Clinical, Diagnostic and Therapeutic Framework of mHSPC and nmCRPC: A Multidisciplinary Consensus Project of the Italian Society for Uro-Oncology (SIUrO)

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Abstract

The recent evidences provided in metastatic hormone sensitive prostate cancer (nmHSPC) and in nonmetastatic castration resistant (nmCRPC) introduced the possibility to adopt Androgen Receptor Signaling inhibitor (ARSi) alone (both settings) or with chemotherapy (in mHSPC). In daily clinical practice there are some opening questions regarding the inclusion of next generation imaging, mainly PSMA-PET, how integrate local treatment as radiotherapy, how to select patients or drugs in a multiple-choice scenario, and how to manage patients with comorbidities and polypharmacy. These issues led the Italian Society for Uro-Oncology (SIUrO) to develop a consensus project involving all of the most important Italian scientific societies engaged in the multidisciplinary and multiprofessional management of the disease. This paper describes the items and statements approved, with the aim to support clinicians in managing metastatic hormone sensitive and nonmetastatic castration resistant prostate cancer patients.

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Introduction

Notable improvements have been recorded in recent years in treating prostate cancer, especially in de novo metastatic hormone sensitive setting (mHSPC), where we have moved from a therapeutic strategy based on androgen deprivation therapy (ADT) alone to intensified treatment by adding to ADT either docetaxel[1,2] or 1 Androgen Receptor Signaling inhibitor (ARSi)[3–5] or by combining even ADT, docetaxel, and 1 ARSi.[6] Besides, prostate radiotherapy (RT) shown to have an impact in the initial therapy of mHSPC.[7]

Thus, apart a limited number of patients with an oligometastatic de novo mHSPC eligible for radiotherapy on primary tumor plus SBRT to oligometastasis with a defined course of ADT±ARSi,[8] in the contemporary landscape the large majority of mHSPC patients should receive ADT plus 1 ARSi, alone or combined with docetaxel.

Regardless the evidence provided by pivotal trials, the massive use of ARSi in treating mHSPC patients opened some practical issues in their daily management.

About 1 of the major challenges is to translate the pivotal trials into the clinical practice, even more considering that in these studies the imaging monitoring have been performed with conventional imaging (CI), while there is an increasing use of next generation imaging (NGI) techniques, mainly PSMA PET, in the daily practice.

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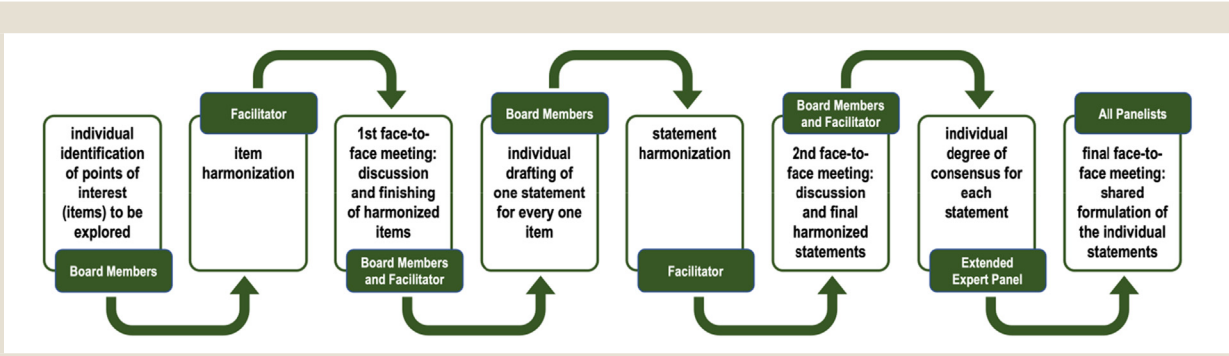
Figure 1 Project workflow.



Despite the choice among the available therapeutic options is mainly driven by disease-related factors, such as disease volume/risk or timing of metastases occurrence (relapsed vs. de novo mHSPC), some patient-related factors (such as chronological age, health status, comorbidities, and concomitant medications) could influence treatment decision.

In this complex scenario the continuum of care may involve the multidisciplinary and multiprofessional team along patient journey.

For this reason, the Italian Society for Uro-Oncology (SIUrO), engaging the leading Italian scientific societies involved in prostate cancer management, organized a Consensus Program with the aim to address some critical issues which emerge in managing ARSi in patients mHSPC.

Material and Methods

Figure 1 shows the workflow of the consensus process, which started using the estimate-talk-estimate (ETE) method.[9,10] ETE (a formal means of reaching consensus that was developed to overcome some of the negative aspects of group dynamics) facilitates group decision making[11,12] by combining assembling of expert opinions on an anonymous basis during surveys with open exchange during workshops.[13] The 10 members of a selected multidisciplinary board (3 medical oncologists, 1 radiation oncologist, 1 urologist, 1 geriatrician, 1 nuclear medicine specialist, 1 radiologist, 1 pharmacologist, 1 pathologist) individually identified 60 points of interest (or items) that, in their opinion, deserved exploration and discussion. These were then harmonized and grouped by a senior urologist (GNC) trained in developing group consensus (the facilitator) into 31 items that were proposed to the board members at a face-to-face meeting. The harmonized items were discussed to reach agreement between the facilitator's work and the experts' opinions, after which the board members individually drew up 1 or more statements concerning each of agreed items. This led to the proposal of 70 statements, which were again subsequently harmonized by the facilitator. 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 25 statements.

