Special Article

Top Ten Lessons Learned from Trials in Oligometastatic Cancers

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Recent evidence supports the role of aggressive local treatment in the oligometastatic setting. In this review, we discuss the top 10 lessons we have learned from trials in oligometastatic cancers. Major lessons learned pertain to definitions of oligometastatic disease, outcomes, toxicity, costs, and the combination of ablative therapies with systemic therapy, including immunotherapy. Barriers to accrual for trials and upcoming phase III trials are also reviewed. These lessons may help to inform clinical practice and may be the basis for future research in the oligometastatic space.

Key words Oligometastatic, Stereotactic, Metastases, Stereotactic ablative radiotherapy, Stereotactic body radiation therapy

Introduction

Weichselbaum and Hellman [1] defined oligometastases as a state of restricted tumor metastatic capacity where radical treatment of metastases may have curative potential. Although this idea of ablating metastases with the goal of cure originated several decades ago, up until the last decade there were no completed clinical trials investigating ablative therapies for treatment of oligometastases. In recent years, several randomized controlled trials (RCTs) published in quick succession (Table 1) generally support the assertion that aggressive local treatment can provide progression-free survival (PFS) and overall survival (OS) benefits in patients with oligometastatic disease. Although these trials differ in their inclusion criteria, treatments delivered, and outcomes, there are some consistent themes and findings that have emerged across trials that can be informative for both clinicians and researchers. In this review, we present the top 10 lessons learned from trials in oligometastatic cancers, which are summarized in Fig. 1.

Lesson #1: There May Never Be an Exact Cut-off for What Constitutes Oligometastatic Disease

There is currently no standard number of metastases that defines oligometastatic disease. Across clinical trials, the definitions of "oligometastatic" vary. Many trials have used up to 3 or up to 5 metastatic lesions as a common definition, but definitions around counting metastases and use of systemic therapy vary. As an example, Table 2 reviews the inclusion criteria of the three RCTs currently published in oligometastatic disease in non–small cell lung cancer (NSCLC) [2-4], which had different cut-offs for the number of metastases, and the counting of lesions. These differences in inclusion criteria make it difficult to arrive at a strict definition of the oligometastatic state. In addition, a recent meta-analysis of both prospective RCTs and retrospective series by Rim et al. [5], found that 48.1% of studies defined oligometastases as up to five lesions, 7.4% up to four lesions and 25.9% as up to 3 lesions. A recommendation from the European Society for Radiotherapy and Oncology (ESTRO) and the American Society for Radiation Oncology (ASTRO) asked participants if oligometastatic disease is defined by a maximum number of lesions and found that the consensus was that the ability to safely deliver curative radiation to metastasis determines the maximum number [6].

Ideally, there would be a strict cut-off for the number of metastases that would render a patient oligometastatic. But if patients are considered to be "oligometastatic" if they have a chance of cure, then it will be difficult to define a hard cut-off, particularly when there is a lack of definition of cure in certain cancers. For some cancers, a 5-year disease-free interval is taken as a definition of cure, but for others it may be 10 years or longer. Even if a clear definition of cure existed for all cancers, determining a hard cut-off of who is curable (e.g., with 3 metastases but not with 4) is unlikely.

If instead we consider patients to be oligometastatic if they merely benefit from ablative treatments (in terms of improved survival) without the requirement for cure, there may never be an upper limit of metastases. The EORTC 40004 trial that showed an OS benefit for radiofrequency ablation (RFA) in colorectal liver metastases allowed up to 9

lesions in the liver [7]. The SABR-COMET-10 trial currently in recruitment assesses the impact of stereotactic ablative radiotherapy (SABR) for up to 10 metastatic lesions [8]. An ongoing trial, ARREST, examines the possible benefits of SABR in more than 10 metastases [9]. There may never be an exact cut-off defining the number of metastases that would benefit from treatment.

