



Stereotactic ablative body radiation for oligometastatic and oligoprogressive disease

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Abstract: Stage IV non-small cell lung cancer (NSCLC) exists on a spectrum, with a subset of patients presenting with oligometastatic disease involving only a limited number of distant sites. For these patients, local consolidative therapy (LCT) has been demonstrated to improve outcomes through ablation or cytoreduction of metastatic disease, as shown in an increasing number of randomized controlled trials. In particular, stereotactic ablative body radiation (SABR) has emerged as a feasible treatment modality for elimination of oligometastatic sites. This focused review examines the underlying biologic mechanisms and clinical data in support of SABR in the setting of oligometastatic NSCLC. Following a comprehensive evaluation of the pertinent retrospective, prospective, and anticipated trials to date, we summarize the evidence regarding patient selection, treatment safety, and technical considerations to provide guidance of this approach for clinicians.

Keywords: Stereotactic ablative body radiation (SABR); stereotactic body radiation therapy (SBRT); lung cancer; non-small cell lung cancer (NSCLC); oligometastatic; oligoprogressive; consolidative radiation

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Introduction

One area in which stereotactic ablative body radiation (SABR) has developed as a viable treatment modality over the past decade has been in metastatic disease. Several related categories of this malignancy have been defined. Oligometastasis is the setting of limited metastases, with the definition of “limited” varying by study. The most common classification is 3 or less metastatic lesions (1,2), though studies with one to eight sites of disease exist. Oligoprogression refers to malignancy that has progressed in a limited number of sites, while oligo-recurrence occurs after definitive treatment for locoregional disease, followed by the manifestation of metastases in a limited fashion. Retrospective and prospective trials have focused on all

three of these scenarios. The aim of the current manuscript is to review the underlying biologic rationale and clinical data for SABR in the setting of oligometastases and oligoprogression to provide a sense of the current state of ablative radiation in these settings, with regard to which patients may be candidates for this approach, what high impact trials are currently addressing this issue, and where future directions may lie.

The role of SABR in the context of the oligometastatic biologic state

Emerging preclinical and clinical evidence over the past two decades support the existence of a distinct oligometastatic biologic state. First described in the landmark review of

1995 by Weichselbaum and Hellman (3) and updated in 2011 with more recent results (4), an underlying premise for this clinical entity is that multiple steps are required for metastases to occur (5). These include loss of cellular adhesion, increased motility, entrance and survival in the circulation, and entrance/survival into distant sites. If any of these steps are disrupted by the host, or if the tumor does not have the capacity to complete an individual step, the process of metastasis is disrupted. Furthermore, cellular and host factors may predispose a tumor to only invade and colonize in certain structures, thus leading to a full and almost continuous spectrum of disease that spans from completely localized to widely disseminated. Another approach to understanding the biologic state is to compare it to Darwinian evolution on a more macroscopic scale (5). Specifically, several host factors influence survival and progression of disease, such as hypoxemia, growth factors, external exposures, and the inherent immune response, which are then balanced with the “fitness” of an individual malignant cell to survive in any given structure. The balance that is achieved between the “environment” (e.g., host) and the “organism” (e.g., tumor cell) then dictates where on the spectrum of metastasis an individual tumor lies (6).

Several lines of evidence exist to support these broad hypotheses. In one study, autopsies and genomic profiling were performed on seven patients with pancreatic cancer who had dissemination to several metastatic sites. The investigators then compared the accumulation of mutations in individual lesions, to determine if patterns could be identified. They found that mutations accumulated in a manner that was dependent on the site of metastasis, thus suggesting a “hierarchy” of metastasis to the peritoneum, the liver, and finally the lung. They then used mathematical modeling to determine the time from transformation to a tumor cell, to the formation of a parental clone, to progression to subclones with metastatic capacity, and finally disseminated metastases (7). These findings thus support a “spectrum” theory of metastasis.

In another collection of studies, Weichselbaum and colleagues have identified microRNAs preclinically that appear to mediate an oligometastatic phenotype (8,9). In one study, the investigators identified three microRNAs in the 14q32 cluster that suppressed several steps of metastases, including cellular adhesion and invasion. Furthermore, these factors inhibited metastatic development in animal models of lung colonization through breast cancer (8). In another study, Weichselbaum and colleagues found that patients who failed to develop oligometastases could be

identified through unique features of the microRNA-200 family. Through development of an oligometastatic-polymetastatic xenograft model, the authors found that enhancement of microRNA-200c resulted in polymetastatic progression (9). Data such as these support the mechanism of specific molecular factors determining the extent of progression along the metastatic spectrum in an individual patient. If they could ultimately be targeted, there is great potential for both limiting the extent of metastasis in an individual patient and identifying a predictive biomarker for oligometastasis that could be used to select patients for aggressive local therapy.

