methods

Figure 1 shows the workflow of the consensus process, which was developed by the end of 2023 using the estimate-talk-estimate method.[23,24] Estimate-talk-estimate (a formal means of reaching consensus that was developed to overcome some of the negative aspects of group dynamics) facilitates group decision making by assembling expert opinions on an anonymous basis during surveys with open exchange in dedicated workshops. The 13 members (radiation oncologists) of the board individually identified 37 points of interest (or items) that, in their opinion, deserved exploration and discussion. These were subsequently harmonized and grouped by a senior clinical epidemiologist trained in developing group consensus (the facilitator) into 9 items that were proposed to the board members at a face-to-face meeting. The harmonized items were discussed to reach an agreement between the facilitator's work and the experts'

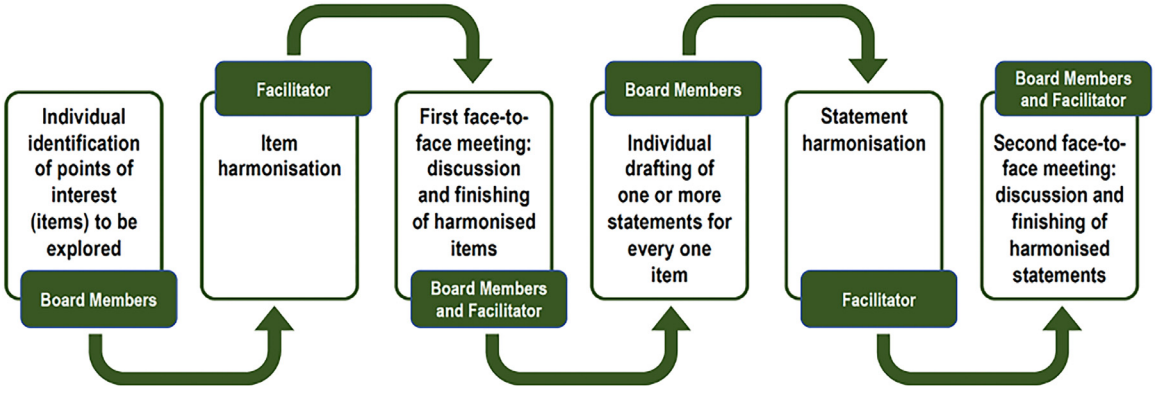

Figure 1 Project workflow.

opinions, resulting eventually in 7 conclusive items. Thereafter, the board members individually drew up 1 or more statements concerning each of agreed items. This led to the proposal of 31 statements, which were again subsequently harmonized by the facilitator into 24 statements. At a second face-to-face meeting, the board members and the facilitator reviewed and further discussed the harmonized statements, and finally agreed on a total of 12 statements.

Results

The final 7 items and 12 statements are shown in Table 1.

Discussion

Patient selection for RT to the primary tumor

Statement: All the newly diagnosed mHSPC patients should be discussed by the multidisciplinary team to evaluate the possibility of offering RT to the primitive tumor, regardless of disease burden

The strongest evidence in this scenario comes from 1 of the arms of the STAMPEDE trial,[9] where the authors demonstrated an absolute survival benefit for patients with low metastatic burden who received SOC and RT to the primary tumor, compared to the ones receiving SOC only. No improvement of survival was

Table 1 Overview of the final 7 items and 12 statements defined by the board members

