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THE ROLE OF STEREOTACTIC ABLATIVE RADIOTHERAPY IN THE TREATMENT OF OLIGOMETASTATIC DISEASE – A CLINICAL REVIEW

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ABSTRACT

Oligometastatic disease (OMD) is defined as an intermediate stage between localised cancer and widespread metastasis. The objective of this paper is to critically evaluate the clinical efficacy and safety of stereotactic ablative body radiation (SABR) in the treatment of OMD.

This evaluation is based on a review of randomised trials from 2012 to 2025. A comprehensive analysis of pivotal clinical trials has revealed that the utilisation of ablation therapy is associated with a substantial enhancement in progression-free survival and overall survival, particularly in carefully selected patient populations. This assertion is corroborated by empirical evidence from studies conducted on prostate cancer (STOMP, ORIOLE) and specific subgroups of lung cancer (SINDAS). However, a discrepancy in outcomes was observed between patients receiving modern immunotherapy (NRG-LU002) and those treated for breast cancer (NRG-BR002), indicating a significant correlation between the efficacy of SABR and tumour biology, as well as the systemic treatment regimen employed.

A thorough analysis of the existing evidence was conducted, encompassing the limitations arising from population heterogeneity, inadequate sample sizes in clinical trials, and the paucity of large-scale phase III trials for numerous histopathological types. The review also underscores the pivotal function of meticulous patient selection based on biomarkers, including circulating tumour DNA.

The clinical findings suggest that SABR is a safe and highly effective method that allows for the deferral of toxic systemic treatment in selected patients. However, definitive standards for all subgroups will be established by ongoing phase III trials.

KEYWORDS

Oligometastatic Disease, Stereotactic Ablative Radiotherapy, Ablation, Overall Survival, Targeted Therapy, Biomarkers

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Introduction

Oligometastatic disease (OMD) has remained one of the most fascinating and controversial concepts in oncology for over three decades. The initial characterisation of this phenomenon was provided by Hellman and Weichselbaum (1995), who described it as an intermediate state between localised disease and full tumour generalisation. This concept posits the existence of a limited capacity of the tumour to metastasise and a potentially biologically distinct evolution of the disease. This definition has enabled the development of curative treatment strategies in a clinical setting that were previously the domain of palliative care (Weichselbaum & Hellman, 2011).

This paradigm shift would not have been possible without technological advances. The advent of sophisticated imaging methodologies, such as positron emission tomography (PET) in conjunction with computed tomography (CT) scanning, utilising prostate-specific membrane antigen (PSMA) as a target, and enhanced magnetic resonance imaging, has facilitated the detection of metastatic lesions at an earlier stage. This has enabled the identification of a patient population with limited metastasis, in whom local treatment could have therapeutic significance rather than being purely symptomatic (Lievens et al., 2020). Concurrently, there has been rapid development in stereotactic radiotherapy techniques, including stereotactic ablative radiotherapy (SABR) and stereotactic body radiation therapy (SBRT). These devices enable the precise delivery of high doses of radiation, while causing minimal damage to healthy tissue (Mangoni et al., 2022).

Initially, the evidence supporting this concept derived from observational studies and prospective clinical series (Milano et al., 2012; Salama & Milano, 2014), which suggested long-term disease control and, in selected patients, even long-term progression-free survival (PFS). Nevertheless, the true breakthrough materialised with the advent of the first randomised clinical trials. The SABR-COMET trial demonstrated a significant prolongation of overall survival (OS) and PFS following SABR compared with standard treatment

(Palma et al., 2019, 2020). Despite its inherent limitations, the study provided the first evidence that, in patients with oligometastases, the use of ablative therapy can have a significant impact on survival.

However, subsequent organ-specific clinical trials have revealed a far more complex picture, in which the efficacy of local treatment depends heavily on the biology of the tumour and the type of systemic therapy used. In prostate cancer, as evidenced by the STOMP and ORIOLE trials, it has been demonstrated that metastasis-directed therapy (MDT) can safely delay the initiation of androgen deprivation therapy (ADT) (Ost et al., 2018; Phillips et al., 2020). Conversely, the most recent data have served to temper the prevailing enthusiasm. In the NRG-BR002 trial, which involved breast cancer patients (Chmura et al., 2022), and in a significant proportion of lung cancer patients treated with modern immunotherapy in the NRG-LU002 trial (Iyengar et al., 2024), no benefit was demonstrated from the addition of SABR. The findings indicate that the physical destruction of visible lesions does not invariably result in the cessation of microscopic disseminated disease.

In response to this clinical heterogeneity, attempts have been made to standardise definitions. International expert consensus groups, including the European Society for Radiotherapy and Oncology (ESTRO), the American Society for Radiation Oncology (ASTRO) and the European Organisation for Research and Treatment of Cancer (EORTC), have proposed a classification system that takes into account the primary disease dynamics, the location and number of metastases, and the response to systemic treatment (Guckenberger et al., 2020; Lievens et al., 2020). It has been emphasised that OMD is not a uniform clinical condition, but rather a broad spectrum with extremely varied prognoses.