Indeed, there is an increasing rationale for utilizing SABR in the setting of oligometastasis and oligoprogression due to two major systemic therapy developments. First, the advent of targeted therapy has improved prognosis greatly for patients with metastatic disease, such that patients who initially present with polymetastases can then experience remarkable responses that result in a small number of active sites. The second scenario has arisen with the incorporation of immunotherapy into large populations of patients with metastatic disease. Indeed, several lines of preclinical data support the abscopal effect of radiation therapy (RT) in this context, and that RT can affect immune upregulation (10,11). Thus, the combination of radiation and immunotherapy could have synergistic local and synergistic distant effects in eradicating metastatic disease. These concepts are currently being explored in ongoing prospective trials.

Data supporting aggressive consolidation therapy in the oligometastatic state

Observational trials (retrospective and single-arm prospective studies)

Most studies that have assessed the role of local consolidative therapy (LCT) in the setting of oligometastases have been retrospective and single-arm prospective trials (*Table 1*) (5). In comparative effectiveness analyses, multiple studies have demonstrated a benefit in progression-free survival (PFS) ± overall survival (OS) for patients with up to 5 sites of disease. For example, the previously cited meta-analysis of seven observational cohort trials demonstrated a 2-year survival rate of 52.1% in patients with up to 5 synchronous metastases receiving “aggressive thoracic therapy”, defined as surgery or radiotherapy >40 Gy, compared to those patients that did not receive this treatment (21). The

Table 1 Selected studies of consolidative local therapy in the setting of oligometastatic NSCLC

Study (reference)	Randomized	Year	No. patients	No. sites	RT regimen	Outcomes	Toxicity
Gomez <i>et al.</i> (2)	Yes (phase II)	2016	44	≤3	SABR, surgery, hypofractionated RT, conventional RT	Median PFS 11.9 months (vs. 3.9 with MCT, P=0.0054)	Similar in both arms; no grade ≥4
Iyengar <i>et al.</i> (12)	Yes (phase II)	2018	29	≤5	SABR, hypofractionated RT	Median PFS 9.7 months (vs. 3.5 with MCT, P=0.01)	Similar in both arms; no grade 5
Palma <i>et al.</i> (13)	Yes (phase II)	2012	99 (exp.)	≤5	SABR	Not yet reported	Not yet reported
Iyengar <i>et al.</i> (14)	No (phase II)	2014	24	≤6	SABR	Median PFS 14.7 months; Median OS 20.4 months	Grade 3 (8%)
Collen <i>et al.</i> (15)	No (phase II)	2014	26	≤5	SABR (50 Gy in 10 fxs)	Median PFS 11.2 months; Median OS 23 months	Grade 3 (8%)
De Ruysscher <i>et al.</i> (16)	No (phase II)	2012	39	≤4	Surgery, SABR, conventional RT	Median PFS 12.1 months; Median OS 13.5 months	Grade 3 esophagitis (15%), pneumonitis (3%)
Downey <i>et al.</i> (17)	No (phase II)	2002	23	1	Surgery	Median OS 11 months	Not reported in detail
de Vin T <i>et al.</i> (18)	Retrospective	2014	309	≤5	SABR	Median OS 24 months	Not reported in detail
Hasselle <i>et al.</i> (19)	No (prospective)	2012	25	≤5	Hypofractionated RT	Median PFS 7.6 months; Median OS 22.7 months	Grade 3 (8%)
Sheu <i>et al.</i> (1)	Retrospective	2014	90	≤3	SABR, surgery, conventional RT	Median OS 27.1 months; PFS 11.3 months	Not reported in detail
Khan <i>et al.</i> (20)	Retrospective	2006	23	≤2	Surgery, SABR, conventional RT	Median OS 20 months	Grade ≥3 pneumonitis (9%); no grade 5

NSCLC, non-small cell lung cancer; No, number; exp, expected; RT, radiation therapy; SABR, stereotactic ablative body radiation; PFS, progression-free survival; MCT, maintenance chemotherapy; OS, overall survival.

