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Salvage Therapy for Locoregional Recurrence After Stereotactic Ablative Radiotherapy for Early-Stage Non-Small Cell Lung Cancer

Eric D. Brooks, MD, MHS[1,*], **Vivek Verma, MD**[2,*], **Suresh Senan, MD**[3], **Thierry De Baere, MD**[4], **Shun Lu, MD**[5], **Alessandro Brunelli, MD**[6], **Joe Y. Chang, MD, PhD**[1,†] **International Association for the Study of Lung Cancer Advanced Radiation Technology Committee**

[1]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA [2]Department of Radiation Oncology, Allegheny General Hospital, Pittsburgh, PA, USA [3]Department of Radiation Oncology, Amsterdam University Medical Center, Amsterdam, Netherlands [4]Département d'imagerie, Institut de Cancérologie Gustave Roussy, Villejuif, France [5]Department of Medical Oncology, Shanghai Chest Hospital, Shanghai Jiao University, Shanghai, China [6]Department of Thoracic Surgery, St. James's University Hospital, Leeds, United Kingdom

Abstract

Although isolated local (LRs) and regional recurrences (RRs) constitute a minority of post-stereotactic ablative radiotherapy (SABR) relapses, their management is becoming increasingly important as the use of SABR continues to expand. However, few evidence-based strategies are available to guide treatment of these potentially curable recurrences. On behalf of the Advanced Radiation Technology Committee (ART) of the International Association for the Study of Lung Cancer (IASLC), this article was written to address management of recurrent disease. Topics discussed include diagnosis and workup, including the roles of volumetric and functional imaging as well as histopathologic methods; clinical outcomes after salvage therapy; patterns of recurrence after salvage therapy; and management options. Our main conclusions are that survival for patients with adequately salvaged LRs is similar to that for patients after primary SABR without recurrence, and survival for those with salvaged RRs (regardless of nodal burden or location) is similar to that of patients with *de novo* stage III disease. Although more than half of patients who undergo salvage do not develop a second relapse, the predominant pattern of second failure is distant, especially for RRs. Management requires rigorous multidisciplinary coordination. Isolated LRs can be managed with resection and nodal dissection, repeat SABR, thermal ablation, or systemic therapies. RRs can be treated with combined chemoradiotherapy, radiation or chemotherapy alone, or supportive services. Finally, regular and structured follow-up is recommended after post-SABR salvage therapy.

[†]**Corresponding Author:** Joe Y. Chang, MD PhD, FASTRO, Department of Radiation Oncology, Unit 97, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX USA. Phone: 713-563-2337; Fax: 713-563-2331; jychang@mdanderson.org.

[*]These authors contributed equally to this work.

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INTRODUCTION

Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiation therapy (SBRT), has become the first-line therapy for medically inoperable early-stage non-small cell lung cancer (NSCLC). Ample evidence supports the efficacy and low toxicity associated with SABR.[1–7] For these reasons, many anticipate that SABR may also be effective for medically operable disease. Preliminary comparisons of SABR vs. surgery for early-stage NSCLC indicate that cure rates are similar but SABR has considerably fewer side effects, [2, 8–10] and several randomized trials comparing SABR to surgical resection continue to accrue patients (e.g., NCT02984761 NCT02468024, NCT02629458). However, concerns remain regarding SABR for first-line treatment of operable disease. For example, SABR cannot address potential disease in the remainder of the involved lobe or regional lymphatics. Moreover, a recent phase II trial of neoadjuvant SABR followed by lung resection for patients with operable disease has triggered debate regarding how best to define local recurrence after SABR.[11] Nevertheless, recurrences after SABR are uncommon; the intra-lobar local disease control rate is in excess of 90% and the local/regional disease control rate is 85% or more.[1–7,12] Findings from several phase II trials have shown rates of isolated local recurrences (iLRs) of up to 6%, and up to 8% for isolated regional recurrences (iRRs).[3–4,6].

Salvage of iLRs and iRRs is crucial for several reasons. First, such failures are potentially curable, and untreated recurrences pose a mortality risk. Second, evidence-based clarification of the role of a particular modality for salvage would affect its use in clinical practice. As an example, relapses after initial resection have historically been treated with other resection techniques, but SABR may have a role in that setting, despite the general lack of data at this time.[6,13–18] Likewise, use of salvage surgery or salvage SABR for post-SABR recurrences has also not been well defined. Third, documentation of the safety and effectiveness of various salvage approaches may affect their use in the primary setting. For example, in early-stage laryngeal or anal cancer, first-line organ-sparing approaches are standard of care, and surgical resection is reserved for salvage.[19–20] This issue is also important for NSCLC, in that organ-sparing approaches may be desirable for patients who are frail, have comorbid conditions, are of advanced age, have compromised baseline cardiopulmonary function, and may have continued organ damage from persistent smoking. [21–23]

Regardless, the use of SABR will continue to increase as the number of elderly patients with comorbid conditions continues to grow, and forms a greater proportion of all patients with potentially inoperable early-stage lung cancer that would be appropriate for SABR therapy. [24] From 2008 through 2013, use of SABR for early-stage NSCLC nearly tripled.[25] As more patients undergo SABR, more patients will experience post-SABR recurrences that will

require salvage, and evidence-based recommendations for the management of such cases become increasingly important. The perceived lack of options in these cases was captured in the current guidelines from the National Comprehensive Cancer Network (NCCN): "… Recurrent and metastatic disease have historically been regarded as *incurable*…However, selected limited locoregional recurrences *may* be treated with curative intent".[26] Notably, treatment for patients who develop distant disease after SABR should follow the principles of treatment for stage IV disease.

