



Unravelling oligometastatic disease from the perspective of radiation and medical oncology. Part II: prostate cancer and colorectal cancer

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Received: 29 July 2022 / Accepted: 18 November 2022 / Published online: 16 December 2022
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Abstract

Oligometastatic disease (OMD) defines a status of cancer that is intermediate between localized and widely spread metastatic disease, and can be treated with curative intent. While imaging diagnostic tools have considerably improved in recent years, unidentified micrometastases can still escape from current detection techniques allowing disease to progress. The variety of OMD scenarios are mainly defined by the number of metastases, the biological and molecular tumour profiles, and the timing of the development of metastases. Increasing knowledge has contributed to the earlier and improved detection of OMD, underlining the importance of an early disease control. Based on increasing detection rates of OMD in the current real clinical practice and the lack of standardized evidence-based guidelines to treat this cancer status, a board of experts from the Spanish Societies of Radiation Oncology (SEOR) and Medical Oncology (SEOM) organized a series of sessions to update the current state-of-the-art on OMD from a multidisciplinary perspective, and to discuss how results from clinical studies may translate into promising treatment options. This experts' review series summarizes what is known and what is pending clarification in the context of OMD in the scenarios of Non-Small Cell Lung Cancer and Breast Cancer (Part I), and Prostate Cancer and Colorectal Cancer (Part II), aiming to offer specialists a pragmatic framework that might contribute to the improved management of patients.

Keywords Oligometastatic disease · Prostate cancer · Colorectal cancer · Locoregional treatment · Systemic therapy · SABR · SBRT · SRS

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Introduction

The concept of “oligometastatic disease” (OMD) proposed by Hellman and Weischselbaum in 1995 changed the understanding of cancer as a systematic disease and mooted the existence of an intermediate status between localized and metastasized disease, defined by an indolent tumour biology and a limited metastatic potential [1, 2]. OMD was initially defined as a limited number of metastases in locations amenable to local approaches. The main implication in clinical practice is that local control of the primary tumour (i.e., using metastases-directed therapies [MDT]) may lead to longer disease-free intervals (DFI) and potential cure of patients. In this particular scenario, the role of systemic therapy was not well determined [2]. A consensus statement published by the European Society of Radiotherapy and Oncology (ESTRO) and the American Society of Radiation Oncology (ASTRO) proposed that OMD should be determined by the image-based detection of ≤ 5 metastases involving ≤ 3 organs [3], although ongoing studies may cause these numbers to change in the near future [4, 5]. The European Organisation for Research and Treatment of Cancer (EORTC) and ESTRO recently developed the first comprehensive system for OMD characterisation, nomenclature, and classification in which a total of nine subtypes of OMD were determined [6].

There is scant high-level evidence supporting standardized clinical guidelines for OMD management. Several clinical variables have to be considered when personalizing treatments, including the patient’s general performance status, primary tumour and OM locations, tumour burden, cancer kinetics, or the temporal pattern of OM development [7]. Therapeutic goals must also be established according to the different presentations of OMD. Advances in the field have changed the therapeutic goal from a palliative intent to an attempt to achieve optimal and durable local control of the disease and, potentially, cured patients [8–12]. Newer MDT using ablative radiation techniques (ART) (such as stereotactic radiosurgery [SRS] or stereotactic ablative radiotherapy [SABR, also known as stereotactic body radiation therapy or SBRT]) to manage isolated metastases have prolonged survival and improved patients’ quality of life (QoL) when used alone or in combination with systemic therapies [13] (see Part I of this two-part review series for further information).

In the current landscape, new therapeutic approaches are being investigated based on the biological and genetic/molecular features of OMD with the aim of understanding this entity in depth and refining the selection of patients and the planning of personalized treatment strategies.

The aim of this second article of the two-part expert review series on OMD was to provide an update on the current knowledge of OMD in prostate cancer and colorectal

cancer. The available evidence from retrospective and randomized clinical studies will be discussed along with the current challenges posed by the treatment of these patients (see Part I of this article series for a review of OM non-small cell lung cancer and breast cancer).

Oligometastatic disease in prostate cancer

The definition of an oligometastatic status in the context of prostate cancer (PC) is still a matter of intense debate. The main criteria used to define OM PC include the following: (1) number (1–5) and location of metastatic lesions (visceral, bone or nodal metastases); (2) time of OMD onset (synchronous with the untreated primary tumour or metachronous with recurrences occurring after treatment of primary tumours [oligorecurrent disease]); (3) progression of limited metastatic disease during systemic treatment (which defines oligoprogressive disease); and (4) the castration status of PC patients (hormone-sensitive or castration-resistant) [6]. This heterogeneity in OMD scenarios is barely reflected in representative clinical trials in which only a few of the possible scenarios have been specifically investigated. Some OMD definitions are based on the disease burden, so patients presenting OMD may be included in the “low-volume” subpopulation of metastatic hormone-sensitive PC patients (mHSPC) in accordance with the criteria established in the CHARTED clinical trial [14].

Since the EORTC-ESTRO consensus established the use of conventional imaging to diagnose OMD [6], the arrival of next generation imaging (NGI) techniques has significantly improved the diagnosis of locoregional and distant spread of disease. The sensitivity of conventional computed tomography (CT) and bone scans ranges from 60 to 80%, but in PC with low levels of prostate-specific antigen (PSA), both techniques offer poor diagnostic power. Pelvic multiparametric magnetic resonance imaging (MRI) has significantly upgraded the imaging-based diagnosis of primary tumours and locoregional spread of the disease. Whole-body MRI performs well in the detection of bone lesions, but has a lower diagnostic accuracy for the identification of lymph node metastases (LNM) at the time of selecting patients for radical multimodal therapies. PET/CT scanning with radiolabelled tracers (such as ^{11}C -Choline, ^{18}F -PSMA or ^{68}Ga -PSMA) provides the best detection rates for the assessment of nodal, bone and visceral OMD in PC with very low PSA levels. In the setting of biochemically recurrent PC or advanced PC with shorter PSA doubling time, ^{68}Ga -PSMA sensitivity is 92% [15]. Consequently, the European Association of Urology (EAU) guidelines recommended PSMA-PET/CT in biochemical PC recurrence to guide subsequent treatment decisions, especially in patients who are candidates for curative salvage treatment [16]. The updated

Radiographic Assessments for Detection of Advanced Recurrence guidelines (RADAR III) recommended the use of available NGI techniques in the setting of metastatic PC (mPC) according to the stage of the advanced disease and in selected groups of patients with disease progression, for whom more aggressive treatments against stage M1 metastatic disease can be considered. In the setting of stage M0 castration-resistant PC (CRPC), RADAR III recommend the use of NGI techniques in patients with PSA doubling time of less than 6 months and propose early M1 treatments as an optimal strategy to prevent further progression [17].

Treatment challenges in de novo oligometastatic and oligorecurrent PC

Locoregional treatments and multimodal regimens

Based on evidence supporting the benefit of radiotherapy (RT) in survival rates, the European Association of Urology (EAU) guidelines recommend the use of RT in mHSPC patients with low-volume PC [18]. However, in the group of PC patients with de novo synchronous OMD or low-volume metastatic disease, the use of various cytoreductive treatments, such as cytoreductive radical prostatectomy (CRP) or external beam radiotherapy (EBRT), can achieve control of localized and potentially distant cancer [2, 19]. Nevertheless, no randomized controlled trials (RCT) have compared the use of CRP versus RT in de novo OM PC and consequently, no evidence supports the recommendation for its use in this setting. Retrospective series analyses suggested the safety and feasibility of CRP and a prolonged overall survival (OS) in selected patients [20–22]. Retrospective data also showed the benefit of adding radical local ablative treatments (as CRP or EBRT) to ongoing systemic androgen deprivation therapy (ADT) [23]. This approach is mainly aimed at treating primary PC tumours and reducing both tumour self-seeding and patients' exposure to systemic agents.