MD Anderson propensity-matched retrospective trial comparing 90 patients between 1998 and 2012 with up to 3 metastatic lesions who received comprehensive local therapy *vs.* those that did not demonstrated an OS benefit, with a hazard ratio of 0.37 (1). And in a secondary analysis of two prospective studies assessing patients with both oligometastatic and polymetastatic disease, patients who received more aggressive radiation to the primary tumor, defined as a dose of ≥ 63 Gy, had better OS, with a 3-year OS rate of 17% *vs.* 2% in those patients that did not undergo this treatment (22). These findings were similar to another report demonstrating that both higher dose to the tumor, again defined as a threshold of ≥ 63 Gy, was associated with improved OS (23). Taken together, studies such as these suggest that oligometastases represents a unique disease entity for which aggressive treatment can improve OS. It was this rationale through an analysis of the 94,708 patients in the International Association for the Study of Lung Cancer (IASLC) database that informed the proposed revision for the 8th edition of the TNM staging system, in which oligometastatic disease is classified as a new “M1b” category, defined relatively narrowly as a single metastatic lesion (24).

Limitations of non-randomized prospective studies

While mounting clinical evidence has supplemented the biologic data for an oligometastatic state that should be classified and treated differently than polymetastatic disease, it is important to understand the unique limitations of the data within this context (5). These caveats have been described well in a recent review on this topic (25). The first is that on the spectrum of consensus levels of evidence, retrospective and single-arm prospective trials (with comparisons to historical controls) are low on this scale. Second, a specific issue to analyses of LCT in the setting of oligometastases is the issue of immortal time bias (5). Specifically, when comparing two groups of patients that have oligometastatic disease, one of which has received aggressive local therapy and one that has not, the group that has received surgery/radiation by definition needed to survive long enough to undergo this treatment to be included in this group. Therefore, patients that succumb early to the disease or progress early enough that local therapy is not an option will be excluded. This period in which patients cannot fail treatment is referred to as immortal time (5). It is thus unclear from examining observational data alone if the apparent superiority with

aggressive local treatment is secondary to an actual causative effect in the setting of indolent disease, or whether the patients that are treated with aggressive therapy appear to fare better because in these cohorts of patients, examined retrospectively, the selection of patients for aggressive treatment occurred preferentially because of favorable prognostic factors. While some of these characteristics can be controlled in multivariate analysis (performance status, number of sites of disease) others, such as the treating physician's general impression of a patient, are not as easily incorporated into statistical analyses (5).

Barriers to randomized trials and goals in designing effective randomized clinical studies

Over the past decade, there have been several randomized studies that have been designed with the purpose of comparing standard of care (e.g., maintenance therapy) with LCT in the setting of oligometastatic disease (5). Until recently, however, all of these trials had been closed due to poor accrual (26). The lack of accrual was likely due to several reasons. First, in the context of retrospective data suggesting a benefit there was a lack of equipoise among many physicians with regards to optimal treatment (5). Second, many patients may have been hesitant to be randomized to clinical trials of LCT *vs.* maintenance therapy due to the off-trial option of LCT. Prior analyses have demonstrated that if an off-trial option in the experimental arm is available, randomized studies become less efficient, with accrual time increasing substantially (27). Finally, many studies may have included relatively stringent inclusion criteria or treatment regimens, attempting to answer a more specific scientific question at the expense of accrual (5).

From these previous studies, several features can be incorporated into future randomized studies to enhance accrual. These include limiting off-trial availability options in the experimental arm when a randomized study is open, broadening inclusion criteria to take into account varying practices among physicians and institutions, presuming that the overall scientific question is not compromised, and educating both participating physicians and potential patients about the current level of evidence supporting the experimental regimen (5). In addition, in a secondary analysis of three prospective studies, it was found that the earlier a patient is approached for participation into a clinical trial, the more likely they are to agree to randomization (28). This finding is likely

secondary to patients anticipating randomization early in treatment, versus having a preconception about the optimal approach based on initial discussions such that there is increased resistance to potentially being randomized to an alternative arm.

