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Consensus statements on ablative radiotherapy for oligometastatic prostate cancer: A position paper of Italian Association of Radiotherapy and Clinical Oncology (AIRO)

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ABSTRACT

Oligometastatic prostate cancer comprises a wide spectrum of conditions, ranging from de novo oligometastatic cancer at diagnosis to oligometastatic castration-resistant disease, which are distinct entities in terms of biology and prognosis.

In order to clarify and standardize the clinical role of ablative radiotherapy in oligometastatic prostate cancer, the Italian Association of Radiotherapy and Clinical Oncology (AIRO) formed an expert panel to review the current literature and develop a formal consensus.

Oligometastatic prostate cancer was defined as the presence of up to three metastatic lesions involving bones or nodes outside pelvis. Thereafter, four clinical scenarios were explored: metastatic castration-sensitive disease at diagnosis and after primary treatment, and metastatic castration-resistant disease at diagnosis and during treatment, where the role of ablative radiotherapy was defined either in conjunction with systemic therapy or as the only treatment in selected cases.

This paper summarizes the current literature about these issues and the proposed recommendations.

1. Introduction

The 'oligometastatic' concept was initially proposed by Hellman and Weichselbaum in 1995 (Hellman and Weichselbaum, 1995), to identify patients with an intermediate stage of cancer disease, between localized and widespread metastatic. More recently, the same authors (Weichselbaum and Hellman, 2011) underlined the promising role of local treatments as potentially curative in strictly selected subgroups of patients with limited burden of metastatic disease. This supported the assumption that oligometastatic disease could be defined as a distinct clinical entity.

Since 2015, more than 600 papers have been published about oligometastatic cancer, and one out of five specifically focused on prostate cancer patients. In 2015, the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) (Gillessen et al., 2015) stated that 'the presence of ≤3 synchronous metastases (bone and/or lymph nodes) is the most meaningful definition of oligometastatic prostate cancer'. However, in 2017 the APCCC (Gillessen et al., 2018) thoroughly

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explored the oligometastatic concept highlighting several topics of debate, including number and site of lesions, castration-sensitive or castration-resistant setting, synchronous versus metachronous metastases and imaging modality used to identify metastases.

Indeed, oligometastatic prostate cancer comprises a spectrum of numerous conditions, ranging from de novo oligometastatic cancer at diagnosis to oligometastatic castration-resistant disease, which differ widely. These distinct settings entail wide variations in terms of biology, benefit from treatments and prognosis (Francini et al., 2018; Gravis et al., 2018).

The emerging interest for oligometastatic prostate cancer, the increasing adoption of metastasis direct therapy (MDT, either surgery or ablative radiotherapy [RT]) (Ost et al., 2015), and the recent availability of prospective studies (Ost et al., 2018; Palma et al., 2012; Siva et al., 2018) even in the absence of data from randomized phase III trials encouraged the Italian Association of Radiotherapy and Clinical Oncology (AIRO) to form an expert panel to review the current literature and develop a formal consensus about the use of ablative RT in oligometastatic patients.

We herein report the results of this expert-opinion consensus from AIRO.

2. Methods

The statements formulated refer to four clinical scenarios: metastatic castration-sensitive disease at diagnosis and metastatic castration-sensitive disease after primary treatment (controlled primary), newly diagnosed metastatic castration-resistant disease (mCRPC) and, finally, mCRPC on therapy. In all cases, the sites of metastases are lymph nodes outside pelvis or bone; visceral metastasis are excluded for their poor prognosis (Gandaglia et al., 2015). The number of metastases was defined as ≤ 3.

A two-step Delphi together with a modified RAND-UCLA Appropriateness Method (RAM Fitch, 2001) were applied for this project.

Before the consensus process, a systematic literature review with evidence synthesis was conducted to provide the expert panel with all pertinent information that guided evidence-based decision-making. Twelve expert panelists, selected among the uro-oncological working group of AIRO for their clinical and scientific activity in oligometastatic prostate cancer even with drugs, were asked to independently draw, in a Delphi mode, a therapeutic statement for each clinical scenario. Patient selection and amount of disease were to be precisely defined, together with the strength of the recommendation. The core panel overseeing the consensus process (RMD & GLP) reviewed and synthesized panelists' statements.