Two RCTs (HORRAD and STAMPEDE) tested the potential of adding prostate EBRT to ADT to improve survival in mPC. In the H arm of the STAMPEDE trial, prostate-targeted RT improved OS in newly diagnosed mPC patients with low-volume disease compared to the use of systemic therapy alone [24], while the HORRAD study found no evidence of OS benefit despite a confirmed improved PSA-progression-free survival (PSA-PFS) [25]. However, a beneficial effect on survival was found in the post hoc analysis of the subgroup of patients with low-volume disease (< 5 bone metastases).

Large RCTs incorporating CRP in the treatment of newly diagnosed mPC patients have not yet reported on the outcomes measured and analysed (Table 1).

In the scenario of oligorecurrent PC, a growing body of evidence suggests a beneficial impact of MDT (as SABR or EBRT) on resistant cancer clones, as these treatments can delay the initiation of androgen receptor (AR)-targeted therapies [26].

Two prospective phase 2 studies, STOMP and ORIOLE, confirmed the high efficacy of MDT in the management of metastases. The STOMP trial results showed a prolonged ADT-PFS, although the impact on OS is still unknown [19, 27, 28]. On the other hand, the ORIOLE trial confirmed higher PFS and distant metastasis-free survival in PC patients with no untreated lesions according to PET-PSMA imaging, compared with patients who received selected metastases-directed SABR based on conventional imaging (CT or bone scan). A retrospective study reported higher rates of ADT-PFS with the use of ⁶⁸Ga-prostate-PSMA PET-CT-guided MDT compared with ¹⁸F-fluorocholine PET-CT-guided MDT [29]. Recently, a prospective study has shown promising results with ¹⁷⁷Lutetium (Lu)-PSMA-617 radioligand therapy in oligorecurrent mHSPC [30], providing additional information on the best imaging techniques to guide MDT.

Systemic multimodal regimens

For decades, the conventional standard of care (SOC) for mPC patients was based on systemic therapy with ADT. The addition of chemotherapy (ChT, docetaxel) to ADT showed improved outcomes [31], as confirmed by the results of the CHAARTED and STAMPEDE docetaxel trials in mHSPC [14, 32, 33] (Table 2) that prompted changes in the SOC of mHSPC patients.

The LATITUDE and STAMPEDE abiraterone trials showed similar substantial survival improvement in selected patients and confirmed a delayed transition of de novo mHSPC to mCRPC after treatment with androgen receptor-signalling inhibitors (ARSi), including abiraterone acetate plus prednisone (AAP), ADT, and docetaxel [34, 35] (Table 2). The risk criteria for the stratification of patients were based on the criteria of high/low-volume disease or high/low risk established in the CHAARTED and LATITUDE studies, respectively. LATITUDE high-risk patients were defined by at least two of the following: ≥ 3 bone metastases (BM), presence of 1–3 visceral metastases, and Gleason score ≥ 8 [34, 35]. High-volume disease was defined in the CHAARTED trial by ≥ 4 BM with ≥ 1 located outside the vertebral column and pelvis along with the presence of visceral lesions, while low-volume disease was defined as non-high-volume disease [14]. According to the CHAARTED criteria that have been widely accepted as prognostic predictors and used as stratification factors in subsequent clinical trials, most OMD patients would

Table 1 Prospective and ongoing randomized controlled clinical trials in cytoreductive prostatectomy to treat primary tumour in de novo hormone-sensitive metastatic prostate cancer (mHSPC) and metastatic prostate cancer (mPC)

	Clinical trial/trial ID	Phase	Inclusion	Study arm	Study arm	Primary end-point	Completion date
Feasibility studies	TRoMbone ISRCTN15704862	NA	De novo OM PC	Standard ST	Standard ST+CRP (including ePLND)	F/S	2018
Local cytoreduction	LOMP II NCT03655886	Phase 2	Newly diagnosed mPC	Standard ST+CRP	Standard ST+EBRT	FR	2022
	FUSCC-PMPCa NCT02742675	Phase 2	OM PC	ADT	ADT+CRP or ERBT	PFS	2023
	g-RAMPP NCT02454543	NA	De novo OM PC	Best ST	Best ST+CRP (including ePLND)	CSS	2026
	SIMCAP NCT03456843	Phase 2	Newly diagnosed mPC	Standard ST	Standard ST+CRP (including ePLND)	FFS	2022
	NCT03988686	NA	OM PC	Standard ST	Standard ST+CRP	TTCR	2022
Multimodal treatments	IP2-ATLANTA ISRCTN58401737	Phase 2	De novo OM PC	1) SOC 2) Standard ST+minimally invasive LAT (including ePLND or MDT) 3) CRP (including ePLND) or EBRT (including PLNRT or MDT)		PFS	2024
	SWOG 1802 NCT03678025	Phase 3	Any M1 on conventional imaging	Standard ST	Standard ST+CRP or EBRT	OS	2028/2031

ADT androgen deprivation therapy, CSS cancer specific survival, EBRT external beam radiotherapy, ePLND extended pelvic lymph node dissection, FFS failure free survival, F/S feasibility and safety, FR feasibility of randomization, MDT metastasis-directed therapy, NA not applicable, OM PC oligometastatic prostate cancer, OS overall survival, PLNRT pelvic lymph node radiotherapy, SOC standard of care, ST systemic therapy, TTCR time to castration resistance

be included into the CHARTED low-volume disease group. A post hoc analysis of the STAMPEDE trial, which used the metastatic burden criteria established in the CHARTED trial, confirmed longer 5-year survival rates with the addition of docetaxel in PC patients with low-burden OMD (72% vs. 34% in patients with high-burden disease) [36].

In the CHARTED trial, the addition of docetaxel to ADT did not provide a benefit in OS in the low-volume subgroup. Exploratory post hoc analysis of the low-volume mHSPC subgroups included in the STAMPEDE, ENZAMET, ARCHES, and TITAN trials suggested an OS benefit with the combination of ARSi (enzalutamide or apalutamide) or with docetaxel and ADT, but none of these trials were designed or powered to specifically answer this question [37–43] (Table 2). Recently, the prospective RCT PEACE-1 (NCT01957436) and ARASENS (NCT02799602) provided evidence that the triplet of ADT plus docetaxel plus ARSi improves OS versus ADT plus

docetaxel in patients with mHSPC. The PEACE-1 trial included only de novo mHSPC, and the subgroup analysis confirmed these results in patients with high-volume disease. No information was available from the ARASENS trial on outcomes in the high- or low-volume subgroups [44, 45].

Treatment challenges in oligoprogressive CRPC

CRPC patients with no metastases (M0 CRPC) who progress to oligometastatic status during SOC treatment with ADT and ARSi (such as enzalutamide, apalutamide or darolutamide) are defined as oligoprogressive PC patients. In mCRPC, different therapeutic strategies may be used [46]. It is still unknown if different radiobiological features can be defined among the variety of OM CRPC scenarios, or if early metastases ablation can affect cancer clonal evolution.

Table 2 Phase 3 randomized controlled trials investigating multimodal approaches with docetaxel or second-generation hormonal treatment in patients with metastatic hormone-sensitive prostate cancer (mHSPC/ mCSPC)

	Clinical trial/ID	HVD/HRD	LVD	Inclusion criteria	Median FUP	Control arm	Study arm	Primary outcomes
Docetaxel	GETUG-AFU 15 NCT00104715 [102, 103]	47.5% HVD	52%	mHSPC	83.9 m	ADT	ADT + DOC	Median OS: 48.6 m vs. 62.1 m (HR 0.88) Median OS in HVD: 35.1 m vs. 39.8 m (HR 0.78) Median OS in LVD: 83.4 m vs. NR (HR 1.02) Median OS: 47.2 m vs. 57.6 m (HR 0.72) Median OS in HVD: 34.4 m vs. 51.2 m (HR 0.72) Median OS in LVD: 63.5 m vs NR Median OS: 71 m vs 81 m (HR 0.78) Median OS in HVD: 35.2 m vs 39.9 m (HR 0.81) Median OS in LVD: 76.7 m vs. 93.2 (HR 0.76) Median OS: 34.7 m vs. NR (HR 0.62) Median rPFS: 14.8 m vs. 33 m (HR 0.47) Median OS at 51.8 (HR 0.66)
	CHAARTED NCT00309985 [14, 33]	65% HVD in DOC group	35%	mHSPC	53.7 m	ADT	ADT + DOC	
	STAMPEDE- Docetaxel NCT00268476 [32, 36]	43% HVD	33%	Newly diagnosed PC (HRD, locally advanced or mHSPC)	43 m	ADT	ADT plus DOC plus prednisone	
Abiraterone	LATITUDE NCT01715285 [34, 35]	100% 79.6%HRD	–	mHSPC	30.4 m	ADT	ADT + abiraterone + prednisone	
	STAMPEDE Abiraterone NCT00268476 [104]	Not reported	–	Newly diagnosed PC (HRD, locally advanced or mHSPC)	40 m	ADT	ADT + abiraterone + prednisone	3-year OS: 76% vs. 83% (HR 0.63)