Another framework when considering oligometastatic disease is the classification published by the European Society for Radiotherapy and Oncology and European Organization for Research and Treatment of Cancer [10]. The classification differentiates into 9 classes based on prior history of poly-metastatic disease, prior history of oligometastatic disease, timing of oligometastatic development, systemic therapy at oligometastatic diagnosis and progression status at oligometastatic diagnosis. Other patient factors, such as the size of the metastasis, location of the metastasis and progression interval, also determine prognosis. As a result of all these factors, a definition of oligometastatic disease based solely on number of metastases will be elusive.

Lesson #2: Most RCTs Indicate That There Is Benefit from Ablative Therapies

A number of RCTs have suggested the possible benefit of ablative therapies (including radiation, surgery or thermal ablation) in patients with oligometastatic cancers. This includes trials with specific histology including lung cancer [2-4], prostate cancer [11-13], colorectal cancer [7,14], breast cancer [15] as well as trials that include multiple histologies [16]. A summary of these RCTs is provided in Table 1. A selection of these trials will be highlighted here.

Gomez et al. [2] conducted a phase II RCT that included 49 patients diagnosed with NSCLC who had 1-3 oligometastases with no progression following first-line systemic therapy. They had found local consolidative therapy (radiation or surgery) was associated with improved PFS and OS as compared to patients on maintenance systemic therapy or observation. The trial was stopped early by the Data Safety and Monitoring Committee due to significant improvement of PFS in the local consolidative arm (11.9 months vs. 3.9 months) in initial analysis [2]. Long-term analysis also demonstrated an OS benefit (41.2 months vs. 17.0 months) [17]. Similarly, a phase II RCT trial by Iyengar et al. [3] evaluated patients with NSCLC and up to 6 sites of disease following first-line chemotherapy randomized to maintenance chemotherapy plus SABR or maintenance chemotherapy alone also demonstrated a PFS benefit (9.7 months vs. 3.5 months).

EXTEND is a phase II basket trial for multiple solid tumors investigating if metastatic-directed therapy improves PFS.

The prostate cancer sub-study, recently presented at ASTRO 2022, enrolled 87 men with up to 5 metastases on androgen deprivation therapy (ADT). Patients were randomized to ADT plus radiation or continuing with ADT alone. The addition of radiation showed PFS benefit (median, not reached vs. 15.8 months; hazard ratio [HR], 0.25; p < 0.001) [13]. Also in prostate cancer, the STOMP trial demonstrated radiotherapy (RT) or surgery to oligometastases improved androgen-deprivation-therapy-free survival and the ORIOLE trial demonstrated SABR improved PFS in castration-sensitive oligometastatic prostate cancers [11,12]. Pooled analysis from these two latter trials found a PFS benefit with treatment compared to observation (11.9 months vs. 5.9 months) [18].

The SABR-COMET trial included 99 patients of multiple tumor histologies with 1-5 metastases who received local definitive treatment randomized to standard of care plus SABR or standard of care alone [16]. In the initial report, SABR was associated with a 13-month improvement in median OS (median survival, 41 months in the SABR arm vs. 28 months in the control arm), but the impact of SABR on OS has increased with increasing follow-up. In the most recent report, more than 5 years after completion of accrual, the gain in median survival had improved to 23 months (53 months vs. 28 months, respectively) [19].

As demonstrated, most RCTs have suggested benefit in PFS and/or OS, except two trials, one in colorectal cancer and one breast cancer. PulMiCC enrolled patients with colorectal primary and lung metastases randomized to surgery or active monitoring. No OS benefit was observed, however, this trial unfortunately closed due to poor enrollment [14]. The NRG-BR002 was a randomized phase II/III trial in oligometastatic breast cancer randomizing standard of care plus surgery/radiation or standard of care alone. There was no benefit seen in PFS or OS, however median follow-up was relatively short at less than 3 years, and long-term follow-up is still pending [15].

