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EDITORIAL

Stereotactic body radiation therapy: A good dance partner of oligometastatic non-small cell lung cancer to the sound of SINDAS study

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Abstract

The European Organization for Research on Treatment of Cancer Research published a consensus statement to establish the key criteria to define oligometastatic disease (OMD). According to those criteria, all lesions (both primary and metastatic) should be amenable to radical intent treatment with acceptable toxicity. Several retrospective studies have shown that adding local ablative therapy to the treatment of OMD improves outcomes; however, due to the diverse selection criteria and treatment strategies used in those studies, it is difficult to compare directly results to draw definitive conclusions. In recent years, prospective phase II trials, such as the SABR-COMET and "Oligomez" trials, have shown that stereotactic body radiation therapy (SBRT) improves outcomes in patients with OMD. More recently, interim results of the randomised phase 3 SINDAS trial were reported at the annual meeting of the American Society of Clinical Oncology 2020 demonstrating that upfront SBRT added to systemic treatment with tyrosine kinase inhibitors yielded a significant benefit in both progression-free survival and overall survival in patients with epidermal growth factor receptor-mutant oligometastatic non-small cell lung cancer. In the present editorial, we review the definition and historical context of advanced non-small

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cell lung cancer with OMD. In addition, we review the scientific evidence for local ablative therapy and SBRT and discuss the results of recently published prospective studies. We also discuss in depth the results of the SINDAS study, including the strengths and weaknesses of the study and the barriers to extrapolating these results to routine clinical practice.

Key Words: Oligometastatic; Non-small cell lung cancer; Stereotactic body radiation therapy; SINDAS; Local ablative therapy; Epidermal growth factor receptor mutations; Epidermal growth factor receptor-mutated

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Core Tip: In this editorial, we review the definitions and historical context of advanced non-small cell lung cancer with oligometastatic disease. We also review the scientific evidence for local ablative therapy and stereotactic body radiation therapy as well as the results of recently-published prospective studies. Finally, we provide an in-depth analysis of the interim results of the SINDAS trial, particularly its strengths and weaknesses, and the barriers to extrapolating these findings to real-life clinical practice.

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INTRODUCTION

Concept and historical context of oligometastatic non-small cell lung cancer

The concept of oligometastatic disease (OMD) was first coined by Hellman and Weichselbaum to describe patients with a limited number of metastatic lesions and sites, representing an intermediate state between localised and disseminated disease[1]. Depending on how OMD is defined, the number of metastases can vary from a single metastatic lesion in one organ to several metastases in several organs[2]. Recently, the European Organization for Research on Treatment of Cancer Research published a consensus statement to establish the key criteria to define OMD. According to those criteria, all lesions (both primary and metastatic) should be amenable to radical intent treatment with acceptable toxicity[3]. That consensus statement also established the maximum number of metastatic lesions (n = 5) and involved organs (n = 3) detected by 18F-fludeoxyglucose positron-emission tomography-computed tomography and brain magnetic resonance imaging. Due to differences in the criteria used to define OMD, it is difficult to ascertain the true incidence, although estimates suggest that approximately 25% of patients present five or fewer metastases at diagnosis[2]. Numerous studies, mostly retrospective[4], have shown that ablative therapies are an effective treatment to achieve disease control and to extend survival in patients with OMD. A meta-analysis of seven retrospective studies involving a total of 776 patients diagnosed with OMD (one to five metastases) found that ablative therapy significantly improved survival outcomes[5]. Nevertheless, data obtained from the application of next-generation sequencing techniques, which allow for phylogenetic analysis of the tumour and metastases, suggest that even a limited number of metastases (one to three) can rapidly multiply, leading to disseminated disease over time[6]. For this reason, ablative therapy applied to those limited number of progenitor cells could prevent the development of polymetastatic disease[6].

For many years, the most common treatment approach (55% of cases) in these patients was surgical resection of the metastatic lesions[7]. Due to technological advances in radiation therapy — mainly the emergence of stereotactic body radiation therapy (SBRT) — it is now possible to administer high dose, highly conformal radiation to small volumes. Consequently, we can now treat brain metastases as well as lesions in other locations (lung, liver, spine, and even multiple sites), achieving local control rates ranging from 70% to 90% with low rates (< 10%) of grade 3 or higher

toxicity[8].