Table 2 (continued)

Clinical trial/ID	HVD/HRD	LVD	Inclusion criteria	Median FUP	Control arm	Study arm	Primary outcomes
Enzalutamide ENZAMET NCT02446405 [39]	48% HVD	44%	mHSPC	34 m	ADT+NSAA (±DOC)	ADT + enzalutamide (±DOC)	3-year OS: 72% vs. 80% (HR 0.67) Proportion alive at 3 years in HVD: 0.64 vs. 0.71 Proportion alive at 3 years in LVD: 0.82 vs. 0.90
ARCHES NCT02677896 [41, 42]	63% HVD	37%	De novo and oligo-recurrent mHSPC	14.4 m	ADT	ADT + enzalutamide	Median rPFS: 19 m vs. NR (HR 0.39) Median rPFS in HVD: 13.8 m vs. NR Median rPFS in LVD: 22.1 m vs. NR
Apalutamide TITAN NCT02489318 [37, 38]	63% HVD	37.3%	mHSPC	24 m	ADT	ADT + apalutamide	Median OS: 73.5% vs. 82.4% (HR 0.67) Median rPFS: 47.5% vs. 68.2% (HR 0.48) Median PFS in HVD: 14.9 m vs. NE (HR 0.53) Median PFS in LVD: 30.5 m vs. NE (HR 0.36)

Primary outcomes in patients with low-volume disease are highlighted in bold

ADT androgen deprivation therapy, DOC docetaxel, HR hazard ratio, HRD high-risk metastatic disease, HVD high-volume disease, LVD low-volume disease, m months, mHSPC metastatic hormone-sensitive prostate cancer, NR not reached, NSAA conventional non-steroidal anti androgen, OS overall survival, PC prostate cancer, rPFS radiographic progression-free survival

Locoregional treatments and multimodal regimens

Oligoprogressive CRPC remains an incurable disease with a life expectancy of only 2–3 years, and specialists have not yet agreed on a therapeutic approach [47]. The safety and feasibility of SABR in oligorecurrent and oligoprogressive CRPC is supported by retrospective studies [26, 48, 49]. In oligoprogressive CRPC patients, Triggiani and cols (2019) confirmed a 2-year distant PFS (D-PFS) of 21.6% and a median 2-year systemic treatment-free survival of 41.3 months [48].

The prospective multicentre phase 2 SBRT-SG 05 (NCT02192788) trial showed that the association of SBRT and ADT in oligorecurrent HSPC and CRPC patients was safe and provided favourable clinical outcomes in both subgroups of patients. Specifically in CRPC, after a median follow-up of 41 months, 42.9% of patients were free from disease progression at last follow-up, with no need to start ARSi [50]. The application of SBRT during the interruption of systemic hormone therapy confirmed a local control (LC) rate of 100% and a biochemical control rate of 97.5% [51].

Finally, in previously treated mCRPC patients, the randomized phase 2 SABR-COMET trial showed that the use of SABR in a limited number of PC patients receiving SOC increased both PFS and OS with optimal safety and toxicity when compared with SOC alone [52].

Several ongoing clinical trials will provide relevant information on the potential of combined regimens with local therapies, SBRT, and hormonal therapies, and on the outcomes obtained after therapy intensification in oligorecurrent CRPC [53] (Table 3).

The expert view

Advances made in recent years in the field of mHSPC now allow us to offer multiple alternatives for the systemic treatment of this disease. The role of treatment of the primary

tumour (with radiation therapy) is clearly relevant in the setting of low-tumour-burden mHSPC. Pending results from larger ongoing surgical studies, the results of the H arm of the STAMPEDE study confirmed a statistically significant benefit, according to CHARTED criteria, of 8% in overall 3-year survival in patients with low-tumour volume who received radiation therapy to the primary tumour. Although this differentiation of patients with low- or high-tumour volume was not specified as a stratification factor in the original study design, a subsequent in-depth analysis showed that it could be considered as such for all purposes. The authors concluded that radiation therapy to the primary tumour should be considered the new SOC in low-volume mHSPC, as this strategy did not increase local symptomatic events in treated patients. This indication in turn raises some uncertainty as to the extent of the benefit of this treatment in patients who also receive systemic treatment with docetaxel or abiraterone acetate, enzalutamide or apalutamide, since only 18% of patients in the H arm of the STAMPEDE study received chemotherapy and none received ARSi. A conclusive response to this question is expected once the final results of the PEACE-1 study evaluating the role of RT are published (NCT01957436).

As previously discussed, the combination of ADT with docetaxel, abiraterone, enzalutamide or apalutamide prolongs OS in the entire HSPC patient population. Although no formal subgroup analysis was planned in these studies, the magnitude of the benefit of these combinations seems to be more evident in patients with synchronous high-volume disease, but there is also evidence of a benefit in the low-volume subpopulation. Based on exploratory retrospective pooled analysis of these studies, some authors recommend that the use of new hormonal agents and MDT should be considered in the setting of OMD [54], particularly in the context of clinical trials that evaluate the role of both systemic and local MDT in this scenario. These trials should define the role of MDT in the treatment of OMD, as well

Table 3 Ongoing clinical trials in PC patients

Clinical Trial/Trial ID	Trial design	Inclusion criteria	Study arm	Study arm	Primary endpoint	Completion date
ARTO NCT03449719	Phase 2	mCRPC	Abiraterone acetate	Abiraterone acetate ± SABR	PSA response rate	2022
PILLAR NCT03503344	Phase 2	mCRPC	Best ST	Best ST plus CRP or RT	PSA response rate	2023
PEACE-V NCT03569241	Phase 2	Oligorecurrent PC	ADT + MDT (including PLND or SABR)	ADT + MDT (including PLND or SABR) + WPRT	Metastasis-FS	2023
NCT03902951	Phase 2	Oligorecurrent PC		ADT + abiraterone acetate + apalutamide + SABR	PSA response rate	2023
PCS IX NCT02685397	Phase 2/3	Oligorecurrent mCRPC	ADT + enzalutamide	ADT + enzalutamide + SABR	rPFS	2025
START-MET NCT05209243	Phase 3	mHSPC	ADT + ARSi + EBRT	ADT + ARSi + EBRT + SBRT	rPFS	2025

ADT androgen deprivation therapy, ARSi androgen receptor-signalling inhibitor, EBRT external beam radiotherapy, FS free survival, mCRPC metastatic castration-resistant prostate cancer, mHSPC metastatic hormone-sensitive prostate cancer, MDT metastasis-directed therapy, PC prostate cancer, PLND pelvic lymph node dissection, rPFS radiographic progression-free survival, ST systemic treatment, PSA prostate-specific antigen, SABR stereotactic ablative radiotherapy, SBRT stereotactic body radiation therapy, WPRT whole pelvic radiotherapy

as the need for, and optimal duration of, systemic therapy for the management of OMD. The recommended objectives of these trials should be time to radiographic progression, clinical progression, OS and QoL. Well-designed trials with stratification and an adequate number of patients, as well as a multidisciplinary approach are strongly recommended to achieve these goals.

A summary of current recommendations on the management of OMD in PC is presented in Table 4.

