

Original Article

Recommendations for radiation therapy in oligometastatic prostate cancer: An ESTRO-ACROP Delphi consensus



Thomas Zilli^{a,b,c,*}, V  rane Achard^{b,c}, Alan Dal Pra^d, Nina Schmidt-Hegemann^e, Barbara Alicja Jereczek-Fossa^{f,g}, Andrea Lancia^h, Gianluca Ingrossoⁱ, Filippo Alongi^{j,k}, Shafak Aluwini^l, Stefano Arcangeli^m, Pierre Blanchard^{n,o}, Antonio Conde Moreno^p, Felipe Cou  nago^{q,r,s}, Gilles Cr  hange^t, Piet Dirix^u, Alfonso Gomez Iturriaga^v, Matthias Guckenberger^w, David Pasquier^{x,y}, Paul Sargos^z, Marta Scorsetti^{aa}, St  phane Supiot^{ab}, Alison C. Tree^{ac}, Almudena Zapatero^{ad}, Jennifer Le Guevelou^{b,c}, Piet Ost^{ae,af}, Claus Belka^e

^a Department of Radiation Oncology, Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland; ^b Department of Radiation Oncology, Geneva University Hospital, Geneva, Switzerland; ^c Faculty of Medicine, Geneva University, Geneva, Switzerland; ^d Department of Radiation Oncology, University of Miami Miller School of Medicine, Miami, FL, United States; ^e Department of Radiation Oncology, LMU University Hospital Munich, Munich, Germany; ^f Department of Oncology and Hemato-oncology, University of Milan, Milan; ^g Division of Radiotherapy, IEO European Institute of Oncology, IRCCS, Milan; ^h Department of Radiation Oncology, Policlinico San Matteo Pavia Fondazione IRCCS, Pavia, Italy; ⁱ Department of Radiation Oncology, Department of Medicine and Surgery, University of Perugia, Perugia; ^j Advanced Radiation Oncology Department, IRCCS Sacro Cuore Don Calabria Hospital, Cancer Care Center, Negrar di Valpolicella; ^k University of Brescia, Brescia, Italy; ^l Department of Radiation Oncology, University Medical Center Groningen, Groningen, the Netherlands; ^m Department of Radiation Oncology, School of Medicine and Surgery, University of Milan Bicocca, Milan, Italy; ⁿ Universit   Paris Saclay, Villejuif, France; ^o Inserm U1018 Oncostat, Department of Radiation Oncology, Gustave Roussy, Villejuif, France; ^p Radiation Oncology Department, Hospital Universitario y Polit  cnico La Fe, Valencia, CEU Cardenal Herrera University, Castell  n; ^q Department of Radiation Oncology, Hospital Universitario Quir  nsalud Madrid; ^r Department of Radiation Oncology, Hospital La Luz, Madrid, Spain; ^s Medicine Department, School of Biomedical Sciences, Universidad Europea, Villaviciosa de Od  n, Madrid, Spain; ^t Department of Radiation Oncology, Institut Curie, Paris, France; ^u Department of Radiation-Oncology, Iridium Network, Antwerp, Belgium; ^v Biocruces Health Research Institute, Cruces University Hospital, Basque Country University (UPV/EHU), Barakaldo, Bizkaia, Spain; ^w Department of Radiation Oncology, University Hospital Z  rich, University of Z  rich, Z  rich, Switzerland; ^x Academic Department of Radiation Oncology, Centre Oscar Lambret; ^y CRISTAL UMR CNRS 9189, Lille University, Lille; ^z Department of Radiotherapy, Institut Bergoni  , Bordeaux, France; ^{aa} Radiotherapy and Radiosurgery Department, IRCCS Humanitas Research Hospital, Via Manzoni 56, Rozzano, 20089 Milan, Italy; ^{ab} Department of Radiation Oncology, Institut de Canc  rologie de l'Ouest Ren   Gauducheau, Saint-Herblain, France; ^{ac} Department of Radiotherapy, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom; ^{ad} Department of Radiation Oncology, Health Research Institute, University Hospital La Princesa, Madrid, Spain; ^{ae} Department of Human Structure and Repair, Ghent University, Ghent, Belgium; ^{af} Department of Radiation Oncology, Iridium Network, GZA ziekenhuizen, Wilrijk, Belgium

ARTICLE INFO

Article history:

Received 3 October 2022

Accepted 7 October 2022

Available online 10 October 2022

Keywords:

Prostate cancer

Radiotherapy

SBRT

Elective nodal radiotherapy

Oligometastases

ESTRO-ACROP

ABSTRACT

Background and purpose: Oligometastatic prostate cancer is a new and emerging treatment field with only few prospective randomized studies published so far. Despite the lack of strong level I evidence, metastasis-directed therapies (MDT) are widely used in clinical practice, mainly based on retrospective and small phase 2 studies and with a large difference across centers. Pending results of ongoing prospective randomized trials, there is a clear need for more consistent treatment indications and radiotherapy practices.

Material and methods: A European Society for Radiotherapy and Oncology (ESTRO) Guidelines Committee consisting of radiation oncologists' experts in prostate cancer was asked to answer a dedicated questionnaire, including 41 questions on the main controversial issues with regard to oligometastatic prostate cancer.

Results: The panel achieved consensus on patient selection and routine use of prostate-specific membrane antigen positron emission tomography (PSMA PET) imaging as preferred staging and restaging imaging. MDT strategies are recommended in the *de novo* oligometastatic, oligorecurrent and oligoprogressive disease setting for nodal, bone and visceral metastases. Radiation therapy doses, volumes and techniques were discussed and commented.

* Corresponding author at: Department of Radiation Oncology, Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland Via Ospedale, CH-6500 Bellinzona, Switzerland.

E-mail address: Thomas.Zilli@eoc.ch (T. Zilli).

Conclusion: These recommendations have the purpose of providing standardization and consensus to optimize the radiotherapy treatment of oligometastatic prostate cancer until mature results of randomized trials are available.

© 2022 The Author(s). Published by Elsevier B.V. Radiotherapy and Oncology 176 (2022) 199–207 This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

The widespread use of next-generation imaging for staging and restaging of prostate cancer has been associated with an increasing number of patients diagnosed with oligometastatic disease [1–3]. Systemic therapies including androgen deprivation therapy (ADT) with or without androgen receptor pathway inhibitors (ARPI) remain the standard treatment for these patients [4–8]. Due to the limited metastatic burden and often favorable outcomes, metastasis-directed therapies (MDT) have been investigated in retrospective studies and prospective trials as a therapeutic alternative to improve progression-free survival or postpone the use of systemic therapies [6,7], both in the hormone-sensitive and castration-resistant settings [9–11].