Lesson #3: In Choosing a Treatment Modality, the Evidence Best Supports SABR, But Other Modalities Have Advantages in Certain Situations

In the RCTs listed in Table 1, the vast majority of patients accrued were treated with SABR or other hypofractionated radiation approaches. Of the eight positive trials listed, five used SABR only [3,4,12,13,16], one used RFA [7], and two allowed radiation and/or surgery but approximately 75% of those patients received radiation [2,11]. A meta-analysis of 54 prospective and retrospective studies also found that 77.8% used radiation, 46.3% used surgery and 18.5% used RFA as

Table 1. Summary of selected randomized trials conducted in oligometastatic cancers

Type of treatment	Histology	Trial name/Author	Benefit
SABR	NSCLC	Iyengar et al. [3]	PFS (9.7 vs. 3.5 mo)
		SINDAS/Wang et al. [4]	OS (25.5 vs. 17.4 mo) PFS (20.2 vs. 12.5 mo)
	Prostate	ORIOLE/Phillips et al. [12]	PFS (not reached vs. 5.8 mo)
		EXTEND/Tang et al. [13]	PFS (not reached vs. 15.8 mo)
	Multiple	SABR-COMET/Palma et al. [16]	OS (41 vs. 28 mo) PFS (12 vs. 6 mo)
RT or Surgery	NSCLC	Gomez et al. [2]	OS (41.2 vs. 17.0 mo) [17] PFS (11.9 vs. 3.9 mo)
	Prostate	STOMP/Ost et al. [11]	ADT-free survival (21 vs. 13 mo)
	Breast	NRG BR-002 [15]	None
Surgery	Colorectal	PulMiCC/Treasure et al. [14]	None
RFA	Colorectal	EORTC 40004/Ruers et al. [7]	OS (45.3 vs. 40.5 mo) PFS (16.8 vs. 9.9 mo)

ADT, androgen deprivation therapy; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; RFA, radiofrequency ablation; RT, radiation therapy; SABR, stereotactic ablative radiotherapy.

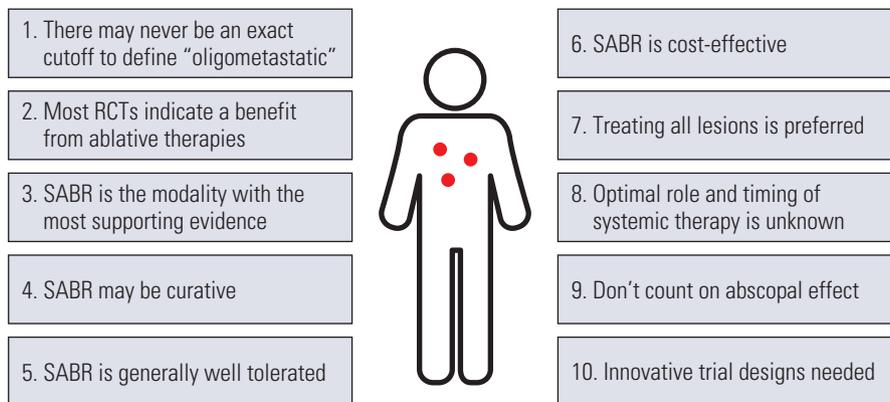Top ten lessons from trials in oligometastatic cancers

1. There may never be an exact cutoff to define "oligometastatic"

2. Most RCTs indicate a benefit from ablative therapies

3. SABR is the modality with the most supporting evidence

4. SABR may be curative

5. SABR is generally well tolerated

6. SABR is cost-effective

7. Treating all lesions is preferred

8. Optimal role and timing of systemic therapy is unknown

9. Don't count on abscopal effect

10. Innovative trial designs needed

Fig. 1. Summary of top ten lessons from trials in oligometastatic cancers infographic. RCT, randomized controlled trial; SABR, stereotactic ablative radiotherapy.

the modality of choice for local consolidative therapy in oligometastases [5].