SBRT is less aggressive than surgery but with comparable effectiveness, which explains why interest in this treatment modality for OMD continues to grow. Advances in our understanding of lung cancer, the development of more efficacious therapies such as targeted treatments for genetic mutations [epidermal growth factor receptor (EGFR) and anaplastic lymphocyte kinase, among others], and the emergence of immunotherapy have altered the course of metastatic non-small cell lung cancer (NSCLC). Nonetheless, prospective data supporting the value of ablative therapy remain scant, and most of the available evidence for this strategy comes from retrospective studies showing that local ablative therapy (LAT) yields better outcomes than systemic treatment alone[7].

The first prospective phase II trial of LAT (surgery or radiotherapy) was conducted in 39 patients with NSCLC with ≤ metastases, with most patients having only a single lesion (n = 37; 87%). In that trial, median overall survival (OS) was 13.5 mo, with a 12-mo survival rate of 56.4%[9]. In a recent update of that trial, 5.1% of patients were still alive at 6 years of follow-up[10]. It is important to note that SBRT was not widely available when that study was performed and was not used in the trial. More recently, findings from several prospective randomised trials have provided valuable data to facilitate treatment decision-making in this clinical setting.

THE MAIN PROSPECTIVE STUDIES

The SABR-COMET study was a prospective phase II clinical trial involving 99 patients with different types of oligometastatic tumours (maximum of five metastatic sites). Patients were randomised to receive SBRT plus standard systemic therapy or systemic therapy alone[11]. Median OS and progression-free survival (PFS) were significantly longer in patients treated with SBRT *vs* conventional treatment [OS: 41 mo *vs* 28 mo; hazard ratio (HR) 0.57, 95% confidence interval (CI), 0.30-1.10, P = 0,09; PFS: 12 mo *vs* 6 mo; HR 0.47, 95%CI, 0.30-0.76, P = 0.0012]. That study used a randomised phase 2 screening design with a two-sided α of 0.20 and power of 80%, which is higher than the 0.05 level used in phase 3 designs, recognising that positive results should not be considered definitive. However, only 18 patients had a primary lung tumour, so it is difficult to reach any definitive conclusions about the true value of SBRT in this population. Moreover, the SBRT group was comprised mainly of patients with breast or prostate cancer, both of which have a less aggressive natural history than lung cancer, which could have influenced the results. A post-hoc analysis that excluded patients with breast and prostate cancer found a significant benefit for LAT, with a 5-year survival rate of 33% *vs* 16% in patients who received standard treatment.

The findings from several phase II clinical trials in patients with lung cancer have recently been reported. Iyengar *et al*[12] carried out a phase II trial of 29 patients with oligometastatic NSCLC who showed disease response/stabilization after induction chemotherapy. Patients were randomised to maintenance chemotherapy or consolidation SBRT to all metastatic sites followed by maintenance chemotherapy. A significant increase in PFS was observed for patients who received radical treatment (9.7 *vs* 3.5 mo; P = 0.01), with excellent local control in the irradiated sites and no increase in toxicity. Gomez *et al*[13] reported the findings from a phase II trial involving 49 randomised patients with advanced lung cancer and ≤ 3 metastases at diagnosis. After completion of induction chemotherapy, patients were randomised to consolidation SBRT and maintenance with systemic therapy *vs* systemic therapy alone. The combined treatment yielded significantly better PFS (14.2 mo *vs* 4.4 mo; P = 0.022) and OS (41.2 mo *vs* 17 mo; P = 0.017). More recently, the interim results of the SINDAS trial were reported at the annual meeting of the American Society of Clinical Oncology 2020. SINDAS is a randomised phase III trial designed to explore the role of upfront SBRT in combination with first- or second-generation EGFR tyrosine-kinase inhibitors (EGFR-TKI) *vs* EGFR-TKI alone as first-line treatment in patients with oligometastatic (≤ 5 metastatic lesions) lung cancer with EGFR activating mutations[14]. In that trial, 136 patients were randomised to receive TKI (n = 65) or TKI plus SBRT (n = 68). The interim findings showed a significant benefit for the experimental arm in both PFS (20.2 *vs* 12.5 mo; HR 0.61, 95%CI, 0.3949-0.9697, P < 0.001) and OS (25.5 *vs* 17.4 mo; HR 0.68, 95%CI, 0.4654-1.001, P < 0.001), without any additional toxicity. Moreover, there were no between-group differences in the distribution of adverse effects ≥ grade 3 nor in toxicity-related mortality (Table 1).