Radiotherapy (RT) modalities have been increasingly implemented in the clinical practice as MDT strategies for treatment intensification of oligometastatic prostate cancer patients. Different MDRT (metastasis-directed radiotherapy) strategies including whole pelvis elective nodal irradiation (WPRT) and stereotactic body radiotherapy (SBRT) with or without systemic therapy have been tested, with nevertheless a large variability in terms of doses, volumes, and treatment planning optimization [12].

As MDT strategies have been increasingly offered in clinical practice even in the absence of level I evidence, there is a need to improve consistency and harmonize treatment indications and radiotherapy practices. The aim of these European Society for Radiotherapy and Oncology (ESTRO) Guidelines Committee recommendations is to provide consensus and standardization on specific items of interest for the Radiation Oncology community for the treatment of oligometastatic prostate cancer patients, including radiotherapy doses, volumes, and techniques as well as treatment indications and combination with systemic therapies.

Materials and methods

Between October and December 2020, a panel of nine radiation oncology experts on prostate cancer developed a dedicated questionnaire including 41 questions addressing the main controversial questions on the management of oligometastatic prostate cancer (Suppl. Table 1). The questionnaire was divided in four major sections as follows:

- A. Patient and disease characteristics (8 questions) [3],
- B. Synchronous *de novo* oligometastatic hormone-sensitive prostate cancer (7 questions),
- C. Metachronous oligometastatic (oligorecurrent) hormone-sensitive prostate cancer (6 questions),
- D. Oligoprogressive castration-resistant prostate cancer (3 questions),
- E. Target volumes and dosimetric considerations (17 questions).

There were 37 multiple-choice, mutually exclusive questions, and 4 open questions. Between December 2020 and March 2021, the questionnaire was electronically submitted to 25 European radiation oncology experts in three rounds using the Google Forms platform in accordance with the Delphi methodology (Fig. 1). Nineteen participants were male, and six were female. All panelists worked in an academic setting.

An anonymized summary of the individual answers was sent to all participants before the next round. Based on participants' feed-

back, some questions were slightly modified in the second and third rounds. Consensus was defined as an agreement of more than 80% among participants, and questions achieving consensus were excluded for the next round. Sixty to 80% rates were considered as agreement. The study was approved by the ESTRO Guidelines Committee, and the final version was approved by all the authors. This study did not require ethical committee approval as no patient data were involved.

Results

Among the 27 contacted experts including the 9 radiation oncologists involved in the development of the questionnaire, 25 participated in the study completing in all cases all the three rounds of the Delphi consensus. In the end of the 3rd round, consensus was reached in 11 out of 41 questions (27%), with 2 questions reaching consensus during the first round. In the second and third rounds consensus was reached in 4 and 5 questions, respectively. Evolution of the agreement is illustrated on Fig. 1, while the major findings are summarized on Table 1.

Patient and disease characteristics

In the first round, 88% of experts agreed that age should not be considered an exclusion criterion for selecting patients for MDRT strategies. Consensus (84%) was also reached to recommend confirmatory biopsies to suspicious lesions before MDRT only in selected cases. In the second round, consensus (88%) was obtained to recommend MDT for patients with *de novo* oligometastatic, oligorecurrent, and oligoprogressive prostate cancer, while 12% of the experts recommended MDT only for *de novo* oligometastatic and oligorecurrent patients (after the first round, the corresponding figures were 68% and 20%, respectively, while 12% of the experts recommended MDT for oligorecurrent disease only). After the third round, 80% of the experts agreed to recommend MDRT for a maximum of 5 lesions (80%), while 12% of the panelists recommended no upper limit if MDRT can be safely delivered. A 88% consensus was reached to treat oligometastatic patients with lymph nodes, bone and visceral metastases but only for selected cases. Prostate-specific membrane antigen positron emission tomography (PSMA PET) imaging was recommended by 88% of the experts as the preferred staging modality to select patients for MDRT strategies. On the other hand, no consensus was reached for life expectancy, not considered a criterion to avoid MDT for 72% of the experts, while 20% recommend MDT only for patients with a life expectancy of at least 5 years. Similarly, no consensus was reached regarding patient selection on the basis of PSA level, PSA doubling time nor Gleason score.

Synchronous *de novo* oligometastatic hormone-sensitive prostate cancer

No consensus was reached during the first round. During the second round, consensus was reached only on the use of PSMA PET imaging as confirmatory imaging in oligometastatic *de novo* prostate cancer patients initially staged with standard imaging (84% agreement). Most panelists (76%) considered complete eradication of all visible disease burden for patients with pelvic and extrapelvic lymph nodes including bone metastases. Although con-

