Radiotherapy for oligometastatic non-small cell lung cancer: a narrative review

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Abstract: Preclinical and early clinical evidence suggest that radical radiotherapy of oligometastatic disease in non-small cell lung cancer (NSCLC) patients can impact outcomes with relatively limited toxicity. Whilst data from phase 2 randomized trials suggesting an improved overall survival (OS) with this treatment is promising, it has also illustrated the heterogeneity in this patient population and treatment. Oligometastatic disease in itself comprises a broad spectrum of patients, in terms of tumor load and location, stage of the disease and treatment history. This real-life variety in patient characteristics is often reflected in studies to a certain extent, hinting to the fact that all might benefit from radical radiotherapy to limited metastatic disease, yet leaving the question unanswered as to whom the ideal candidate is. Furthermore, differences between and within studies with regards to treatment modality, timing, radiation technique, and radiation dose are substantial. Also, preclinical and early clinical trials suggest that radiotherapy can work synergistically with checkpoint inhibitors by acting as an *in situ* cancer vaccine, therefore the combination of these two treatments in oligometastatic patients might entail the largest benefit. Ongoing randomized controlled phase 3 trials and prospective registry trials will further elucidate the true extent of benefit of this local treatment strategy and aid in identifying the ideal patient population and therapy. The current narrative review summarizes the clinical evidence on radiotherapy for oligometastatic NSCLC and highlights the remaining unknowns.

Keywords: Oligometastatic; non-small cell lung cancer (NSCLC); radiotherapy

Introduction

Over the past three decades, it became clear that the oligometastatic disease state—as initially described by Hellman and Weichselbaum—is a separate clinical entity on the spectrum of metastatic disease (1). Retrospective studies indicated that patients with metastatic disease most often first progress in sites of known disease rather than in new sites (2-4), leading to the hypothesis that radical treatment of visible lesions might impact the disease course. In the case of limited metastatic disease, eradication of all disease might abrogate further dissemination and could potentially lead to cure. Progress in both radiation and surgical techniques has allowed the relatively safe radical treatment of metastases. Whilst systemic therapy used to be the only mainstay for patients with spread disease, clinical evidence now corroborates the hypothesis that radical treatment of oligometastatic disease might impact survival (5-11).

Whereas some patients with non-small cell lung cancer (NSCLC) may naturally exhibit a more indolent disease course, with development of oligometastatic rather than polymetastic disease—at diagnosis or as a first presentation

of disease recurrence—progress in systemic therapies, including targeted treatments and checkpoint inhibitors (12,13), has resulted in a selection of patients showing a significantly prolonged disease course in which treatment can sometimes induce an oligometastatic state in initially polymetastatic patients. As a result, it is plausible that the patient population exhibiting an oligometastatic phenotype has grown over the past decades.

Furthermore, the diagnosis of this oligometastatic presentation is predominantly based on imaging (14). Highly sensitive imaging via positron emission tomography-computed tomography (PET-CT) has been the standard of care imaging technique in patients with NSCLC for over a decade, which has perhaps led to more frequent diagnoses of the oligometastatic disease state in this tumor type as compared to others where less sensitive imaging techniques were used. This may explain the early adoption of studies on radical treatment of oligometastatic disease in this tumor type (6,15,16).

In other disease types, such as prostate cancer, ablative radiotherapy has been given in an attempt to defer systemic therapy and its related negative impact on quality of life (17). Given the limited toxicity, radical radiotherapy of oligometastatic disease might indeed form an appealing option in frail patients, not amenable to aggressive systemic therapy. This may especially hold true for the NSCLC population, given the etiological association with smoking, with many patients having multiple comorbidities and a limited performance status. Still, given the quickly progressing nature of lung cancer, where even in those who can tolerate systemic agents outcome remains grim (18), radical radiotherapy for oligometastatic disease is typically given as an additional treatment with the aim of consolidating or prolonging the effect of systemic therapy (5,6,15,16). Moreover, data are emerging suggesting that radiotherapy might also be able to synergize and reinforce systemic treatment.