Oligometastatic disease in colorectal cancer

Around 50% of colorectal cancer (CRC) patients will develop metastases (M1), whether synchronous or metachronous, from the primary tumour [55]. Most CRC metastases develop in the liver and the lung [56]. The therapeutic approach currently consists of systemic treatments and achieves a median OS of approximately 2 years [57, 58]. Available imaging techniques for OM CRC detection include ultrasound, CT, MRI, and PET/CT, modalities that offer varying grades of sensitivity. In this clinical context, PET/CT has become a useful diagnostic tool due to its higher specificity and ability to rule out extrahepatic disease (EHD). It is also useful when combined with CT or MRI for evaluating the resectability of metastatic lesions, especially liver metastases (LM) [59–62]. As a variety of factors influence the diverse presentations of OMD, a proper prognostic algorithm for OM CRC might also consider patient characteristics (such as ECOG or comorbidities), tumour burden (including number, locations and size of M1), and the biological features of the cancer (CRC mutational status).

RAS and *BRAF* gene mutations have been negatively associated with PFS, OS, and recurrence-free survival after LM resection [63], and define a cohort of CRC patients with poor prognosis, for whom hepatectomy may be discarded and alternative systemic therapies must be considered. In a

study that included 134 CRC patients with OM in the liver, three robust subtypes of de novo metastatic CRC (mCRC) were identified using integrative molecular analysis. These subtypes showed clearly different outcomes with differential 10-year OS rates ranging from 19 to 94%, helping identify patients who might benefit from a primary therapeutic modality (based on one or more focal treatments of limited metastases) or the use of systemic therapies with or without regional approaches [64]. This trial provided interesting evidence that supported the biological basis of curable OM CRC and the inclusion of tumour molecular profiling as a crucial prognostic tool that could help clinicians when making everyday clinical decisions.

The randomized phase 3 KEYNOTE-177 trial showed that the use of first-line immunotherapy in a subgroup of newly diagnosed mCRC patients with high microsatellite instability and mismatch-repair deficiency (MSI/dMMR) significantly improved PFS when compared with ChT with or without immunotherapy (16.5 vs. 8.2 months), with around 60% of patients surviving at 5 years from M1 diagnosis [65]. These results supported the prognostic utility of molecular profiling, but also suggested the potential benefits of combining local ablative and systemic treatments in order to significantly increase “long-term” survival in this patient population.

Treatment alternatives in oligometastatic CRC

Locoregional treatments and multimodal regimens

Surgery Based on radiological imaging using established parameters, only 20% of mCRC patients have resectable LM at diagnosis [66, 67]. Thus, patients might be classified as fit or unfit for LM resection and, depending on each context, different strategies and therapeutic approaches must be offered [68]. Complete surgical resection (R0) of LM in

Table 4 Summary of recommendations on the management of OMD in prostate and colorectal cancer

Recommendations
1. Multidisciplinary tumour boards might guide treatment decisions
Prostate Cancer
2. In PC patients with OMD, we recommend the maintenance of ST while primary tumour is locally treated
3. Adding MDT to ST in patients with OMD seems to be a reasonable option, particularly in the context of prospective clinical trials, whenever possible
4. For the great majority of mHSPC patients, ADT alone is no longer the SOC
Colorectal Cancer
5. In CRC patients, the most useful tools for a proper and individualized therapeutic decision making are as follows: radiologic response to previous ST, tumour biology, location and size of metastases, the time of OMD presentation with respect to the primary tumor, clinically relevant comorbidities, primary tumour’s feasibility treatment and ECOG PS
6. In CRC patients with OMD, ST is the preferred option to achieve a global disease control
7. In OM CRC patients, the combination of local MDT (TAT; SABR) with ST is an option that may be evaluated in selected patients. It is crucial to maintain the use of ST while tumours are under local MDT

selected CRC patients provides higher 5-year survival rates (40%–50%) than systemic treatment alone [69, 70]. Long-term survival rates after LM resection may be affected negatively by several factors, including the presence of positive margins after primary tumour resection, synchronous OMD or metachronous OMD with a DFI < 12 months, > 4 LM tumours, or high serum levels of carcinoembryonic antigen (CEA) are well established prognostic factors. Moreover, in large mCRC series, patients, who achieved partial or complete response to prior ChT showed better outcomes after LM resection [71].

Resection of extrahepatic metastases may lead to 35% 5-year survival rates, confirming that patients with LM or extrahepatic disease (EHD) undergoing metastasectomy could also achieve comparable survival benefits [72]. In other scenarios with worse prognosis and evolution, such as peritoneal carcinomatosis, outcomes from surgical resection are sometimes better than those obtained with systemic therapy alone in selected cases [73].

Surgery and perioperative chemotherapy Recurrence after surgery may occur due to persistent microscopic residual disease. In this situation, the use of perioperative ChT achieves longer CRC survival. The randomized phase 3 EORTC 40,983 trial confirmed longer PFS and treatment-free intervals in CRC patients with resectable LM who received perioperative oxaliplatin and fluoropyrimidine-based ChT compared with surgery alone [74]. OS was also longer, although not statically significantly, in the perioperative ChT group compared to the surgery group. A meta-analysis of 18 studies with more than 6,000 mCRC patients also confirmed that neoadjuvant ChT prior to hepatic resection can improve survival outcomes [75]. Based on these results, clinical guidelines for CRC management recommended this multimodal approach with perioperative ChT as the SOC of mCRC patients with resectable LM [62].

Radiofrequency ablation and microwave ablation The ESMO consensus clinical guidelines recommend the use of other alternatives to surgery, in combination with systemic therapies if needed [62]. Image-guided percutaneous thermal ablative therapies (TAT) that include radiofrequency ablation (RFA) or microwave ablation (MWA) emerged as effective alternatives for the treatment of unresectable LM. Results of the randomized phase 2 CLOCC trial, that included more than 119 mCRC patients with unresectable LM, showed that the combined use of RFA with systemic therapy (with/without surgical resection) yields significantly higher survival rates than ChT alone [76].

In the absence of RCTs that directly compare the efficacy and safety of TAT versus surgery, most evidence comes from retrospective analyses. Although no evidence has yet supported any significant benefit with TAT versus surgery, a

similar long-term benefit of TAT in lesions < 3–4 cm has been reported, with 5-year OS rates of 40%–50% [77–80]. A recent observational study that recruited > 400 OM CRC patients to compare the efficacy of R0 LM resection compared to complete TAT of resectable/ablative lesions ≤ 5 cm, showed longer PFS after surgical resection of metastatic lesions > 3 cm in high-risk patients. Nevertheless, the use of both approaches to treat LM ≤ 3 cm achieved comparable liver PFS [81]. More recently, similar efficacy results have been reported after TA of CRC lung metastases (≤ 2 lesions of ≤ 2 cm). The reported 5-year OS rate was higher than 30%–40%, and median OS ranged from 33 to 68 months [82]. In this study, high CEA levels and a DFI < 12 months were negative survival prognostic factors. Altogether, these results suggest that TA of pulmonary and liver metastases could lead to optimal long-term LC.

SABR

The randomized phase 2 SABR-COMET trial demonstrated longer OS and PFS in the subset of OM CRC patients undergoing SABR compared with palliative SOC [52]. Based on accumulating evidence, current clinical guidelines recommend the use of SABR as an alternative therapeutic approach for the management of OM in mCRC patients [62, 68, 83]. Despite the lack of consensus on the optimal dose and fractionation, retrospective data suggest that the efficacy of SABR on LC may be influenced by the dose escalation schedule, which should be planned taking into account the number and volume of target lesions. Higher LC and OS rates have been reported in high-volume tumours (≥ 40 cm³) after irradiation with a biologically effective dose (BED) > 100 Gy [84].

A systematic review of SABR efficacy in the treatment of liver and lung metastases in cohorts of CRC patients reported 2-year OS rates of 65%–76% and a median PFS of 9–14 months for lung metastases, and 2-year OS rates of 26%–83% and median PFS of 10.8–34.4 months for LM, along with low toxicity [85]. Several prospective phase 1 and 2 studies reported similar results with 2-year OS rates of 30%–83% [86]. The delivery of SABR to LNM has shown superior clinical outcomes than in visceral metastases, with higher 1-year LC rates, and improved PFS when pelvic and extrapelvic LNM are targeted [87].