Notwithstanding the early clinical reports that were promising, the topic of OMD treatment remains a controversial area. A number of studies have been conducted to date, incorporating small patient cohorts, a variety of tumour types and a range of therapeutic strategies. Furthermore, the distinguishing biological characteristics between patients with 'true' oligometastases and those in whom the period of limited spread is merely a transient state remain unclear. The resolution of these uncertainties is dependent on ongoing phase III trials.

In summary, the available evidence suggests that SABR is a promising therapeutic approach for treating OMD in carefully selected patients, enabling a delay in the initiation of systemic therapy, prolonging PFS and improving OS. However, further studies are required to identify the patient group that would most benefit from this approach. The objective of this paper is to undertake a critical review of the role of SABR in the treatment of OMD, with particular emphasis on the limitations of this method's efficacy, strategies for combining it with systemic therapy, and modern biomarker-based patient selection, as set out in the latest clinical reports.

Methodology

A comprehensive literature review was conducted to assess the role of SABR in the treatment of OMD in patients with various types of malignant tumours. To identify relevant studies, a comprehensive search strategy was conducted using multiple electronic databases, including PubMed/MEDLINE, Embase, the Cochrane Library, and the ClinicalTrials.gov registry. The selection of sources enabled the analysis of primary data from clinical trials, systematic reviews, guidelines and reports on ongoing research projects.

The search strategy was based on a combination of keywords relating to OMD and local therapies. The most relevant terms included: 'oligometastases', 'oligometastatic disease', 'stereotactic ablative radiotherapy', 'stereotactic body radiation therapy', 'local consolidative therapy', 'metastasis-directed therapy', as well as terms describing related clinical situations, such as 'oligorecurrence' or 'oligoprogression'. The findings of this study are constrained to English-language publications between 2012 and 2025. Furthermore, seminal works that defined the concept of OMD (Hellman & Weichselbaum, 1995; Weichselbaum & Hellman, 2011) were included in the analysis. This, combined with the latest research, allowed for a comprehensive assessment of the impact of ablative techniques on survival parameters.

Studies that met the following methodological criteria were included: randomised controlled trials, prospective phase II and III studies, and meta-analyses based on primary data. Current guidelines from scientific societies, including ASTRO and ESTRO (Iyengar et al., 2023), provide a significant addition to the existing literature. The analysis incorporated studies that involved the ablation of all identifiable metastatic lesions. The outcomes were then compared with those achieved through standard systemic treatment or observation methods. This approach ensured the reliability of the clinical comparisons.

Publications with lower levels of evidence, such as single case reports and small single-centre series, were excluded from the primary efficacy assessment. Narrative reviews were excluded from the evaluation of survival data. However, selected ones were included as supplementary literature, necessary for describing

biological phenomena and technological perspectives. An exception to the rigorous inclusion criteria was also made for large, multicentre retrospective studies (including pooled analyses) and prospective registry studies. The inclusion of these studies in the analysis was driven by their distinctive value in identifying prognostic factors (Hong et al., 2018) and verifying the safety profile in real-world clinical practice (Chalkidou et al., 2021). However, studies focusing exclusively on immunotherapy (without a local ablation component) and studies in which patients were not stratified according to the extent of metastasis were excluded from the analysis.

A further analysis of the bibliographies of key clinical trials was conducted, as well as analyses concerning major solid tumours. While patients with lung and prostate cancer are the most frequently represented groups in the literature, the review also deliberately included key reports evaluating the efficacy of SABR in other tumours, such as breast cancer, colorectal cancer and renal cell carcinoma.

The collected research material was then utilised to analyse key issues, including the evolution of the definition of OMD, the efficacy of SABR as a potentially curative method, the impact of metastasis ablation on OS and PFS, and changes in eligibility criteria taking tumour biology into account. The safety profile of radiotherapy was also assessed, along with preliminary reports on combining SABR with systemic therapy in sequential and concurrent regimens.

Results

Despite the fact that the concept of OMD has been utilised in the field of oncology for a period of three decades, a universal definition of this condition has yet to be established. Contemporary expert bodies, including ASTRO, ESTRO and EORTC, are moving away from viewing OMD as a simple point on the disease timeline, treating it instead as a broad spectrum of states with varied prognoses and biology (Guckenberger et al., 2020; Lievens et al., 2020).

The most commonly used criterion remains the quantitative aspect. In the majority of clinical trials and in routine clinical practice, the presence of one to five metastatic lesions is generally considered to indicate an oligometastatic condition. While this threshold is to a certain extent arbitrary, it is derived from early observations suggesting that a small number of lesions reflects a less aggressive tumour phenotype that remains sensitive to radical local treatment (Hellman & Weichselbaum, 1995; Salama & Milano, 2014). However, it is imperative to acknowledge that the numerical criterion constitutes a necessary but insufficient condition. It is equally important to consider the technical feasibility of safely ablating all visible lesions and controlling the primary tumour.

As knowledge has advanced, the definition of OMD has evolved to account for the dynamics of metastasis. The establishment of distinct clinical subtypes is of fundamental importance for the selection of treatment strategies (Guckenberger et al., 2020).