The statements generated in this way were then presented via an on-line scoring platform to the 45 members (41 voted) of an extended multidisciplinary panel of experts who expressed their degree of consensus by means of a RAND 9-point numerical rating scale ranging from 1 = totally disagree to 9 = totally agree. A median score of ≥7 was considered the threshold of consensus for each statement according to the RAND/UCLA Appropriateness Method User's Manual.[14] A final face-to-face meeting, held on December 2 2022, allowed the members of the board and the expert panel to come to a final shared formulation of the 25 statements. It is worth noting that all the members of the board and the panel were involved in the global care of prostate cancer patients at different Italian centers in the context of a multidisciplinary team. Given the nature of the consensus technique, a senior clinical epidemiologist (GP) assured scientific and methodological accuracy.

Items, Statements and Rationale

All the items (10) and statements (25) are listed in Table 1 .

1. **Imaging for studying metastatic Hormone Sensitive Prostate Cancer (mHSPC)**

1.1 *Bone scintigraphy and contrast enhanced CT remains preferred imaging methods for studying the extension of disease in mHSPC.*

1.2 *In patients with mHSPC at conventional imaging (CT and Bone scintigraphy), PSMA PET should not be routinely performed.*

1.3 *CT and bone scintigraphy could be used in monitoring and to evaluate response to treatment.*

1.4 *In patients with mHSPC, PSMA PET could be used to identify further site of disease, but we lack data on main outcome (overall survival).*

Bone scintigraphy and contrast enhanced CT remains preferred imaging methods for studying the extension of disease in mHSPC.[15,16]

Despite many papers have demonstrated a better accuracy for NGI as compared to CI in prostate cancer, these studies regarded primary prostate cancer staging or biochemical recurrence, rather than mHSPC.[16] In fact, compared to CI, in mHSPC NGI contributes to identify a greater number of lesions, without a real impact on patient management.[17]

Therefore, in mHSPC patients diagnosed with CI, PSMA PET should not be performed.[18]

Conversely, NGI should be performed only when it leads to a change in patients' management and not just to provide further information that not ultimately support clinical decisions. At present time, there are no data supporting a clinical usefulness of

Table 1 Items and Statements Approved During Plenary Session

Item	Statement
Imaging for studying metastatic Hormone Sensitive Prostate Cancer (mHSPC)	Bone scintigraphy and contrast enhanced CT remains preferred imaging methods for studying the extension of disease in mHSPC
	In patients with mHSPC at conventional imaging (CT and Bone scintigraphy), PSMA PET should not be routinely performed
	CT and bone scintigraphy could be used in monitoring and to evaluate response to treatment.
	In patients with mHSPC, PSMA PET could be used to identify further site of disease, but we lack data on outcome (OS)
Imaging for studying nonmetastatic Castration Resistant Prostate Cancer (nmCRPC)	Bone scintigraphy and contrast enhanced CT remains preferred imaging methods for studying the extension of disease in patients with nmCRPC
	CT and bone scintigraphy could be used monitoring and to evaluate response to treatment
	In patients with nmCRPC, PSMA PET could be used to identify further site of disease, but we lack data on outcome (OS)
	In patients with nmCRPC already studied with conventional imaging, the clinical utility of PET has never been demonstrated. Therefore, the use of PET, even in possible oligometastatic setting, should be discussed in a multidisciplinary team
	In patients with nmCRPC at convention imaging and undergoing ARSis treatment, next generation imaging should not be used to reevaluate patients.
If PET is indicated, which radiopharmaceutical should be used?	PSMA PET should be regarded as most accurate PET methods in patients with PC: different tracers (such as Choline or Fluciclovine) should only be used in selected cases
Biological characteristics	Predictive biomarkers of resistance to ARSi - Molecular alterations of the Androgen Receptor (AR) have been identified as possible mechanisms of resistance to ARSi therapy, including the AR splice variant AR-V7, AR amplification, and AR activating point mutations, which confer different sensitivity to ARSi
	Possible role of liquid biopsy in monitoring patients before and during ARSi therapy - Although liquid biopsy has proved to be a valid tool for the identification of biomarkers (prognostic and predictive), to date there are no validated prospective data available to recommend its use to monitor response to ARSi in prostate cancer
Correct clinical assessment of the patient (fit, unfit, frail)	Evaluation of "health status" and life expectancy - Health status and life expectancy are more important factors than the patient's chronological age alone. Health status can be defined by examining both physical and cognitive performance, with the aim of categorizing the patient into FIT, UNFIT (VULNERABLE) and FRAIL states.
	Impact of comorbidity and level of dependence on the therapeutic process - Comorbidities and the patient's level of dependence can significantly influence the therapeutic process, as they can cause poly-pharmacotherapy and interfere with treatments and life expectancy. The driver in the therapeutic process must always be the neoplastic pathology. Comorbidity can be assessed and "weighed" through specific scores (for example CIRS-G) and managed according to the chosen treatment, and not vice versa
	Osteosarcopenia and metabolic syndrome: correct management and prevention, appropriate use of Bone Targeted Agents (BTA) - In patients undergoing treatment with androgen deprivation ± ARSi, first-level preventive diagnostics are recommended, including quantitative measurement of lean muscle mass and a qualitative assessment of physical performance. The patient undergoing androgen deprivation therapy ± ARSi must be provided with all recommendations regarding lifestyle, diet and physical activity capable of preventing osteosarcopenia and metabolic syndrome. BTA must be used regularly at the dosages and with the schedules used in the prevention of osteopenia
Characteristics of patients and choice of treatment in patients with de novo mHSPC	Choice criteria between ARSi+ADT and docetaxel+ADT: the choice should be made according to the disease burden and patient's comorbidities, concomitant medications and performance status
	Choice criteria for choosing ARSi to be added to ADT: the choice should be made according to both the patient's clinical status and the ARSi toxicity profile
	Criteria for the selection of patients to be applied for triplet (ADT + docetaxel +ARSi): the addition of an ARSi should be considered in all patient fit for the combination of ADT and docetaxel
	Selection criteria for patients eligible for combined local and systemic treatments: patients with de novo mHSPC and up to 3 bone lesions should be evaluated for radiation treatment to the primary tumor and/or secondary lesions. The possibility of combining local and systemic treatments (ADT+ARSi) should be evaluated on a case-by-case basis in a multidisciplinary context with careful definition of the benefit/harm ratio