The purpose of this article is to highlight the nuances of diagnosing recurrent disease in patients treated with SABR, many of whom have complex comorbidities that led to their being referred for SABR in the first place. We offer insight into the rationale for salvage management, and to describe evidence for the various salvage options to direct clinical decision-making in this unique but important setting.

DIAGNOSIS AND WORKUP OF SUSPECTED RECURRENCE

Diagnosing recurrent disease after SABR, particularly suspected LRs or RRs, can be challenging, largely because benign processes (e.g., fibrosis and reactive lymphadenopathy) are difficult to distinguish from true recurrences. Therefore, a central principle for diagnosing recurrences is the need for thorough multidisciplinary evaluation and individualized diagnostic management.

Imaging

The evaluation process for suspected recurrence should commence with a complete interval history and physical examination, including an evaluation of risk factors for recurrent disease. Contrast-enhanced thoracic computed tomography (CT) scans should be obtained 3–6 months after curative SABR for early-stage NSCLC; evidence of suspicious lesions on those images should prompt positron emission tomography (PET)/CT to support the diagnosis of LR, identify areas for biopsy, and detect potential distant failures, the most common pattern of recurrence.[1] Brain magnetic resonance imaging (MRI) should be considered for patients with regional or distant metastases, particularly in patients with driver mutations such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Thus, although brain MRI should be performed for patients with confirmed or highly suspected iRR, the rate of synchronous brain metastases is unknown for iLR. However, because the presence of intracranial disease would drastically change management, and because iLR would ideally require confirmation before aggressive consolidative approaches are pursued, brain MRI in the iLR setting can be considered judiciously.

Evaluation of post-SABR images should include close attention to the thorax, not only because it is the single most common site of post-SABR recurrence[1] but also to detect second primary lung neoplasms. Imaging of the irradiated site after SABR remains among the most challenging aspects of follow-up, but the importance of multidisciplinary assessment of the findings cannot be understated. The following characteristics on CT have been identified as being predictors of LR: enlarging lesions with soft tissue density on multiple images obtained over a prolonged interval (e.g., >6 months); craniocaudal growth

(because SABR often involves depositing dose in a coplanar ‘horizontal’ manner, the appearance of growth outside this ‘dose plane’ is particularly worrisome); bulging margins; and disappearance of the linear margin.[27–28]

Although PET/CT can be more sensitive than CT for staging primary NSCLC,[29] its usefulness for detecting in-field recurrence after SABR remains challenging. False-positive findings from radiation-related inflammation and fibrosis are common, particularly on PET/CT images obtained within 6 months of SABR and those on which the tumor maximum standardized uptake value (SUV_{max}) is less than 5.[30–31] PET/CT findings may be more reliable for detecting true recurrences if the tumor SUV_{max} is at least 5 and the scan is obtained at least 6 months after SABR.[32–33] In any case, PET/CT should be considered on a case-by-case basis based on careful multidisciplinary evaluation of CT findings.

Histopathology

The gold standard for the diagnosis of LR remains biopsy; core biopsy is preferred over fine-needle aspiration because the former can provide information such as molecular profiling, PDL1 expression, and other relevant markers. Moreover, fine-needle aspiration for recurrence has been associated with a higher rate of nondiagnostic findings (e.g., 20% vs. 3% for diagnosing primary disease[34]). Nevertheless, biopsy has some notable shortcomings that should be considered. First, pathologic diagnosis of irradiated tissue can be challenging when the post-SABR interval is short, and false-positive findings are likely.[11] Also, tissue biopsies are sampling procedures; false-negative results remain a concern even with high-quality image guidance (e.g., CT), especially for lesions smaller than 1−1.5 cm.[35–36] Thus, the presence of fibrosis as well as difficulties in distinguishing viable tumor from necrotic radiation-related changes can further increases the false-negative rate. Core biopsies can also be associated with complications, such as clinically significant hemoptysis, pulmonary hemorrhage, and pneumothorax, which could be more common in the presence of lung parenchymal fibrosis. One meta-analysis reported a complication rate of nearly 40% for core biopsy procedures, including major complications in 6%.[37]

Nodal sampling of suspected iRR (ideally guided by endobronchial ultrasonography or mediastinoscopy) can provide pathologic evidence of RR and its anatomic location, particularly when imaging findings are questionable. Nodal sampling can also be useful for delineating the specific stations to be covered with salvage radiotherapy, as LRs after SABR have been associated with occult nodal disease in 25%−33% of cases,[38–40] suggesting that endobronchial sampling be considered on an individualized basis.[41] Moreover, because the presence of distant relapses dictates management regardless of nodal status, pathologic nodal sampling procedures may not change the management strategy for patients with documented distant disease. Regardless of iLR or iRR status, as discussed below, such patients are at highest risk for distant failure (and in the case of iLR, for subsequent LR or RR events). As such, histopathology could identify actionable mutations for drug therapy which we argue should be considered in iLR and iRR cases given the patterns and rates of second failure. Overall, we propose that use of pathologic nodal assessment after SABR be limited to patients with locally (case-by-case) or regionally (all) recurrent disease (either proven or

strongly suspected), no evidence of distant failure, and the fitness to tolerate these procedures with minimal complications.