One important question when designing randomized trials in oligometastatic non-small cell lung cancer (NSCLC) is what endpoints are clinically relevant? While OS is certainly the “gold standard,” other endpoints could certainly have utility in defining the role of LCT, though with reduced time to accrual. The primary alternative to OS has been PFS, and certainly many oncologic therapeutic regimens has received Food and Drug Administration approval and have been incorporated into national guidelines as a result of meeting this endpoint (5). One limitation to PFS in the context of surgery/RT for metastatic disease is that it could be argued that the impact is attenuated because patients treated with an aggressive regimen will inherently have less failure at the sites that have been ablated. That is, patients in the alternative systemic therapy arm will be at risk for recurrence in all sites of disease, whereby patients in the LCT arm will have a minimal risk of failure in the sites that have undergone ablation (29). Therefore, alternative endpoints may be useful in strengthening PFS data. These include time to failure in a new lesion, quality of life (QOL) endpoints, and cost-effectiveness data. Incorporation of these endpoints as secondary aims will potentially provide stronger evidence than PFS alone that LCT is a high-quality treatment option (5).

Randomized trials

To the best of our knowledge, the first multi-institutional, randomized, phase II study was recently completed comparing the role of aggressive LCT in patients with ≤ 3 metastases who did not progress on standard front-line systemic therapy (FLST)/observation (*Table 1*) (5). The hypothesis was that consolidative therapy would improve PFS in this setting (2). Eligible patients required: (I) histologic confirmation of NSCLC; (II) stage IV; (III) ≤ 3 sites of disease at post-FLST; and (IV) no RECIST progression during FLST or before randomization. Appropriate FLST was defined as either ≥ 4 cycles of platinum doublet therapy or ≥ 3 months of epidermal growth factor receptor (EGFR)/anaplastic lymphoma kinase (ALK) inhibitor for patients with EGFR mutations/ALK rearrangements, respectively. Patients were randomized to either LCT (chemo-radiation or surgical resection of all

sites) \pm ongoing maintenance therapy/observation (MT/O) *vs.* MT/O alone. The MT/O was physician choice (from predefined standard-of-care options). Randomization was balanced dynamically on five prognostic factors: number of metastases, response to FLST, central nervous system (CNS) metastases, intrathoracic nodal status, and EGFR/ALK status. The primary endpoint was PFS, powered to detect an increase from 4 to 7 months (HR =0.57) using intention-to-treat (ITT) analysis (5). The planned study size was 94 randomized patients, with interim analysis planned at 44 patients. PFS and OS were assessed, and in an exploratory analysis, the time to developing a new lesion was compared between the two arms with a log-rank test [time to new site failure (TNSF)].

On the recommendation of the Data Safety Monitoring Board, the study was terminated early due to efficacy with LCT. Forty-nine patients were randomized from 2/2013–1/2016. Of the patients that underwent randomization to the LCT arm, 20% of them underwent surgery as part of their LCT regimen. Eight patients had EGFR/ALK alterations. The median follow-up time for PFS was 18.7 months for all patients. The median PFS time in the LCT arm was 11.9 (90% CI: 5.72–20.90) months, compared to 3.9 (90% CI: 0.18–0.66) months in the no LCT arm (HR =0.35; $P=0.005$) (2). The LCT arm also had improved TNSF, with 11.9 months compared to 5.7 months in the no-LCT arm ($P=0.0497$). Toxicity was similar between the two arms, with no grade 4–5 toxicity. OS data is immature, with only 14 deaths recorded. However, the investigators concluded that in patients with oligometastatic NSCLC without progression after FLST, immediate LCT improved PFS compared to standard treatment alone (5).

These results were further supported in another phase II randomized study examining the role of consolidative RT in the setting of oligometastases (primary + up to 5 metastatic sites). In this single-institution trial, patients received front-line systemic therapy and then were randomized to hypofractionated consolidative RT \pm maintenance chemotherapy *vs.* maintenance chemotherapy alone (5). While this study was similarly terminated early, in the 29 patients that were randomized, there was found to be a substantial improvement and similar tripling in PFS for patients in the consolidation arm (12). Taken together, these studies support a PFS benefit with aggressive consolidation in the setting of limited metastatic NSCLC (5).

In addition to the trials above, the recently completed COMET study compares the efficacy of standard of care RT *vs.* ablative radiation (SABR) in the setting of multiple

oligometastatic tumor types, defined as up to 5 lesions (5). In this Canadian study, patients are randomized to one of these two arms with a 2:1 ratio favoring the experimental arm, and a primary endpoint of OS. Secondary endpoints include QOL, toxicity, and PFS (13).