Table 1 Prospective clinical trials in oligometastatic disease

Trial	Ref.	Design	Population	Number of lesions	Local treatment	PFS	OS
SABR-COMET	Palma *et al*[11]	Phase II, *n* = 99	≤ 5 locations; different tumour types (lung cancer; *n* = 18)	1-5	SABR	12 mo *vs* 6 mo, (*P* = 0.0012)	41 mo *vs* 28 mo, (*P* = 0.09)
	Iyengar *et al*[12]	Phase II, *n* = 29	Lung cancer patients treated with induction chemotherapy followed by standard maintenance treatment (+/-SBRT)	1-5	SABR	9.7 mo *vs* 3.5 mo, (*P* = 0.01)	Not reported
"Oligomez"	Gomez *et al*[13]	Phase II, *n* = 49	Lung cancer patients treated with induction chemotherapy followed by standard maintenance treatment (+/-SBRT)	1-3	XRT or Surgery	14.2 mo *vs* 4.4 mo, (*P* = 0.022)	41.2 mo *vs* 17 mo, (*P* = 0.017)
SINDAS	Wang e *et al*[14]	Phase III, *n* = 133	Front line treatment for EGFR + NSCLC patients with ≤ 5 metastases. EGFR-TKI *vs* SBRT + EGFR-TKI	1-5	SBRT	20.2 mo *vs* 12.5 mo, (*P* < 0.01)	25.5 mo *vs* 17.4 mo, (*P* < 0.01)

EGFR: Epidermal growth factor receptor; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival; SBRT: Stereotactic body radiation therapy; TKI: Tyrosine kinase inhibitor.

DISCUSSION

The SINDAS trial provides new, high-grade evidence to support the benefits of LAT with SBRT at diagnosis for the treatment of oligometastatic NSCLC[14]. The main strength of that trial is the randomised phase III design. Other important strengths include the homogeneous population (NSCLC with EGFR mutations) and the well-balanced patient cohort (despite a few exceptions, discussed below). In addition, the timing of SBRT (applied at diagnosis) was the same in all patients. This aspect is important because it eliminates the possible interference of SBRT timing on outcomes. Notwithstanding these advantages, one of the main limitations of that trial is that it is not possible to extrapolate the results to routine clinical practice due to the high screening failure rate. Only 136 of the 631 patients screened over a 3-year period were eligible for randomisation, a screening failure rate of nearly 78%, which underscores the difficulty of identifying "ideal" oligometastatic candidates. Other limitations are the inclusion of patients with EGFR exon 20 insertions. These patients received first-generation TKIs rather than the more modern, superior systemic treatment strategies involving second and third-generation TKIs or combination therapy (chemotherapy + TKIs). In addition, the trial excluded patients with brain metastases, which is one of the most common metastatic sites[15].

Another notable limitation of the SINDAS trial is the lack of balance between treatment arms in the proportion of patients with exon 20 insertions (12% of the control arm *vs* only 4% in the SBRT group), a relevant difference given the worse prognosis in these patients[16]. This was confirmed on the multivariate analysis (exon 19 *vs* exon 20/21; HR 0.091, 95%CI, 0.022-0.381, *P* = 0.001) and for which we will probably have a more effective targeted treatment in the future[17]. In addition, patients in the control arm received proportionally more gefitinib than erlotinib. Although these agents are both first-generation inhibitors, no comparative studies have been performed and thus they may present small differences in efficacy and toxicity. Other factors that could limit the validity of the results and their extrapolation to real-world clinical settings are the small number of patients and the fact that the trial involved only Chinese patients, who may differ in some ways from western populations. In addition, we do not know the proportion of patients with the T790M resistance mutation, which is a relevant point given that patients with progressive disease were treated with chemotherapy alone as salvage therapy, a suboptimal treatment in patients with the T790M mutation, which could have had a major impact on OS[18].