SURVIVAL AND SUBSEQUENT DISEASE PROGRESSION AFTER SALVAGE

Review of existing data on outcomes of salvage therapies and patterns of subsequent failure is essential to identify optimal salvage strategies. At this time, the existing data are sparse and are mostly retrospective reviews of small numbers of patients with heterogeneous conditions, largely originating from centers that were early adopters of lung SABR. As a result, identifying patients for particular salvage strategies should be done on an individual basis and based on rigorous multidisciplinary assessment.

Survival after Salvage Therapy

The largest study of post-SABR salvage to date was published in 2018 by investigators at MD Anderson Cancer Center.[12] That study reported survival outcomes for 102 patients whose iLRs or iRRs after SABR were salvaged with a variety of different treatment types, including repeat irradiation, surgery, thermal ablation, or systemic therapy.[12] The median follow-up times in that study were 57 months from initial SABR and 39 months from recurrence. The most prominent finding was that the median overall survival (OS) time for patients who received salvage therapy was considerably longer than those who did not receive salvage (35.5 months vs. 7.3 months). Although patients who did not have salvage therapy often had poor performance status or could not tolerate further treatment, all such patients experienced progressive disease, suggesting that disease progression may have affected the OS findings. These findings supported those of a similar study by Senthi and colleagues, who noted that salvage therapy for limited recurrent disease was associated with prolonged survival.[1] Although recurrent NSCLC has historically been associated with poor OS, the improved prognosis associated with “oligo-recurrent NSCLC” suggests that salvage therapy should be offered more proactively than has been done in the past.

In support of this argument was another finding that the OS for patients who received salvage for iLR was similar to the OS for patients without recurrence after primary SABR,[12] which strongly implies that having an iLR is unlikely to affect OS as long as it is adequately salvaged. This in turn suggests that patients with locally recurrent disease should undergo curative-intent approaches (including local definitive therapy) whenever possible. It also reinforces the need for close post-SABR surveillance to identify salvageable iLR promptly.

Regarding RR (whether isolated or in combination with LR), the OS time for patients undergoing salvage therapy was similar to that for patients with newly diagnosed stage III (node-positive) disease,[12] which corroborates the findings of another small study.[42] This is noteworthy for multiple reasons. First, *de novo* diagnosis of stage III NSCLC in the contemporary era is not considered particularly unfavorable because treatment outcomes have improved.[43] Second, RRs after SABR may reflect occult nodal disease at time of SABR, which would have been addressed during lobectomy.[8] This phenomenon has been observed in surgical series, where nodal upstaging after lobectomy for cN0 disease led to OS similar to that of patients initially diagnosed with cN+ disease.[44] Because unexpected discovery of pN+ disease after resection should prompt consideration of

chemo(radio)therapy, post-SABR RRs should similarly prompt consideration of similar salvage regimens, as discussed in a subsequent section.

Patterns of Subsequent Progression

Despite the limited data available at this time, an understanding of post-salvage progression patterns (and the natural history thereof) has important implications for the choice of salvage therapy. In 50% to 60% of cases – the majority -- patients who have salvage therapy do not experience further recurrence.[12, 38–40, 42, 45–46] Of those who do have a second recurrence, the predominant pattern is distant failure.[12, 38–40, 42, 45–46] Distant failure rates are ~20% after LR,[39–40, 42, 45–46] ~40% after RR that is not treated with chemotherapy,[42] and less than 30% after salvage with chemotherapy.[12] These findings, although preliminary, imply that systemic therapy could have a critical role for iRR, similar to that for nodal disease in the *de novo* setting.

Distant failure also seems to occur at different locations after salvage for iLR versus salvage for iRR. Although data are limited at this time, in one study about 90% of distant failures after salvaged iLR occur in other pulmonary lobes and are often amenable to further oligometastatic salvage.[12] Conversely, almost half of distant failures after iRR are extrathoracic, which could contribute to the lower survival rates for patients with iRR relative to those with iLR. Nevertheless, the lower risk of extrathoracic dissemination provides another rationale for managing iLRs more aggressively than iRRs.

Second locoregional recurrences after salvage may also be different for those with iLR versus iRR.[12, 46] Among patients with iRR, the overall rate of locoregional second recurrence is low (6%) owing to the preponderance of distant failure. However, among patients with iLR, the location of second recurrences tends to be distributed equally between local and regional sites.