(*continued on next page*)

Table 1 (*continued*)

Item	Statement
Is there still a role for ADT monotherapy in denovo mHSPC?	ADT monotherapy should not be considered except in the case of severe comorbidities and/or short life expectancy
Local treatment of lesions detected by next generation imaging (PET-PSMA etc.) only	In patients with sites of disease at next generation imaging (PET-PSMA, other) but not at conventional imaging, decision about systemic and/or local treatment should be discussed within a multidisciplinary team
Pharmacological properties of ARSi in mHSPC and nmCRPC	In the presence of concomitant therapies, ARSi show different drug interaction profiles.
	Considering the interaction between the oncological and concomitant drug, it is the latter which should preferentially be modified (dose reduction or substitution)
Critical issues in the multidisciplinary and multiprofessional management of mHSPC and nmCRPC patients	Urologic management through the continuum of the mHSPC and nmCRPC patients' treatment - In patients with mHSPC and nmCRPC disease it is proper to systematically monitor upper and lower urinary tract to detect earlier any obstruction or functional disease
	Role of radiotherapy for symptomatic bone lesions and/or bone lesions at risk of fracture - Radiation treatment (including stereotactic radiotherapy) for symptomatic and/or consolidation purposes should be considered in patients with symptomatic bone lesions or lesions at risk of fracture

PSMA PET in mHSPC patients in terms of changing the treatment plan, which is usually based on volume of disease as seen at CI. Preliminary data have shown that volume of disease can be assessed also by NGI,[17] but more studies are required to correlate NGI-detected disease volume (low vs. high) with patients' outcome, as already recognized in CHAARTED and STAMPEDE trials by using CI.[18]

Usually, mHSPC patients are monitored by laboratory and clinical data, and by the same imaging performed at diagnosis on selected time point.[16]

2. **Imaging for studying nonmetastatic Castration Resistant Prostate Cancer (nmCRPC)**

2.1 *Bone scintigraphy and contrast enhanced CT remains preferred imaging methods for studying the extension of disease in patients with nmCRPC*

2.2 *CT and bone scintigraphy could be used in monitoring and to evaluate response to treatment.*

2.3 *In patients with nmCRPC, PSMA PET could be used to identify further site of disease, but we lack data on main outcome (overall survival)*

2.4 *In patients with nmCRPC already studied with conventional imaging, the clinical utility of PET has never been demonstrated. Therefore, the use of PET, even in suspicious of oligometastatic disease, should be discussed in a multidisciplinary team.*

2.5 *In patients with nmCRPC at convention imaging and undergoing ARSi treatment, NGI should not be used to reevaluate patients.*

There is a growing debate regarding the use of imaging techniques in nmCRPC, as introduction of NGI have dramatically increased the number of patients classified as nmCRPC at CI that show metastases at PSMA PET.[19] However, all pivotal studies performed in nmCRPC patients have been done using CI, thus NGI could simply lead to a stage migration with low impact on treatment strategy (eventually adding radiation to main systemic treatment which is mainly based on ARSi use in mCRPC first-line). Therefore, further studies should evaluate the impact of NGI on major clinical outcomes in nmCRPC.