The current article reviews clinical evidence on radiotherapy in oligometastatic NSCLC patients, and digs deeper into the interplay between patient and tumor characteristics, and radiation techniques and doses utilized for this treatment, whilst highlighting the remaining unknowns. Literature was searched via PubMed using the terms 'non-small cell lung cancer', 'oligometastatic', 'radiotherapy', 'radical treatment' and variants thereof, whilst focusing on prospective trials. Additional relevant publications were found by hand searching reference lists. We present the following article in accordance with the Narrative Review reporting checklist (available at http://

dx.doi.org/10.21037/tlcr-20-1051).

Clinical evidence

Multiple single-arm prospective studies, three randomized phase II trials and the interim results of a phase III randomized controlled trial evaluating local consolidative treatment in patients with oligometastatic NSCLC have been reported (https://cdn.amegroups.cn/static/public/tlcr-20-1051-1.pdf).

Gomez *et al.* (6,7) performed a randomized phase II trial, comparing local consolidative therapy to standard maintenance treatment or observation in NSCLC patients without progression after approximately three months of first line treatment, being chemotherapy or epidermal growth factor receptor (EGFR) inhibitors (in case of EGFR mutation) or anaplastic lymphoma kinase (ALK) inhibitors (in case of ALK rearrangement). Patients with a maximum of three (extra- or intracranial) metastases after three months of systemic treatment were allowed, hence including both genuine and induced oligometastatic disease (19). Regional nodal disease was allowed and collectively counted as one lesion. Consolidative therapy could be either surgery or radiotherapy, whereby stereotactic radiotherapy, hypofractionated radiotherapy and concurrent chemoradiotherapy were options; dose-fractionation regimens were at physician's discretion. The trial was terminated early after randomization of 49 patients, as an interim analysis indicated a 99% probability of superiority of the experimental arm. A median progression-free survival (PFS) of 14.2 months was noted in the local consolidative therapy arm, versus 4.4 months in the control arm, translating into a significant overall survival (OS) benefit (median of 41.2 months OS in the experimental arm versus 17 months in the control arm). Importantly, this OS benefit was observed even though crossover was permitted, with 9 of 24 patients in the control arm receiving local consolidative therapy upon progression. This suggests that local consolidative therapy is ideally given early in the disease course, without waiting for progression. Yet, even delayed local ablation given at the time of progression partly compensated for the loss in outcome of not giving immediate treatment, be it with the risk of losing a subset of patients to polymetastatic disease or declining performance status. Notably, time to appearance of a new lesion was also longer in the experimental arm, being 14.2 months as compared to 6.0 months. This again suggests that residual macroscopic tumor deposits may be the first focus

of subsequent metastatic spread, that can be prevented or delayed by local therapy. No grade 4 or 5 adverse events were noted.

A similar phase II trial by Iyengar *et al.* (5) was conducted in NSCLC patients with up to six extracranial disease sites, including the primary, without progressive disease after induction chemotherapy. Patients with targetable genetic changes or uncontrolled/untreated intracranial disease were not allowed. Randomization was performed between maintenance chemotherapy and stereotactic body radiotherapy (SBRT) or hypofractionated radiotherapy to all visible disease followed by maintenance chemotherapy. Twenty-nine patients were included and randomized. Median PFS was significantly longer in the experimental arm at 9.7 months, as compared to 3.5 months in the maintenance chemotherapy arm. Median OS was not reached in the experimental arm and 17 months in the control arm. No grade 4 or 5 toxicity was reported in the radiotherapy arm.

The phase III SINDAS trial (8) recently reported interim results. This trial compared first-line TKI with or without upfront local radiotherapy in oligometastatic EGFR mutated NSCLC patients. Patients were allowed to have a maximum of five metastatic lesions. SBRT was administered at a dose of 25–40 Gray (Gy) in five fractions to all disease sites. A planned interim analysis after randomization of 133 patients showed a significantly improved PFS from 12.5 to 20.2 months, as well as an improved OS from 17.4 to 25.5 months. No excess toxicity was noted between arms, no grade 5 events were observed. Of interest, so far 631 patients were screened for this trial, illustrating the difficulty of finding the correct patient population. Screening numbers are unfortunately not available for the trials by Gomez *et al.* and Iyengar *et al.*