Collectively, these findings suggest that LR and RR after initial SABR represent two distinct clinical entities and thus should be managed in ways that reflect the two distinct outcomes. Understanding the nature of post-salvage failures after LR versus those after RR should form the basis of salvage management, as described further below and in Figures 1 and 2.

MANAGEMENT STRATEGIES FOR ISOLATED LOCAL RECURRENCES (Figure 1)

Surgery

Use of resection for salvage therapy has two major advantages. First, the presence of a LR implies that the original tumor had some resistance to radiation, and thus surgical resection may be beneficial to avoid treating potentially radioresistant disease with similar techniques. Surgery may be especially preferred if the LR is located directly within the SABR field or in a “high-risk” area (i.e., close to organs at risk in the mediastinum, which are common for central lesions), both of which would make repeat use of SABR challenging. Second, because recurrence after most iLRs are non-disseminated locoregional failures (and because 90% of distant failures occur within the thorax), the ability to remove tumor tissues and

evaluate regional lymphatics is critical for potentially preventing further locoregional recurrence and for guiding adjuvant therapy. It might also be more beneficial for larger tumor recurrences where SABR and thermal ablation are known to be less effective in providing long-term control. The primary drawback to surgery is its feasibility for patients who had been poor candidates for surgery in the first place (thereby leading to the choice of SABR for primary treatment). The risk of complications for patients with previously irradiated tissue and poor tolerance for surgery may be higher as well.[12, 38–40, 45, 47] Moreover, the presence of fibrotic tissue in about 50% of patients after SABR may complicate salvage resection by requiring open techniques or a greater extent of resection.[38–40, 45, 47] However, for "fit" patients who can tolerate surgery, delivering SABR before resection does not increase the surgical risk or impair quality of life.[11] Whether these findings can be extrapolated to "marginally fit" patients remains unclear.

Thus, judicious and careful examination of operative risks in the salvage setting is critical to ensure that treatment-related morbidities and mortality are minimized. Notably, if surgical assessment was done before SABR, it should be repeated in full because of the potential for disease that is initially inoperable (at the time of SABR) to convert to operable (at the time of recurrence), if comorbidities can be adequately managed.[12, 38–40, 47] We strongly recommend that salvage surgery should be considered by experienced clinicians at high-volume centers with strong multidisciplinary coordination. Even at such institutions, postoperative complications remain relatively common, although in most studies these complications are associated with 0% 90-day mortality and high (approaching 90%) locoregional control rates over the short term.[12,38–40,45,47–50] (Table 1).

Investigations of surgical salvage after SABR are summarized in Table 1. Lobectomy is considered the standard of care in the primary setting, as it has the advantage of removing sufficient tissue to avoid the potential for intralobar failure. However, many clinicians perform sublobar resections for select cases,[26] pending the publication of randomized data (NCT02468024). We recommend that sublobar resections should involve anatomic segmentectomies with systematic lymph node dissection whenever possible, rather than wedge resections.[51] Sublobar techniques may be appropriate (1) if the risk of operative morbidity is deemed to be lower than that for lobectomy, (2) if the patient would benefit from resection but has borderline pulmonary function precluding lobectomy, or (3) if re-SABR would be technically challenging. If a patient is eligible for a sublobar resection and no contraindications for re-SABR are present, multidisciplinary evaluation, with patient preferences accounted for, should be used to choose between the two.

Repeat SABR

Although repeat SABR can be challenging owing to complicated treatment planning and theoretical concerns regarding whether radiation should be used to treat presumably radioresistant disease (specifically in-field), repeat SABR has the important advantage of avoiding the morbidity and complications of surgery. Some limited studies of repeat SABR used for LR are summarized in Table 2. Although variations in the extent of dose overlap (e.g., within 1 cm of the original field[46,52] versus >1 cm[12]) among these studies are probably a source of selection bias, the principles of repeat SABR are similar to those for primary

disease treatment, including the need to consider the size and location of the disease, tumor motion, high-quality image guidance, and delivery of biologically effective doses (BEDs) of >100 Gy (although whether higher BEDs are required for recurrent disease remains controversial).[46,53,54] Overall, repeat SABR has led to excellent rates of short-term local control (nearly 90%), acceptable rates of regional control (>80%), and relatively low rates of grade ≥3 events (<10%)[12,28,41,46,52,55–57] (Table 2).

The dosimetric objectives, however, for repeat SABR remain somewhat unclear. Toxic effects seem to be correlated with the composite dose to mediastinal structures and unirradiated lung, rather than the dose received by lung volumes previously treated to high doses.[54–55] This observation likely stems from the high-dose lung volumes being relatively nonfunctional,[58] but the interval between SABR and repeat SABR is likely important as well. Although most LRs appear more than 1 year after SABR, more rapid recurrences of NSCLC (e.g., ≤16 months) may reflect disease that is radioresistant to SABR and thus may not respond as well to reirradiation.[59] As such, the other definitive local therapies (surgery and thermal ablation) may be considered.