Spinal metastases can be detected in advanced stages of mCRC. Most of the studies that evaluated SABR efficacy in vertebral metastases included patients with different cancer histologies and used highly hypofractionated irradiation or radiosurgery with a single dose of irradiation [88]. The most common fractionation schemes have achieved 2-year LC rates of 82%–96% [89]. In selected patients with no vertebral compression (Bilsky grade 0–Ib), radioresistant histopathology, estimated survival > 6 months, and Karnofsky

performance status (KPS) > 70, SABR to vertebral metastases yielded high rates of pain control (around 85%) and radiological responses (90%). Delivery of high SABR BED to the spine resulted in prolonged LC, and palliative pain relief was reported in both spinal and non-spinal metastases [90–92].

There are no direct comparisons of efficacy of SABR with other local approaches in OM CRC. Only two studies that included mCRC patients with unresectable LM treated with RFA or SRS/SABR (according to the characteristics of lesions) reported higher 1- and 2-year LC rates with SRS/SABR compared to RFA, especially in lesions ≥ 2 –3 cm. Nevertheless, no significant differences in OS or toxicity were found [93, 94]. A recent meta-analysis has confirmed high LC associated with the use of SABR on LM [95].

Cost-effectiveness and maintaining good QoL in CRC patients are other key factors to consider at the time of therapeutic decision-making [96]. Cumulative evidence has shown that the safety and tolerability of SABR confers good QoL in mCRC patients with LM [96]. Moreover, the cost-effectiveness of this approach makes it an optimal alternative to standard therapies [97, 98].

The expert view

Many years of clinical experience support the efficacy of surgical resection as the standard approach to manage OM CRC. Surgery offers many advantages including access to tissue samples for biopsy and an optimal visualization of the metastatic lesions or affected organs, favouring accurate diagnosis. However, its invasive nature means patient recovery times are longer and morbidity is higher than with ART. Although currently available data, coming mainly from clinical series and small phase II trials, are limited, ART offers long-term LC and longer PFS, and the low number of associated side effects allow patients to continue simultaneous systemic treatments. From a palliative point of view, ART in mCRC with multiple M1 also improves some common disease-related symptoms, such as pain. However, the time to response to ART is longer when compared with surgical resection, and close follow-up with regular radiological testing is required. In this scenario, ART can play a crucial role in the treatment of all OM or recurrences not amenable to surgical resection, offering high efficacy, an interesting safety profile, and preserved QoL. Further clinical studies will evaluate intensification therapies and new clinical tools that help specialists evaluate the response to ST and improve the selection of patients suitable for treatment with ART.

Percutaneous and image-guided RFA or MWA are minimally invasive techniques that have a similar efficacy to SABR, as confirmed in retrospective clinical series. The efficacy of RFA and SABR depends mainly on the size and location of target lesions, as well as the energy delivered.

With these alternatives it is important to consider certain technical and anatomical aspects to minimize side effects or avoid potential damage in adjacent tissues or blood vessels. Another detrimental factor to bear in mind is the potential cell cancer seeding in intravascular locations due to the trajectory of catheter during the RFA procedure.

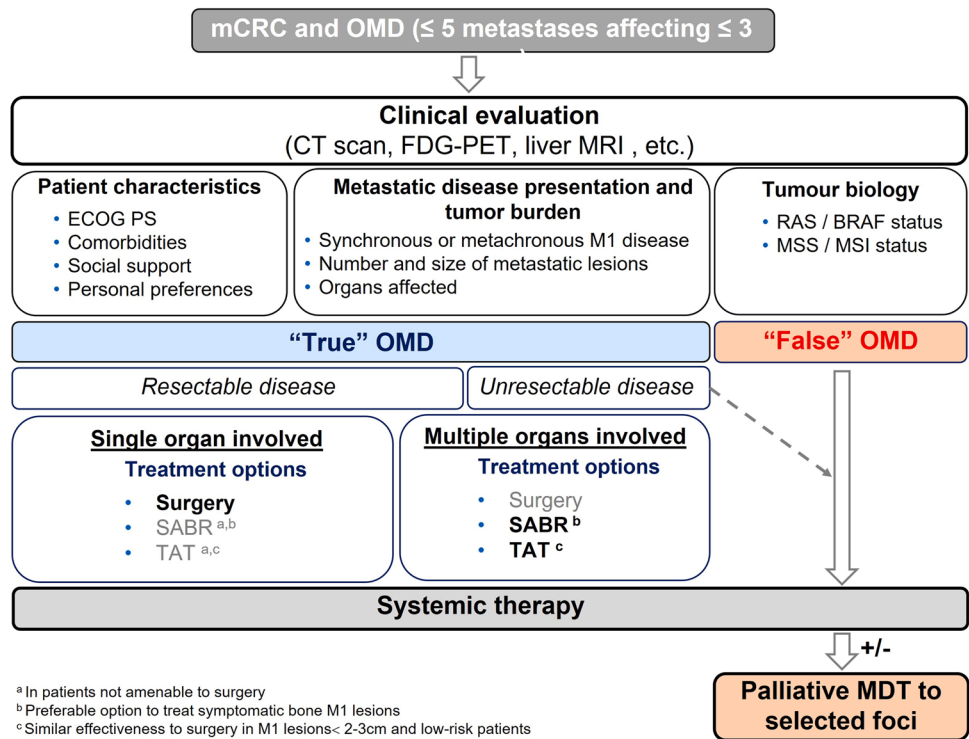
In this clinical context, then, patient selection is a crucial step towards optimizing long-term results and minimizing potential side effects. The expert should examine multiple scenarios with different prognosis, therapeutic approaches, and outcomes to select the most optimal therapeutic alternative for oligorecurrent versus oligoprogressive or even widespread mCRC (Fig. 1):

- (1) First, a complete diagnostic analysis and metastatic work-up with imaging (body-TC, FDG-PET and sometimes liver MRI can be helpful in this sense) are essential to establish the tumour burden (number and size of M1, organs involved, etc.) and to determine if there is a true oligometastatic or pseudo-oligometastatic disease that has already disseminated with undetected M1 (“false OMD”). In the first scenario, LC is crucial. Thus, local therapeutic approaches (such as surgery or metastases-directed therapies, TAT or SABR, depending on patient and disease characteristics) generally combined with systemic therapies are key to achieving a long-term OS or even cure. However, in patients with “false OMD”, systemic therapy is the preferred option for achieving global disease control, while local therapies with palliative intent may be only considered in selected cases.
- (2) Classical clinical prognostic scales [99] and some individual factors, such as radiologic response to previous systemic therapy [71] or tumour biology profile (as RAS/BRAF mutational status) [63, 100], are probably as useful as the patient’s general status (ECOG) and presence of clinically relevant comorbidities when selecting the optimal therapeutic approach for each patient.
- (3) The feasibility of primary tumour control is also crucial for decision-making. The time of OMD presentation, whether synchronous or metachronous with primary tumour, is an important factor as these two clinical presentations have different prognosis (synchronous OM CRC is well established as a negative prognosis factor).

Finally, given the complexity of OM CRC, multidisciplinary tumour committees are an essential tool to appropriately guide treatment decisions [101].

A summary of recommendations on the management of OMD in CRC is presented in Table 4.

Fig. 1 Proposed therapeutic algorithm for OM CRC patients with different presentations of metastatic disease. *CT* computed tomography, *ECOG PS* ECOG performance status, *MDT* metastasis-directed therapy, *MRI* magnetic resonance imaging, *MSI* microsatellite instability, *MSS* microsatellite stable, *OMD* oligometastatic disease, *PET* positron emission tomography, *SABR* stereotactic ablative radiotherapy, *TAT* thermal ablative therapy



Conclusions

OM patients have been acknowledged as a defined group that, due to their better prognosis, can be classified separately from multimetastatic patients, and it has been determined that local therapies improve not only PFS but also OS in this group. Consequently, this approach should be always considered and analysed in this clinical setting. Systemic treatment is still the cornerstone intervention in most metastatic patients, while recent developments in molecular selection of therapies have yielded encouraging results. The combination of local therapies with systemic therapies may then confer a clinically significant survival advantage.

Local ablative therapies such as TA and MWA are minimal invasive techniques that are highly effective and safe and associated with a short recovery time. However, local control achieved with these approaches may be limited by the size or location of the metastases.