The SABR-COMET trial (9,10) was a randomized phase II basket trial in patients with a maximum of five extra- or intracranial metastases and a previously treated and controlled primary tumor of any origin. Randomization occurred 2:1 to either SBRT to all metastases and standard of care systemic treatment, or standard of care systemic treatment alone. Doses for SBRT ranged from 30–60 Gy in 3-8 fractions, or 16–24 Gy in a single fraction for brain or vertebral metastases. Ninety-nine patients were enrolled, of which 66 in the experimental arm. In both arms, 18% of patients had a primary lung cancer, yet it is unknown how many of these patients had NSCLC. PFS was significantly longer in the experimental arm as compared to the control

arm, at 11.6 versus 5.4 months respectively. Median OS was significantly improved to a larger extent than PFS from 28 months in the control arm to 50 months in the experimental arm. Even though baseline characteristics between both arms were not balanced with more prostate cancer patients in the experimental arm, a post hoc sensitivity analysis excluding these patients continues to show a significant survival improvement due to the addition of SBRT. In contrast to the findings of Gomez *et al.*, no difference was noted between arms for the time to new metastasis. In this trial, consolidative radiotherapy unfortunately came at a cost: SBRT treatment was associated with a 20% increase in grade 2 or higher toxicity, while three patients experienced grade 5 toxicity, with their death possibly, probably or definitely related to treatment.

The majority of trials did not observe excess toxicity in the radiotherapy arm, which is corroborated by single arm prospective trials reporting grade 3 adverse events generally in less than 10% of patients, and grade 4 adverse events only very rarely (3,5,8,15,20-25). In contrast, higher toxicity was noted in the SABR-COMET trial, the trial by Gomez *et al.* and the trial by De Ruysscher *et al.* (6,7,9,10,16) Most strikingly, the SABR-COMET trial (9,10) reported a 20% increase in grade 2 or higher toxicity, observed in 9% of patients in the control arm versus 29% of patients in the SBRT arm. Grade 3 toxicity was limited, with dyspnea and pain being observed in the SBRT arm in only 1 and 3 patients respectively; in the control arm one patient with grade 3 fatigue was the only grade 3 adverse event. Sadly, three deaths occurred in the SBRT arm, i.e., due to a radiation pneumonitis after SBRT to a central lung metastasis, a pulmonary abscess at the location of previous SBRT, and a subdural hemorrhage occurring after reparative surgery for an SBRT-related perforated gastric ulcer. The earliest single-arm prospective trial by De Ruysscher *et al.* (16) investigated upfront radical treatment, be it (a combination of) surgery, radiotherapy or radiochemotherapy, of all visible disease—including the primary—in 39 newly diagnosed oligometastatic NSCLC patients. No grade 4 or 5 toxicity was observed, yet 15% of patients experienced grade 3 oesophagitis and one patient had a grade 3 cough. In the trial by Gomez *et al.*, 5 out of 25 patients in the experimental arm had grade 3 adverse events, as compared to 2 patients in the control arm (6,7). These findings suggest that whilst radiotherapy to visible disease in oligometastatic patients is tolerated well in the majority of patients, a small risk for severe, potentially

lethal, toxicity exists.

Radiation techniques and the search for the ideal dose

Radiation treatments in the studies varied from SBRT, to hypofractionated radiotherapy and conventional radio(chemo)therapy, where the latter may have been delivered with 3D-conformal radiotherapy as well as using intensity modulations. Given this discrepancy and lack of randomization between techniques, it is impossible to ascertain whether there is a preferred—more effective—radiotherapy approach in this setting (3,5-10,15,16,20-25).