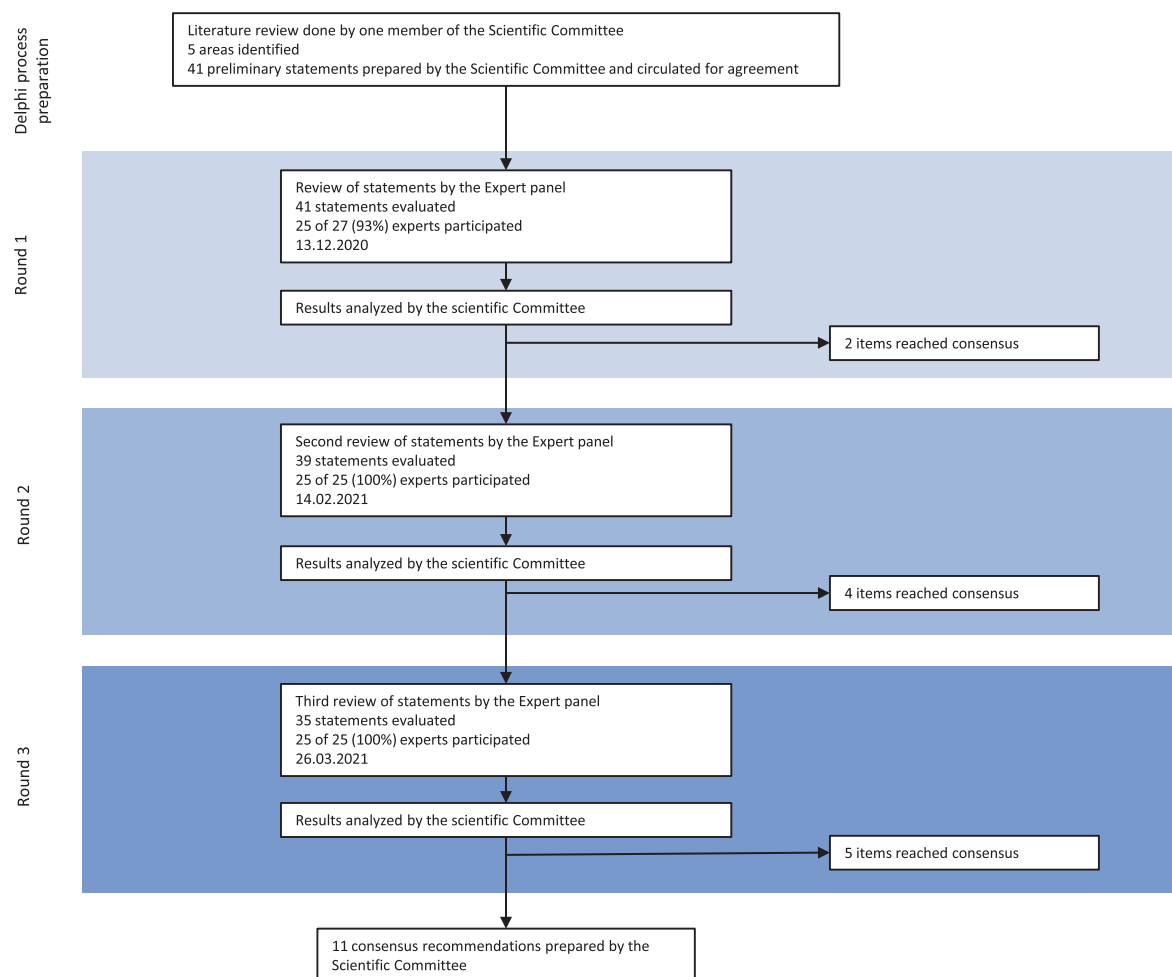


Fig. 1. Study flow diagram of the 3 rounds of the Delphi consensus.

sensus was not reached, 76% of the experts agreed that systemic therapies and treatment of the primary tumor with or without inclusion of pelvic lymph nodes and all metastatic sites is the preferred treatment option for these patients, while systemic therapy and treatment of the primary alone was recommended by 24% of the panelists. When treating the primary with local radiotherapy, experts were divided in recommending as systemic treatment ADT (52%) or ADT with ARPI (40%). The same figures were 64% and 36% for ADT and ADT + ARPI, respectively, when the primary was treated together with the metastatic sites. In this situation, the recommended duration of androgen suppression was between 18 and 36 months for 76% of the panelists, while only a minority recommended a lifelong systemic therapy. Overall survival, progression-free survival, and impact on quality of life and patient reported outcomes were rated as the most important endpoints in this setting (Fig. 2).

Metachronous oligometastatic (oligorecurrent) hormone-sensitive prostate cancer

Consensus was reached after the second round only for the use of PSMA PET as the preferred imaging modality to confirm metachronous oligorecurrent prostate cancer (96% agreement). While the time interval between the primary treatment and the oligorecurrence was not considered a criterion to recommend MDRT for 68% of the panelists, experts were divided in recommending MDRT alone of all metastatic sites (36%) versus systemic therapy and MDRT of all sites (60%) as best treatment options for these patients

(1 expert uncertain). Short course (≤ 6 months) standard ADT using luteinizing hormone-releasing hormone (LH-RH) agonist/antagonists was the preferred systemic therapy option for 60% of the experts. As for patients with *de novo* oligometastatic prostate cancer, the most important endpoints to consider were overall survival, progression-free survival and impact on quality of life and patient reported outcomes (Fig. 2).

Oligoprogressive castration-resistant prostate cancer

Agreement on use of PSMA PET as confirmatory imaging to recommend MDRT for oligoprogressive patients increased from 40% in the first round to 60% in the second round and finally to 80% in the 3rd round. In the third round, MDRT of all lesions without switch of systemic therapy reached consensus (84% agreement), while 16% recommended use of MDRT only in the context of clinical trials. The most important endpoints to consider for MDRT strategies were overall survival, progression-free survival, quality of life and patient-reported outcomes. Ability to stay on the same systemic treatment was another endpoint of MDRT for many experts (Fig. 2).

Target volumes and dosimetric considerations

For the treatment of bone disease, 68% of the panelists agreed to treat bone lesions when the PET uptake is associated with the presence of a radiologically visible lesion. For spinal lesions, consensus was reached to treat the visible lesion (gross tumor volume, GTV)

Table 1

Consensus recommendations for treatment of oligometastatic prostate cancer.

	Response	Agreement level
Patient and disease characteristics		
1. Is age a criterion for the indication of MDRT?	No	Consensus Round 1: 88%
2. Is life expectancy a criterion for the indication of MDRT?	No	Agreement Round 1: 60%; round 2: 72%; round 3: 72%
3. Is the number of metastases a criterion for the indication of MDRT?	Yes, maximum 5	Agreement Round 1: 68%; round 2: 80%; round 3: 80%
4. For which site of metastatic involvement do you recommend MDRT?	For nodes, bone and visceral, but only for selected patients	Consensus Round 1: 56%; round 2: 76%; round 3: 88%
5. For which presentation setting (de novo, oligorecurrent, oligoprogressive) do you recommend MDRT?	For de novo, oligorecurrent and oligoprogressive	Consensus Round 1: 68%; round 2: 88%
7. Which imaging modalities do you recommend to select candidates for MDRT?	PSMA PET imaging	Consensus Round 1: 64%; round 2: 80%; round 3: 88%
8. Do you recommend a confirmatory biopsy to suspicious lesions for MDRT?	Only for selected cases	Consensus Round 1: 84%
Synchronous de novo oligometastatic castration-sensitive PCa		
9. For patients with untreated primary with de novo oligometastatic PCa on conventional imaging, which confirmatory imaging do you recommend?	PSMA PET imaging	Consensus Round 1: 60%; round 2: 84%
10. For patients with untreated primary with de novo oligometastatic PCa, which type of treatment do you recommend?	Systemic therapy and treatment of the prostate (\pm pelvic nodes) and all metastatic lesions	Agreement Round 1: 68%; round 2: 76%; round 3: 76%
13. For patients with untreated primary with de novo oligometastatic PCa treated to primary and all metastatic lesions, which duration of systemic therapy do you propose?	Long-course, 18–36 months	Agreement Round 1: 72%; round 2: 72%; round 3: 76%
14. For patients with untreated primary with de novo oligometastatic PCa treated to the primary, for which SITES do you consider using MDRT?	Pelvic and extra-pelvic nodal disease + bone lesions	Agreement Round 1: 52%; round 2: 60%; round 3: 76%
Metachronous oligometastatic (oligorecurrent) castration-sensitive PCa		
16. For patients with rising PSA after radical treatment, which imaging modalities do you recommend to confirm a diagnosis of metachronous oligometastatic PCa?	PSMA PET imaging	Consensus Round 1: 80%; round 2: 96%
17. For patients with oligorecurrent PCa, is the time interval between the primary treatment and the oligorecurrence a criterion for the indication of MDRT?	No	Agreement Round 1: 46%; round 2: 64%; round 3: 68%
19. For patients with oligorecurrent PCa, which type of systemic treatment do you recommend?	LH-RH agonist/antagonists	Agreement Round 1: 64%; round 2: 64%; round 3: 76%
Oligoprogressive castration resistant PCa		
22. For patients with rising PSA in a castration resistant phase, which imaging modality do you recommend to confirm a diagnosis of oligoprogressive PCa?	PSMA PET imaging	Agreement Round 1: 40%; round 2: 60%; round 3: 80%
23. For patients with oligoprogressive PCa (with no visceral metastases), which treatment do you recommend?	MDRT of all lesions without switch of systemic therapy	Consensus Round 1: 56%; round 2: 76%; round 3: 84%
Target volume and dosimetric considerations		
25. For bone lesions, when do you consider MDRT?	There is an uptake on PET but must be associated with the presence of a radiologically visible lesion	Agreement Round 1: 72%; round 2: 72%; round 3: 68%
26. For vertebral bone lesions, when you consider a MDRT, do you treat:	The lesion (GTV) and the vertebral body (CTV)	Consensus Round 1: 60%; round 2: 76%; round 3: 84%
28. For extraspinal bone lesions, when you consider a MDRT, do you treat:	The lesion (GTV) and a 4–5 mm isotropic CTV	Agreement Round 1: 32%; round 2: 44%; round 3: 68%
30. If the dose is prescribed at the isodose, please specify at which percentage (e.g. 80%)	80%	Consensus Round 1: 72%; round 2: 87%
36. For ENRT, which treatment template do you recommend?	NRG based with upper level at the aortic bifurcation (L4–5 interspace)	Agreement Round 1: 36%; round 2: 68%; round 3: 79%
38. For oligorecurrent PCa patients relapsing after a previous RP and not previously irradiated on the PB, in which cases do you treat the PB?	Only in presence of histological risk factors (pT3a, pT3b, pT4 and/or R1)	Agreement Round 1: 36%; round 2: 56%; round 3: 68%