During the conclusive meeting, the expert panelists voted the appropriateness of a particular intervention for the patient through a 9-point Likert scale. In RAM, a rating between 1 and 3 was considered "inappropriate" (risks outweigh benefits), 4–6 was "uncertain", and 7–9 was considered "appropriate" (benefits outweigh risks). The experts were given the opportunity to discuss individual views on the appropriateness of the intervention in each clinical scenario. At the end of the discussion, each panelist could reconsider his/her own original rating and re-rate the clinical scenario. A clinical scenario was deemed as appropriate if the median rate was ≥ 7. Agreement among panelists was also recorded.

3. Results

3.1. First clinical scenario: oligometastatic prostate cancer at diagnosis

In this scenario, patients have been diagnosed with de novo oligometastatic disease and have not yet received any treatment for their prostate cancer.

The treatment of metastatic disease at diagnosis has suddenly changed in recent years: indeed, the STAMPEDE (James et al., 2016, 2017), CHAARTED (Kyriakopoulos et al., 2018) and LATITUDE (Fizazi et al., 2017) trials have recorded impressive survival benefit adding docetaxel (DOC) or abiraterone acetate + prednisone (AAP) to standard androgen deprivation therapy (ADT) in metastatic castration-sensitive prostate cancer (CSPC).

While the STAMPEDE trial, exploring either DOC or AAP, did not identify a special patient population benefitting from this kind of combined therapy, CHAARTED and LATITUDE did.

The CHAARTED trial, in its preliminary (Sweeney et al., 2015) and updated analysis (Kyriakopoulos et al., 2018), confirmed the role of DOC + ADT in patients with high-volume disease (defined as the presence of visceral metastases and/or at least four bone lesions with at least one lesion outside of the vertebral column and/or pelvis). In LATITUDE (Fizazi et al., 2017), patients were enrolled if at least two of the three following criteria were present: Gleason score $\geq$ 8, at least three bone lesions, presence of measurable visceral metastases.

Therefore, in oligometastatic disease, two scenarios could be possible: a patient eligible to ADT only or to ADT + AAP.

Three analyses of a large population-based cancer database with propensity score-matched analysis (Rusthoven et al., 2016; Löppenberg et al., 2017; Culp et al., 2014) recorded a survival benefit adding local therapy to ADT compared to ADT alone. These data are consistent with biological data of persistent prostatic disease at the primary site after ADT even when patients were treated with DOC (Tzelepi et al., 2011).

Moreover, STAMPEDE (Parker et al., 2018) recently explored the potential benefit of adding RT on primary site with standard of care (SOC) in metastatic patients at diagnosis. The majority of patients (82%) received ADT only for their metastatic disease, and the use of prostate RT provided a survival benefit (HR: 0–68; 95%CI 0.52-0-90) in low metastatic burden as defined by CHAARTED (Sweeney et al., 2015).

The panel reached a median value of 8 (range 6–9), with a consensus of 91% for this statement: in an oligometastatic patient with up to three metastases (node or bone), RT with radical intent to primary and metastatic sites along with ADT, could be offered as alternative to ADT alone.

Furthermore, an oligometastatic patient at diagnosis could be eligible to ADT + AAP if a Gleason score $\geq$ 8 with three bone lesions and without visceral metastases have been diagnosed.

Even if the LATITUDE trial included patients who had received previous palliative RT only, the STAMPEDE trial (James et al., 2017) explored RT on primary site concurrently with ADT and AAP in locally advanced non-metastatic disease, recording a benefit in failure-free survival without any alert for toxicity. Moreover, in LATITUTE, AAP could be started within three or fewer months from ADT start, allowing to administer RT on primary site and AAP in a sequential treatment strategy.

Therefore, based on the absence of major local toxicity adding RT to ADT + AAP with the potential benefit on survival in treating primary site in oligometastatic disease, patient with oligometastatic disease eligible for systemic therapy with ADT + AAP could receive irradiation of primary tumor at diagnosis, in an expert multidisciplinary setting.

The panel reached a median value of 7 (range 3–8), with a consensus of 54%, for this statement: In an oligometastatic patient with three bone metastases eligible to ADT plus AAP, RT with radical intent to primary and metastatic sites could be offered together with ADT + AAP.