- Synchronous (de novo) disease: At the time of diagnosis of the primary tumour, limited metastasis is detected. These patients may benefit from aggressive combination therapy targeting both the primary tumour and the metastases.
- Metachronous disease: The emergence of metastases occurs subsequent to the conclusion of curative treatment (e.g. surgery) and following a period of complete remission. This course frequently suggests a more indolent tumour biology.

In the context of recurrent and progressive disease, additional categories have been identified:

- Oligorecurrence: This is defined as the emergence of limited metastases in patients who have previously undergone radical treatment, with no evidence of uncontrolled disease in other sites. This group constitutes the archetypal cohort eligible for SABR, a concept that has been extensively researched, particularly in the context of prostate cancer trials (Ost et al., 2018).
- Oligoprogression: This is defined as disease progression in a limited number of lesions during active systemic therapy, whilst disease control is maintained in all other sites. The implementation of SABR in the management of these progressive lesions, known as ‘escape’ lesions, has the potential to enhance the clinical benefits of the ongoing systemic treatment.
- Oligopersistence: This condition manifests as a response to systemic treatment, such as chemotherapy or targeted therapy, where the majority of lesions regress, yet a few foci remain active. The focal point of current research endeavours is the ablative treatment of these residual lesions (Gomez et al., 2016).

The advent of contemporary diagnostic methodologies, underpinned by highly sensitive techniques such as PET/CT and PET-PSMA, has given rise to a phenomenon known as stage migration, also referred to as the

'Will Rogers effect'. This development has led to a notable differentiation in patient populations, as evidenced by recent studies in contrast to historical cohorts (Lievens et al., 2020).

For the purposes of this paper, a definition has been adopted that combines the aforementioned criteria and allows for a consistent analysis of the studies discussed below. Oligometastatic disease is characterised by the presence of a limited number of metastatic lesions (no more than five) that can be effectively treated with radical local therapy. This definition encompasses both synchronous and metachronous conditions, as well as oligorecurrence and oligoprogression, provided that the objective of the intervention is the complete eradication of all active lesions.

Local treatment techniques and eligibility for SABR

The successful implementation of the oligometastatic treatment concept requires the use of methods that ensure high precision in destroying the lesion whilst maximally sparing healthy tissue. Historically, the role in question was fulfilled by surgery. However, stereotactic radiotherapy has gained a dominant position in the last decade.

SBRT, frequently referred to as SABR, differs fundamentally from conventional radiotherapy. The fundamental principle underpinning this approach involves the precise delivery of a high dose of radiation (typically ranging from 6 to 20 Gy per fraction) in a limited number of fractions (most commonly between 1 and 5). This method enables an ablative effect that is biologically equivalent to surgical resection (Mangoni et al., 2022).

The following key technical features are associated with SABR:

- High-dose gradient: A significant reduction in dose to the periphery of the tumour volume (Target Volume) serves to minimise the burden on adjacent critical organs.
- Image verification: It is imperative that advanced imaging systems (e.g. cone beam computed tomography, optical systems) are utilised prior to and during each fraction in order to meticulously monitor tumour motion and patient positioning with millimetre accuracy.
- Immobilisation: The utilisation of dedicated stabilisation systems (masks, vacuum mattresses), frequently in conjunction with respiratory management techniques (e.g. breath-hold or respiratory gating), is a common practice.

The biological effects of such fractionation extend beyond the scope of conventional DNA damage. The involvement of vascular mechanisms (destruction of tumour microcirculation) and the potential stimulation of the immune response have been postulated (Mangoni et al., 2022).

Although radiotherapy forms the cornerstone of non-invasive treatment, other methods, such as surgical metastasectomy and thermal ablation, are used in certain clinical situations.

The determination of eligibility for local treatment in OMD must be informed by a comprehensive evaluation of the benefits versus risks. According to the ASTRO and ESTRO guidelines (Iyengar et al., 2023), the ideal candidate for SABR should meet the following technical criteria:

- The status of performance: ECOG 0–1, indicating that the patient is eligible for treatment and has a high probability of recovery.
- The location of the lesion: The ability to safely administer an ablative dose without exceeding tolerance limits for critical organs (e.g. spinal cord, brainstem, intestines) is paramount.
- The size of the tumour: In the case of smaller lesions (typically measuring less than 5 centimetres), the prognosis with regard to local control is more favourable. Conversely, for larger tumours, there is an increased risk of underdosing or toxicity.

In the studies analysed, toxicity assessment is routinely based on the CTCAE (Common Terminology Criteria for Adverse Events) scale. The nature of high doses carries a risk of rare but serious complications, such as vertebral compression fractures, pulmonary fibrosis or gastrointestinal ulcers (Lehrer et al., 2021). It is imperative that precise planning and strict adherence to dose limits are considered as absolute prerequisites.

The subsequent section will discuss the most significant phase II trials and the initial reports from phase III trials on the use of SABR in OMD, which have shaped the current clinical approach.

The SABR-COMET trial – various tumour sites

The SABR-COMET (Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases) trial, as published by Palma et al. (2019), was the inaugural multicentre, randomised phase II trial to assess the impact of SABR on OS. The trial enrolled 99 patients with various types of cancer (most commonly breast, lung, colorectal and prostate cancer) who had between one and five metastases. Patients were randomly assigned in a 1:2 ratio to a group receiving standard palliative care (SOC) or SOC combined with SABR to all metastatic lesions.