Table 1 (continued)

	Response	Agreement level
39. For oligorecurrent PCa patients relapsing after a previous definitive irradiation of the prostate, in which cases do you recommend additional investigations to rule out a local relapse?	Only in selected cases if imaging is suspicious for local recurrence	Consensus Round 1: 58%; round 2: 72%; round 3: 88%
41. Which definition of biochemical failure do you use after MDRT and concomitant ADT and a post-treatment normalized testosterone?	Phoenix definition (nadir + 2 ng/ml) for de novo and oligorecurrent with prostate (treated with primary definitive radiotherapy) and any PSA rise above 0.20 ng/ml with a confirmatory rise at least 2 weeks later for patients previously treated with RP	Agreement Round 1: 42%; round 2: 60%; round 3: 76%

Abbreviations: MDRT, Metastasis-directed radiotherapy; PCa, prostate cancer; PSMA PET, Prostate-specific membrane antigen positron emission tomography; ENRT, Elective nodal radiotherapy; PB, Prostate bed; RP, Radical prostatectomy; ADT, Androgen deprivation therapy.

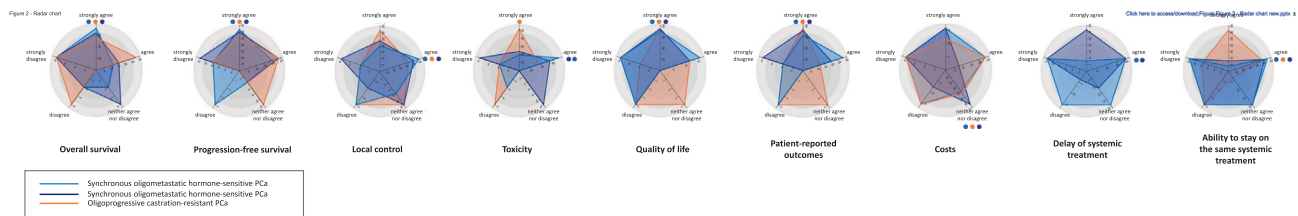


Fig. 2. Importance of different endpoints for metastasis-directed radiotherapy (MDRT) in de novo oligometastatic, oligorecurrent and oligoprogressive castration-resistant prostate cancer. Axis are in percentage. Color points correspond to the higher percentage of each category.

and the entire vertebral body (clinical target volume, CTV) (84% agreement), using mostly a simultaneous integrated boost technique (56% agreement). For extraspinal bone lesions, the majority of the experts recommended to treat lesions with a variable CTV margin (4–5 mm, 1–3 mm, non-isotropic margin based on anatomy for 68%, 16% and 12% of the panelists, respectively). Practices differed with regards to dose prescription, as 60% of the panelists voted for an homogeneous dose prescription on the planning target volume (PTV), and 40% voted for a dose prescription to an isodose line (80% isodose line recommended by the 87% of the 15 voting experts). The most recommended fractionation for spinal lesions SBRT was 35 Gy in 5 fractions (42%, $n = 10$), followed by 30 Gy in 3 fractions (37.5%, $n = 9$), and use of simultaneous integrated boost (SIB) in 3 or 5 fractions recommended by 33% of the experts ($n = 8$) (Fig. 3). For the treatment of extra-spinal bone metastases, a 3-fraction SBRT schedule (i.e., 30 Gy in 3 fractions) was recommended by 72% of the experts ($n = 18$).

For the treatment of pelvic nodal disease, elective nodal irradiation (ENRT) with a boost on the suspicious lymph nodes was recommended as preferred option by 60% of the experts ($n = 15$). The use of SBRT or ENRT based on the number of involved lymph nodes was proposed by 28% of the experts. However, criteria for such approach were divergent, including 33% of the panelists recommending ENRT for patients with 1 single lesion and SBRT for patients with 2–5 lymph nodes, and 33% proposing SBRT for 1–3 lesions and ENRT for 4–5 lymph nodes. For SBRT, a dose of 30 Gy in 3 fractions was the preferred treatment schedule (64%, $n = 16$), while 35 Gy in 5 fractions was proposed by 48% of the experts ($n = 12$). For ENRT treatments, a dose of 45 Gy in 25 fractions with a SIB technique to the positive lymph nodes (2.2–2.7 Gy per fraction) was recommended by 60% of the experts. A dose of 50 Gy in 25 fractions or doses of more than 50 Gy in 30 fractions were proposed in the 24% and 20% of the cases, respectively. An agreement was reached in the 3rd round on the use of the NRG template with an upper level at the aortic bifurcation (L4–5 interspace) for ENRT volumes delineation (79% agreement) [8].

Inclusion of the prostate bed in the ENRT volume in previously not irradiated patients reached an agreement of 68% for patients presenting high risk factors (pT3a/b–pT4 disease and/or R1). The treatment of the prostate bed based on the evidence of local

relapse on multiparametric magnetic resonance imaging (mpMRI) or next-generation imaging was proposed by 20% of the experts. Regarding the need to rule out intraprostatic local relapse in oligorecurrent patients already treated with definitive irradiation of the prostate, a consensus was reached by 88% of the experts to recommend further investigations only for selected cases when imaging is suspicious for a local recurrence. After pelvic salvage lymph-node dissection, whole pelvic radiotherapy with or without concomitant ADT was proposed by 52% of the experts only in case of persistent postoperative PSA. Observation was recommended by 16% of the experts, while SBRT with or without ADT was proposed as salvage treatment option only in case of persistent PSA and visible target by 20% of the panelists.