There are several advantages of using SABR as the local therapy of choice in oligometastatic disease. SABR is non-invasive and can be delivered in the outpatient setting. SABR is also generally well-tolerated with few side effects (this will be further discussed in lesson #5). Perhaps most importantly for patients with metastases in multiple organs, SABR has the ability to treat numerous lesions in different locations in the same session. However, there are disadvantages to SABR to be borne in mind. SABR, unlikely surgery, does not provide material for pathologic analysis. A metastatic lesion can usually be treated only once with SABR, and certain medical

conditions (such as interstitial lung disease) can put patients at high risk of toxicity with radiation treatment. In addition, there can be difficulty assessing response to SABR treatment using frameworks such as the Response Evaluation Criteria in Solid Tumors (RECIST) criteria due to radiation-induced changes from treatment, sometimes leading to uncertainty about treatment success. For example, it has been demonstrated that the RECIST criteria have a poor predictive positive value in lung SABR [20], and these uncertain findings can lead to additional investigations.

Surgical intervention also has advantages: it allows for the ability to confirm pathology and to obtain tissue for molecular testing. However, surgery requires selection of candidates

Table 2. Summary of selected randomized trials in oligometastatic NSCLC

	Gomez et al. [2]	Iyengar et al. [3]	SINDAS (Wang et al.) [4]
Population	NSCLC	NSCLC	NSCLC EGFRm
Prior systemic therapy	Yes	Yes	No
Primary tumor	Allowed	Allowed	Allowed
Regional nodes	Allowed (together=1 lesion)	Allowed	Allowed (not counted in total)
No. of metastases	Up to 3 after systemic therapy	Up to 6	Up to 5

EGFRm, epidermal growth factor receptor mutant; NSCLC, non–small cell lung cancer.

sufficiently fit for an operation and usually requires hospitalization with time for post-operative recovery, which can delay systemic treatment. Ultimately, the choice of surgery vs. radiation may not impact outcome: the trial by Gomez et al. [2] demonstrated that local consolidative therapy including radiotherapy or surgery improved PFS in oligometastatic NSCLC, but did not detect differences in outcomes in patients who received radiotherapy vs. those who received surgery.

Another treatment option consists thermal ablative techniques, including RFA, microwave ablation or cryoablation. Ablation is suitable for patients who have comorbidities that increase their risk of surgical intervention. Advantages of ablation include that the procedure is minimally invasive and repeatable. However, ablation may be difficult with larger lesions or lesions that are not easily accessible (i.e., adjacent to critical organs). In addition, there is a heat sink effect when the lesion is in proximity of large blood vessels that may also limit the effectiveness of the treatment.

Regardless of the treatment modality, it is important to optimize and personalize treatments to patients with oligometastatic disease though a multi-disciplinary decision approach. The best candidates for local oligometastatic treatments include patients with good performance status, low burden of disease, effective systemic therapy options and small lesions where treatment is unlikely to cause toxicity [21].

Lesson #4: SABR May be Curative, Although Most Patients Progress with New Metastasis

SABR may potentially play a role in curing patients with oligometastatic disease. In long-term analysis of the SABR-COMET study that included 8-year follow-up described above, approximately one in five patients in the SABR arm achieved survival beyond 5 years without recurrence or progression. This plateau and stabilization of survival outcomes was evident particularly at years 4-8 following SABR treatment. In comparison, no patients in the control arm survived

beyond 5 years without progression or death [22]. These data suggest SABR may be potentially curative in select patients, however additional long-term analyses across trials will be needed to further support this.

Progression in the oligometastatic setting can happen quickly. In the SABR-COMET trial, the median PFS was 5.4 months with palliative standard of care treatment without SABR and 11.6 months with standard of care plus SABR [16]. A meta-analysis of prospective trials including patients with oligometastatic cancers treated with SABR reported a 1-year PFS rate of 51.4% [23]. This suggests approximately half of oligometastatic patients progress at one year even if they receive radiation.

Most patients recur with new metastases. The SABR-5 trial was a population-based single-arm phase 2 study of 381 patients that demonstrated that treatment with SABR in patients with oligometastatic disease resulted in a median PFS of 15 months [24]. Local control rates were 93% at 1-year and 87% at 3-years, suggesting SABR is effective in stabilizing the targeted lesion, however patients still progress with metastases in other sites.

For patients who recur, some can receive salvage therapy with repeat SABR. In the SABR-5 trial, 47 patients (12%) received a second course of SABR to new metastatic sites upon disease progression. Two patients underwent a third course of SABR, and one patient underwent a fourth course in this study [25]. Patients treated with SABR for oligometastatic should undergo surveillance with imaging and consideration of salvage SABR treatment if indicated.