Ongoing randomized trials in the setting of oligometastatic NSCLC

Several current trials are examining the role of aggressive therapy in the setting of oligometastatic NSCLC. The SARON trial from the United Kingdom compares the treatment regimens of chemotherapy + RT *vs.* chemotherapy alone in the setting of oligometastatic NSCLC (NCT02417662). Planned enrollment for the trial is 340 patients, with a primary outcome of OS. In a phase II/III intergroup study being performed in the United States (NRG-LU002), patients with up to 3 sites of disease receive frontline systemic therapy (5). Patients that do not progress are then randomized in a 2:1 fashion to local consolidation therapy and maintenance systemic therapy *vs.* maintenance systemic therapy alone. In addition, other ongoing trials demonstrate the extrapolation of the indication and definition of oligometastatic NSCLC to determine which patient subsets may benefit from aggressive local therapy. An example of these are the LONESTAR and NORTHSTAR studies. In LONESTAR, patients with metastatic disease (no limit to number of sites) are treated with front-line nivolumab and ipilimumab and are then randomized to further immunotherapy *vs.* LCT followed by immunotherapy. The primary endpoint is OS, and as many sites can be treated as are clinically feasible. In the partner trial NORTHSTAR, a similar paradigm is utilized, though patients receive frontline osimertinib and are then randomized to consolidation to as many sites as are feasible *vs.* continued osimertinib, with a primary endpoint of PFS (5).

The choice between surgery and RT as consolidation is likely to be physician and patient dependent. None of the current data compares the two approaches, and the MD Anderson phase II study implies that either treatment can be used. Given that the phase III study in the United States also will include both modalities, if LCT is shown to provide a benefit, the likely conclusion will be that each patient should be evaluated by a multidisciplinary team and a tailored approach made for both the primary tumor and the metastatic site. Certainly, the recent influx of studies demonstrating a benefit to aggressive therapy in

oligometastases has the potential to dramatically broaden the indications for surgical resection, not just in lung cancer but across a spectrum of primary tumor sites (5).

Selection of patients for treatment with oligometastases

Number of sites/lesions

The most common method used to stratify patients with oligometastatic disease utilizes the number of total metastatic sites or lesions. And indeed, much observational and single arm data suggests that a lower number of lesions is associated with improved prognosis (5). A phase II dose-escalation radiation trial from the University of Chicago assessed outcomes in multiple histologic types and found that the number of sites was the primary prognostic factor for survival (30). In a recent systematic review of seven eligible retrospective observational cohort studies, which included 668 patients with oligometastatic disease (defined by up to 5 synchronous metastases), the authors found that those patients with a single organ involvement had substantially improved OS, with a HR of 0.49 (95% CI: 0.31–0.75) (21). And in another study reporting on 156 patients with 228 brain metastases, the number of brain metastases was noted to be an independent prognostic factor for survival (31). Indeed, the threshold of oligometastatic disease is currently under debate, with some arguing that 4–5 metastases do not fit the criteria of oligometastases (5). However, this cohort of patients continues to be included in prospective clinical trials addressing this disease.

Synchronous vs. metachronous oligometastatic disease

Virtually all comparisons of synchronous *vs.* metachronous metastatic disease have demonstrated improved outcomes with metachronous lesions (5). One study assessed outcomes of 72 patients with synchronous *vs.* metachronous solitary brain metastases in NSCLC and found that patients with metachronous metastases had a median survival of 33.3 months, compared to 8.6 months with a synchronous lesion (P=0.001) (32). In a review of surgical outcomes in the setting of oligometastatic lung cancer, it was also found that most studies observed improved survival when surgery was performed for metachronous *vs.* synchronous disease (33). And in a systematic review of 757 patients in several institutions with stage IV NSCLC and 1–5 metastases, only metachronous metastases and

lower N-stage were associated with an improved survival group in recursive partitioning analysis (34). These data highlight that, while the focus of many trials is that of synchronous disease, it is also important to explore optimal patient selection for aggressive treatment in the setting of oligorecurrence (5).