After the third round, a 76% agreement was reached on the definition of biochemical failure after MDRT and concomitant ADT in the context of a post-treatment normalized testosterone level (Phoenix definition, nadir + 2 ng/mL, for de novo and oligorecurrent patients with prostate in place and PSA > 0.2 ng/mL for patients in the post-prostatectomy setting). Twenty percent of the experts considered biochemical failure as any elevation above the baseline PSA (pre-MDRT) followed by a confirmatory PSA level.

Discussion

Oligometastatic prostate cancer is an emerging clinical situation, with MDT strategies frequently proposed in the clinical routine despite the lack of strong clinical evidence [13]. Radiotherapy has played a major role from the beginning in MDT strategies, with nevertheless huge variabilities across trials in terms of radiation doses and volumes and combination with systemic therapies [12,14]. Using the Delphi consensus methodology, these ESTRO Guidelines Committee recommendations aim for standardization and consensus on radiotherapy treatment of oligometastatic prostate cancer patients providing useful insights for the Radiation Oncology community while waiting for the results of ongoing randomized clinical trials and prospective registries.

To date the definition of an oligometastatic disease relies entirely on imaging. The effectiveness of MDT techniques is therefore strongly dependent on the ability of imaging modalities to

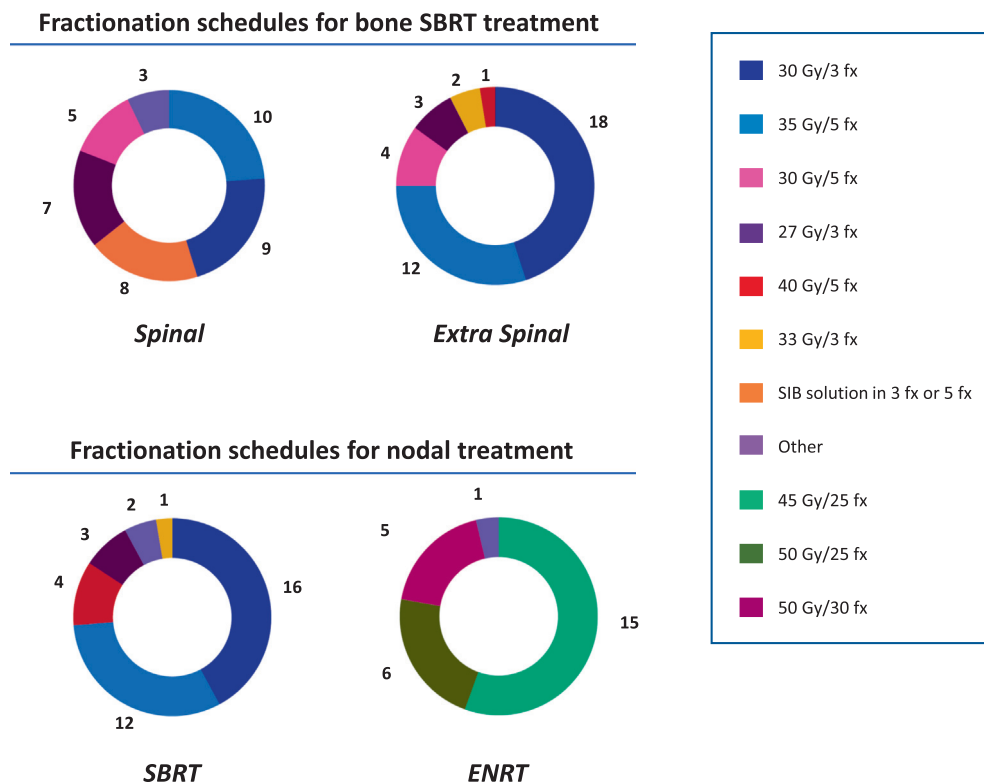


Fig. 3. Fractionation schedules for bone and nodal treatments (more than one schedule recommended by the 25 experts). *Abbreviations:* SBRT = stereotactic body radiation therapy; ENRT = elective nodal radiation therapy; fx = fractions; SIB = simultaneous integrated boost.

identify early metastases. In parallel with the widespread use of next-generation imaging for prostate cancer (Suppl. Fig. 1), PSMA PET was recommended homogeneously by panelists as the best imaging modality to select candidates for MDRT in all oligometastatic settings. PSMA PET has been demonstrated to provide superior accuracy for identifying bone and/or pelvic nodal lesions than conventional CT and bone scanning in the initial staging [15] as well as for the restaging of recurrent disease, improving the detection rate of metastases particularly at low PSA levels (33% for PSA < 0.2 ng/mL and 45% for PSA between 0.2 and 0.5 ng/mL) [16]. In patients with castration-resistant disease at high risk for metastatic disease with no evidence of metastatic disease on conventional imaging, PSMA imaging was able to identify in 44% of the cases a PSMA-positive pelvic nodal disease and in 55% distant metastases, including a 14% rate of patients harboring oligometastatic disease [17]. Of note, although some differences have been reported in performance of [68 Ga] versus [18F]-labelled PSMA tracers [18], total consolidation of all PSMA-avid disease sites with MDRT was associated with an improved outcome compared to MDRT directed on lesions visualized on standard imaging only [11].

As far as patient selection is concerned, according to the current recommendations, all oligometastatic prostate cancer patients could be considered for MDRT, regardless of their age (consensus), life expectancy (agreement), and disease status (oligorecurrent, oligoprogressive or de novo). While concerns have been raised about prognosis of patients developing metastases shortly after primary treatment, data are lacking on the role of a minimal time-interval to recommend MDRT for metachronous oligometastatic disease. Pending further evidence on patient and treatment factors, time interval between the primary treatment and the oligorecurrence has not been recommended as a criterion in selecting patients for MDRT. The panel agreed on 5 lesions detected on PSMA-imaging as an upper limit to consider MDRT, as stated in

previous ESTRO recommendations [19]. Given the paucity of data on the role of MDT in patients with visceral metastases [20–22], treatment of these patients with MDRT has not been contraindicated by experts, but limited to selected cases based on clinical judgement.