3.2. Second clinical scenario: metachronous oligometastatic castration-sensitive prostate cancer (CSPC)

In this scenario, patients have been treated with radical prostatectomy or radical RT and have no evidence of tumor recurrence at the primary site. Therefore, patients eligible for salvage RT after radical prostatectomy, or those suitable for local treatment after radical RT are excluded.

These patients are defined as oligo-recurrent due to a new evidence of a metastatic site after primary treatment. Two systematic reviews (Ost et al., 2015; Ploussard et al., 2015) addressed the role of metastasis-directed therapy (either surgery or RT) with local radical intent, showing that half of the patients are progression-free at 1–3 years.

Furthermore, relapses after ablative RT on nodal sites often consist in nodal oligometastatic recurrence (Ost et al., 2016). Moreover, data from literature show extremely low toxicity rates after RT (Ost et al., 2015).

STOMP is a small phase II trial (Ost et al., 2018) comparing MDT versus surveillance in patients with biochemical recurrence after primary prostate cancer treatment. All included patients had three or fewer extra-cranial metastatic lesions observed by choline positron emission tomography–computed tomography (PET-CT). Results showed a significant benefit in terms of ADT-free survival in patients treated with MDT (23 vs 13 months) with very mild toxicity (no grade 2–5 events, 17% of grade 1 toxicity).

Even if ADT-free survival may appear as a weak end-point, a significant percentage of patients undergoing ADT for metastatic disease could develop hypercholesterolemia and osteoporosis during treatment (up to 31% and 19%, respectively). Moreover, the 10-year cumulative incidence of ischemic and thrombotic events during ADT ranges between 24% and 33% (Hershman et al., 2016). Besides this, benefit of immediate versus delayed ADT could be questioned considering results from the CaPSURE study [Cancer of the Prostate Strategic Urologic Research Endeavor; Garcia-Albeniz et al., 2015], which did not show any survival benefit for immediate versus delayed ADT.

Therefore, delaying ADT could yield significant benefit in this setting.

Finally, repeated treatment should be reserved to those patients with oligo-progressive disease after more than one year (surveillance group in STOMP trial).

The panel reached a median value of 9 (range 8–9), with a consensus of 100%, for this statement: in an oligometastatic patient with primary tumor controlled and up to three metastases (node or bone), RT with radical intent to metastatic sites could be offered as alternative to ADT to delay systemic treatment.

3.3. Third clinical scenario: oligometastatic castration-resistant prostate cancer (CRPC) at its first occurrence

In this scenario, patients have evidence of metastatic castration-resistant prostate cancer (mCRPC) as defined by the European Association of Urology (EAU) guidelines (Cornford et al., 2017) during ADT, without any previous systemic treatment, such as DOC or AAP, for metastatic CSPC.

At present, three systemic options are available in Italy for these patients, all with an impact on survival: DOC (Tannock et al., 2004), AAP (Ryan et al., 2015), and enzalutamide (ENZA) (Beer et al., 2017). Even if DOC has been tested in both symptomatic and asymptomatic patients, in the APCCC 2017 meeting there was consensus of 86% in offering AAP or ENZA (Androgen Receptor Target Agent – ARTA) in asymptomatic or minimally symptomatic men with mCRPC. In the same conference, 54% of panelists suggested to include local treatment in oligometastatic CRPC.

Therefore, in oligometastatic CRPC two scenarios are possible: patients eligible to receive RT with ADT in order to delay ARTA beginning, or patients eligible to ADT + ARTA who could add RT to oligometastatic sites.

Two retrospective analyses (Muldermans et al., 2016; Triggiani et al., 2017) revealed high activity for irradiation to oligometastatic sites, similarly to what has been observed in castration-sensitive patients (local control up to 95%). Furthermore, data from these experiences underline that ARTA start could be delayed up to 11 months. Therefore, effective systemic treatments are available for this clinical scenario, and the addition of RT alone to ADT should be limited to carefully selected patients.

Firstly, not all mCRPC patients show the same clinical behavior, since a prostate-specific antigen (PSA) doubling time of 6 months or less is correlated with a high proportion of new bone metastases (Smith et al., 2005, 2013). Moreover, the time to develop a castration-resistant phenotype could help to distinguish slowly progressive from more aggressive disease (James et al., 2015). Finally, use of metabolic imaging could provide more information about the burden of disease (Kwee et al., 2014), and help to direct MDT (Ceci et al., 2016).