In parallel to the techniques used and the association to chemotherapy—or not—the administered doses varied substantially between and within studies (3,5-10,15,16,20-25), ranging from a biologically effective dose (BED) of 39 Gy (for 30 Gy in ten fractions) to 151 Gy (for 54 Gy in three fractions) (for an α/β =10). Local control of lesions treated with radiotherapy in these trials varied between 63% and 100% and was better than in the control arms (5-7,9,10). Even though multiple retrospective and prospective series in metastases from various primary tumors indicate better local control with higher biologically effective radiation doses (6,22,26-37), further prospective data regarding the ideal dose is awaited. Higher doses resulting in better local control was not clearly observed in the majority of prospective trials including lung cancer patients, nor was it evident when comparing between trials (3,5-10,15,16,20-25). A previous retrospective analysis of SBRT for lung metastases has suggested the dose-response plateaus at 160 Gy BED [planning target volume (PTV) maximum dose], yielding a tumor control probability of 90%. If administered in three fractions, this corresponds to the PTV encompassing doses of 11.2–16.8 Gy (60–90% of the maximum dose) (38). The safety of such high SBRT doses in, for instance, lung oligometastases has been extrapolated from stage I NSCLC and was confirmed in three dose-escalation studies in the oligometastatic setting (20,22,25,38). As suggested by Guckenberger et al. (38), it is however uncertain whether the maximum tolerated dose in the setting of oligometastatic disease is preferable, as the evidence is based on phase I trials where patients on average had 1–2 lung metastases. Yet in everyday clinic, many patients have more than one or two metastases to be treated, and are likely to progress at a certain point, perhaps needing further local radiotherapy to other lesions. Furthermore, as is evidenced by the SABR-COMET trial, there is a risk, albeit small, for important—even lethal—toxicity (9,10), and previous

reports have shown that the higher the dose, the higher the risk of toxicity (39).

Even though tumor control probability at a certain radiation dose is likely to be similar regardless of the location of the metastasis, similar radiation doses (40,41) do not entail the same toxicity risk in different organs or for different lesion sizes. For instance, a safe dose for a small peripheral lung metastasis (e.g., 60 Gy in three fractions), would be too toxic and unacceptable for a very large peripheral lung metastasis, or a gastro-intestinal or central lung metastasis. In the latter situation, it is necessary to limit the radiation dose to ensure a safe treatment, which unfortunately will reduce the probability of tumor control, similar to what has been observed in risk-adapted SBRT for early-stage NSCLC (42). The SABR-COMET trial also showed that even when dose prescriptions are altered and reduced to meet normal tissue safety constraints, toxicity cannot be ruled out, illustrating the difficulty of risk prediction (9,10).

The ideal radiation dose should therefore balance both the benefit of tumor control probability and the risk of toxicity in light of the lesion location, the lesion size, and potential multiple radiation courses, with safety of SBRT being the absolute priority (32).

Outcome per location: an intricate interplay of dose, volume and primary tumor

The location and size of the oligometastasis will therefore affect the deliverable radiation dose, which in turn influences the tumor control probability. This interplay can explain why different local control rates are observed based on the organ of the metastasis. Furthermore, the evidence concerning these local control rates tends to come from multiple different tumor types with varying radiosensitivity, in patients who may or may not have been receiving systemic treatment. All of these factors will alter the tumor control probability, adding other layers of complexity.

The SABR-COMET trial noted different local control rates depending on the organ of the metastasis, with 100% for adrenal metastases, 72% for bone metastases, 51% for lung metastases and 50% for liver metastases (9,10). For adrenal metastases, this high local control rate is however not concordant with previous reports, showing 1- and 2-year local control rates after radiotherapy for adrenal metastases of 55–73% (43-45) and 27–46.6% (44-47), respectively. This is contrary to bone metastases, where in general high local control rates after radiotherapy have been reported,

ranging between 80–96% and 73–93% at 1- and 2-year, respectively (48-57).

Nonetheless, a handful of retrospective series on metastatic NSCLC patients with bone metastases unfortunately suggest poor outcomes for these patients with a 2-year survival of only 13% (58-61). The discrepancy between these good local control rates and poor outcomes is presumably due to the limited amount of data available for this specific population, making treatment recommendations difficult (58-61).

Rusthoven et al. reported on a phase I/II dose escalation trial in patients with pulmonary metastases. SBRT dose was escalated from 48 to 60 Gy in three fractions in 38 patients (of whom five with a primary lung tumor). Local control rates were excellent at 100% and 96% at 1- and 2-year follow-up respectively (20). Similar high local control rates in the order of magnitude of 90% at 1 year and 80% at 2 years have been reported in retrospective studies, again including a multitude of primary tumors (39,62-64). De Rose et al. reported on 60 NSCLC patients with 90 lung metastases treated with SBRT (64). SBRT dose was 60 Gy in three to eight fractions for lesions up to 2 cm, and 48 Gy in four fractions for lesions between 2–5 cm. Using this dose-adapted scheme to mitigate toxicity, a 2-year local control rate of 88.9% was observed. Of interest, these high local control rates are in the same order of magnitude as what has been reported in early-stage NSCLC treated with SBRT (65). In a retrospective multi-centre series of 399 patients with primary NSCLC and 397 patients with pulmonary metastases from various primary origins, similar tumor control probabilities were found in both groups (38).