If repeat SABR is to be used, several strategies can be used to provide high BED (>100Gy) while minimizing the risk of toxic effects, based on lessons learned from primary SABR. These strategies include use of extended hypofractionated regimens (e.g., 8- to 10-fractions),[60] non-daily delivery to allow normal tissue repair,[61,62] simultaneous integrated boosting to deliver a lower dose to the planning target volume while maintaining higher doses to gross disease,[63] methods of reducing tumor motion with respiration, and avoiding hypofractionation in and around the mediastinum which can damage major vessels and cause deadly bleeding (surgery or other techniques may be considered in these cases).[64]

Thermal Ablation

Thermal ablation refers to a heterogeneous set of procedures often performed by interventional radiologists (radiofrequency, microwave, and cryoablation); the vast majority of reports involve radiofrequency ablation. Thermal ablation treatments are more invasive than SABR but are generally less invasive than resection; both general anesthesia and conscious sedation can be used.[65–68] Although thermal ablation is not often used for primary disease, it may be indicated in some cases of recurrent disease for patients who are not candidates for surgery or repeat SABR. Thermal ablation may be most attractive for in-field SABR recurrences (i.e., potentially radioresistant disease), especially those that cannot be resected with surgery.

Use of thermal ablation is guided by several principles.[65–68] First, patients must be able to tolerate a small pneumothorax, which can occur in up to 40% of cases, although fewer than 20% require chest tube placement. Second, thermal ablation can be used to target tumors 1 cm or more from critical central thoracic structures; however, for lesions less than 1 cm from mediastinal critical structures, thermal ablation carries risks of excessive toxicity and potentially a lack of efficacy owing to thermal energy being carried away via convection by the great vessels. Third, thermal ablation results in suboptimal local control for tumors ≥3 cm in diameter.

A small study comparing rates of 90-day mortality and grade ≥3 adverse events for 31 patients treated with SABR (n=15), surgery (n=10), or thermal ablation (n=6) for LR reported rates of 40% after surgery, 7% after SABR, and 0% after thermal ablation.[12] Rates of subsequent LR seemed to be similar among all three groups, but the numbers of patients in each group were too small for reliable survival or other comparisons.

Systemic Therapies

Because the most common location of relapse after salvage for iLR is distant (followed by regional), post-salvage systemic therapy should be considered in such cases. Although use of adjuvant systemic therapy may reduce relapse after primary treatment,[69] no studies of repeat SABR for iLR reported to date have included systemic therapy, and hence firm recommendations cannot be made. However, an accruing randomized trial is evaluating SABR versus nivolumab+SABR for both primary and iLR disease (NCT03110978), which is important because immunotherapy for relapsed NSCLC is not approved for post-SABR recurrence, only for post-chemotherapy recurrence.

Systemic therapy alone is an option for salvage if local therapies are contraindicated, but this approach is usually not considered curative.[70] Nevertheless, national guidelines recommend a variety of potential agents, including cytotoxic therapy (e.g., platinum doublets, pemetrexed, or other acceptable agents), immunotherapy (e.g., anti-PD-1/PD-L1), or targeted therapy (e.g., EGFR or ALK inhibitors), as well as enrollment in a clinical trial.[26] Notably, many of the aforementioned agents require biopsy to establish the molecular profile or PD-L1 expression, which may not be possible in the salvage setting but provides rationale for its use.

MANAGEMENT STRATEGIES FOR REGIONAL RECURRENCES (Figure 2)

Chemoradiotherapy

Because survival for patients receiving salvage treatment for RR (either in isolation or with LR) can be similar to those with *de novo* stage III disease,[12,42] and because distant failure is common in such cases, salvage therapy should ideally mimic that for *de novo* unresected stage III NSCLC (i.e., chemoradiotherapy with a platinum doublet). Although concurrent chemoradiotherapy improves survival over sequential chemoradiotherapy for primary disease,[71] this may not be true for salvage therapy, when the overall disease bulk is much smaller and toxicity may be amplified (as is evidenced in studies on RR comparing radiation alone versus chemoradiation).[12, 42] Thus, clinicians should carefully consider the risks and benefits of concurrent versus sequential therapy on an individual basis for each patient.[41] Moreover, although giving durvalumab after chemoradiotherapy is now the standard of care for *de novo* stage III NSCLC,[43] no data exist at present to support its use after RR; as such, individualized multidisciplinary discussion is recommended to consider off-label indications of expensive immunotherapeutic agents.[72,73]

Mediastinal radiotherapy for RR after SABR has been even less well studied. Elective nodal irradiation has no role in locally advanced disease,[74] as corroborated by the low rate of out-of-field RRs after salvage.[12, 41] Thus, elective nodal irradiation is not recommended for RR

after SABR, and providers should be aware of the need to balance potential oncologic gain with the risk of treatment-related toxic effects. With regard to dose and fractionation, the two most common regimens are conventionally fractionated (i.e., 60–70 Gy in 2-Gy fractions, or a simultaneous integrated boost to gross disease with the planning target volume kept to 60 Gy in 30 fractions)[12, 41] and mildly hypofractionated (45–60 Gy in 15–20 fractions).[12, 41] Due to toxicity, concurrent chemotherapy or other systemic drugs are not routinely recommended with hypofractionated courses but can be given beforehand or afterwards depending on patient tolerance.