All these aspects confirm that mCRPC patients represent a heterogeneous cancer population in which unknown biological factors could play a relevant role in distant spread.

Therefore, considering the available treatment options in this setting, focal treatment with RT plus ADT in oligometastatic mCRPC patients at first observation could be proposed in highly selected patients only. Strict follow-up should be provided in order to begin ARTA if biochemical, clinical or metabolic progression appears within 6 months.

The panel reached a median value of 8 (range 5–8), with a consensus of 91% for this statement: in an asymptomatic or minimally symptomatic mCRPC patient, with a PSA doubling time > 6 months, time to castration-resistant phenotype > 12 months and oligometastases up to three nodal or bone lesions detected by metabolic imaging, RT with radical intent to metastatic sites could be offered as alternative to ARTA to delay systemic treatment.

Conversely, if a patient is eligible to ARTA, the benefit of adding ablative RT is unknown. For sure, no safety alert should be expected considering data from COU-AA 301 (Logothetis et al., 2012; Fizazi et al., 2012). In fact, with a 20.2-month median follow-up, more than 60% of patients received RT to bone without any new safety signals. Prospective data could be provided by the currently ongoing Italian randomized phase II trial designed to detect the amount of benefit of focal RT in this setting [ARTO trial (EUDRACT: 2016-005284-13)].

The panel reached a median value of 8 (range 6–9), with a consensus of 91%, for this statement: in an asymptomatic or minimally symptomatic mCRPC patient with up to three metastases (node or bone) and eligible to ADT plus ARTA, RT with radical intent to metastatic sites could be offered along with this systemic treatment.

3.4. Fourth clinical scenario: oligometastatic castration-resistant prostate cancer (CRPC) during treatment with Androgen Receptor Target Agent (ARTA)

In this scenario, patients with mCRPC on treatment with AAP or ENZA develop an oligo-progression. Therapeutic strategies including RT for oligo-progressive disease have been already defined in different settings, e.g. for lung cancer patients with oncogene-addicted tumors (Basler et al., 2017). Furthermore, 60% of panelists attending the APCCC 2017 meeting supported the addition of a local treatment to systemic therapies.

The Prostate Cancer Clinical Trials Working Group 2 (PCWG2 (Scher et al., 2008)) encouraged the continuation of systemic treatment in case of worsening of an isolated disease site. More recently, PCWG3 (Scher et al., 2016) underlined that if '*multiple sites of disease continue to respond but one to two sites grow, focal therapy such as radiation or surgery could be administered to the resistant site(s) and systemic therapy continued*'.

The feasibility of adding RT to AAP has been reported in (Saad et al., 2012), and its activity in (Detti et al., 2017). A post-hoc exploratory analysis of the COU-AA-301 randomized trial (Saad et al., 2012) revealed that palliative RT to bone was safely administered with AAP in patients experiencing localized progression at a single site, supporting the maintenance of AAP in men receiving palliative RT who were gaining benefit from this agent. Moreover, an Italian experience (Detti et al., 2017) recorded a PFS of 9.6 months after irradiation on site of oligo-progression.

Data from COU-AA 302 (Ryan et al., 2013) and PREVAIL (Beer

Table 1
Statements with appropriateness and agreement among panelists (see text for details).

Statement	Appropriateness	Agreement
First clinical scenario: oligometastatic prostate cancer at diagnosis		
In an oligometastatic patient with up to three metastases (node or bone), RT with radical intent to primary and metastatic sites along with ADT, could be offered as alternative to ADT alone	8 (6-9)	91%
In an oligometastatic patient with three bone metastases eligible to ADT plus AAP, RT with radical intent to primary and metastatic sites could be offered together with ADT + AAP	7 (3-8)	54%
Second clinical scenario: metachronous oligometastatic castration-sensitive prostate cancer (CSPC)		
In an oligometastatic patient with primary tumor controlled and up to three metastases (node or bone), RT with radical intent to metastatic sites could be offered as alternative to ADT to delay systemic treatment	9 (8-9)	100%
Third clinical scenario: oligometastatic castration-resistant prostate cancer (CRPC) at its first occurrence		
In an asymptomatic or minimally symptomatic mCRPC patient with a PSA doubling time > 6 months, time to castration-resistant phenotype > 12 months, and oligometastases up to three nodal or bone lesions detected by metabolic imaging, RT with radical intent to metastatic sites could be offered as alternative to ARTA to delay systemic treatment	8 (5-8)	91%
In an asymptomatic or minimally symptomatic mCRPC patient with up to three metastases (node or bone) and eligible to ADT plus ARTA, RT with radical intent to metastatic sites could be offered along with this systemic treatment	8 (6-9)	91%
Fourth clinical scenario: oligometastatic castration-resistant prostate cancer (CRPC) during treatment with Androgen Receptor Target Agent (ARTA)		
In an asymptomatic or minimally symptomatic oligoprogressive mCRPC patient, with up to two nodal or bone lesions, in treatment with ARTA from at least from 6 months, RT with radical intent to sites of progressive disease could be offered as an alternative to the change of systemic treatment	8 (6-9)	91%