Item	Statement
1. Patient selection for RT to the primary tumor	1.1 All the newly diagnosed metastatic hormone-sensitive prostate cancer patients should be discussed by the multidisciplinary team to evaluate the possibility of offering RT to the primary tumor, regardless of disease burden
2. Integrating systemic therapy with RT to the primary tumor	2.1: In mHSPC patients, RT to the primary tumor can integrate any of the systemic approaches currently recommended in the metastatic setting
	2.2: No significant increase in toxicity has been reported from the combination of RT and systemic therapy in this patient cohort
3. Timing of RT on primary tumor	3.1: RT to the primary tumor can be administered concomitantly to hormonal therapy (ADT + ARSI), and in any case within 6 months from its start
	3.2: If docetaxel is administered, it may be appropriate to postpone the start of prostate RT until after last chemotherapy administration
4. Doses and target volumes of radiation therapy to the primary tumor	4.1 Treatment volumes should include the prostate and the seminal vesicles
	4.2 Radiation therapy should be delivered with radical intent. Either a normofractionated or a hypofractionated regimen can be adopted
5. Metastasis-directed therapy (MDT) indications	5.1 MDT could be proposed in oligometastatic prostate cancer (OMPC), defined by molecular (next-generation) imaging as the presence of maximum 3-5 bone lesions, without visceral metastasis
	5.2 MDT should be delivered if treatment with radical intent is feasible both on primary tumor and metastatic sites
6. MDT RT schedule and technique	6.1 MDT by SBRT should be delivered together with primary treatment
	6.2 Treatment dose and volume should be those used with radical intent
7. Implication of *BRCA/HRR* determination	7.1 In mHSPC, the determination of *BRCA/HRR* should not influence RT indication both on primary tumor or metastatic sites

Abbreviations: ADT = androgen deprivation therapy; ARSI = androgen receptor signaling inhibitor; MDT = metastasis-directed therapy; mHSPC = metastatic hormone-sensitive prostate cancer; OMPC = oligometastatic prostate cancer; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

documented in the high metastatic burden group. The definition and criteria for differentiating between low and high metastatic burden were taken from the CHAARTED study,[2] and included the absence/presence of visceral metastases and the number of bone lesions detected at conventional imaging, irrespective of the extent of nodal involvement. The amount of bone lesions seems to inversely correlate with the benefit of RT in terms of overall survival (OS) and failure-free survival.[8] Another smaller randomized trial, the HORRAD, explored the potential benefit of adding RT to the primary in a cohort of predominantly high-burden metastatic PCa patients.[25] Similar to the STAMPEDE, no OS advantage was shown in the overall population; however, a trend toward significant improvement in survival was observed in an unplanned subgroup analysis of patients having < 5 metastatic lesions (hazard ratio, 0.68).[8]

Novel insights on the role of irradiation in the setting of de novo mHSPC can be inferred from the late breaking results of the randomized phase 3 PEACE-1 study,[10] in which a 4-arms design was conceived, with RT being added to SOC ± abiraterone and tested against patients receiving only SOC with and without ARSI.[26]

Although a clear OS benefit was not documented by the authors, there was a significant improvement of radiographic progression-free survival (PFS) in the patients' cohort with low-volume disease who received RT in addition to SOC + abiraterone.[10]

Of note, the analysis of the secondary endpoints of the trial demonstrated a statistically significant benefit of adding RT both in terms of safety and efficacy, with delayed serious genitourinary events in the irradiated patients and increased time to castration resistance in those receiving RT + abiraterone.[10]

Based on these results, the coadministration of RT + ADT + ARSI may be considered a standard treatment approach in men with low-burden de novo mHSPC. Furthermore, RT may be considered in selected men with high-burden mHSPC.

Integrating systemic therapy with RT to the primary tumor

Statement: In mHSPC patients, RT to the primary tumor can integrate any of the systemic approaches currently recommended in the metastatic setting

Statement: No significant increase in toxicity has been reported from the combination of RT and systemic therapy in this patient cohort

ADT still represents the backbone of the treatment of de novo mHSPC, but it can no longer be considered the SOC in this setting when administered alone. During the last decades, several randomized studies have shown that combining ADT with other systemic therapies leads to better oncological outcomes.[2-4] In the CHAARTED study, upfront docetaxel administered at the time of ADT start improved survival by 13.6 months (hazard ratio, 0.61) if compared to hormonal therapy alone.[2] Similar outcomes were obtained from the investigators of the arm C of the STAMPEDE.[3] In the LATITUDE trial, the addition of abiraterone was associated with a significantly longer OS (hazard ratio, 0.62) than ADT alone.[4] These first practice-changing studies paved the way for treatment intensification in the setting of mHSPC; data from ARCHES,[27] TITAN,[28] and ENZAMET[29] further demonstrated how doublet therapy with second generation antiandrogen outperforms first line ADT, whereas PEACE 1[26] and ARASENS[6] provided us with the first evidences of the benefit of the triplet therapy (ADT + Docetaxel + ARSI) over ADT ± docetaxel, especially in the setting of high-volume de novo disease. Such an intensified approach may be considered for selected fit patients, as long as triplet therapies are associated with worse safety profiles than ARSI doublets.[30]