Lesson #5: SABR Is Generally Well Tolerated (But Serious Toxicities Can Occur)

The original SABR-COMET study reported a 29% rate of grade 2 or higher toxicity, including 3 deaths in the SABR arm that were possibly, probably, or definitely related to treatment [16]. However, larger trials have demonstrated much lower toxicity estimates. The SABR-5 single-arm phase II clinical trial specifically investigated the toxic effects with

SABR for up to 5 oligometastases, using a population-based approach in order to ensure excellent ascertainment of outcomes. SABR-5 reported the rate of grade ≥ 2 toxicity was 18.6% and the rate of grade ≥ 3 toxicity was less than 5% [25]. In the real-world setting, outcomes of a national prospective registry-based observational study of patients with extracranial oligometastases undergoing SABR in the National Health Service in the UK have been published. In this cohort of 1,422 patients, the most common grade 3 adverse event was fatigue (2.0%), and the most common grade 4 event was elevated liver enzymes (0.6%). No treatment-related deaths were reported in this cohort [26]. A meta-analysis of 21 prospective trials characterizing the safety of SABR in oligometastatic cancer found the estimate for acute grade ≥ 3 toxicity rates under the random-effects model to be 1.2% and the estimate for late grade ≥ 3 toxicity was 1.7% [23]. This further supports SABR is associated with relatively low risk of toxicities.

Quality of life was also reported in long-term analysis of the SABR-COMET trial, demonstrating that SABR did not result in a detriment in quality of life [19,27]. A meta-analysis that included data from SABR-COMET, STOMP and a prospective trial in prostate cancer found that there was no difference in health-related quality life (HRQOL) at 12 months from baseline between patients who received SABR to those who did not. A small deterioration in HRQOL was seen in all patients at 12 months [28]. Therefore, SABR is generally well tolerated treatment with likely minimal impact to quality of life.

Lesson #6: SABR Is Cost-Effective

An economic evaluation of SABR from a health care system planning and resource perspective is also important to consider. Costs of treatment including medications and radiation are often highest in stage IV cancers [29]. Cost-effectiveness studies usually comprise of models that determine the costs associated with each quality-adjusted life-years (QALY) gained from a treatment intervention, known as the incremental cost-effectiveness ratio (ICER). This is usually compared to a "willingness-to-pay" (WTP) threshold which has been historically $50,000 per QALY, although more recently $100,000 per QALY is standard. An intervention is deemed cost-effective if the ICER is below the WTP threshold.

Several studies have demonstrated that SABR is cost-effective in the oligometastatic setting. A systematic review found nine studies evaluating the cost-effectiveness of SABR for oligometastases. Of the nine studies, five of the studies were specific to histology including lung, liver and prostate while four of the studies were based on studies with mixed histology. All but one study confirmed that SABR was cost-effective with a ICER ratio ranging between $28,000 per QALY to $55,000 per QALY. The median probability of achieving cost-effectiveness in these studies was approximately 61% at a $50,000 per QALY and 78% at a $100,000 per QALY WTP threshold [30]. Based on the current evidence, this is suggestive that SABR appears to be a cost-effective approach for oligometastases.

Qu et al. [31] demonstrated that SABR was cost-effective in 97% of all iterations with a WTP threshold of $100,000 per QALY based on the SABR-COMET trial. In a sensitivity analyses, the number of metastases treated with SABR was the parameter with the greatest influence on model output: more lesions requiring SABR made the strategy less cost-effective. SABR was cost-effective across the 95% confidence PFS HR reported in SABR-COMET (0.29-0.76) for three metastases, cost-effective at a PFS HR below 0.72 in four metastases and cost-effective at a PFS HR below 0.44 in 10 metastases, suggesting that trials including more metastases will have to demonstrate a larger PFS benefit for SABR to remain cost-effective.