Finally, if a RR is accompanied by local failure, treatment options include fractionated radiotherapy that encompasses the LR in the treatment volume or, alternatively, managing the RR independently, with local therapy given for the LR. If surgery is used for local therapy, another option to address mediastinal disease is a therapeutic nodal dissection (provided that doing so does not increase operative risks). However, some form of adjuvant management would be required regardless of whether a dissection takes place, for the reasons noted above.

Radiotherapy or Systemic Therapy Alone

Delivery of either radiation or chemotherapy alone should be considered suboptimal therapy, but this approach may be required if patients are not candidates to receive combined chemoradiotherapy. As noted previously, chemotherapy alone is not considered curative and should not be used as a substitute for local therapy. Similarly, radiotherapy alone is inadequate for locally advanced disease given the rate of micrometastatic disease at presentation.[75] These principles should be used in counseling patients who are ineligible for chemoradiotherapy.

Supportive Services

A diagnosis of recurrent cancer often weighs heavily on patients, both emotionally and physically. Despite encouraging survival after multidisciplinary salvage approaches, some patients may refuse or be ineligible for curative-intent therapy. Compassionate counseling and timely coordination of services such as case management, palliative care, and onco-psychology may be of great importance to these patients, and may well improve quality of life and patient-specific outcomes.[76] These professionals may also be helpful to encourage patients to be more accepting of therapeutic options (oncologic or non-oncologic). Nevertheless, clinicians and ancillary staff should respect patient autonomy and seek to make the appropriate referrals based on the patient’s reaction to the diagnosis and recommended management.

FOLLOW-UP CONSIDERATIONS

Follow-up after primary SABR usually includes an interval history and physical examination along with thoracic CT but can vary based on institutional and clinician preference. Such follow-up is generally recommended every 3–6 months for the first 1–2 years, every 6–12 months for the next 3–5 years, and annually thereafter. NCCN guidelines recommend follow-up every 3–6 months for the first 3 years, every 6 months for the next 2 years, and

annually thereafter.[26] The European Society for Medical Oncology recommends biannual follow-up for 3 years followed by annually thereafter.[77] The International Association for the Study of Lung Cancer endorses imaging every 3–6 months for the first year, followed by every 6–12 months for the next 3 years, and annually thereafter.[78] A recent consensus panel has proposed follow-up at 3 and 6 months, then every 6 months until the end of year 2, and annually thereafter.[79].

Follow-up after salvage requires particular attention. Because second recurrences often occur within a year of salvage therapy,[12, 46] close follow-up (e.g., every 3 months) during this period is critical to ensure that second recurrences are captured before distant dissemination of disease. Notably, this close follow-up should be independent of the pre-salvage follow-up schedule. For example, if a patient is being followed up every 6 months when an LR/RR is detected, then more frequent follow-up thereafter is indicated. How long the post-salvage follow-up should be remains an open issue because of the rarity of experiencing a second recurrence and the limited follow-up data available for such patients.

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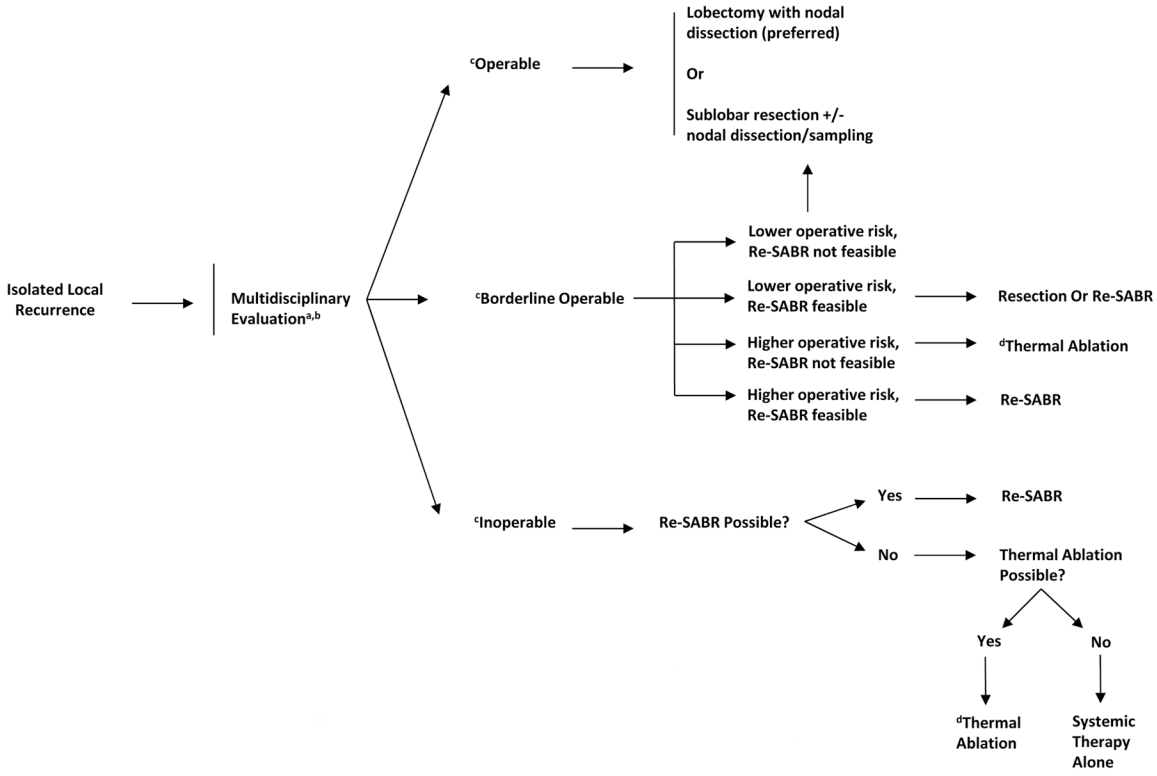