In the global scenario, the addition of prostate RT to systemic treatment has shown to improve oncological outcomes in mHSPC patients with no increase of toxicity burden, but rather delaying serious genitourinary events.[10]

Considering that ADT alone can now be regarded as an undertreatment, is worth noting that PEACE 1 also demonstrated that RT + ADT has a poorer performance versus RT + ARSI + ADT but also versus ARSI + ADT.[26]

Timing of RT

Statement: RT to the primary tumor can be administered concomitantly to hormonal therapy (ADT + ARSI), and in any case within 6 months from its start

Statement: If docetaxel is administered, it may be appropriate to postpone the start of prostate RT until after last chemotherapy administration

Concomitant RT + ADT has traditionally represented the preferred therapeutic approach for high-risk PCa patients with localized or locally advanced tumor. Several landmark phase 3 trials[31-35] have demonstrated the benefit of adding hormonal treatment to RT in this clinical scenario.

Furthermore, 3 randomized, multicenter phase 3 trials compared RT-ADT to ADT alone (Widmark et al[36] and Brundage et al[37] [n = 1205], Mottet et al[38] [n = 264]) in locally advanced PCa and also showed a statistically

significant benefit of long-term oncological outcomes in favor of the combination arm.

The same population was analyzed in the STAMPEDE trial,[3] where the association of RT to the primary site administered concurrently with ADT and abiraterone showed a benefit in Failure-Free Survival without raising significant toxicity. This sequential strategy may therefore be reproduced in the (oligo)metastatic setting, where RT to the primary tumor can be safely offered at diagnosis and an ARSI can be started within 3 months from ADT start, as for registrative studies.[6,27,28]

When the addition of docetaxel was permitted, it was given upfront.[3] Combined chemotherapy-radiation offers the possibility of improved tumor response both through direct cytotoxic mechanisms and enhanced radiation effects, but normal tissue tolerance might represent an issue when the 2 therapies are administered concomitantly.

In the STAMPEDE trial, RT was offered within 3 to 4 weeks after last chemotherapy dose. More specifically, in the group of irradiated patients, median time to RT was 35 days after randomization and 95 days from ADT start (which was commenced before randomization in most patients).[9] No significant toxicity issues were recorded in the group of patients receiving docetaxel. Furthermore, adding RT to systemic therapy proved to be beneficial in delaying the onset of serious genitourinary events in the PEACE 1 trial,[10] where patients assigned to receive RT were planned to start the treatment at least 3 weeks (but not more than 8 weeks) after docetaxel completion. For this reason, if RT on primary is proposed in a patient undergoing triplet therapy (ADT + docetaxel + ARSI), it should preferably be postponed until chemotherapy completion.

Doses and target volumes of RT to the primary tumor

Statement: Treatment volumes should include the prostate and the seminal vesicles

Statement: RT should be delivered with radical intent. Either a normofractionated or a hypofractionated regimen can be adopted

According to the 2018 ESTRO consensus guidelines on target delineation in PCa,[39] at least 2.2 cm of the proximal seminal vesicles should be included in the target volume of PCa patients presenting with high-risk disease. However, in the STAMPEDE protocol, the planning target volume for RT to the primary tumor in low-burden mHSPC was obtained from the prostate only, plus an anisotropic margin of 10 mm in all directions, with the exception of the posterior margin (8 mm).[9]