Similarly to mHSPC (see statement 1.3), the routine use of NGI with the aim of evaluating response to treatment in nmCRPC patients is not recommended but should be limited to selected patients and proposed into a multidisciplinary setting. Again, since no data exist in favor of the use of NGI, an approach based on CI should be considered.[16]

There are currently several ongoing RCTs which explore the role of PSMA PET in patients with nmCRPC to drive the therapy: when these trials will be concluded, we will finally have reliable information on the role of PSMA PET in this setting. At present PSMA PET could be indicated in selected patients after a multidisciplinary evaluation, mainly to identify sites of disease not detected at CI but being aware of lack of outcome data.[5]

3. **If PET is indicated, which radiopharmaceutical should be used?**

3.1 *PSMA PET should be regarded as most accurate PET methods in patients with PC: different tracers (such as Choline or Fluciclovine) should only be used in selected cases.*

It has been largely demonstrated that PSMA PET is the most accurate imaging method in prostate cancer patients, both in localized disease for N and M staging and at biochemical recurrence onset.[17,20,19,21] It is much more sensitive than other PET tracers (such as Choline and Fluciclovine)[22] which should be considered only in very selected cases (like in cancers with low expression of PSMA). Among the several PSMA tracers available, the choice of the tracer depending on many factors such as logistic, availability, expertise and others.

4. **Biological characteristics**

4.1 *Molecular alterations of the androgen receptor (AR) have been identified as possible mechanisms of resistance to ARSi therapy, including the AR splice variant AR-V7, AR amplification, and AR activating point mutations, which confer different sensitivity to ARSi.*

4.2 *Although liquid biopsy has proved to be a valid tool for the identification of biomarkers (prognostic and predictive), to date there are no validated prospective data available to recommend its use to monitor response to ARSi in prostate cancer.*

Prostate cancer is characterized by several molecular alterations in frequently altered genes, including AR, Rb1, TP53, BRCA, PTEN, PIK3CA, CTNNB1, ATM, PALB2, CHEK2, CDK12 and many others, representing a clinical challenge for patients' management, particularly in terms of treatment resistance.[23,24] Considering the driver event of prostate cancer growth, the therapeutic strategies are directed to block the dependence on hormonal-driven signaling (i.e., CYP17A1, AR).[25] Growing number of evidence confirmed that prostate cancer progression during AR-deprivation therapies remains mainly dependent on persistent AR signaling.[26–29]

In these cases it has been observed an abnormally active AR function due to the selective pressure of treatments, including gene amplifications, activating mutations, alternative splice variants.[30,23]

AR-V7, AR overexpression, AR point mutations in the ligand binding domain (LBD) and reactivation of androgen synthesis has been reported.[23] Mutations in the LBD of the AR (i.e., W741L/C, H875Y/T, T878A and F877L) or AR copy number gain are commonly associated with a gain of function, altering the specificity and response to androgens and steroid hormones.[31,32] Molecular alterations of the AR have been identified as possible mechanisms of resistance to ARSi therapy, including the AR splice variant AR-V7, AR amplification, and AR activating point mutations, which confer different sensitivity to ARSi.

Interestingly, preclinical evidence suggested that AR mutations confer different response to different AR-directed treatments.[33] The AR-V7 splice variant has been correlated in different studies to shorter response to enzalutamide.[26–28]

However, even if that evidence is very strong in literature, there are no prospective data suggesting a possible use of these alterations to stratify patients candidate to receive ARSi.

Liquid biopsy has been widely studied in prostate cancer to predict resistance to AR-directed therapies and is a standard of care in other solid tumors, including lung and breast cancer.[34] A number of retrospective studies confirmed the utility of using different analytes in liquid biopsy, such as circulating tumor cells (CTCs), circulating free DNA (cfDNA) or microvesiscles (mEV) to predict response and resistant to AR-directed agents, looking particularly for AR variants.[26–29]

However, the limitation of a possible use of the liquid biopsy in prostate cancer is not related to the liquid biopsy itself. Liquid biopsy preanalytic and analytic processes are nowadays very well standardized in referral centers and the risks for false negative/positive results are minimized due to highly sensitive and specific technological molecular platforms.[35] On the contrary, the lack of a validated biomarker to stratify patients makes of the liquid biopsy an un-useful tool.

Although liquid biopsy has proved to be a valid tool for the identification of biomarkers (prognostic and predictive), to date there are no validated prospective data available to recommend its use to monitor response to ARSi in prostate cancer.

5. **Correct clinical assessment of the elderly patient (fit, unfit, frail)**

5.1 *Health status and life expectancy are more important factors than the patient's chronological age alone. Health status can be defined by examining both physical and cognitive performance, with the aim of categorizing the patient into FIT, UNFIT (VULNERABLE) and FRAIL states.*

5.2 *Comorbidities and the patient's level of dependence can significantly influence the therapeutic process, as they can cause poly-pharmacotherapy and interfere with treatments and life expectancy. The driver in the therapeutic process must always be the neoplastic pathology. Comorbidity can be assessed and "weighed" through specific scores (for example CIRS-G) and managed according to the chosen treatment, and not vice versa.*

5.3 *In patients undergoing treatment with ADT ± ARSi, first-level preventive diagnostics are recommended, including quantitative measurement of lean muscle mass and a qualitative assessment of physical performance. The patient undergoing ADT ± ARSi must be provided with all recommendations regarding lifestyle, diet and physical activity capable of preventing osteosarcopenia and metabolic syndrome. Bone target agents (BTA) must be used regularly at the dosages and with the schedules used in the prevention of osteopenia.*