Lymph nodes represent the most frequent site of failure in prostate cancer, with the majority of the patients relapsing in the pelvis [23]. Disparities exist with regards to the management of nodal oligorecurrence across panel experts, yet 60% of them recommend use of ENRT with a boost to suspicious lymph nodes, including irradiation of the prostate bed in case of adverse pathological findings. Comprehensive pelvic irradiation with ENRT is supported by surgical series data and analyses of patterns of relapse showing better outcome results with template-based extended or super-extended bilateral lymph node dissection compared to selective nodal dissection [24,25]. The OLIGOPELVIS GETUG P07 trial demonstrated a promising 46% biochemical relapse-free survival rate at 3-years in oligorecurrent patients treated to the whole pelvis (54 Gy in 30 fractions) with boost to suspicious lymph nodes (66 Gy in 30 fractions) combined with 6 months of ADT [26]. In contrast to elective radiotherapy doses used in OLIGOPELVIS GETUG P07 trial, the majority of the panel experts favored lower ENRT doses (i.e., 45 Gy in 25 fractions) to possibly limit long-term bowel toxicities. A 79% agreement was reached in recommending the upper limit of the nodal target volume at the level of the common iliac vessels as proposed by the latest NRG consensus [27] to improve coverage of common sites of recurrence after prostate radiotherapy [28]. Focal SBRT (30 Gy in 3 fractions or 35 Gy in 5 fractions) without concurrent systemic therapy is also proposed by some experts as treatment strategy for delaying start of palliative ADT [10,11,20]. Considering that patterns of relapse remain nodal and oligometastatic for the majority of the patients [29], the best treatment strategy to manage nodal oligorecurrence remains undetermined [12]. Although the treatment strategy may

be related to the nodal burden at recurrence [14], results of the ongoing PEACE V – STORM phase II trial, randomizing pelvic nodal oligorecurrent prostate cancer patients between SBRT vs ENRT in combination with 6 months of ADT, will certainly help to establish the best salvage treatment strategy for this population [30,31]. Likewise, radiotherapy may be beneficial for oligometastatic prostate cancer in the para-aortic lymph nodes, and the use of focal SBRT vs larger target volumes requires further investigation [32].

For vertebral bone metastases, while there are not sufficient data to address the optimal radiotherapy dose for all clinical situations, improved local control rates have been documented when biologically effective doses (BED) of more than 100 Gy (α/β ratio of 3) are delivered [20]. Recommended schedules for spinal SBRT included 35 Gy in 5 fractions, 30 Gy in 3 fractions or 27 Gy in 3 fractions, or with SIB, usually prescribed at the target volume [33]. Extra-spinal SBRT schedules were less heterogeneous, and the most prescribed schedules were 30 Gy in 3 fractions and 35 Gy in 5 fractions. With regards to target volumes, implementation of guidelines for spinal [34,35] and non-spinal SBRT [36] are recommended also for oligometastatic prostate disease. For spinal SBRT, integration of a clinical target volume encompassing the vertebral body is recommended to avoid marginal failures [37,38]. Caution should be taken when recommending MDRT for bone lesions with a PSMA uptake only and no radiological correlate on CT scan as they often represent benign lesions [18,39,40]. Use of confirmatory MRI imaging or biopsies can be considered in selected cases.

The survival benefit observed with combination treatments in patients with *de novo* hormone-sensitive metastatic prostate cancer has defined a new standard of care, even for patients with low-volume disease [4–6,8]. On the other hand, for *de novo* oligometastatic patients, the use of ablative SBRT to all metastatic sites detected on next-generation imaging remains a very appealing strategy even if the definite long-term benefits remain unknown [41]. Despite the fact that level I evidence supports the treatment of the primary only in patients with low-volume metastatic disease [42], a comprehensive treatment of all metastatic sites was recommended by 76% of the experts, mostly in combination with ADT and ARPI (40%). This compares favorably with the 61% of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022 consensus meeting panelists recommending a systemic therapy plus local treatment of the primary and MDT in oligometastatic synchronous prostate cancer patients with 1–3 bone lesions on next-generation imaging (data unpublished). In contrast with current guidelines [7], agreement was achieved to limit systemic treatments for a total duration of 18–36 months when an ablative treatment of all disease sites is performed, with addition of ARPI to ADT considered an option by 36% of the panelists. Due to the experimental character of this therapeutic approach, careful patient selection and close follow-up remains mandatory with enrollment of patients in clinical trials or prospective registries highly encouraged. Interestingly, ongoing randomized trials like GETUG AFU 26/PRESTO (NCT04115007) and STAMPEDE will help define the role and impact of SBRT in this disease setting. In patients with metachronous disease, the addition of a short-course ADT to MDRT was recommended by 60% of the experts, probably based on the potential progression-free survival benefit observed in retrospective series [20]. Nevertheless, based on the promising results of prospective trials [43,44], MDRT alone without concomitant systemic therapy remains an option for 36% of the experts. The results of the ongoing randomized phase III ADOPT trial (NCT04302454) are awaited to better define the role of addition of ADT to MDRT in this disease setting [45]. For oligoprogressive disease, consensus has been reached in proposing MDRT as treatment modality to prolong the efficacy of ongoing systemic treatments and delay the use of next-line therapies. Nevertheless,

data remain scarce and mainly based on retrospective series [46,47].

In conclusion, in the rapidly evolving field of oligometastatic prostate cancer, MDRT plays a central therapeutic role, from the *de novo* disease to the oligorecurrent and castration-resistant settings. These ESTRO Guidelines Committee recommendations provide the radiation oncology community with a useful reference in an attempt to establish standardization and consensus on the best radiotherapy strategies for oligometastatic prostate cancer. Although consensus has been reached on some topics, many open questions remain unanswered and enrollment of patients in clinical trials to create level I evidence is highly encouraged. Ongoing studies will hopefully help improve treatment outcomes for these patients in the coming years.

Disclaimer

ESTRO cannot endorse all statements or opinions made on the guidelines. Regardless of the vast professional knowledge and scientific expertise in the field of radiation oncology that ESTRO possesses, the Society cannot inspect all information to determine the truthfulness, accuracy, reliability, completeness or relevancy thereof. Under no circumstances will ESTRO be held liable for any decision taken or acted upon as a result of reliance on the content of the guidelines.

The component information of the guidelines is not intended or implied to be a substitute for professional medical advice or medical care. The advice of a medical professional should always be sought prior to commencing any form of medical treatment. To this end, all component information contained within the guidelines is done so for solely educational and scientific purposes. ESTRO and all of its staff, agents and members disclaim any and all warranties and representations with regards to the information contained on the guidelines. This includes any implied warranties and conditions that may be derived from the aforementioned guidelines.