Concerning RT schedules, STAMPEDE offers the possibility of treating the primary either with 36 Gy in 6 consecutive weekly fractions of 6 Gy, or 55 Gy in 20 daily fractions (2.75 Gy/day over 4 weeks of treatment). However, during the last decades, the advances in radiation treatment and the diffusion of image guided RT protocols allowed for more conformal dose delivery to the target with a major sparing of the surrounding healthy tissues, and patients treated with RT in the PEACE 1 and HORRAD trials received a total dose of 74 Gy in 37 fractions.[10,25] For this reason, the panel felt that, despite data coming from STAMPEDE trial, lower doses may be insufficient for obtaining a good probability of local control. Based on this assumption, almost two-thirds of the panelists of the Advanced Prostate Cancer Consensus Conference (APCCC) recommended a schedule of 78 to 80 Gy in 39 to 40 fractions (or any equivalent hypofractionated schedule) for the treatment of low-volume OMPC patients.[20]

MDT indications

Statement: MDT could be proposed in OMPC, defined by molecular next-generation imaging as the presence of maximum 3 to 5 bone lesions without visceral metastasis

The treatment landscape for OMPC has undergone radical changes in recent decades, thanks to the introduction of multimodality therapies, resulting in significant improvements in oncologic outcomes.[40] Nevertheless, a consensus on a common and unique definition of OMPC has yet to be achieved, primarily due to the varied classifications employed in different clinical trials.[40] An ESTRO-ASTRO Consensus,[41] approaching this status from a radiation oncology perspective, was built on the original definition by Hellman and Weichselbaum.[42] In this context, it is crucial to consider the disease burden, generally defined as having a limited number of metastases (3-5 or fewer) involving few anatomic sites or regions.[41] The choice of imaging modalities to define the OMPC is a crucial point and remains a subject of lively discussion, even within this consensus. The topic of next-generation imaging has been extensively addressed, from the 2017 APCCC consensus[43] to the present day. Most of the evidence suggests greater sensitivity with next-generation imaging compared to computed tomography or bone scintigraphy, particularly in defining OMPC and planning multimodal therapy.[40]

The higher accuracy of prostate-specific membrane antigen (PSMA) positron emission tomography-computed tomography has led to an increased prescription rate whenever available. In 2019, APCCC panelists voted that conventional imaging alone was insufficient for OMPC, particularly in selecting the optimal treatment. However, no consensus was reached on whether patients staged with conventional or next-generation imaging should be treated in the same manner.[40] The ESTRO consensus, as detailed in the paper by Zilli et al,[21] did reach

an agreement on the use of PSMA PET as confirmatory imaging for oligometastatic hormone-sensitive PCa, especially when multimodal therapy (MDT) is considered. Even within this consensus, the issue was discussed, and the conclusion was drawn that, in the context of MDT, next-generation imaging is crucial for defining OMPC. The accurate characterization of OMPC was also a critical point of discussion. In PCa we can refer, as previously mentioned, to the initial definition of high- versus low-volume disease, as applied in the CHAARTED and STAMPEDE trials.[2,3] High volume is defined as the presence of 4 or more bone metastases, with 1 or more outside the vertebral bodies or pelvis, or the presence of visceral metastases, or both. The definition used in the HORRAD trial is based on improved outcomes observed after RT in a subgroup of patients with fewer than 5 bone metastases.[25] Similarly, the STOPCaP meta-analysis[7] indicates that PCa patients with fewer than 5 bone lesions benefit from local RT. Shifting the focus from local to systemic treatment intensification, the LATITUDE trial in metastatic castration-sensitive PCa (mHSPC) introduced a high-risk versus low-risk classification.[4] High-risk patients were defined as those with at least 2 of 3 high-risk features: Gleason score 8 or more, 3 or more bone lesions, and measurable visceral metastasis. In an exploratory analysis by Ali et al,[8] the number of bone metastases was associated with better outcomes from prostate RT, particularly in individuals with 3 or fewer bone lesions or only nonregional nodes.