Health status and life expectancy give us a more precise perception of patients' physiological age than chronological age.[36] Knowing a patient's life expectancy at a given age allows for better balancing of the treatment risk-benefit ratio. It will enable the avoidance of patient overtreatment or undertreatment. It is, therefore, helpful to use tools or scores that allow the quantification of the life expectancy of a patient at a given age. The health status assessment will enable elderly patients to be categorized into FIT, UNFIT (VULNERABLE), and FRAIL.[37] This subdivision corresponds to a different therapeutic and management approach. FIT patients can be considered and treated like younger patients, considering age-related physiological changes. UNFIT (VULNERABLES) patients can be treated and managed like younger patients but with greater attention to the side effects or toxicity of the treatments and to those factors that could cause them to fall into a state of frailty. FRAILTY patients require particular attention as any treatment could facilitate their falling into a state of disability. Health status can be defined by assessing physical and cognitive performance through the tools that constitute the Comprehensive Geriatric Assessment (CGA).[38]

Comorbidities influence therapeutic choices, both because comorbidities are associated with polypharmacy and consequently with a more significant number of side effects related to treatments and because any cancer treatment can exacerbate chronic pathologies.[39] However, it is crucial to consider not the total number of comorbidities or the presence of comorbidities but rather the impact of comorbidities on the individual and the therapeutic choice. To obtain this data, scales, and tools capable of weighting the importance of comorbidities in the patient are helpful; the most useful for this purpose in cancer patients could be the CIRS-G tool.[40] Based on the treatment that is hypothesized to be carried out on a patient, it is possible to modulate the therapy and not vice versa.

The use of ADT involves an alteration of both bone, muscle, and metabolic metabolism. The reduction in muscle quality (sarcopenia) associated with greater bone fragility constitutes the syndrome defined as osteosarcopenia.[41,42] The metabolic alterations found in patients on ADT (increase in fasting glycemic values, dyslipidemia, increase in abdominal adipose tissue, and changes in blood

pressure values) constitute the picture of metabolic syndrome. Metabolic syndrome in turn represents an important cardiovascular risk factor.[43]

It is essential to consider how both metabolic syndrome and osteosarcopenia represent preventable and treatable syndromes. For this reason, lifestyle changes, increased protein intake, reduced dietary intake of carbohydrates and fats, and physical activity aimed at maintaining muscle tone-tropism can control and avoid the development or evolution of these syndromes.[38] In consideration of the alterations regarding bone health, control of calcium, phosphorus, and vitamin D values should be carried out in all patients, as well as the use of bone target agents in preventing osteopenia.

6. **Characteristics of patients and choice of treatment in patients with de novo mHSPC**

6.1 *The choice between ARSi+ADT and docetaxel+ADT should be made according to the disease burden and patient's comorbidities, concomitant medications and performance status.*

6.2 *The choice of ARSi to be added to ADT should be made according to both the patient's clinical status and the ARSi toxicity profile.*

6.3 *The addition of an ARSi should be considered in all patient fit for the combination of ADT and docetaxel.*

6.4 *Patients with de novo mHSPC and up to 3 bone lesions should be evaluated for radiation treatment to the primary tumor and eventually to secondary lesions. The possibility of combining local and systemic treatments (ADT+ARSi) should be evaluated on a case-by-case basis in a multidisciplinary context with careful definition of the benefit/harm ratio*

Since docetaxel and ARSi clearly demonstrated a survival advantage in mHSPC patients, clinicians could use both strategies in daily clinical practice. In this view, it could be of interest to define criteria to choose between the available strategies.

The first criterion is related to both the disease burden and the timing of metastases detection. According to the pivotal trials results, docetaxel efficacy appeared to be limited to high volume de novo mHSPC, since in the remaining clinical conditions (relapsed and/or low volume disease) the addition of this agent to ADT failed to demonstrate any survival improvement compared to ADT alone.[44,45] Although post hoc analyses of STAMPEDE trial suggested that the beneficial effect of docetaxel did not vary according to the metastatic burden,[1] in the clinical practice it is mainly used in high volume de novo mHSPC patients.

On the contrary ARSi demonstrated to be efficacious regardless disease burden and metastases timing.[3–5]

The other criterion concerns the degree of fitness for chemotherapy. In the case of elderly patients, they were developed scales able to predict the risk of toxicity. The CARG toxicity tools is a quick and simple instrument freely available online which was developed and validated for patients aged $\geq$ 65.[46] The CRASH score incorporates validated GA tools as well as clinical variables and adjusts for chemotherapy intensity, but it was validated for patients aged $\geq$70 and is more time consuming compared to the CARG score.[47] However, these instruments are not validated in younger patients and their real use of these instruments in elderly population in the daily clinical practice is very limited. Thus, in absence of a clear definition of chemo-fitness (or unfitness), this remains a more intuitive than objective concept, mainly driven by the clinician's experience and depending on patient's comorbidities (and concomitant medications) and performance status.

The same criteria could be used to choose between docetaxel and ARSi for addition to ADT in mHSPC.

To date, the addition of 3 different ARSi to ADT demonstrated a survival improvement in mHSPC patients. The pivotal trials with enzalutamide and apalutamide had similar inclusion criteria and demonstrated a survival advantage regardless the disease burden and metastases timing.[3–5] On the contrary, LATITUDE trial, which tested the addition of abiraterone to ADT, enrolled only mHSPC de novo high-risk patients.[48] Accordingly, abiraterone is indicated in mHSPC patients meeting the LATITUDE trial criteria, although the posthoc analysis of STAMPEDE trial suggested that it is active in both low- and high-risk patients.[49]

Beyond the disease characteristics (in terms of both volume/risk and metastases timing), the choice drivers can be related to the toxicity profile and the potential drug-by-drug interactions with concomitant medications.