Figure 1.

Proposed management algorithm for isolated local recurrence after stereotactic ablative radiotherapy.

[a]Multidisciplinary evaluation including thoracic surgeons, radiation oncologists, medical oncologists, and interventional radiologists

[b]Systemic therapy may be carefully considered in conjunction with locally directed therapy for iLR or iRR given the rates of distant metastases observed

[c]Operable status pertains to both operability of disease (extent) and patient tolerance. All patients should be formally evaluated by a treating thoracic surgeon. Operability frequently pertains to sufficient pulmonary function (predicted postoperative diffusing capacity for carbon monoxide and forced expiratory volume in 1 second >40%) and patients deemed adequate risk candidates by a thoracic surgeon. However, in light of other less invasive and effective options (re-SABR and thermal ablation) the decision to operate needs to be weighed carefully in this select patient population.

[d]Thermal ablation includes percutaneous destruction of tumor via minimally invasive catheter maneuvering by interventional radiologists or surgeons using radiofrequency ablation, ultrasound ablation, cryoablation, microwave ablation, or lase ablation.

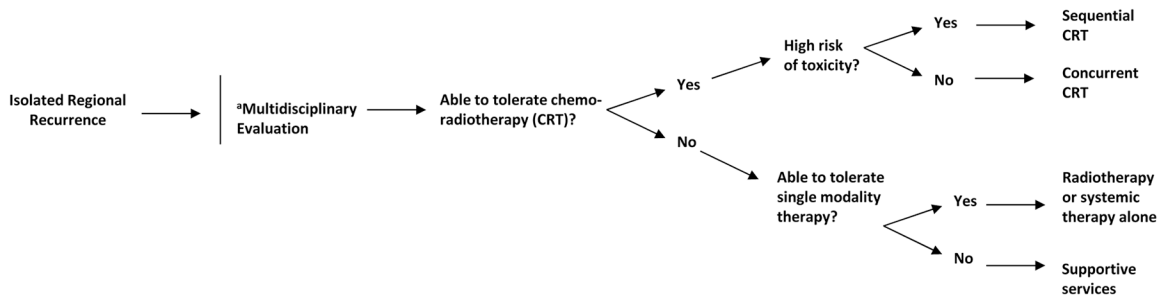

Figure 2.

Proposed management algorithm for isolated regional recurrence after stereotactic ablative radiotherapy.

[a]Multidisciplinary evaluation including thoracic surgeons, radiation oncologists, medical oncologists, and interventional radiologists

Table 1.

Selected studies of surgery as salvage after initial stereotactic ablative radiotherapy