SABR has also been shown to be a cost-effective intervention when compared to other local ablative therapies. In oligometastatic liver cancer and hepatocellular carcinoma, SABR was found to be the most cost-effective intervention when compared to surgery or RFA [32]. Reassessment of costs with longer-follow up as well as with phase III trial data will be required. In addition, costs in combination of other new systemic treatments such as immunotherapy will need to be considered to determine the most cost-effective standard of care for oligometastatic patients.

Lesson #7: Treating All Lesions Is Preferred

In the oligometastatic setting, there is growing evidence that aggressively treating all oligometastatic lesions is associated with improved outcomes. The ORIOLE trial evaluated patients with metastatic hormone sensitive prostate cancer randomized to SABR or observation. The study had found that patients who underwent total metastatic ablation (based on PSMA PET) compared to subtotal metastatic ablation had better PFS (not reached vs. 11.8 months) and distant-metastasis–free survival (29.0 months vs. 6.0 months) [12]. In addition, a retrospective study of 401 patients with mixed histology undergoing SABR for one to five metastases for oligometastases at the Peter MacCallum Cancer Centre found that total metastatic ablation was prognostic for OS (adjusted HR, 0.8) and PFS (adjusted HR, 0.6) as compared to patients with subtotal ablation. This effect was consistent in meta-

chronous vs. synchronous disease subgroups [33]. Treating all metastatic lesions may reduce the risk of new metastases developing from untreated lesions. In addition, consolidating all oligometastatic lesions decreases the overall tumor burden and can lead to a synergistic effect in combination with systemic therapy including targeted therapies/immunotherapy (further discussed in lesson #8).

Lesson #8: Optimal Role and Timing of Systemic Therapy Is Unknown

The Norton-Simon hypothesis states that cancer cell death in response to treatment is inversely proportional to tumor burden at time of treatment [34]. Specifically, a given systemic therapy at a given dose is less effective as the overall tumor burden increases. Reducing the overall tumor burden with local treatments such as SABR could allow systemic therapy to become more effective in achieving cell kill.

The majority of published RCTs in the oligometastatic setting were conducted prior to the adoption of several novel systemic treatments, that are now part of standard practice, including immunotherapy and some newer targeted agents. As a result, their optimal combination with SABR continues to remain largely unknown. A meta-analysis of 51 studies including all disease sites report that the potential combination of SABR and immune checkpoint inhibitors (based on prospective/retrospective studies with an arm treated with any combination of radiation and immunotherapy) is associated with similar toxicity profiles to immune checkpoint inhibitors alone (based on phase III/IV trials that compared any immunotherapy to placebo) [35]. As a result, the combination of SABR and immunotherapy has a potential role to improve oncological outcomes without compromising patient quality of life.

Currently, the optimal sequencing of systemic therapy and ablative treatment remains unknown. In some RCTs, including the Gomez trial and the Iyengar trial, patients received chemotherapy prior to ablative therapy (Table 2) [2,3]. However, some trials included targeted therapies/ immunotherapies following SABR. The phase III SINDAS trial that evaluated patients with epidermal growth factor receptor (*EGFR*)–mutated NSCLC with 1-5 metastases randomized to receive SABR followed by tyrosine kinase inhibitor had PFS and OS benefit [4]. A phase trial II by Bauml et al. [36] found that local therapy (surgery or stereotactic radiotherapy) followed by pembrolizumab in oligometastatic NSCLC was associated with improved PFS with no reduction in quality of life. The RAPPORT phase I/II trial demonstrated that SABR followed by pembrolizumab was well-tolerated and had excellent local control in low-volume

metastatic kidney cancer [37]. In addition, analysis of the SABR-5 trial revealed initiation or change in systemic treatment around the time of SABR before any disease progression was associated with improved PFS (HR, 0.50) [24]. There is a need to explore the combination of SABR and immunotherapy in future clinical trials, particularly in clarifying not only the timing of systemic treatment but also dose/fractionation when SABR is integrated with targeted therapy/ immunotherapy.