Enzalutamide and apalutamide, which present a similar molecular structure and the same mechanism of action, show a slightly different toxicity profile: their most frequent class side effects are hypertension, falls and fractures.[3–5] The only distinctive side effect in their toxicity profile is rash, which is usually reported in patients treated with apalutamide.[4]

The toxicity profile of abiraterone is quite different from that of the previous ARSi, being mainly related to hypertension, hypokalemia, transaminases increase, and cardiac disorders.[48]

The potential interactions between ARSi and concomitantly administered drugs are well known and related to cytochrome-based mechanism of interference, which could increase/reduce the activity of either the anticancer agent or the other drug.[50,27] Although it should be preferred to privilege the activity of the anticancer drug by changing/modulating the other 1, these interactions should be considered in choosing the ARSi to be added to ADT.

Recently, 2 different phase III randomized trials have demonstrated the superiority of triplet combination of ADT + docetaxel + ARSi (abiraterone or darolutamide) over ADT + docetaxel,[51,6] with a frequency of adverse events quite similar in both experimental and control group. Therefore, triplet combination of ADT + docetaxel + ARSi should be offered to patients with de novo mHSPC if they are considered fit for chemotherapy with docetaxel.

Arm H of Stampede trial[7] evaluated the role of adding radiotherapy to primary tumor in de novo mHSPC, recording a survival benefit in low volume disease, that has been introduced in current EAU guidelines.

Moreover, a posthoc analysis on bone metastatic burden[52] showed a survival benefit in treating primary tumor in patients with up to 3 bone metastases.

No specific data about this setting of disease are available for treatment of distant metastasis, other than SABR Comet trial.[53] In this basket trial, Stereotactic Ablative Radiotherapy (SABR) was added to standard systemic treatment in different cancer type, including prostate cancer, showing an improved overall survival over standard treatment alone.

Finally, in APCC 2022 consensus conference[8] 94% of panelists voted to include local treatment of primary in oligometastatic (up to 3 bone metastases) mHSPC with systemic therapy, while 61% of them voted to add metastases directed therapy too.

In STAMPEDE trial,[7] 82% of patients received ADT only as standard of care, and therefore, the inclusion of prostate RT in patients receiving ADT+ARSi should not be based on STAMPEDE trial for indirectness of standard treatment.

Recent data from Peace-1,[54] where patients received abiraterone and/or irradiation with standard of care (SOC), revealed a better radiologic progression free survival (rPFS) and time to serious genitourinary adverse events but not overall survival, for patients receiving SOC+abiraterone+RT over SOC alone, thus confirming the benefit of adding prostate radiotherapy even with abiraterone.

Although evidence does not suggest that prostate radiotherapy leads to improved OS in these patients, incorporating prostate RT in this context is associated with better rates of serious GU events, regardless of the metastatic burden, a remarkable benefit in terms of quality of life.[55]

7. **Is there still a role for ADT monotherapy in de novo mHSPC?**

7.1 *ADT monotherapy should not be considered except in the case of severe comorbidities and/or short life expectancy.*

ADT monotherapy has been the standard of care for over 50 years in mHSPC. Starting from 2015, several trials have demonstrated the superiority of combination therapy with chemotherapy[1,2] and/or a new ARSi,[3–5] over ADT alone.

Consequently, ADT alone should not be offered to patients with de novo mHSPC if they have no contraindications for combination therapy and have an acceptable life expectancy, unless they are willing to accept the potential increased toxicity.

8. **Local treatment of lesions detected by next generation imaging (PET-PSMA etc.) only**

8.1 *In patients with sites of disease at next generation imaging (PET-PSMA, other) but not at conventional imaging, decision about systemic and/or local treatment should be discussed within a multidisciplinary team.*

At present time, there are no data derived from clinical studies that evaluate the prognosis of patients with metastases detected only by PSMA PET or other NGI.

It is therefore unknown whether local treatments resulting from NGI-based upstaging are able to improve patient outcomes.

Therefore, NGI staging and local management of any metastases detected should always be discussed in a multidisciplinary context.

9. **Pharmacological properties of ARSi in mHSPC and nmCRPC**

9.1 *In the presence of concomitant therapies, ARSi show different drug interaction profiles.*

9.2 *Considering the interaction between the oncological and concomitant drug, it is the latter which should preferentially be modified (dose reduction or substitution).*

ARSi have different metabolic profile, which characterizes each drug for a specific profile of interaction with other drugs.[56]

Considering the risk that ARSi may have to be "victim" drugs in case of patients treated with multiple drugs, enzalutamide may be victim of drugs inhibiting or inducing the CYP2C8; apalutamide of drugs that modify the CYP2C8 and 3A4 activity, and darolutamide may be victim of inducers or inhibitors of the CYP3A4, UGT1A9, 1A1. On the contrary, ARSi may be perpetrator-drugs towards other therapies metabolized by CYP3A4, 2D6, 2C9, 2C19 and different transporters such as PgP, OTP.[56]

The drug-drug interaction (DDI) evaluation is a complex and multifactorial process, which includes different variables.