The results obtained were nothing short of groundbreaking. The median OS in the SABR arm was 41 months, compared to 28 months in the control group ($p = 0.09$). With long-term follow-up (over 5 years), this difference became statistically significant, showing an almost doubling of the 5-year survival rate in favour of the ablative treatment (42.3% vs 17.7%; Palma et al., 2020). A substantial prolongation of PFS was also demonstrated. However, it should be noted that the higher efficacy was associated with a higher incidence of grade ≥2 toxicity in the SABR group (29% vs 9%), including three potentially treatment-related deaths. This underscores the need for rigorous assessment of treatment plans.

Prostate cancer trials – STOMP and ORIOLE

In the context of prostate cancer, it is imperative to delay the initiation of ADT to ensure optimal quality of life for patients. The efficacy of this approach is evidenced by the results of the phase II STOMP (Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer) trial, which was conducted by Ost et al. (2018) and which was focused on patients with biochemical recurrence and oligometastases (up to 3 lesions) that had been detected by choline-PET. The findings of the study demonstrated that the utilisation of MDT in the present cohort resulted in a median ADT-free survival duration of 21 months, in comparison to the 13 months observed in the observation group.

In the ORIOLE study (Observation Versus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer), Phillips et al. (2020) demonstrated that in patients with castration-sensitive oligometastatic prostate cancer who underwent SABR, the risk of progression after six months was significantly lower (19%) compared with the observation group (61%). It is important to note that this study emphasised the significance of contemporary imaging techniques: patients in whom all visible lesions on PET-PSMA were ablated demonstrated significantly superior outcomes in comparison to those in whom some lesions were overlooked. This finding was corroborated by a subsequent pooled analysis of both clinical trials (Deek et al., 2022).

Investigations into non-small cell lung cancer (NSCLC)

Gomez et al. (2016) conducted a phase II trial in patients with stage IV NSCLC with ≤3 metastases who had achieved disease stabilisation following induction chemotherapy. Patients were randomised to either maintenance therapy or local consolidative therapy (LCT) using radiotherapy or surgery. The termination of the trial occurred ahead of schedule, owing to the observation of a substantial benefit in the experimental group. The median PFS in the LCT group was 11.9 months, in comparison with 3.9 months in the control group. Moreover, an update of the data (Gomez et al., 2019) also confirmed a significant benefit in terms of OS (41.2 vs 17.0 months). The findings of Iyengar et al. (2018) demonstrated that consolidation with SABR following chemotherapy significantly delays disease recurrence in patients with NSCLC.

A significant development for the subgroup of patients with oligometastatic lung cancer harbouring an epidermal growth factor receptor (*EGFR*) mutation was the publication of the results of the phase III SINDAS trial (Stereotactic Body Radiation Therapy in Newly Diagnosed Advanced Staged Lung Adenocarcinoma; Wang et al., 2023). The findings of the study demonstrated that the combination of SABR and tyrosine kinase inhibitors has been shown to yield dual benefits. The median PFS is extended from 12.5 to 20.2 months and there is a significant improvement in OS from 17.4 to 25.5 months. These results have reinforced the position of SABR as a standard component of care in this specific clinical subgroup.

However, the NRG-LU002 trial (Iyengar et al., 2024) yielded entirely different results. The study population encompassed a more extensive demographic of lung cancer patients who had undergone treatment with contemporary systemic therapy modalities, encompassing immunotherapy. Preliminary analyses indicated that the incorporation of SABR into standard maintenance treatment did not result in a substantial enhancement of either PFS or OS. This suggests that, in the era of highly effective immunotherapy, the role of SABR may be limited to narrower patient groups and should not be used routinely in all patients.

Renal cell carcinoma – confirmation of efficacy in radiation-resistant tumours

The concept of oligometastatic treatment is supported by the results of a single-arm phase II trial conducted by Tang et al. (2021). Renal cell carcinoma, which was historically considered to be a radiation-resistant tumour in the classical fractionation model, has been shown to demonstrate high sensitivity to the ablative doses used in the SABR technique. It has been demonstrated that this approach enables a substantial delay in the initiation of toxic systemic therapy. This is a pivotal finding for patients' quality of life, as it facilitates periodic interruptions in drug treatment while preserving complete autonomy over the management of the disease.

The challenges associated with colorectal cancer – achieving excellent local control without a clear translation into survival

Phase II clinical trials involving patients with colorectal cancer (e.g. the single-arm study by Scorsetti et al., 2015) demonstrate very high local efficacy of SABR – the radiotherapy effectively destroys the irradiated tumours in the liver (local control of 91%). However, in contrast to the outcomes observed in prostate or kidney cancer, where phase II trials have demonstrated significant benefits in delaying disease progression, colorectal cancer often exhibits a local control that is not sufficient to halt further spread. In the study by Scorsetti et al. (2015), only 35% of patients survived two years without progression in other organs. Consequently, there is still a paucity of hard evidence from phase III trials that local ablation in this group unequivocally prolongs OS. It is imperative to exercise caution when making diagnoses, particularly in cases of colorectal cancer metastases, where proven surgical methods or radiofrequency thermal ablation remain the most effective and preferred treatment options.