Intracranial vs. extracranial disease

Historically, intracranial oligometastases have been thought to represent a special subset of metastatic disease amenable to local therapy due to improved prognosis. Indeed, the highest-level data supporting aggressive treatment of oligometastatic disease is the randomized study comparing surgery + RT *vs.* RT alone in the setting of a single brain metastasis (5). Patients randomized to surgery + radiation had an improvement in OS of 40 *vs.* 15 weeks with radiation alone. Notably, of the 48 patients in this trial, 37 had lung cancer (35). The cooperative group trial RTOG 9508 also demonstrated an OS benefit of stereotactic body radiosurgery (SRS) + whole brain radiation therapy (WBRT) *vs.* WBRT alone in patients with 1–3 brain metastases, thus also suggesting that patients with brain metastases can have improved prognosis with more aggressive therapy. It is notable that 64% of patients in RTOG 9508 had a diagnosis of lung cancer (36). Other observational studies have also supported the potential role of aggressive therapy in the setting of a solitary brain metastasis, including a report from MD Anderson Cancer Center that found that patients with a single brain metastasis and N0 disease had a 3-year survival rate that approximated that of patients without metastasis (50%) (37).

It is notable that, while several lines of data have suggested that patients with intracranial metastases have improved prognosis with aggressive local therapy, there is not high-level data demonstrating that, comparing outcomes site by site and controlling for treatment given, the natural history of oligometastatic disease with an intracranial metastasis is more indolent than that of a single site elsewhere (5). In a propensity score-matched analysis of comprehensive local therapy in limited metastatic NSCLC, no difference was observed among the various metastatic sites (1). In fact, some of the basis behind the National Comprehensive Cancer Network (NCCN) guidelines advocating surgery or RT in the context of a solitary metastasis to the adrenal gland or brain (www.nccn.org) may be due to the relatively high incidence of a single metastasis to these sites and the data demonstrating that

a subset of these patients can achieve long-term survival. Similar outcomes may be demonstrated in the future with a solitary metastasis in other locations such as the bone, liver, or abdominal lymph nodes (5).

Regional nodal involvement

Several studies have suggested that decreased regional extent of tumor improves prognosis in the setting of oligometastatic disease (5). Two of these studies have been cited above, that being the MD Anderson study examining aggressive treatment in the setting of a single brain metastasis demonstrating worse outcomes with N1 or N2 involvement (37), and the systematic review of 757 patients with oligometastatic disease (34). In the latter study, recursive partitioning analysis (RPA) demonstrated a 3-year OS of 36% with synchronous metastases and N0 disease *vs.* 13% in synchronous metastases and N1/N2 involvement (34). This correlation has also been demonstrated through at least one surgical series in which patients with synchronous metastatic disease underwent surgery to both sites of disease (38). Patients with regional disease may have worse outcomes both because of the more advanced nature of their malignancy as well as the lower likelihood of controlling intrathoracic disease (surgery/stereotactic body radiation therapy (SBRT) in early stage disease *vs.* chemoradiation with N2 involvement) (5).

Safety and technical considerations for SABR in oligometastatic disease

Most studies examining the role of radiation in oligometastases have utilized SABR. Dose/fractionation regimens have varied, but overall the results support adequate safety profiles in treating multiple sites of disease. In one of the first reports SABR for oligometastases, Salama and colleagues examined 29 patients with metastatic lesions treated to 56 sites between November 2004 and March 2007. Two patients experienced Grade 3 or higher toxicity, including one patient with radiation pneumonitis and one with persistent nausea/vomiting. Notably, though with small numbers, the authors found a dose response in the control of targeted tumors, 57% in those treated to 24 Gy (n=12) to 83% if treated to 36 Gy (n=5) (30). In a comprehensive review of SBRT for oligometastases in multiple disease sites, including lung cancer, Tree and colleagues demonstrated a low rate of high-grade toxicity (5% or less for most studies) (39). In general, we recommend