However, in case of high risk of DDI, considering the small number of options in terms of oncological treatment, it is strongly suggested to modify or replace the concomitant drug, without any change in the ARSi therapy.

10. **Critical issues in the multidisciplinary and multiprofessional management of mHSPC and nmCRPC patients**

10.1 *In patients with mHSPC and nmCRPC disease it is proper to systematically monitor upper and lower urinary tract to detect earlier any obstruction or functional disease*

10.2 *Radiation treatment (including stereotactic radiotherapy) for symptomatic and/or consolidation purposes should be considered in patients with symptomatic bone lesions or lesions at risk of fracture*

Lower urinary tract symptoms (LUTS) are a common complaint in adult men with a major impact on quality of life (QoL) and renal function. The understanding of the urinary tract as a functional unit, and the multifactorial etiology of associated symptoms, means that upper and lower urinary tract symptoms (LUTS) are not only related to Benign Prostatic Hyperplasia (BPH) but may be present also in men treated for prostate cancer.[57]

A medical history focused on assessing LUTS is an integral part of prostate cancer patient medical evaluation during his lifetime.[58] Bladder voiding pattern monitoring is mandatory using validated symptom score questionnaires as International Prostate Symptom Score (IPSS). Moreover, an ultrasound evaluation of the upper and lower urinary tract status has to be regularly scheduled in order to rule out the presence of either hydronephrosis or a significant post void residual urine (PVR) in mHSPC and nmCRPC patients.[59]

Postvoid residual is not necessarily associated with Benign Outlet Obstruction (BOO), since high PVR volumes can be a consequence of obstruction due to prostate cancer or poor detrusor function. PVR urine can be assessed by transabdominal ultrasound (US), bladder scan or catheterization. Monitoring of changes in PVR overtime may allow for identification of patients at risk of acute or chronic urinary retention.[60]

Patients with severe LUTS may also experience hydronephrosis, renal insufficiency or urinary retention. Urinary retention should be treated with a bladder caterer positioning or a cystostomy tube according to the clinical scenario. When hydronephrosis is discovered, it must be immediately managed with the positioning of and indwelling JJ stent or, if not possible, with a nephrostomy tube.

Bone metastases can be divided into: uncomplicated (approximately 2/3 of all) and complicated lesions which has features

suggestive of (impending) fracture and or compression, associated soft tissue mass or neurological deficits.[61,62]

Radiotherapy can achieve, in an uncomplicated lesion, a clinically significant pain response in up to 80% of treated patients with a median response duration of 18 to 21 months.

In complicated bone metastases,[61,62] the most common symptoms include pain and neurologic deficits, while the most serious complications of bone metastases are skeletal-related events (SRE), defined as pathologic fracture, spinal cord compression, pain or other symptoms requiring an urgent surgery or radiotherapy. Finally, diffuse bone metastases may lead to hypercalcaemia that can be fatal if untreated.

For spinal cord compression,[61,62] diagnosis is based on the MRI (or if MRI is not available, CT scan) of the whole spine that should be performed within 24 hours from the occurrence of the neurological symptoms. In case of confirmed single site metastatic spinal cord compression, within 48 hours from the occurrence of paraplegia, life expectancy of >3 months and spinal instability urgent surgical decompression and stabilization followed by postoperative radiotherapy seems the best option. All other patients should be referred for radiotherapy.

Radiotherapy schedules for spinal cord compression: single fraction of 8 to 10 Gy or other schemes (25-20 Gy in 5 fr o 30 Gy in 10 fr); SBRT can be used for selected patients.

Re-irradiation of spinal cord compression seems safe after 6 months providing the cumulative BED (biologically equivalent dose) is 100 to 135.5 Gy

Symptoms of pathological fractures[61,62] include an increase in pain, deformity or loss of weight bearing. Diagnosis is made through plain X-ray or CT or MRI. The risk of pathological fracture is high if there is > 30 mm axial cortical involvement or high SINS (spine instability neoplastic score).[63]

The most commonly used radiotherapy schedules include 8 Gy/fr or 20 Gy in 5 fractions or 30 Gy in 10 fractions may be used to prevent pathological fracture.

If fracture occurs surgery consultation or evaluation by the interventional radiologist (kyphoplasty etc.) is highly recommended.

Discussion

Recent evidences have deeply changed therapeutic approach in both mHSPC[3,4,1,5,7,6,2] and nmCRPC,[64–66] but at the same time, they led to new challenges, mainly to the directness of results in daily practice.

First of all, how are we confident with survival advantages in patients staged with PSMA PET, even if pivotal studies assessed disease by conventional imaging?

In the case of mHSPC, PSMA PET could show more lesions than CI,[17] but it is unclear the impact of this better detection ability on a main outcome as the overall survival. Moreover, we do not know how the results of high- and low-volume disease defined according to the CI-based detection are transferable to those patients staged with PET.[67] For these reasons the panel recommended CI as primary staging. Similarly, the differences observed in a NGI performed after CI add complexity to the subsequent therapeutic decision, particularly when there is a discrepancy between the volume of disease assessed by PET and by CI.