RT, radiotherapy; ADT, androgen-deprivation therapy; AAP, abiraterone acetate and prednisone; PSA, prostate-specific antigen.

Nevertheless, in the present paper no specific data are provided with regard to the most proper technique which radical/ablative refers to, along with the modality to reach this ablation (e.g.: no indication is given on whether to treat the whole lymph nodal station or positive lymph nodes only), because technical and dosimetry issues on RT were beyond the scope of the current consensus.

In conclusion, the present consensus paper might be a useful tool to better define and consolidate the potential indication of RT in oligometastatic prostate cancer patients in order to guide clinicians in decision-making strategy, especially in the modern era of multidisciplinary approach.

et al., 2014) trials showed in placebo group, a radiologic progression within 6 months; therefore, this strategy could be offered to those patients responding to ARTA with a minimum time on treatment of 6 months.

The panel reached a median value of 8 (range 6–9), with a consensus of 91%, for this statement: in an asymptomatic or minimally symptomatic oligoprogressive mCRPC patient, with up to two nodal or bone lesions, in treatment with ARTA from at least from 6 months, RT with radical intent to sites of progressive disease could be offered as an alternative to the change of systemic treatment.

4. Discussion

In the absence of high-quality, level I evidence, two possibilities are available to meet clinical needs: phase III randomized trials or expert opinions. Randomized trials are the best way to evaluate the impact, and its magnitude, of a treatment or diagnostic intervention. However, this approach is not always feasible, especially in a widely heterogeneous population, such as oligometastatic prostate cancer patients.

Besides, if conflicting data, or their controversial interpretation, are present, expert opinions can be helpful in daily clinical practice, even if rejectable after further clinical research.

While agreement was common in most of the proposed clinical scenarios, two areas of disagreement from APCCC 2017 (Gillessen et al., 2018) were deemed as clinically relevant for this expert review from AIRO: treatment of the primary tumor in metastatic disease, and definition and treatment of oligometastatic prostate cancer and its management.

For all statements, a median value ≥ 7 was reached. Moreover, a declaration of appropriateness and agreement among panelists was found when RT is applied in de novo oligometastatic CSPC along with ADT, or as the primary therapy in oligo-recurrent CSPC disease, or when RT is administered together with ARTA in oligo-metastatic CRPC. Table 1 summarizes all statements, with appropriateness and agreement among panelists.

In two cases, the interval of consensus included uncertainty or unsuitability: in a patient with de novo oligometastatic CSPC eligible to ADT + AAP, and in an oligometastatic mCRPC patient where RT could be an alternative to ARTA.

A consensus of 54% only, with one panelist rating 3, was found in including local RT with ADT + AAP in oligometastatic CSPC. This underlines the uncertainty to transfer in clinical practice recent data about the treatment of primary tumor with RT + ADT in metastatic disease (Parker et al., 2018) to another setting (RT + ADT + AAP), even when no alert for toxicity has been raised (James et al., 2017).

Instead, in the case of oligometastatic mCRPC, the expert panel felt that RT should be considered as an alternative to ARTA only in highly selected patients, considering that the efficacy of ARTA in this setting has been proven in several prospective randomized trials.

The panel members are aware that the voting results might lead to the adoption of arguable or controversial interventions and ongoing prospective investigations could better clarify the efficacy and safety of those interventions. Therefore, the panelists recommend participation in clinical trials to reach high-level evidence.

In summary, from the AIRO expert panel, the role of ablative RT emerged as a concrete treatment option for prostate cancer patients in different scenarios representing the various declinations of the oligometastatic setting (Table 1).

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