Conflict of interest

TZ reports speaker and advisory honoraria from Janssen, Amgen, Ferring, Debiopharm Bayer, Astellas and research grants from Varian medical Systems and Debiopharm; AZ reports speaker honoraria from Astellas Pharma and Janssen and advisory board honoraria from Bayer; AGI reports advisory board honoraria from Astellas, Janssen, Bayer and Elekta; FA reports advisory board, consultant and speaker honoraria from Janssen, Ipsen, Ferring, Astellas, Elekta, Varian, Brainlab; ACM reports advisory board honoraria from Astellas, Janssen, IPSEN and Bayer; PS reports advisory board and consultant honoraria from Astellas, AAA, AstraZeneca, Bayer, Janssen, Sanofi; PB reports advisory boards and honoraria from Ipsen, Bayer, Astellas; PO reports consultancy for AAA, Bayer, Curium, Janssen and research grants from Bayer and Varian; BJF reports research funding from AIRC Italian Association for Cancer Research (institutional grants), FIEO-CCM & FUV (institutional grants), Accuray (institutional grant), and travel expenses or speaker fees from Janssen, Ferring, Bayer, Roche, Astellas, Elekta, Carl Zeiss, Ipsen, Accuray, IBA; AT reports research funding and honoraria from Accuray and Elekta, research funding from Varian and honoraria from Janssen.

The other authors declare no competing interests concerning the submitted work.

Acknowledgements

The authors acknowledge the comprehensive review of these recommendations by Dr. Constantinos Zamboglou, Dr. Stephanie

Kroeze, Dr Daniel Taussky and Dr. Giulio Francolini and wish to thank them for their work.

AT would like to acknowledge the support of Cancer Research UK (C33589/A28284 and C7224/A28724). This project represents independent research supported by the National Institute for Health research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Ethics approval and consent to participate

No approval of the local Ethics committees was required.

Funding

No funding was required.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2022.10.005>.

References

- Lancia A, Zilli T, Achard V, Dirix P, Everaerts W, Gomez-Iturriaga A, et al. Oligometastatic prostate cancer: The game is afoot. *Cancer Treat Rev* 2019;73:84–90.
- Farolfi A, Hadaschik B, Hamdy FC, Herrmann K, Hofman MS, Murphy DG, et al. Positron emission tomography and whole-body magnetic resonance imaging for metastasis-directed therapy in hormone-sensitive oligometastatic prostate cancer after primary radical treatment: a systematic review. *Eur Urol Oncol* 2021;4:714–30.
- Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol* 2020;21:e18–28.
- Chi KN, Agarwal N, Bjartell A, Chung BH, de Santana P, Gomes AJ, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *New Engl J Med* 2019;381:13–24.
- Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *New Engl J Med* 2019;381:121–31.
- Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *New Engl J Med* 2017;377:352–60.
- Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. *Eur Urol* 2021;79:263–82.
- Smith MR, Hussain M, Saad F, Fizazi K, Sternberg CN, Crawford ED, et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. *New Engl J Med* 2022;386:1132–42.
- Deek MP, Tapparra K, Phillips R, Velho PI, Gao RW, Deville C, et al. Metastasis-directed Therapy Prolongs Efficacy of Systemic Therapy and Improves Clinical Outcomes in Oligoprogressive Castration-resistant Prostate Cancer. *Eur Urol Oncol* 2021;4:447–55.
- Ost P, Reyniers D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. *J Clin Oncol: Off J Am Soc Clin Oncol* 2018;36:446–53.
- Phillips R, Shi WY, Deek M, Radwan N, Lim SJ, Antonarakis ES, et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. *JAMA Oncol* 2020;6:650–9.
- Achard V, Bottero M, Rouzaud M, Lancia A, Scorsetti M, Filippi AR, et al. Radiotherapy treatment volumes for oligorecurrent nodal prostate cancer: a systematic review. *Acta Oncol* 2020;59:1224–34.
- Marvaso G, Volpe S, Pepa M, Augugliaro M, Corrao G, Biffi A, et al. Oligorecurrent Prostate Cancer and Stereotactic Body Radiotherapy: Where Are We Now? A Systematic Review and Meta-analysis of Prospective Studies. *Eur Urol Open Sci* 2021;27:19–28.
- De Bleser E, Jereczek-Fossa BA, Pasquier D, Zilli T, Van As N, Siva S, et al. Metastasis-directed Therapy in Treating Nodal Oligorecurrent Prostate Cancer: A Multi-institutional Analysis Comparing the Outcome and Toxicity of Stereotactic Body Radiotherapy and Elective Nodal Radiotherapy. *Eur Urol* 2019;76:732–9.
- Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet* 2020;395:1208–16.
- Perera M, Papa N, Roberts M, Williams M, Udovitch C, Vela I, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. *Eur Urol* 2020;77:403–17.
- Fendler WP, Weber M, Iravani A, Hofman MS, Calais J, Czernin J, et al. Prostate-Specific Membrane Antigen Ligand Positron Emission Tomography in Men with Nonmetastatic Castration-Resistant Prostate Cancer. *Clin Cancer Res: Off J Am Assoc Cancer Res* 2019;25:7448–54.
- Evangelista L, Maurer T, van der Poel H, Alongi F, Kunikowska J, Laudicella R, et al. [(68)Ga]Ga-PSMA Versus [(18)F]PSMA Positron Emission Tomography/Computed Tomography in the Staging of Primary and Recurrent Prostate Cancer. A Systematic Review of the Literature. *Eur Urol Oncol* 2022;5:273–82.
- Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. *Radiother Oncol: J Eur Soc Therap Radiol Oncol* 2020;148:157–66.
- Ost P, Jereczek-Fossa BA, As NV, Zilli T, Muacevic A, Olivier K, et al. Progression-free Survival Following Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Treatment-naïve Recurrence: A Multi-institutional Analysis. *Eur Urol* 2016;69:9–12.
- Battaglia A, Devos G, Decaestecker K, Witters M, Moris L, Van den Broeck T, et al. Metastectomy for visceral and skeletal oligorecurrent prostate cancer. *World J Urol* 2019;37:1543–9.
- Connor MJ, Smith A, Miah S, Shah TT, Winkler M, Khoo V, et al. Targeting Oligometastasis with Stereotactic Ablative Radiation Therapy or Surgery in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review of Prospective Clinical Trials. *Eur Urol Oncol* 2020;3:582–93.
- De Bruycker A, Lambert B, Claeys T, Delrue L, Mbah C, De Meerleer G, et al. Prevalence and prognosis of low-volume, oligorecurrent, hormone-sensitive prostate cancer amenable to lesion ablative therapy. *BJU Int* 2017;120:815–21.
- De Bruycker A, De Bleser E, Decaestecker K, Fonteyne V, Lumen N, De Visschere P, et al. Nodal Oligorecurrent Prostate Cancer: Anatomic Pattern of Possible Treatment Failure in Relation to Elective Surgical and Radiotherapy Treatment Templates. *Eur Urol* 2019;75:826–33.
- Fossati N, Scarcella S, Gandaglia G, Suardi N, Robesti D, Boeri L, et al. Underestimation of Positron Emission Tomography/Computerized Tomography in Assessing Tumor Burden in Prostate Cancer Nodal Recurrence: Head-to-Head Comparison of (68)Ga-PSMA and (11)C-Choline in a Large, Multi-Institutional Series of Extended Salvage Lymph Node Dissections. *J Urol* 2020;204:296–302.
- Supiot S, Vaugier L, Pasquier D, Buthaud X, Magne N, Peiffert D, et al. OLIGOPELVIS GETUG P07, a Multicenter Phase II Trial of Combined High-dose Salvage Radiotherapy and Hormone Therapy in Oligorecurrent Pelvic Node Relapses in Prostate Cancer. *Eur Urol* 2021;80:405–14.
- Hall WA, Paulson E, Davis BJ, Spratt DE, Morgan TM, Dearnaley D, et al. NRG Oncology Updated International Consensus Atlas on Pelvic Lymph Node Volumes for Intact and Postoperative Prostate Cancer. *Int J Radiat Oncol Biol Phys* 2021;109:174–85.
- Spratt DE, Vargas HA, Zumsteg ZS, Golja Pernicka JS, Osborne JR, Pei X, et al. Patterns of Lymph Node Failure after Dose-escalated Radiotherapy: Implications for Extended Pelvic Lymph Node Coverage. *Eur Urol* 2017;71:37–43.
- Ost P, Jereczek-Fossa BA, Van As N, Zilli T, Tree A, Henderson D, et al. Pattern of Progression after Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Nodal Recurrences. *Clin Oncol* 2016;28:e115–20.
- De Bruycker A, Spiessens A, Dirix P, Koutsouvelis N, Semac I, Liefhooghe N, et al. PEACE V - Salvage Treatment of Oligorecurrent nodal prostate cancer Metastases (STORM): a study protocol for a randomized controlled phase II trial. *BMC Cancer* 2020;20:406.
- Zilli T, Dirix P, Heikkilä R, Liefhooghe N, Siva S, Gomez-Iturriaga A, et al. The Multicenter, Randomized, Phase 2 PEACE V-STORM Trial: Defining the Best Salvage Treatment for Oligorecurrent Nodal Prostate Cancer Metastases. *Eur Urol Focus* 2021;7:241–4.
- Rich BJ, Montoya C, Jin WH, Spieler BO, Mahal BA, Delgadillo R, et al. Para-Aortic Radiation Therapy for Oligorecurrent Prostate Cancer. *Int J Radiat Oncol Biol Phys* 2022.
- Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys* 2010;37:4078–101.
- Cox BW, Spratt DE, Lovelock M, Bilsky MH, Lis E, Ryu S, et al. International Spine Radiosurgery Consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 2012;83:e597–605.
- Dunne EM, Sahgal A, Lo SS, Bergman A, Kosztyla R, Dea N, et al. International consensus recommendations for target volume delineation specific to sacral metastases and spinal stereotactic body radiation therapy (SBRT). *Radiother Oncol: J Eur Soc Therap Radiol Oncol* 2020;145:21–9.
- Nguyen TK, Chin L, Sahgal A, Dagan R, Eppinga W, Guckenberger M, et al. International Multi-institutional Patterns of Contouring Practice and Clinical