The SINDAS trial did not clarify the role of local treatment of the primary tumour, since that was not included in the protocol. There is some evidence from a meta-analysis of retrospective studies suggesting that aggressive thoracic therapy is associated with better survival[5,15,19]. Despite these limitations, the results of the SINDAS trial demonstrate that the strategy of adding upfront SBRT to systemic treatment with TKIs yielded a significant benefit in both PFS and OS. Given the effectiveness of this treatment strategy, this approach merits consideration in treatment decision-making in the context of routine clinical practice; however, further studies, including randomised clinical trials, are warranted to provide more definitive data.

FUTURE DIRECTIONS

There is a growing body of evidence to support the addition of LAT (such as SBRT) to the treatment of OMD. The current evidence includes retrospective studies showing that LAT provides a survival benefit[19], randomised phase II trials that have prospectively confirmed this benefit with long-term data[11,20,21], and the first randomised phase III trial (SINDAS) whose results provide robust support for this strategy, demonstrating an increase in both PFS and OS[14].

Many doubts remain with the regard to the optimal use of LAT in OMD. The term OMD is still too broad; as a result, the optimal treatment may differ depending on the specific patient subgroup. The multivariate analysis in the SINDAS trial showed that patients with the largest tumours (T3-4 *vs* T1-2; HR for OS 2.06, 95%CI, 1.08-5.5, P = 0.017) and a greater number of metastases (≥ 3 *vs* < 3; HR for OS 1.95, 95%CI, 1.2-3.07, P = 0.04] had worse survival[14]. Moreover, we still do not know which LAT technique is best for the various clinical scenarios due to a lack of head-to-head studies comparing surgery to SBRT or radioablation. That said, if we were forced to select a single approach, it seems reasonable to opt for the least aggressive treatment, which would support the use of SBRT due to its favourable toxicity and morbidity profile.

The optimal timing of SBRT is also unclear. SBRT could be administered as the initial therapy—the approach used in the SINDAS and SABR-COMET trials[11,14]—or as consolidation therapy, as in the "Oligomez" and Iyengar trials[12,13]. The benefit of local treatment of the primary tumour should be confirmed prospectively. The effect of adding immunotherapy in this clinical scenario remains unknown; similarly, the biomarker and molecular profiles that could help to identify the patients most likely to benefit from LAT are not known. In tumours with EGFR mutations, there may be a high degree of discordance between the primary tumour and metastases (Lee *et al*[22] found a discordance rate of 45% between the primary tumour and bone metastases). Indeed, this discordance provides the rationale for treating these foci of TKI-resistant cell clones with LAT and explains why this strategy is effective. Several phase III trials currently underway will help resolve these questions. The NRG LU002 trial (NCT03137771) is being performed to evaluate local ablative consolidation therapy in NSCLC. The SABR-COMET-3 (NCT03862911) and SABR-COMET-10 (NCT03721341) trials are evaluating upfront SBRT in multi-tumour OMD with one to three or four to ten metastases, respectively. A new post-hoc analysis of the SABR-COMET trial data is expected when all patients have reached at least 10 years of follow-up. Other phase II trials are also underway, including CHESS (NCT03965468), which is evaluating the application of immunotherapy, chemotherapy, and radiotherapy, and the NCT03905317 trial, which is evaluating antiangiogenic therapy combined with radiotherapy.

CONCLUSION

In conclusion, although the strong results published in recent years have generated great enthusiasm for including SBRT in the treatment of oligometastatic NSCLC, more research is essential to improve patient selection, identify molecular biomarkers (not only clinical), and determine the optimal timing of SBRT. While SBRT is not likely to be applicable to most patients with oligometastatic NSCLC, it may be an ideal treatment for well-defined subgroups.

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