Lesson #9: Don't Count on the Abscopal Effect

The abscopal effect has been known since at least 1953 when researchers observed that treating a tumor on one side of the mouse with radiation could lead to the shrinkage of an untreated tumor on the contralateral side [38]. The effect is defined by the shrinkage of tumours in parts of the body that was not the direct target of local therapy (such as radiation). There have been a number of preclinical studies that have demonstrated the effect [39]. However, the abscopal effect is a fairly rare phenomenon observed in the clinical setting. A meta-analysis from 1954-2019 found a total of 50 case reports that observed this effect [40].

The abscopal effect is described as a potential hypothesis behind the synergistic effect of SABR and immunotherapy combined therapy. The theory is that SABR improves the efficacy of immunotherapy and thus facilitating regression of metastases not directly treated with SABR.

Randomized trials assessing the abscopal effect have been mostly negative. A pooled analysis of the PEMBRO-RT and MDACC trials assessed metastatic NSCLC patients receiving pembrolizumab with or without radiotherapy found that patients undergoing radiation had a higher abscopal response rate (41.7% vs. 19.7%) [41]. However, other phase II clinical trials that evaluated the combination of SABR and immunotherapy have failed to demonstrate the abscopal effect in a variety of histologies [42] including renal cell carcinoma [43], head and neck [44], NSCLC [45], cervical/ endometrial [46] and colorectal cancer [47]. This includes the ongoing CHEERS trial, a multicenter phase II trial randomizing locally advanced or metastatic patients to receive SABR and anti-PD-(L)1 immunotherapy or immunotherapy alone. Preliminary results presented at ESTRO 2021 found that there was no effect on PFS, with a median PFS of 4.4 months in the experimental arm and median PFS of 2.8 months in the standard arm [42]. Another example is the phase II trial conducted by McBride et al. [44] randomizing metastatic head and neck squamous cell carcinoma to nivolumab plus SABR versus nivolumab alone. There was no significant difference in OS, PFS or response duration [44]. Therefore, at this cur-

Table 3. Summary of selected ongoing phase III randomized trials conducted in oligometastatic cancers

Histology	Trial name	Clinicaltrials.gov No.	No. of metastases	Type of treatment	Primary end point
NSCLC	OMEGA	NCT03827577	1-3	Surgery or SABR or RFA	OS
	SARON	NCT02417662	1-5	RT	OS
	NRG LU002	NCT03137771	1-3	SABR	OS, PFS
Prostate	CORE	NCT02759783	1-3	SABR	PFS
	PLATON	NCT03784755	1-5	Surgery or SABR	Failure-free survival
	PRESTO	NCT04115007	1-5	SABR	Castrate-resistant prostate cancer–free survival
Breast	OLIGOMA	NCT04495309	1-5	SABR	PFS, QoL
Esophageal /Gastric	ECOG-ACRIN EA2183	NCT04248452	1-3	RT	OS
Multiple	SABR-COMET-3	NCT03862911	1-3	SABR	OS
	SABR-COMET-10	NCT03721341	4-10	SABR	OS
	OLIGORARE	NCT04498767	1-5	SABR	OS

OS, overall survival; PFS, progression-free survival; QoL, quality of life; RFA, radiofrequency ablation; RT, radiotherapy; SABR, stereotactic ablative radiotherapy.

rent time, there has been limited evidence of the abscopal effect in RCTs, but future trials that are underway will provide more clarity as they complete accrual [48-50].

Lesson #10: Innovative Trial Designs May Be Needed to Overcome Accrual Difficulties

RCTs are considered the gold standard providing the highest level of evidence for evaluating interventions. However, many trials have difficulty recruiting patients and fail. In a review of phase II/III clinical trials in oncology initiated between 2005 to 2011, approximately 20% of cancer trials failed to complete, with the most common reason being poor accrual (39%) [51]. Nguyen et al. [52] reviewed 134 RCTs involving radiation and found a failure rate of 29.9% with poor accrual also the dominant reason for trial failure (57.5%). Other reasons for trial failure included inadequate funding (15.0%), drug unavailability (7.5%), interim data-monitoring report recommendations (7.5%), and other (12.5%).