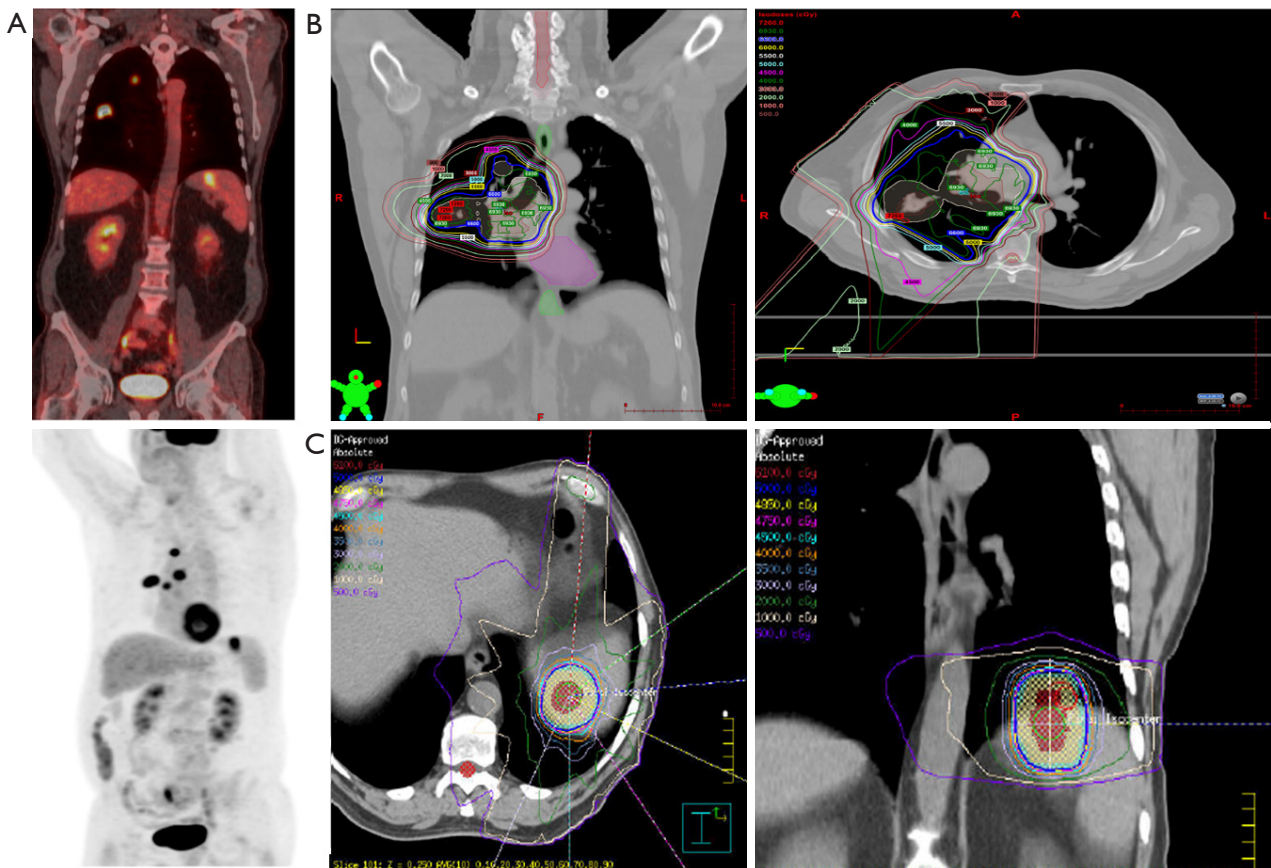


Figure 1 Example case report of the use of SABR in consolidative RT for oligometastatic NSCLC. (A) A 72-year-old male with T3N2M1b NSCLC presenting with 3-cm RUL lesion, 1.5-cm satellite RUL lesion, right hilar and lower paratracheal adenopathy, and solitary splenic lesion, biopsy-proven as oligometastasis. Following induction cisplatin/pemetrexed $\times 4$; (B) he received concurrent chemo-RT to 66 Gy in 33 fxs to the thorax; (C) followed by SBRT to 50 Gy in 4 fxs to the spleen. NED for 30 months until progression and alive nearly 5 years post-RT. SABR, stereotactic ablative body radiation; NSCLC, non-small cell lung cancer; RUL, right upper lobe; SBRT, stereotactic body radiation therapy; NED, no evidence of disease.

that treating clinicians adhere to standard, fractionation-dependent radiation constraints (www.nccn.org), but that current data support treating multiple sites in appropriate clinical circumstances (*Figure 1*).

Conclusions

In summary, oligometastatic NSCLC may reflect a more indolent phenotype of disease amenable to definitive therapy. LCT has been shown to improve outcomes for these patients, as demonstrated by the growing body of supportive evidence. In particular, SABR is an effective and tolerable treatment modality for ablation of metastatic sites and should be considered a feasible tool in the management

of oligometastatic NSCLC. We recommend that SABR be further utilized in the setting of randomized controlled trials in order to elucidate which subgroups of patients are most likely to benefit from local ablative therapy in the oligometastatic setting.

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None.

Footnote

Conflicts of Interest: Note that portions of this review have been previously published in the textbook *Adult Chest*

Surgery, 3rd Edition, “The Role of Surgery in Oligometastatic Disease.”

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