As for liver metastases, a phase I/II trial assessed the safety and local control of SBRT to one to three hepatic metastases. Dose was escalated from 36 to 60 Gy in three fractions, leading to a local control rate of 95% and 92% at 1 and 2 years follow-up respectively (21). Local control was 100% in lesions below 3 cm, but dropped to 77% for lesions beyond 3 cm. A large retrospective analysis of 474 patients who received SBRT to liver metastases, including 29 NSCLC patients, showed a 1-year local control rate of 76.1% for the whole group and 88% for the NSCLC patients (26). This large, real-life multicenter cohort illustrates how differences in dose prescriptions, concomitant systemic therapy and primary tumor histology can affect the outcome. The good local control rate in this study is corroborated by a meta-analysis of retrospective studies comparing SBRT to radiofrequency ablation (RFA) for liver metastases of various origins, showing a 2-year

local control rate of 83.6% for SBRT (66).

Patients with intracranial oligometastases are often studied and reported separately from those with extracranial oligometastases, even though consensus converges towards the inclusion of these patients in future studies on oligometastatic disease (32). Several retrospective analyses have reported on patients with NSCLC and oligometastastic synchronous brain metastases treated with radiotherapy (67-71). Yang et al. focused on patients with thoracic stage I or II NSCLC and one to three synchronous brain metastases without extracranial metastases. All patients underwent Gamma Knife radiosurgery for their intracranial disease to a dose of 15 to 25 Gy, with or without thoracic surgery to the primary. Only two of 31 patients had local intracranial failure, resulting in a 97.1% and 93.5% 1- and 2-year local control rate for metastatic brain tumors (70). Hu et al. (69) reported on patients with a single brain metastasis receiving stereotactic radiosurgery (n=31) or neurosurgical resection (n=53). Local control rates at 1 and 2 years were both 61% for the radiosurgery group, compared to 97% and 88% for the neurosurgical group, respectively. However, due to the retrospective nature of this study, this difference in local control between treatment modality might be due to patient selection. Unfortunately, no randomized data exists comparing radiosurgery to neurosurgery for limited intracranial metastases.

Similarly, no head-to-head comparison exists between radiotherapy and surgery or RFA for extracranial metastatic disease (47). A recent meta-analysis of retrospective studies suggests that SBRT may lead to improved 2-year local control rates as compared to RFA for liver metastases, at 83.6% and 60% respectively (66). This difference in outcome seems to especially hold for lesions larger than 2 cm (72). In retrospective studies, surgery tends to either have similar or better outcomes than radiotherapy (62,66,73). Yet, when comparing different treatment modalities using retrospective data, the results are inherently biased. Even if baseline patient characteristics are matched, there remain unknown variables which can impact on prognosis regardless of treatment. Patients fit for surgery tend to have a better prognosis from the start, with a better performance status, less comorbidities and smaller metastases. This is supported by a study by Soni et al. (74) which compared results of observational studies in the oncological field, to results of subsequent randomized controlled trials seeking to answer the same question. This showed that observational studies are more likely to favor outcomes after surgery than after radiotherapy; a pattern not observed in randomized controlled trials. Hence, in

the absence of randomized controlled trials comparing SBRT to other loco-regional treatment strategies, no firm conclusions can be drawn.

How to select the right patient that will benefit from radiotherapy?