A lesson from breast cancer

Despite the enthusiasm generated by the successes observed in many cancers, the clinical picture is not uniform across all histological types. The results of the NRG-BR002 trial, which was exclusively dedicated to patients with oligometastatic breast cancer, provide an important point of reference (Chmura et al., 2022). The findings of this randomised trial did not demonstrate a statistically significant benefit from the addition of ablative treatment to standard systemic therapy, either in terms of PFS or OS. This outcome constitutes a substantial corroboration of earlier retrospective observations, including the analysis by Hong et al. (2018), which indicated long-term survival in this cohort. The authors of the NRG-BR002 study indicate that the favourable prognosis in this group is attributable to the high efficacy of contemporary systemic treatment and the specific biology of breast cancer, rather than to the ablative intervention itself. The absence of any additional benefit suggests that early microscopic spread may predominate in these patients. In such cases, local ablation of visible lesions has no real impact in the face of effective systemic therapy. This underscores the imperative for exercising extreme caution when extrapolating findings from studies of other cancers to the population of breast cancer patients.

Evidence from meta-analyses and systematic reviews

Recent meta-analyses (2019–2024) have corroborated the phase II findings across a more extensive population base. A comprehensive meta-analysis, published by Lehrer et al. (2021), provided key evidence for the general population, encompassing various types of cancer collectively. The authors analysed data from 21 studies involving a total of 943 patients with OMD. The results confirmed the high efficacy of local treatment: one-year OS was 85.4%, and one-year local control reached 94.7%. The present study demonstrates that the ablation of lesions is an effective method of destroying disease foci in the short and medium term, regardless of the primary site, ensuring high local efficacy.

However, the strength of the evidence regarding survival benefits is inconsistent and depends heavily on the histopathological type of tumour, as demonstrated by dedicated meta-analyses:

- NSCLC: Meta-analyses of studies involving patients treated with conventional chemotherapy and targeted therapies (e.g. Rim et al., 2023) consistently indicate that the addition of local treatment is associated with a significant reduction in the risk of death and progression. It has been demonstrated that LCT extends the median PFS by an average of 6–8 months in comparison with systemic treatment alone. However, it is important to acknowledge that these studies merely summarise earlier research conducted on older generations of patients and do not fully reflect the latest challenges of the immunotherapy era, as presented in the NRG-LU002 study. This contemporary era necessitates a growing need for treatment to be tailored to the individual characteristics of each patient.

- Prostate cancer: Integrated long-term follow-up data (e.g. the combined analysis of the STOMP and ORIOLE trials conducted by Deek et al., 2022) confirm the sustained clinical benefit of MDT. This analysis demonstrated a significant prolongation of PFS in comparison with observation alone. In the context of the diverse biology of tumours, this study also demonstrated that outcomes following the administration of SABR can be stratified based on the tumour's mutational profile. Research has demonstrated that patients exhibiting high-risk mutations (in genes such as ATM, BRCA1/2, Rb1 or TP53) demonstrate inferior outcomes following ablation in comparison to patients who do not exhibit such mutations. This finding signifies the potential for enhanced, personalised patient selection for local treatment.
- Breast and gastrointestinal cancers: In these histological types, the benefits of SABR in terms of extending OS are significantly less consistent (Lehrer et al., 2021). The accumulated data suggest that these cancers are more frequently characterised by aggressive microscopic spread, which limits the long-term benefits of local ablation of visible lesions.

A significant finding from the aforementioned study by Lehrer et al. (2021) is the confirmation of the high safety profile of the SABR technique. Notwithstanding the assertive nature of the treatment, the estimated risk of severe toxicity (grade 3–5) was determined to be minimal, ranging from 1–5% for both acute and late complications. This indicates that, in the general population, the risk of severe complications is considerably lower than the observed result in the small group in the SABR-COMET study (29%; Palma et al., 2019), thereby enabling clinicians to address concerns regarding the safety of this method with greater confidence. The findings of the meta-analysis suggest that the safety profile is closely dependent on the location of the irradiated lesions. The highest risk applies to centrally located lung tumours (risk of bleeding) and lesions situated in the immediate vicinity of nerve plexuses (Lehrer et al., 2021; Rim et al., 2023). It is important to note that any toxicity does not result in long-term deterioration in quality of life. Randomised trials demonstrate that there are no significant differences in patient well-being between those undergoing SABR and those treated solely with systemic therapy (Palma et al., 2020). The safety of the method has been definitively confirmed by data from real-world clinical practice. A substantial British registry study encompassing over 1,400 patients has demonstrated that the high efficacy and low toxicity of SABR are sustained even beyond the rigorous confines of experimental trials (Chalkidou et al., 2021).