ARTs are non-invasive and have demonstrated a high level of disease control and safety. Their main advantages include the fact that they can be applied to different solid organs at the same time (including bone or CNS) and their apparent cost-effectiveness.

Given that the combination of systemic and local treatments could provide clinically relevant survival benefits in selected patients, in the context of OMD, we recommend maintaining the indication for systemic treatment while the primary tumour is treated locally. The management of OM PC and CRC should be led by a multidisciplinary team in

order to optimize the choice of all available alternatives and improve efficacy, based on the individual patient’s performance status, tumour molecular characteristics, and location and size of the metastases, among other factors.

Acknowledgements The authors would like to thank Dr Álvaro Rodríguez-Lescure (former president of SEOM) and Dr Jorge Contreras Martínez (former president of SEOR) who facilitated the organization of the “I Jornada Virtual de Consenso SEOM-SEOR sobre el Abordaje Multidisciplinar de la Enfermedad Oligometastásica”, and Dr Juan de la Haba Rodríguez. (SEOM), Dr. Manel Algara López (SEOR), Dr Ana Fernández Montes (SEOM), and Dr Carmen Rubio Rodríguez (SEOR) for their valuable contribution as moderators of the sessions. The authors would like to thank Dr Susana Cañón-Sánchez (from Statistics Consulting S.L., Valencia, Spain) for providing scientific support and medical writing services.

Author contributions All authors were involved in the conception of this work, drafting and/or revising the manuscript, and approved the final version.

Funding This work was funded by SEOR and SEOM.

Availability of data and material Not applicable.

Declarations

Conflict of interest JAA has received speaker honoraria from Astellas Pharma, Pfizer and Bristol-Myers Squibb, and consultancy fees from Pfizer, Astellas Pharma, Janssen-Cilag, MSD Oncology, BMS, Merck, AstraZeneca, Bayer, Eisai and Novartis. AGdA, has received research funding from Astellas, travel grants from Astellas, Jansen, Sanofi, BMS, Roche, Pfizer, MSD and Ipsen; and honoraria for speaking engagements, membership of advisory boards and continuing medical education from Janssen, Astellas, Sanofi, Bayer, Roche, Ip-

sen, BMS, MSD, Pfizer, Merck, Eusa Pharma, Eisai and Astra Zeneca. JdCC has received consultancy fees from AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Hoffmann-La Roche and Takeda; RCh-S, has received honoraria for speaking engagements from Astrazeneca, Fresenius-Kabi, Grunenthal and Adventia Pharma; and declares financial relationship with Fresenius-Kabi and Adventia Pharma. EFF has received consultancy honoraria from Amgen, Astrazeneca, Bayer, Bristol Myers Squibb, Daiichi Dankyo, Eli Lilly, F. Hoffmann-La Roche, Glaxo Smith Kline, Janssen, Merck Sharp and Dome, Merck Serono, Novartis, Peptomyc, Pfizer, Sanofi and Takeda and speaker honoraria from Amgen, Astrazeneca, Bristol Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Janssen, Medscape, Merck Sharp and Dome, Peervoice, Pfizer, Medical Trends, Merck Serono, Sanofi, Takeda and TouchOncology. All other authors declare no relevant financial or non-financial interests to disclose.

Informed consent For this type of study formal consent is not required.

Ethical approval This article does not contain any studies with human participants or animal performed by any of the authors.

References

- Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13(1):8–10.
- Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol*. 2011;8(6):378–82.
- 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*. 2020;148:157–66.
- Olson RA, Jiang W, Liu MC, Bergman A, Schellenberg D, Mou B, et al. Population based phase II trial of stereotactic ablative radiotherapy (SABR) for up to 5 oligometastases: preliminary results of the SABR-5 trial. *Int J Radiat Oncol Biol Phys*. 2021;111(3):S4.
- Palma DA, Olson R, Harrow S, Correa RJM, Schneiders F, Haasbeek CJA, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of 4–10 oligometastatic tumors (SABR-COMET-10): study protocol for a randomized phase III trial. *BMC Cancer*. 2019;19(1):816.
- 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(1):e18–28.
- Szturcz P, Nevens D, Vermorken JB. Oligometastatic disease management: finding the sweet spot. *Front Oncol*. 2020;10(2872):617793.
- Salama JK, Milano MT. Radical irradiation of extracranial oligometastases. *J Clin Oncol*. 2014;32(26):2902–12.
- Palma D, Senan S. Stereotactic radiation therapy: changing treatment paradigms for stage I nonsmall cell lung cancer. *Curr Opin Oncol*. 2011;23(2):133–9.
- Rusthoven KE, Hammerman SF, Kavanagh BD, Birtwhistle MJ, Stares M, Camidge DR. Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? *A Patterns Fail Anal Acta Oncol*. 2009;48(4):578–83.
- Rusthoven KE, Kavanagh BD, Cardenes H, Stieber VW, Burri SH, Feigenberg SJ, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol*. 2009;27(10):1572–8.
- de Vin T, Engels B, Gevaert T, Storme G, De Ridder M. Stereotactic radiotherapy for oligometastatic cancer: a prognostic model for survival. *Ann Oncol*. 2014;25(2):467–71.
- Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet*. 2004;363(9422):1665–72.
- Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. *J Clin Oncol*. 2018;36(11):1080–7.
- Perera M, Papa N, Christidis D, Wetherell D, Hofman M, Murphy D, et al. Effect of PSA on diagnostic yield of 68Ga-PSMA PET in advanced prostate cancer: a systematic review and meta-analysis. *Eur Urol Suppl*. 2016;15(12):e1540.
- Mottet N, Cornford P, van den Bergh, R.C.N., Briers, E., UOMO), E.P.A.E.P.C.C.E., De Santis, M., et al., *EAU Guidelines*. <https://uroweb.org/guidelines/2019>. 2019.
- Crawford ED, Koo PJ, Shore N, Slovin SF, Concepcion RS, Freedland SJ, et al. A clinician's guide to next generation imaging in patients with advanced prostate cancer (RADAR III). *J Urol*. 2019;201(4):682–92.
- 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(2):263–82.
- Radwan N, Phillips R, Ross A, Rowe SP, Gorin MA, Antonarakis ES, et al. A phase II randomized trial of observation versus stereotactic ablative radiation for oligometastatic prostate cancer (ORIOLE). *BMC Cancer*. 2017;17(1):453.
- Gratzke C, Engel J, Stief CG. Role of radical prostatectomy in metastatic prostate cancer: data from the Munich cancer registry. *Eur Urol*. 2014;66(3):602–3.
- Sooriakumaran P, Karnes J, Stief C, Copsey B, Montorsi F, Hammerer P, et al. A multi-institutional analysis of perioperative outcomes in 106 men who underwent radical prostatectomy for distant metastatic prostate cancer at presentation. *Eur Urol*. 2016;69(5):788–94.
- Leyh-Bannurah SR, Gazdovich S, Budaus L, Zaffuto E, Briganti A, Abdollah F, et al. Local therapy improves survival in metastatic prostate cancer. *Eur Urol*. 2017;72(1):118–24.
- Rusthoven CG, Jones BL, Flaig TW, Crawford ED, Koshy M, Sher DJ, et al. Improved survival with prostate radiation in addition to androgen deprivation therapy for men with newly diagnosed metastatic prostate cancer. *J Clin Oncol*. 2016;34(24):2835–42.
- Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet*. 2018;392(10162):2353–66.
- Boeve LMS, Hulshof M, Vis AN, Zwiderman AH, Twisk JWR, Witjes WPJ, et al. Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: data from the HORRAD trial. *Eur Urol*. 2019;75(3):410–8.
- Triggiani L, Alongi F, Buglione M, Detti B, Santoni R, Bruni A, et al. Efficacy of stereotactic body radiotherapy in oligorecurrent and in oligoprogressive prostate cancer: new evidence from a multicentric study. *Br J Cancer*. 2017;116:1520–5.