- Target Volume Recommendations for Stereotactic Body Radiation Therapy for Non-Spine Bone Metastases. *Int J Radiat Oncol Biol Phys* 2022;112:351–60.
- [37] Chang EL, Shiu AS, Mendel E, Mathews LA, Mahajan A, Allen PK, et al. Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. *J Neurosurg Spine* 2007;7:151–60.
- [38] Koyfman SA, Djemil T, Burdick MJ, Woody N, Balagamwala EH, Reddy CA, et al. Marginal recurrence requiring salvage radiotherapy after stereotactic body radiotherapy for spinal metastases. *Int J Radiat Oncol Biol Phys* 2012;83:297–302.
- [39] Grunig H, Maurer A, Thali Y, Kovacs Z, Strobel K, Burger IA, et al. Focal unspecific bone uptake on [(18)F]-PSMA-1007 PET: a multicenter retrospective evaluation of the distribution, frequency, and quantitative parameters of a potential pitfall in prostate cancer imaging. *Eur J Nucl Med Mol Imaging* 2021;48:4483–94.
- [40] Letang A, Crombe A, Rousseau C, Sargos P, Merlin C, Cantarel C, et al. Bone Uptake in Prostate Cancer Patients: Diagnostic Performances of PSMA-RADS v1.0, Clinical, Biological, and 68 Ga-PSMA-11 PET Features to Predict Metastasis After Biochemical Recurrence. *Clin Nucl Med* 2022;47:e529–39.
- [41] Gillesen S, Attard G, Beer TM, Beltran H, Bjartell A, Bossi A, et al. Management of Patients with Advanced Prostate Cancer: Report of the Advanced Prostate Cancer Consensus Conference 2019. *Eur Urol* 2020;77:508–47.
- [42] Parker CC, James ND, Brawley CD, Clarke NW, Ali A, Amos CL, et al. Radiotherapy to the prostate for men with metastatic prostate cancer in the UK and Switzerland: Long-term results from the STAMPEDE randomised controlled trial. *PLoS Med* 2022;19:e1003998.
- [43] Holscher T, Baumann M, Kotzerke J, Zophel K, Paulsen F, Muller AC, et al. Toxicity and Efficacy of Local Ablative, Image-guided Radiotherapy in Gallium-68 Prostate-specific Membrane Antigen Targeted Positron Emission Tomography-staged, Castration-sensitive Oligometastatic Prostate Cancer: The OLI-P Phase 2 Clinical Trial. *Eur Urol Oncol* 2022;5:44–51.
- [44] Glicksman RM, Metser U, Vines D, Valliant J, Liu Z, Chung PW, et al. Curative-intent Metastasis-directed Therapies for Molecularly-defined Oligorecurrent Prostate Cancer: A Prospective Phase II Trial Testing the Oligometastasis Hypothesis. *Eur Urol* 2021;80:374–82.
- [45] Janssen J, Staal FHE, Brouwer CL, Langendijk JA, de Jong IJ, van Moorselaar RJA, et al. Androgen Deprivation therapy for Oligo-recurrent Prostate cancer in addition to radiotherapy (ADOPT): study protocol for a randomised phase III trial. *BMC Cancer* 2022;22:482.
- [46] Ingrosso G, Detti B, Fodor A, Caini S, Borghesi S, Triggiani L, et al. Stereotactic ablative radiotherapy in castration-resistant prostate cancer patients with oligoprogression during androgen receptor-targeted therapy. *Clin Trans Oncol: Off Publ Fed Span Oncol Soc Natl Cancer Inst Mexico* 2021;23:1577–84.
- [47] Franzese C, Perrino M, Marzo MA, Badalamenti M, Baldaccini D, D'Agostino G, et al. Oligoprogressive castration-resistant prostate cancer treated with metastases-directed stereotactic body radiation therapy: predictive factors for patients' selection. *Clin Exp Metastasis* 2022.