Whom is regarded as an oligometastatic patient and which treatments are offered tends to differ from physician to physician and has shifted over time, with a tendency to reserve radical local therapy such as SBRT for patients not progressing after systemic therapy (75). Furthermore, as compared to the theoretical definition of oligometastatic disease based on number of lesions, in the real-life setting, physicians tend to be more restrictive as to who they label as oligometastatic (75). Multiple studies have evaluated and suggested clinical prognostic markers to guide patient selection (19,76-79), however, these are all based on retrospective data, and have not yet been prospectively validated. It also remains uncertain whether these prognostic factors merely allow selection of patient groups with a better prognosis per se, or whether they can truly predict who will benefit from radical treatment of their oligometastases. Aside from the fact that the cut-off of oligometastatic disease is generally arbitrarily set to a maximum of three or five metastases, this clinical and radiological entity that is referred to as 'oligometastatic disease' comprises a broad and variable spectrum of disease states, with presumably substantially different underlying tumor biology (19). This variability is also reflected in the prospective and randomized trials evaluating the benefit of local consolidative therapy in NSCLC patients with limited metastatic burden, which often included patients from different parts of the oligometastatic spectrum, based on divergent inclusion criteria (https://cdn.amegroups.cn/static/public/tlcr-20-1051-1.pdf) (3,5-10,15,16,20-25).

The maximum number of metastases, the activity of the lesions (i.e., new, stable or progressing), the setting (i.e., synchronous, metachronous, or induced oligometastasis, or oligorecurrent, oligopersistent or oligoprogressive), all or not in the context of systemic treatment and whether or not regional nodal metastases were included in the number of lesions; all these factors showed high variability (3,5-10,15,16,20-25). Gomez et al. (6,7) allowed patients with up to three synchronous or metachronous metastatic lesions and counted the lesions after first-line systemic treatment, hence allowing patients with prior polymetastatic disease. Regional nodal disease was collectively counted

as one lesion. The trial by Petty et al. (3) allowed patients with up to five synchronous or metachronous metastatic lesions with a maximum of three lesions in any extracranial organ. Regional nodal disease was allowed and was not counted towards this number. De Ruysscher et al. (16) only allowed patients with synchronous oligometastatic disease with a maximum of five metastases, yet strikingly the eventual patient population was more restrictive, consisting of 87.2% of patients with a single metastasis, 10.3% with two metastases, 2.6% with three metastases and none with more. Regional nodal disease was likely not counted as metastatic disease. The randomized trial by Iyengar et al. (5) included patients with a maximum of six synchronous extracranial metastases, including the primary but not involving the gastro-intestinal tract or the skin. The single arm trial by the same group (15) included patients with the same number and sites of metastases, yet progressive after at least one line of chemotherapy. It is uncertain whether induced oligometastatic disease was allowed in this trial. Important to note, even though the extent and number of nodal metastases are often disregarded in trials, in other words, accounted for in the loco-regional disease, their presence might significantly impact the prognosis (80). A recent pan-European consensus report recommended that mediastinal lymph nodes should not be considered as a metastatic site in oligometastatic NSCLC, yet should be regarded as regional disease. They do however acknowledge that the extent of nodal disease impacts radical treatment options, as was previously also suggested on the basis of a meta-analysis (79,81). Further prospective evidence on this topic remains necessary. Furthermore, not only the extent of local disease is of importance, but also whether or not the disease is controlled. There is a discrepancy between trials whether or not patients with active and progressing local disease were allowed and if so, how this was treated (3,5-10,15,16,20-25). Also, not all trials mandated the use of PET-CT imaging to determine the number of metastases, while using less sensitive imaging might lead to different oligometastatic patient populations. For example, a patient with three metastases on CT imaging might have additional small PET-avid lesions, occult on CT, and hence only be regarded as oligometastatic when using CT imaging, not when using PET-CT. By using less sensitive imaging patients will be down-staged and the resultant oligometastatic population will inherently have a worse prognosis than the oligometastatic population based on PET-CT (82).

From the above it becomes evident that the large heterogeneity in clinical practice (75,83) is reflected in

prospective radiotherapy research on oligometastatic disease where the included patients are heterogeneous between and within trials (3,5-10,15,16,20-25). This hints to the fact that a variety of patients might benefit from local radiotherapy to visible disease, yet leaves us in the dark as to whom the ideal candidates are. Targeted biomarkers aiding in patient selection for this treatment would be useful, yet are unfortunately still awaited.

Future perspectives in this rapidly evolving field

Results from randomized phase 2 trials suggest that radical treatment of oligometastases in NSCLC patients can prolong OS. Yet, multiple phase 3 trials, such as the SABR-COMET-3, SARON and OMEGA trial, are currently ongoing and awaited to confirm this benefit.