Discussion

The clinical trial and meta-analyses results presented provide a complex and heterogeneous picture of the efficacy of SABR, which is closely dependent on the type of tumour and its biology. Despite the well-established benefits of high precision and low toxicity associated with ablative radiotherapy, the observed variability in therapeutic response among diverse patient demographics necessitates a paradigm shift from a purely technical approach to one that is more biological and strategic in nature. In this context, contemporary oncology is evolving beyond the binary distinction between local and systemic treatment, seeking synergies between these two modalities. Four primary strategies for combining them are currently identified, each with distinct biological and clinical objectives:

1. Consolidation following initial systemic treatment

This strategy has been the subject of retrospective studies in NSCLC by teams including Gomez et al. (2016) and Iyengar et al. (2018). The strategy involves the use of initial systemic treatment as a tool for selecting patients with a favourable prognostic profile. In patients who have achieved at least disease stabilisation, SABR is applied to all remaining metabolically active lesions (so-called residual disease). The objective of this study is to eradicate drug-resistant cell clones that have demonstrated resistance to initial therapeutic interventions. This approach, originally tested in the era of conventional chemotherapy and targeted therapies, has been shown to allow for the eradication of tumour foci. Furthermore, older meta-analyses have demonstrated that this approach significantly improves OS. However, it should be noted that in the era of widespread use of highly effective maintenance immunotherapy, the universality of this strategy is currently being re-evaluated, including through the results of the NRG-LU002 trial (Iyengar et al., 2024). Consequently, the utilisation of SABR for consolidation is undergoing a transition from a conventional standard of care to a methodology applied exclusively to a select group of patients.

2. Oligoprogression – extending the current line of therapy

Oligoprogression is a phenomenon that is characteristic of targeted therapies (e.g. kinase inhibitors in lung cancer with *EGFR/ALK* mutations). The conventional approach would entail the transition to subsequent-line therapy, which is frequently characterised by increased toxicity and reduced efficacy. The utilisation of SABR for progressive disease facilitates the eradication of the resistant clone and the continuation of the current systemic treatment. Research indicates that this approach significantly prolongs the time to treatment change, thereby ensuring the patient continues to receive a well-tolerated drug. This approach, aimed at maintaining the continuity of effective systemic therapy, is now officially recommended by the joint ASTRO/ESTRO guidelines (Iyengar et al., 2023).

3. Interaction with immunotherapy: the abscopal effect

The most recent and promising development in this field is the combination of SABR with checkpoint inhibitors. The abscopal effect hypothesis proposes that the administration of a high dose of radiation results in the release of significant quantities of tumour antigens from the irradiated tumour site. This phenomenon functions as an in situ vaccine, thereby stimulating the immune system to target non-irradiated micrometastases (Nabrinsky et al., 2022; Reynders et al., 2015). Although spectacular abscopal effects are rare in clinical practice, studies (including the phase II PEMBRO-RT trial in lung cancer) suggest that irradiation of a single metastasis may enhance the response to systemic immunotherapy, even though this trial did not formally meet its stringent endpoint (Theelen et al., 2019). A plethora of studies are currently underway to ascertain the optimal sequence (i.e. whether to irradiate before or during drug administration) and dosage to maximise this synergistic effect (Mangoni et al., 2022; Reynders et al., 2015).

4. Combination with radioisotopes

In the search for synergy, the combination of SABR with systemic radioisotopes has also been investigated. However, the recently published results of the phase II RAVENS trial have served to temper this enthusiasm (Wang et al., 2025). The study demonstrated that the addition of radium-223 to SABR did not result in a prolongation of PFS when compared with stereotactic radiotherapy alone. This outcome serves to confirm the high efficacy of SABR in isolation (as a local monotherapy). It issues a warning against the routine combination of methods without the evidence from clinical trials, as this may generate unnecessary costs and toxicity without clinical benefit.

The integration of SABR with systemic therapy necessitates close collaboration between the radiotherapist and the clinical oncologist. It is imperative to accurately ascertain the opportune moment for intervention (consolidation vs oligoprogression) and to meticulously monitor safety, particularly in scenarios where high-dose radiation is employed in conjunction with novel therapeutic agents. This precautionary approach is driven by the potential for unanticipated toxicities, including pneumonia (Iyengar et al., 2023; Lehrer et al., 2021; Theelen et al., 2019).

The role of biomarkers and modern imaging in patient selection

The transition from an anatomical paradigm (number and size of metastases) to a biological one signifies a pivotal shift in the eligibility criteria for the treatment of oligometastases. The extant body of evidence suggests that a low number of metastases alone does not guarantee success if the tumour exhibits aggressive microscopic biology. Consequently, contemporary patient selection is predicated on two fundamental pillars: advanced molecular imaging and liquid biomarkers.

The most striking illustration of this paradigm shift in eligibility is evident in the case of prostate cancer. Conventional diagnostic methods (bone scintigraphy, computed tomography) frequently proved incapable of accurately gauging the true extent of the disease. The advent of PET targeting the prostate-specific membrane antigen (PSMA) has profoundly transformed the conceptualisation of oligometastases in this cohort. The ORIOLE trial (Phillips et al., 2020) demonstrated that the efficacy of SABR is closely correlated with imaging accuracy. Patients in whom all lesions visible on PET-PSMA were irradiated demonstrated significantly superior PFS outcomes in comparison to those in whom some lesions (not visible on standard CT) were omitted. This finding was subsequently corroborated by meta-analyses (Deek et al., 2022). Presently, PET-PSMA is being established as the gold standard for patient selection, with the capacity to exclude patients with occult multifocal metastases who would not benefit from local treatment.