Nevertheless, when evaluating the treatments efficacy by imaging, it would be appropriate to re-stage patients with the same imaging performed at the diagnosis.[16]

The situation is even more complex for patients classified as nmCRPC at CI, where PSMA PET could detect active disease in up to 98% of the patients.[19] In these cases, although 55% of patients have metastatic spread of the disease, the impact of transition from nmCRPC to mCRPC on therapeutic proposal may be marginal since ARSi are a therapeutic option in both disease settings. Noteworthy, the challenge is related to the choice among the different ARSi since the available agents are not the same in the different settings: apalutamide, darolutamide and enzalutamide in nmCRPC,[64–66] and abiraterone and enzalutamide in mCRPC.[68,69] A significant issue can be due to the pelvic disease detection, where SBRT may have a potential role.[70]

Considering these reflections, the panel deemed useful to stage these patients with CI, unless an oligoprogressive disease can be suspected mainly in patients with nonhigh risk disease. As regards the re-evaluations and the impact of PET on prognosis, the same considerations made for mHSPC were maintained.

An additional issue concerning the use of PET as NGI is related to the tracer choice: the recommended tracer is PSMA, while choline and fluciclovine should be reserved to selected cases, or if PSMA is not available in a reasonable period of time or in case of low expression of PSMA.

In mHSPC, studies have shown the addition of ARSi to ADT alone[3–5] or to ADT and docetaxel[51,6] produced survival benefits compared to ADT alone. Thus, although it is clear that ADT alone should be offered only to patients with severe pathologies and short life expectancy and conversely all mHSPC should receive 1 ARSi alone or with docetaxel, which criteria should we use for choosing among the available ARSi?

The first criteria considered relevant by the panel were the volume/risk of disease (low vs. high) and the timing of onset (de novo vs. metachronous). The volume criteria discriminate the use of chemotherapy and, thus, the type of ARSi which should be proposed. Data from ARASENS[6] and PEACE-1[51] studies mainly supported the use of triplet in de novo high volume mHSPC patients: accordingly, in patients fit for chemotherapy for whom the triplet can be considered as a therapeutic option, the proposable ARSi are either darolutamide or abiraterone. Conversely, when the triplet is not an option (due to either disease or patient characteristics) the proposable agents are abiraterone,[48] apalutamide,[4] or enzalutamide.[3,5]

Additional drivers for ARSi choice (in both mHSPC and nmCRPC settings) are the toxicity profile of each agent, possible drug-by-drug interactions (DDI) and therefore comorbidities and concomitant must be considered.

In clinical practice many elderly patients suffered of several comorbidities and a clinical classification of the patient (fit, unfit, frail) assessed by geriatric scales is very helpful in driving the treatment choice.[37]

It is important to note that different tools can value comorbidities in different way.[40] Charlson Comorbidity Index gives more importance to cancer status (up to 6 points in case of metastatic disease) while Cumulative Illness Rating Scale (CIRS) differentiate

between number and severity of comorbidities. CIRS-G, weighting the importance of comorbidities in cancer patient, seems the most useful tool for this purpose.[40]

Osteosarcopenia[41,42] and metabolic syndrome[43] are 2 well-known side effects of androgen deprivation therapy (ADT) and should be managed by prevention. Physical performance has been shown to be associated with adverse outcomes in older patients with cancer[38] and should be measured with quantitative measurement. Therefore, patients should receive all recommendations regarding lifestyle, diet and physical activity capable of preventing osteosarcopenia and metabolic syndrome, as well as receiving BTA with the schedules used in the prevention of osteopenia.

In this setting another important issue underlined by the panel is the polypharmacy and possible interactions, prioritizing oncological treatment and remodulating or modifying the concomitant therapy for comorbidities.

Another element of interest was the use of local treatments in mHSPC disease.

The data from arm H of the Stampede trial[7] showed a survival benefit from the addition of RT to primary in addition to SOC, with up to 80% of recruited patients receiving ADT only. A posthoc analysis revealed a better survival advantage in treating primary in those patients with up to 3 bone lesions. Therefore, data are lacking on the potential impact of RT in the ADT+ARSI combination, considered the standard systemic treatment in low volume, as well as in the treatment of metastatic sites. Therefore, the panel considered that in this context, only a multidisciplinary discussion, evaluating the risk/benefit ratio on the individual patient, can express a judgment on the feasibility of a multimodal approach that integrates systemic treatment with local treatment.

Finally, particular attention should be paid to patients throughout their disease course, as they could develop obstructive symptoms linked to the primary tumor or painful symptoms linked to metastases bone.

In this context, active monitoring of urinary symptoms could show early-stage symptoms, avoiding or delaying, as far as possible, the placement of nephrostomies or cystotomies.[57,60,58,59]

Similarly, radiation treatment could guarantee a reduction in pain symptoms, or in well-defined cases with uncomplicated lesions, allowing ablative therapy.[61,62] In the case of complicated lesions, bone stabilization should be performed before any radiation treatment.[63]

In this complex and evolving scenario of prostate cancer, either diagnostic or therapeutic, the panel underline in this paper the elements to consider when transferring data from clinical studies to daily practice, allowing clinicians to have a practical and reasoned help for their individual patients.

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