27. Ost P, Reynders 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*. 2018;36(5):446–53.
28. 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(5):650–9.
29. Mazzola R, Francolini G, Triggiani L, Napoli G, Cuccia F, Nicosia L, et al. Metastasis-directed therapy (SBRT) guided by PET-CT (18)F-CHOLINE versus PET-CT (68)Ga-PSMA in Castration-sensitive oligorecurrent prostate cancer: a comparative analysis of effectiveness. *Clin Genitourin Cancer*. 2021;19(3):230–6.
30. Prive BM, Peters SMB, Muselaers CHJ, van Oort IM, Janssen MJR, Sedelaar JPM, et al. Lutetium-177-PSMA-617 in low-volume hormone-sensitive metastatic prostate cancer: a prospective pilot study. *Clin Cancer Res*. 2021;27(13):3595–601.
31. Gonzalez Del Alba A, Mendez-Vidal MJ, Vazquez S, Castro E, Climent MA, Gallardo E, et al. SEOM clinical guidelines for the treatment of advanced prostate cancer (2020). *Clin Transl Oncol*. 2021;23(5):969–79.
32. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multi-arm, multistage, platform randomised controlled trial. *Lancet*. 2016;387(10024):1163–77.
33. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373(8):737–46.
34. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352–60.
35. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2019;20(5):686–700.
36. Clarke NW, Ali A, Ingleby FC, Hoyle A, Amos CL, Attard G, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. *Ann Oncol*. 2019;30(12):1992–2003.
37. Chi KN, Agarwal N, Bjartell A, Chung BH, de Santana Gomes AJP, Given R, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2019;381(1):13–24.
38. Chi KN, Chowdhury S, Bjartell A, Chung BH, de Santana Gomes AJP, Given R, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. *J Clin Oncol*. 2021;39(20):2294–303.
39. Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med*. 2019;381(2):121–31.
40. Hoyle AP, Ali A, James ND, Cook A, Parker CC, de Bono JS, et al. Abiraterone in “high-” and “low-risk” metastatic hormone-sensitive prostate cancer. *Eur Urol*. 2019;76(6):719–28.
41. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2019;37(32):2974–86.
42. Azad AA, Armstrong AJ, Alcaraz A, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, et al. Efficacy of enzalutamide in subgroups of men with metastatic hormone-sensitive prostate cancer based on prior therapy, disease volume, and risk. *Prostate Cancer Prostatic Dis*. 2022;25(2):274–82.
43. Armstrong AJ, Azad AA, Iguchi T, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, et al. Improved survival with enzalutamide in patients with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2022;40(15):1616–22.
44. Fizazi K, Carles Galceran J, Foulon S, Roubaud G, McDermott R, Fléchon A, et al. LBA5 A phase III trial with a 2x2 factorial design in men with de novo metastatic castration-sensitive prostate cancer: overall survival with abiraterone acetate plus prednisone in PEACE-1. *Ann Oncol*. 2021;32:S1299.
45. Smith MR, Hussain M, Saad F, Fizazi K, Sternberg CN, Crawford ED, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med*. 2022;386(12):1132–42.
46. Gómez-Caamaño A, González-San Segundo C, Henriquez I, Maldonado X, Zapatero A. Consensus on management of castration-resistant prostate cancer on behalf of the urological tumours working group (URONCOR) of the Spanish society of radiation oncology. *Clin Transl Oncol*. 2019;21(4):420–32.
47. Gillessen S, Armstrong A, Attard G, Beer TM, Beltran H, Bjartell A, et al. Management of patients with advanced prostate cancer: report from the advanced prostate cancer consensus conference 2021. *Eur Urol*. 2022;82(1):115–41.
48. Triggiani L, Mazzola R, Magrini SM, Ingrosso G, Borghetti P, Trippa F, et al. Metastasis-directed stereotactic radiotherapy for oligoprogressive castration-resistant prostate cancer: a multicenter study. *World J Urol*. 2019;37(12):2631–7.
49. Yoshida S, Takahara T, Arita Y, Ishii C, Uchida Y, Nakagawa K, et al. Progressive site-directed therapy for castration-resistant prostate cancer: localization of the progressive site as a prognostic factor. *Int J Radiat Oncol Biol Phys*. 2019;105(2):376–81.
50. Conde-Moreno AJ, Lopez F, Hervas A, Morillo V, Mendez A, Puertas MDM, et al. Phase II trial of SBRT and androgen deprivation for oligometastases in prostate cancer. *Int J Radiat Oncol Biol Phys*. 2021;111(3):S59.
51. Conde-Moreno AJ, Lopez F, Hervas A, Morillo V, Mendez A, Puertas MDM, et al. Phase II trial of SBRT and androgen deprivation for oligometastases in prostate cancer. *Int J Radiat Oncol Biol Phys*. 2021;111(3S):S59.
52. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. *J Clin Oncol*. 2020;38(25):2830–8.
53. G.A.P consortium, De Bruycker A, Tran PT, Achtman AH, Ost P. Clinical perspectives from ongoing trials in oligometastatic or oligorecurrent prostate cancer: an analysis of clinical trials registries. *World J Urol*. 2021;39(2):317–26.
54. Sweeney CJ, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Overall survival of men with metachronous metastatic hormone-sensitive prostate cancer treated with enzalutamide and androgen deprivation therapy. *Eur Urol*. 2021;80(3):275–9.
55. Leporrier J, Maurel J, Chiche L, Bara S, Segol P, Launoy G. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. *Br J Surg*. 2006;93(4):465–74.
56. Vatandoust S, Price TJ, Karapetis CS. Colorectal cancer: metastases to a single organ. *World J Gastroenterol*. 2015;21(41):11767–76.
57. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Kaiser F, Al-Batran SE, et al. FOLFIRI plus cetuximab or bevacizumab for advanced colorectal cancer: final survival and per-protocol