Another significant development is the analysis of circulating tumour DNA (ctDNA). The level of ctDNA in the blood is a sensitive marker of minimal residual disease. As demonstrated in the relevant literature, including the work of Chaudhuri et al. (2017), clinical trials have repeatedly indicated that patients with detectable ctDNA following radical treatment are significantly more likely to experience rapid metastasis.

As proposed by Moding et al. (2021), the application of these findings directly to OMD is a potential avenue for future research. The identification of patients with a biologically oligometastatic condition may be facilitated by the use of low or undetectable levels of ctDNA as a biomarker. These tumours exhibit low metastatic activity, thus rendering them an optimal candidate for the implementation of SABR. High concentrations of this marker, despite the absence of visible changes on CT scans, may suggest aggressive microscopic disease, necessitating intensive systemic treatment as a primary approach.

In the context of contemporary local treatment modalities, the molecular status of the tumour assumes a pivotal role, both in the initial assessment of metastasis and at the onset of oligoprogression. The most salient example of this phenomenon is NSCLC. The presence of activating mutations (e.g. *EGFR, ALK*) has been demonstrated to promote clonal evolution. In the context of targeted therapy (tyrosine kinase inhibitors), a single, resistant clone is frequently selected within a solitary lesion, while the remaining sites of disease remain entirely under systemic control. The recognition of this biology is therefore justified, and local ablation of the progressive lesion is recommended as an alternative to altering the entire treatment regimen (Iyengar et al., 2023; Rim et al., 2023).

The integration of the aforementioned data results in the formulation of a novel decision-making model. The ideal candidate for SABR is currently not only a patient with few lesions visible on imaging, but above all a patient with metabolically (PET) and molecularly (ctDNA) confirmed limited disease activity (Moding et al., 2021; Phillips et al., 2020). Such rigorous selection helps to avoid exposing patients to unnecessary toxicity, particularly those in whom the tumour process is already systemic in nature, even in the absence of visible macroscopic lesions.

Nevertheless, before such sophisticated biological stratification can be considered standard clinical practice, it is essential to critically evaluate the quality of the available data. The growing body of reports supporting the use of SABR in OMD has led to a notable increase in clinical enthusiasm. However, it is crucial to exercise caution and acknowledge the methodological limitations of existing studies, as well as the systemic risks involved. The integration of this approach within established treatment protocols has given rise to numerous contentious debates.

1. Population heterogeneity and challenges in phase III trials

The majority of the extant high-quality evidence derives from phase II trials. Despite the randomisation of these trials, they are characterised by small group sizes (typically fewer than 100 patients), which increases the risk of statistical error. A further challenge is the considerable heterogeneity of the enrolled patients. “Pan-cancer” trials, such as SABR-COMET (Palma et al., 2019), are a notable example of this approach, as they group patients with cancers of completely different biology into a single cohort. It is challenging to provide an unequivocal assessment of whether the observed benefit is attributable to the intervention itself (SABR) or to more favourable patient selection (i.e. selection of patients with a better prognosis).

It is important to note that the most recent randomised trials (phase III trials) have produced equivocal results. Whilst the SINDAS trial ultimately confirmed the efficacy of SABR in a specific population of lung cancer patients with an *EGFR* mutation (Wang et al., 2023), in breast cancer groups (NRG-BR002; Chmura et al., 2022) and in the general population of lung cancer patients treated with immunotherapy (NRG-LU002; Iyengar et al., 2024), no benefit from the addition of local treatment was demonstrated. This indicates that, with a few exceptions, there remains a paucity of robust, positive evidence from large phase III trials that would justify the routine and widespread use of this method for most cancers.

2. The risk of overtreatment

Due to the phenomenon of stage migration (also known as the ‘Will Rogers effect’), the high sensitivity of PET-CT methods means that patients with minimal metastasis who would previously have been classified as having limited-stage disease are now classified as oligometastatic. However, there is a valid concern that some of these newly detected lesions are indolent and would not affect the patient’s survival, even if left untreated. In such circumstances, the administration of SABR exposes patients to treatment-related toxicity and stress without conferring any tangible survival benefit. The most significant challenge in diagnosis is distinguishing between patients for whom ablation is required and those for whom it is not (Lievens et al., 2020).

3. Toxicity and quality of life

Despite the findings of meta-analyses indicating a low rate of severe complications (Lehrer et al., 2021), the possibility of such complications occurring cannot be discounted entirely. The SABR-COMET study documented treatment-related fatalities, including pneumonia and haemorrhage, thereby underscoring the potency of ablative radiotherapy as a therapeutic modality (Palma et al., 2019). Nevertheless, concerns persist

regarding the long-term ramifications on patients' quality of life. Whilst the deferral of chemotherapy is undoubtedly beneficial, chronic complications following radiation therapy (e.g. pulmonary fibrosis, nerve plexus damage, vertebral fractures) may only manifest many years later. The follow-up period in many studies is still too short to fully assess these risks. Nonetheless, the long-term results of the SABR-COMET study are encouraging, as no new, serious complications were observed after a period of more than five years of follow-up, and patients' quality of life did not deteriorate (Palma et al., 2020).