Furthermore, a recent Italian consensus has defined both low-volume and oligometastatic disease as the presence of up to 3 nonvisceral lesions[22]; according to the authors, MDT could be considered, albeit selectively, if the oligometastatic disease definition is applied to patients with 4 or 5 metastases. Several phase 2 trials have investigated the role of MDT in this scenario. The SABR-COMET trial[44] included patients with 1 to 5 metastatic lesions and controlled primary tumors, demonstrating a significant impact on OS with MDT with ablative intent. Two other trials, ORIOLE and STOMP, specifically enrolled patients with metachronous oligometastatic castration-sensitive PCa and showed benefits in both PFS and androgen deprivation-free survival.[11,12] The STOMP trial enrolled patients with 3 or fewer metastases detected by choline PET-CT, randomized to surveillance or MDT (surgery or stereotactic body radiation therapy [SBRT]).[12] The ORIOLE trial randomized mHSPC patients with 1 to 3 lesions detectable by conventional imaging or PSMA PET to receive SBRT or observation.[11] More recently, the EXTEND study,[15] a basket randomized trial, enrolled 87 PCa patients with OMPCa and 5 or fewer metastases. The trial compared MDT with intermittent ADT against ADT alone, with the former demonstrating improved PFS and eugonadal PFS. The debate around the number of lesions to warrant MDT has been ongoing. In the ESTRO consensus,[21] an agreement was reached in round 2, establishing a maximum of 5 lesions as a criterion for MDT. However, in the APCCC 2022 consensus,[20] the agreement was not reached and a specific cut-off number of lesions to define patients as having oligometastatic disease was not determined (66% voted for 3 or fewer). Additionally, for patients with 1 to 3 bone lesions on PSMA PET, 50% voted to treat as M0 plus MDT.

After a prolonged discussion on the number of lesions to consider for MDT eligibility, members of this consensus decided to vote. Fifty percent of the panelists voted for 3, and the other 50% voted for 5. Consequently, the consensus was obtained considering patients eligible for MDT if they present with "maximum 3 to 5 bone lesions."

Statement: MDT should be delivered if treatment with radical intent is feasible both on primary tumor and metastatic sites

The rationale behind MDT is not only to achieve local control but also to hamper disease progression, delaying the onset of castration-resistant PCa, prolonging disease-free survival and the need to change systemic therapies.[45,46] Control of both primary and metastatic sites is therefore crucial. All the previously mentioned trials investing MDT used SBRT or surgery to treat metastatic sites with a radical intent; moreover, in all these trials, primary tumor was controlled.[11,12,15,44] Over half of the panelists at the 2019 APCCC voted to treat all secondary lesions with ablative treatment together with the treatment of the primary tumor in in "de novo" oligometastatic patients.[20] Also, the ESTRO consensus addressed this issue, reaching an agreement of 76% in the second round for treating de novo oligometastatic patients by combining systemic therapy with RT both to the primary (± pelvic nodes) and all secondary lesions.[21]

Several trials [NCT02716974, NCT06150417] are investigating the combination of systemic SOC (including docetaxel or ARSI) with MDT of all known metastases and primary RT, delivered with ablative doses (Biologically Effective Dose > 100 Gy). The ongoing ADOPT trial (NCT04302454) is evaluating the role of adding ADT to MDT, whereas the currently recruiting PERSIAN trial (NCT05717660) is testing the role of MDT associated with ADT and apalutamide in oligometastatic hormone-sensitive PCa.

MDT RT schedule and technique

Statement: SBRT as MDT should be delivered together with the treatment of the primitive tumor

Statement: Treatment dose and volume should be those used with radical intent

Timing of RT in mHSPC largely depends on systemic treatments adopted. In general, following the approach of

the STAMPEDE trial, RT was administered "as soon as practicable," typically within 3 to 4 weeks after the last dose of docetaxel.[9] The percentage of de novo OMPCa in studies investigating multimodal therapy with ablative intent, including RT to the primary tumor, is very low. However, to achieve a radical intent, there is currently no apparent rationale to delay MDT following primary RT.

Different doses and volumes have been employed in MDT across studies addressing this topic, with SBRT being the main technique used in most cases. In the SABR-COMET study, doses ranging from 30 to 60 Gy administered in 3 to 8 fractions, or 16 to 24 Gy in a single fraction (for bone/brain), were employed.[44] The STOMP trial used 30 Gy in 3 fractions,[12] whereas the ORIOLE study implemented a range of 19.5 to 48 Gy in 3 to 5 fractions, depending on site and location.[11] In the POPSTAR trial, a single fraction of 20 Gy was administered.[47] The use of heterogeneous dose/fractionation schedules, different imaging tools, and limited follow-up duration complicate the selection of a single approach. However, achieving excellent local control has been possible with the delivery of a biological equivalent dose exceeding 100 Gy, and this has been accomplished without a high incidence of toxicity.[48]