- analysis of FIRE-3, a randomised clinical trial. *Br J Cancer*. 2021;124(3):587–94.
58. Venook AP, Niedzwiecki D, Lenz H-J, Innocenti F, Mahoney MR, O'Neil BH, et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). *J Clin Oncol*. 2014;32(18 suppl):LBA3–LBA3.
 59. Floriani I, Torri V, Rulli E, Garavaglia D, Compagnoni A, Salvolini L, et al. Performance of imaging modalities in diagnosis of liver metastases from colorectal cancer: a systematic review and meta-analysis. *J Magn Reson Imaging*. 2010;31(1):19–31.
 60. Ramos E, Martinez L, Gamez C, Torras J, Valls C, Rafecas A, et al. Use of PET-CT in pre-surgical staging of colorectal cancer hepatic metastases. *Cir Esp*. 2008;84(2):71–7.
 61. Maffione AM, Lopci E, Bluemel C, Giammarile F, Herrmann K, Rubello D. Diagnostic accuracy and impact on management of (18)F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. *Eur J Nucl Med Mol Imaging*. 2015;42(1):152–63.
 62. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386–422.
 63. Modest DP, Ricard I, Heinemann V, Hegewisch-Becker S, Schmiegel W, Porschen R, et al. Outcome according to KRAS-, NRAS- and BRAF-mutation as well as KRAS mutation variants: pooled analysis of five randomized trials in metastatic colorectal cancer by the AIO colorectal cancer study group. *Ann Oncol*. 2016;27(9):1746–53.
 64. Pitroda SP, Khodarev NN, Huang L, Uppal A, Wightman SC, Ganai S, et al. Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. *Nat Commun*. 2018;9(1):1793.
 65. Andre T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383(23):2207–18.
 66. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg*. 2004;240(4):644–57.
 67. Pawlik TM, Choti MA. Surgical therapy for colorectal metastases to the liver. *J Gastrointest Surg*. 2007;11(8):1057–77.
 68. Vera R, Gonzalez-Flores E, Rubio C, Urbano J, Valero Camps M, Ciampi-Dopazo JJ, et al. Multidisciplinary management of liver metastases in patients with colorectal cancer: a consensus of SEOM, AEC, SEOR, SERVEI, and SEMNIM. *Clin Transl Oncol*. 2020;22(5):647–62.
 69. Allard MA, Adam R, Giuliani F, Lapointe R, Hubert C, Ijzermans JNM, et al. Long-term outcomes of patients with 10 or more colorectal liver metastases. *Br J Cancer*. 2017;117(5):604–11.
 70. Omichi K, Shindoh J, Cloyd JM, Mizuno T, Chun YS, Conrad C, et al. Liver resection is justified for patients with bilateral multiple colorectal liver metastases: a propensity-score-matched analysis. *Eur J Surg Oncol*. 2018;44(1):122–9.
 71. Adam R, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, et al. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist*. 2012;17(10):1225–39.
 72. Adam R, de Haas RJ, Wicherts DA, Vibert E, Salloum C, Azoulay D, et al. Concomitant extrahepatic disease in patients with colorectal liver metastases: when is there a place for surgery? *Ann Surg*. 2011;253(2):349–59.
 73. Hwang M, Jayakrishnan TT, Green DE, George B, Thomas JP, Groeschl RT, et al. Systematic review of outcomes of patients undergoing resection for colorectal liver metastases in the setting of extra hepatic disease. *Eur J Cancer*. 2014;50(10):1747–57.
 74. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2013;14(12):1208–15.
 75. Liu W, Zhou JG, Sun Y, Zhang L, Xing BC. The role of neoadjuvant chemotherapy for resectable colorectal liver metastases: a systematic review and meta-analysis. *Oncotarget*. 2016;7(24):37277–87.
 76. Ruers T, Van Coevorden F, Punt CJ, Pierie JE, Borel-Rinkes I, Ledermann JA, et al. Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. *J Natl Cancer Inst*. 2017;109(9):15.
 77. Gillams AR, Lees WR. Five-year survival following radiofrequency ablation of small, solitary, hepatic colorectal metastases. *J Vasc Interv Radiol*. 2008;19(5):712–7.
 78. Hur H, Ko YT, Min BS, Kim KS, Choi JS, Sohn SK, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. *Am J Surg*. 2009;197(6):728–36.
 79. Kim KH, Yoon YS, Yu CS, Kim TW, Kim HJ, Kim PN, et al. Comparative analysis of radiofrequency ablation and surgical resection for colorectal liver metastases. *J Korean Surg Soc*. 2011;81(1):25–34.
 80. Solbiati L, Ahmed M, Cova L, Ierace T, Brioschi M, Goldberg SN. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. *Radiology*. 2012;265(3):958–68.
 81. Luo M, Chen SL, Chen J, Yan H, Qiu Z, Chen G, et al. Resection vs. ablation for lesions characterized as resectable-ablative within the colorectal liver oligometastases criteria: a propensity score matching from retrospective study. *PeerJ*. 2020;8:e8398.
 82. Delpla A, de Baere T, Varin E, Deschamps F, Roux C, Tselikas L. Role of thermal ablation in colorectal cancer lung metastases. *Cancers (Basel)*. 2021;13(4):908.
 83. (NCNN), N.C.C.N. *NCNN clinical practice guidelines in oncology-Colon Cancer. V3. 2021*. 2021; Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
 84. Mahadevan A, Blanck O, Lanciano R, Peddada A, Sundararaman S, D'Amrosio D, et al. Stereotactic body radiotherapy (SBRT) for liver metastasis - clinical outcomes from the international multi-institutional RSSearch(R) patient registry. *Radiat Oncol*. 2018;13(1):26.
 85. Kobiela J, Spychalski P, Marvaso G, Ciardo D, Dell'Acqua V, Kraja F, et al. Ablative stereotactic radiotherapy for oligometastatic colorectal cancer: systematic review. *Crit Rev Oncol Hematol*. 2018;129:91–101.
 86. Kim M, Son SH, Won YK, Kay CS. Stereotactic ablative radiotherapy for oligometastatic disease in liver. *Biomed Res Int*. 2014;2014: 340478.
 87. Cathail SMO, Smith T, Owens R, Zeniou A, Tsang Y, Holyoake D, et al. Superior outcomes of nodal metastases compared to visceral sites in oligometastatic colorectal cancer treated with stereotactic ablative radiotherapy. *Radiother Oncol*. 2020. <https://doi.org/10.1016/j.radonc.2020.08.012>.
 88. Greco C, Pares O, Pimentel N, Moser E, Louro V, Morales X, et al. Spinal metastases: from conventional fractionated radiotherapy to single-dose SBRT. *Report Pract Oncolo Radiother*. 2015;20(6):454–63.
 89. Soltys SG, Grimm J, Milano MT, Xue J, Sahgal A, Yorke E, et al. Stereotactic body radiation therapy for spinal metastases:

- tumor control probability analyses and recommended reporting standards. *Int J Radiat Oncol Biol Phys.* 2021;110(1):112–23.
90. Ito K, Nakajima Y, Onoe T, Ogawa H, Harada H, Saito M, et al. Phase 2 clinical trial of stereotactic body radiation therapy for painful nonspine bone metastases. *Pract Radiat Oncol.* 2021;11(2):e139–45.
 91. Zeng KL, Tseng CL, Soliman H, Weiss Y, Sahgal A, Myrehaug S. Stereotactic Body radiotherapy (SBRT) for oligometastatic spine metastases: an overview. *Front Oncol.* 2019;9:337.
 92. Wilson DD, Alonso CE, Sim AJ, Peck T, Handsfield LL, Chen Q, et al. STAT RT: a prospective pilot clinical trial of scan-plan-QA-treat stereotactic body radiation therapy for painful osseous metastases. *Ann Palliat Med.* 2019;8(3):221–30.
 93. Jackson WC, Tao Y, Mendiratta-Lala M, Bazzi L, Wahl DR, Schipper MJ, et al. Comparison of stereotactic body radiation therapy and radiofrequency ablation in the treatment of intrahepatic metastases. *Int J Radiat Oncol Biol Phys.* 2018;100(4):950–8.
 94. Stintzing S, Grothe A, Hendrich S, Hoffmann RT, Heinemann V, Rentsch M, et al. Percutaneous radiofrequency ablation (RFA) or robotic radiosurgery (RRS) for salvage treatment of colorectal liver metastases. *Acta Oncol.* 2013;52(5):971–7.
 95. Lee J, Shin IS, Yoon WS, Koom WS, Rim CH. Comparisons between radiofrequency ablation and stereotactic body radiotherapy for liver malignancies: meta-analyses and a systematic review. *Radiother Oncol.* 2020;145:63–70.
 96. Mutsaers A, Greenspoon J, Walker-Dilks C, Swaminath A. Systematic review of patient reported quality of life following stereotactic ablative radiotherapy for primary and metastatic liver cancer. *Radiat Oncol.* 2017;12(1):110.
 97. Jin H, Chalkidou A, Hawkins M, Summers J, Eddy S, Peacock JL, et al. Cost-effectiveness analysis of stereotactic ablative body radiation therapy compared with surgery and radiofrequency ablation in two patient cohorts: metastatic liver cancer and hepatocellular carcinoma. *Clin Oncol (R Coll Radiol).* 2021;33(3):e143–54.
 98. Kumar A, Straka C, Courtney PT, Vitzthum L, Riviere P, Murphy JD. Cost-effectiveness analysis of stereotactic ablative radiation therapy in patients with oligometastatic cancer. *Int J Radiat Oncol Biol Phys.* 2021;109(5):1185–94.
 99. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg.* 1999;230(3):309–18.
 100. Brudvik KW, Kopetz SE, Li L, Conrad C, Aloia TA, Vauthey JN. Meta-analysis of KRAS mutations and survival after resection of colorectal liver metastases. *Br J Surg.* 2015;102(10):1175–83.
 101. Oxenberg J, Papenfuss W, Esemuede I, Attwood K, Simunovic M, Kuvshinoff B, et al. Multidisciplinary cancer conferences for gastrointestinal malignancies result in measurable treatment changes: a prospective study of 149 consecutive patients. *Ann Surg Oncol.* 2015;22(5):1533–9.
 102. Gravis G, Boher JM, Joly F, Soulie M, Albiges L, Priou F, et al. Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial. *Eur Urol.* 2016;70(2):256–62.
 103. Gravis G, Fizazi K, Joly F, Oudard S, Priou F, Esterni B, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2013;14(2):149–58.
 104. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med.* 2017;377(4):338–51.

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