4. Economic considerations and accessibility

The extensive implementation of SABR for the management of OMD introduces substantial systemic challenges. The implementation of this procedure necessitates the utilisation of sophisticated equipment, meticulous planning, and rigorous imaging verification. The method is costly and burdensome for radiation therapy centres. This has given rise to concerns about the potential impact on patients treated for radical indications, such as early-stage lung cancer, who may encounter difficulties in accessing the necessary equipment. Nevertheless, the most recent economic models suggest that, in suitable cases, SABR is a highly "cost-effective" strategy. The extension of patient survival that has been observed as a result of this method is significant, and it is therefore considered to fall within the rigorous cost-effectiveness thresholds for healthcare systems (Kumar et al., 2021).

The final definition of treatment guidelines for OMD is contingent upon the results of large phase III trials that are currently underway. The objective of these trials is to validate previous findings in significantly larger and more precisely defined patient populations. The oncology community is currently awaiting the results of several key studies, including:

- SABR-COMET-3 and SABR-COMET-10: These trials represent a direct continuation of the pioneering studies conducted by Palma's team. The former recruits patients with 1–3 metastases, while the latter pushes the boundaries of the method by including patients with 4-10 metastatic lesions (Palma, 2018, 2019). The results of this study are intended to provide a response to the fundamental question regarding the relationship between clinical benefit and the number of lesions, and to assist in the upper limit of the feasibility of local treatment.
- SABR-SYNC: This is a pivotal phase III trial that is distinguished by its specific target population. The study encompasses patients with newly diagnosed (synchronous) generalised disease, encompassing an untreated primary tumour and up to 10 metastases (Palma, 2023). The objective of this trial is to ascertain whether administering aggressive local treatment (SABR for metastases and treatment of the primary tumour) at the time of diagnosis provides a benefit in comparison with systemic therapy alone.
- SARON: This is a multicenter, British phase III trial in lung cancer. The objective of the trial is to evaluate the addition of SABR to standard chemotherapy (McDonald, 2015). The results of this study are of high statistical power, and it is therefore to be hoped that they will ultimately influence the standards of care and reimbursement for SABR in the NSCLC patient population.

However, all indications suggest that further development in this field will inevitably move towards the close integration of advanced radiotherapy technologies with molecular biology and deep treatment personalisation. Consequently, conventional endpoints such as OS or tumour size on imaging (RECIST criteria), are proving inadequate in the era of precision oncology. Contemporary research protocols (including SABR-SYNC) have introduced translational endpoints, which seek to establish a correlation between clinical outcomes and tumour biology. The assessment of molecular response is achieved through the detection of ctDNA, a highly sensitive marker of minimal residual disease eradication (Moding et al., 2021). Furthermore, the evaluation of immunological profiles, such as T-cell clonality, is imperative to optimise the synergy between radiotherapy and immunotherapy (Mangoni et al., 2022; Reynders et al., 2015).

The utilisation of artificial intelligence for the purpose of conducting in-depth analyses of standard CT images serves to complement contemporary diagnostic methodologies. The employment of radiomics algorithms facilitates the extraction of features that are invisible to the human eye, including the microscopic structure and texture of a tumour, from scans. These tools are currently being tested to predict the sensitivity of lesions to radiation therapy even before treatment begins (Ramasamy et al., 2024). This approach, known as a 'virtual biopsy', facilitates a more precise patient selection process based on digital data from routine procedures.

Conclusions

A thorough analysis of the extant literature in this field enables the formulation of pragmatic recommendations regarding the utilisation of SABR in the treatment of OMD. In view of the extant evidence, the following pillars should underpin management:

1. There is documented evidence of efficacy in specific indications. SABR is an established treatment option in oligometastatic prostate cancer (allowing for the safe deferral of toxic systemic therapy) and in carefully selected subgroups of NSCLC (including patients with *EGFR* mutations).
2. It is important to note the absence of universality and the necessity for caution in certain areas: the use of SABR is not universally applicable to all histologies and treatment regimens. The failure of the study to demonstrate a significant benefit from the addition of SABR to immunotherapy in lung cancer, in addition to the negative results in breast cancer, demonstrates that tumour biology often outweighs the benefit of ablation. Consequently, eligibility in groups such as colorectal cancer still requires the utmost caution.
3. Modern biological assessment: It is imperative to recognise that treatment decisions cannot be based solely on the number of metastases. The utilisation of advanced imaging techniques, such as PET-PSMA and PET-CT, along with the assessment of tumour biology through ctDNA analysis or radiomics, is imperative for the exclusion of patients with occult, systemic disease spread.
4. The necessity for safety and a multidisciplinary approach is paramount. It is evident that the SABR method is a safe procedure, with a risk of serious complications that is less than 5%. However, it is important to note that this is only the case if the strict technical requirements are met. This treatment should always form part of a personalised multidisciplinary strategy (reviewed by a multidisciplinary team), precisely integrating local ablative treatment with optimal systemic therapy.

The OMD paradigm has evolved from a theoretical hypothesis into a viable clinical option. For a carefully selected group of patients, metastatic ablation offers the chance to alter the natural history of the disease – transforming a fatal cancer into a chronic condition that medicine can effectively manage for many years.

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