There are many factors that influence the failure rate of RCTs. In RCTs involving radiation, trials with a surgical comparator was associated with a very high rate of failure (75%). This rate was higher than in surgical oncology trials themselves. Other predictors of failure included government sponsorship, inclusion of a safety endpoint, and studies starting after 2006, this latter finding potentially reflective of increasing administrative burden over time [52]. A survey of investigators participating in SABR-COMET evaluated the factors influencing accrual rates, and found that off-trial availability of SABR was associated with lower accrual rates.

In addition, equipoise of the referring physician was associated with higher accrual rates. This is hypothesized to relate to the initial discussions about SABR with the patient by the referring physician, which could influence the perception of the benefits of treatment and subsequent willingness to enroll in a randomized trial [53].

In light of the difficulties in accruing, trial design may need to take a more pragmatic approach. Ideally, RCTs for oligometastases would include only single histologies, but such trials are at risk of failure due to poor accrual. One example of the challenges of single-histology trials is the Stereotactic Radiation for Oligo-Progressive Cancers (STOP) trial, a multi-center phase II trial randomizing between SABR vs. standard of care systemic treatment for patients with up to 1-5 oligo-progressive lesions. Initially, the trial was designed for patients with NSCLC but it did not meet pre-specified accrual targets. Participating investigators from the Canadian Pulmonary Radiotherapy Investigators group were tasked with the decision of either discontinuing the trial or expanding it to all histologies. The latter option was chosen, and accrual was completed [54]. In trial design, rather than having a perfect answer to a clinical question by designing a perfect trial (i.e., limiting the trial to NSCLC) but risking failure, it is sometimes preferable to take a more pragmatic approach, looking for a good, but imperfect answer from a trial that can complete accrual.

Given the difficulties with accrual, investigators may need to employ innovative new trial designs. An example is the ongoing EXTEND trial, which is a prospective randomized basket trial that evaluates PFS with local consolidative therapy for various oligometastatic histologies. Primary

analysis involves assessing the individual histology baskets separately with planned secondary analyses combining baskets. Prior to the opening of the trial, a "lead-in" phase was conducted to assess the likelihood of accrual in each of these baskets and found that prostate, breast and kidney had the highest enrollment which helped to inform feasibility [55]. The OligoRARE phase III randomized trial takes a different approach to addressing uncommon histologies. OligoRARE only enrols patients with less-common cancer types, specifically excluding patients with oligometastases from lung, breast, colorectal, or prostate origin, with a primary endpoint of OS [56].

Conclusion: We Are Entering the Era of Phase 3 RCTs

At this current time, there is no standard in defining the number of lesions in oligometastatic disease, and we may never have an exact cut-off. There continues to be a range in the number of metastases treated in ongoing clinical trials, with most defining "oligometastatic" as 1-3 or 1-5 lesions (Table 3). Local ablative therapies, including SABR, has shown OS and PFS benefits in phase II RCTs. The advantages of SABR include being a non-invasive, cost-effective treatment that is generally well tolerated with minimal impact on quality of life. There is also some data suggesting that SABR may be potentially curative in select patients and there may be a role of salvage SABR for metastases that emerge after initial ablative therapies. The optimal role and timing of local ablative therapy with systemic therapy including targeted therapy/immunotherapy continues to be unknown and future clinical trials are required to clarify this combination.

Moving forward, phase III trials will conclusively test the benefits of local aggressive treatment in oligometastatic disease. There are phase III trials underway including SABR-COMET-3 (NCT03862911) and SABR-COMET-10 (NCT-03721341) that will assess the impact of SABR in patients with 1-3 and 4-10 metastases respectively in multiple histologies [8,57]. It will also provide histology-specific evidence with a several of histology-specific phase 3 trials underway. Accrual continues to be a challenge in running such randomized trials, as such innovative trial designs are needed to overcome these difficulties.

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Conflicts of Interest
Dr Palma reports a Clinician-Scientist Grant from the Ontario Institute for Cancer Research, royalties from Uptodate.com, and a consultant role with equity at Need Inc, all unrelated to the current work. Remaining author has declared no conflicts of interest.

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