As previously stated, current unresolved issues include the ideal treatment modality. Radiotherapy, surgery and potentially RFA are likely to be options for this radical treatment, as prospective trials have allowed different treatment modalities without indication of a clear benefit of any treatment modality over another. Further evidence to better define the choice for one or the other treatment modality would be optimal, but seeing the large variation in clinical presentation, in a population with often important co-morbidities, the potential benefit and harms of a treatment should always be weighed on a patient by patient basis. This can best be obtained through multidisciplinary team discussion, in the context of a comprehensive cancer center (75,84).

The ideal timing of radiotherapy both in the disease course and relative to systemic treatment is yet to be determined. The trial by Gomez *et al.*, indicating a survival benefit for local consolidative treatment, allowed crossover of patients in the control arm to local consolidative treatment upon progression, which nine of 24 patients in this arm received (6,7). Almost a third of patients in the control arm however progressed into polymetastatic disease, suggesting that radical treatment of oligometastases early in the disease course is key in order not to miss the window of opportunity. Whether or not systemic treatment should be administered sequentially, concomitantly or be withheld when considering radical treatment of visible disease, is unknown. Preclinical and early clinical data suggest that radiotherapy might work in synergy with immunotherapy (85-89). The hypothesis goes that whilst the brake on the immune system is released by checkpoint inhibitors, local radiotherapy instigates the release of tumor-specific antigen and ignites a pro-inflammatory tumor micro-environment, aiding recognition of the malignant cells locally and distant to the irradiated lesion. The latter is coined the 'abscopal' effect (89). Preclinical data suggests that hypofractionated radiotherapy, e.g., 24 Gy in three fractions would be ideal in triggering this effect (90). The accumulating evidence on immunotherapy in NSCLC has recently led to a change in practice in advanced and in locally-advanced disease (91,92). While in the latter the addition of immunotherapy to concurrent chemoradiotherapy has already become the new standard, in oligometastatic disease, radiotherapy to all or part of the macroscopic lesions in combination with immunotherapy might similarly herald advantages in long-term survival through local synergistic effects in the irradiated lesions and a systemic abscopal response in microscopic disease (93).

One of the main questions remains who the ideal candidates are for radical (radiation) treatment of oligometastatic disease. The performed trials often included a highly selected patient population, as illustrated by the SINDAS trial where only about 1 out of 5 screened patients were enrolled in the study so far (8). It is therefore uncertain how results of these trials can be extrapolated to the patients we encounter in the real-world setting. In addition, while the definition of what truly represents oligometastatic disease remains under scrutiny, the different trials have used these definitions in a variable manner, further adding to the difficulty of selecting the right patients for radical treatment of metastases (94). Hence, more evidence, ideally from randomized controlled trials, is still awaited to further support practice. It can nevertheless be anticipated that the broad spectrum of oligometastatic disease, in lung cancer and other cancers, will be difficult to capture solely by clinical trials. Moreover, the available results have already fueled the uptake of SABR for oligometastatic disease in daily practice (95). In order to capture this momentum and learn from the treatments already being clinically delivered, ESTRO and EORTC have jointly initiated OligoCare under the E2-RADIatE platform (EORTC-ESTRO RADiation InfrAstrucTure for Europe, NCT03818503). This international prospective registry trial is aimed at identifying patient, tumor and treatment characteristics that impact OS of patients with oligometastatic NSCLC, colorectal, prostate or breast cancer, treated with radical radiotherapy to all visible disease. As inclusion criteria are purposely broad, this study will hopefully aid in describing patterns-of-care, identifying relevant prognostic and predictive factors, and defining accessibility and cost of radiotherapy in the current clinical setting (19). In addition, by capturing the data following

the EORTC oligometastases characterization system (19), it will hopefully broaden our understanding of the impact of radiotherapy in the distinct oligometastatic disease states and generate hypotheses to be further addressed in formal, randomized controlled trials.

Conclusions

Current clinical evidence from randomized phase 2 trials suggests that radical radiotherapy of oligometastatic disease in NSCLC patients can prolong survival, yet further confirmatory data from randomized controlled phase 3 trials remains awaited. The oligometastatic patient population and the treatments used in trials prove to be heterogeneous, leaving many questions regarding the ideal candidate, treatment modality, timing and radiation dose unanswered. Ongoing and future trials will likely lift the remaining corners of the veil in the upcoming years.

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Footnote

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