An attempt of standardization was undertaken by the ESTRO consensus.[21] For bone metastases with a spinal location, it was recommended to cover both the volume of the visible lesion (gross tumor volume) and the entire vertebral body (clinical target volume). Among the preferred schedules, 35 Gy in 5 fractions received the highest vote (42%), followed by 30 Gy in 3 fractions. Additionally, 33% of the experts recommended a simultaneous integrated boost technique in either 3 or 5 fractions. Regarding extraspinal bone metastasis, a consensus of 68% of the panelists suggested considering an isotropic margin of 4 to 5 mm, based on location and anatomy. This was followed by the preference for a margin of 1 to 3 mm and a nonisotropic expansion. In this setting, a SBRT schedule of 3 fractions was recommended. Regarding dose prescription, 60% of the experts voted in favor of a homogeneous dose on the planning target volume, whereas 40% favored prescription to an isodose (80% isodose line). Opinions were divergent for the treatment of pelvic nodes, whether using whole-pelvis RT or SBRT for single-nodal lesions. However, the most recommended schedule for the treatment of single lymph nodes was 30 Gy in 3 fractions, followed by 35 Gy in 5 fractions.[21]

Due to the various schedules used and the absence of a unanimous opinion, the sole recommendation is to use the dose and fractionation employed for radical intent. This decision should be based on single-center experience and technology. Additionally, reference to existing contouring guidelines, particularly for bone lesions, is advised.

Implication of *BRCA/HRR* determination

Statement: In mHSPC, the determination of *BRCA/HRR* should not influence RT indication both on primary tumor and metastatic sites

In recent decades, the emergence of genomic sequencing has led to the consideration of PARP inhibitors as the SOC for metastatic castration-resistant with relevant alterations in *HRR* genes [20]. Olaparib is approved in Europe for PCa with germline or somatic alterations in *BRCA1* or *BRCA2* genes. In the United States, its approval extends to cases involving additional DNA repair genes.[49] Rucaparib is approved in the United States for germline or somatic *BRCA1/2* mutations.[50] In the PROPEL and MAGNITUDE study,[51,52] a combination of PARP inhibitors with abiraterone was used in an unselected population in the setting of first line of metastatic castration-resistant PCa, with a greater benefit shown in biomarkers positive population.[53]

In the mHSPC setting, studies on the first line association of niraparib + abiraterone or talazoparib + enzalutamide are still ongoing (NCT04497844, NCT04821622).

A recent document of the Italian Association of Medical Oncology gives a recommendation about implementing *BRCA* analysis in metastatic PCa (https://www.aiom.it/wp-content/uploads/2023/04/2023-03_Racc_BRCA_Prostata.pdf).

Overall, as shown in a pooled analysis of STOMP and ORIOLE trial, patients with high-risk mutations (*TP53, RB1, BRCA1/2* or *ATM*) had are more aggressive disease.[14] MDT prolonged PFS compared with surveillance, with the largest benefit observed in patients with a high-risk mutation; more specifically, in the MDT arm, PFS was 13.4 months in those without a high-risk mutation compared with 7.5 months in those with a high-risk mutation, confirming a more aggressive pattern.[14]

In this scenario, molecular biomarkers will have a potentially crucial prognostic and predictive role. However, we need to wait for the results of upcoming studies to bring about further changes in clinical practice.

Nevertheless, the determination and results of *BRCA/HRR* should not influence the choice on RT on primary and metastatic lesions.

Conclusion

There is mounting evidence on the role of RT as part of the multimodality management of mHSPC. Recent findings support its employment not only as MDT, but they also suggest targeting the primitive tumor as it has been shown to provide better oncologic outcomes. However, several issues remain unclear, ultimately leading to a certain heterogeneity among radiation oncologists' conception and application of RT in this setting of patients.

This Experts consensus aims to shed lights on the most commonly debated aspects in daily practice and to standardize the current radiotherapeutic approach in the clinical scenario of mHSPC patients.

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