Study and Reference	No. of Patients	Population	Techniques	Median time, SABR to surgery (mo)	Median follow-up time, mo	Significant Findings	Outcomes	Toxic Effects/Complications
Neri et al, 2010 [48]	2	iLR in initially inoperable cases	VATS lobectomy, segmentectomy	14	17	Complete resection in both patients	Both alive and disease-free at 2 and 32 months after resection	Postoperative pulmonary fistula (n=1) treated with surgery and pleurodesis
Chen et al, 2010 [45]	5	iLR in initially operable cases	Lobectomy	17	27	No significant fibrosis/ adhesions impairing dissection	All patients alive at last follow-up	None
Allibhai et al, 2012 [38]	4	iLR in initially inoperable cases	Lobectomy	15	31	Adhesions in all cases; required conversion to open procedure and partial chest wall resection (n=1 each)	All patients alive and disease-free at last follow-up	None
Taira et al, 2014 [49]	2	iLR in patients initially operable or inoperable	Wedge resection	37	--	Neither case had viable tumor cells in resection specimen	Not reported	Not reported
Hamaji et al, 2015 [50]	12	iLR in patients initially operable (9/12) and inoperable (3/12)	Open lobectomy (n=6), VATS lobectomy (n=3), VATS segmentectomy (n=2), open wedge resection (n=1)	15	55	Nodal dissection done in 11 patients, two of which were positive and offered adjuvant chemotherapy	Median CSS and OS from salvage surgery were 83 months	Intraoperative bleeding (n=1) requiring conversion to open lobectomy; prolonged air leak (n=3)
Verstegen et al, 2016 [39]	9	iLR (n=7) in initially operable cases; remainder with regional (n=1) or single distant metastasis (n=1)	Open lobectomy (n=5), VATS lobectomy (n=1), sleeve lobectomy (n=1), wedge resection (n=1), pneumonectomy (n=1)	22	19	Adhesions limited (n=3) or extensive (n=2), one of which required conversion to pneumonectomy; complete resection in all but one patient	Median OS 26 months; two patients failed (one with regional/distant, the other distant alone)	Grade 2 infection (n=2), grade 3 air leak requiring new chest tube (n=1); no 30-day mortality and 11% (n=1) 90-day mortality
Antonoff et al, 2017 [47]	21 *	iLR in initially inoperable (18/21) cases	Open lobectomy (n=8), robot/VATS lobectomy (n=2), wedge resection (n=3), segmentectomy (n=1), pneumonectomy (n=1)	16	17	Complete resection in all; nodal dissection in all patients (n=2 pN1, n=1 pN2, n=1 pM1)	Median OS 14 months	Of all patients, any complication (n=6) and ICU admission (n=2). Prolonged air leak (n=2), atrial arrhythmia (n=3), pulmonary artery thrombosis requiring pneumonectomy (n=1); 30- and 90-day mortality 5%
Brooks et al, 2018 [12]	10	iLR in initially inoperable cases	Lobectomy (n=6), sublobar (n=4)	--	39	Complete resection in all patients	100% local control and 90% regional control	40% with grade 3+ toxicities, including respiratory distress (n=1), pleural effusion (n=1), atrial fibrillation (n=1); no 90-day mortality

* 15 with non-metastatic disease

Abbreviations: SABR, stereotactic ablative radiotherapy; iLR, isolated local recurrence; VATS, video-assisted thoracoscopic surgery; CSS, cancer-specific survival; OS, overall survival

Table 2.

Selected studies of radiation as salvage after initial stereotactic ablative radiotherapy*

Study and Reference	No. of Patients	Population	Initial SABR	Median time between SABR and reSABR, mo	Median follow-up time, mo	Re-Treatment	Local (Regional) Control	Toxic Effects/Complications
Peulen et al, 2016 [28]	29**	iLR of previously SABRed patients with NSCLC (n=10) or metastases (n=19); central (n=11) or peripheral (n=21)	20–45 Gy in 1–5 fractions	14	12	SABR, 20–45 Gy in 1–5 fractions; chemo in 12 patients	5m LC 52%	Twelve grade 3 events, most commonly cough/dyspnea; two grade 4 events including vena caval stenosis and tracheal fistula; three grade 5 bleeds; no grade >3 toxicities in peripheral re-SABR
Valakh et al, 2013 [55]	9	iLR of previously SABRed patients with primary NSCLC (n=8), all peripheral	30–60 Gy in 3–5 fractions	11	22	SABR, 30–60 Gy in 3–5 fractions	2y LC 75%	Three grade 3 events (dyspnea, chest wall pain); no grade 4–5 events
Hearn et al, 2014 [46]	10	iLR of previously SABRed patients; all but two peripheral	30–50 Gy in 1–5 fractions	15	14	SABR, 50–60 Gy in 3–5 fractions	60% LC at last follow-up	No grade 3+ events
Kennedy et al, 2019 [52]	21	iLR of previously SABRed patients; central (n=6) or peripheral (n=15)	50–60 Gy in 3–5 fractions	23	24	SABR, 50–60 Gy in 3–5 fractions	2y LC 81%	No grade 3+ events
Manabe et al, 2018 [56]	26	iRR of patients previously SABRed (n=14) or resected (n=12)	48–60 Gy in 4–10 fractions	12	35	CFRT, 54–66 Gy in 27–33 fractions; chemo in 3 patients	1y LRC 76%	One grade 3 toxicity (dermatitis), 1 grade 5 pneumonitis
Kilburn et al, 2014 [57]	12	iRR of patients previously SABRed (n=9), hypofractionated (n=2), or both (n=1)	50–60 Gy in 3–5 fractions	15	10	CFRT, 60–70.2 Gy in 23–36 fractions; chemo in 2 patients	2y LRC 100%	One grade 3 dyspnea; no grade 4–5 events
Ward et al, 2016 [41]	15	iRR of patients previously SABRed	30–60 Gy in 1–10 fractions	11	--	45 Gy in 15 fractions (53%) or 50–60.4 Gy in 20–33 fractions (33%); chemo in 6 patients	1y LRC 84%	No grade 3+ events
Brooks et al, 2018 [12]	46	iRR of patients previously SABRed	50 Gy in 4 fractions or 70 Gy in 10 fractions	--	39	CRT (n=26), most commonly (n=24) with 60–70 Gy in 30–35 fractions; chemo only (n=12), RT only (n=8)	92% LRC (CRT) and 100% LRC (RT only) at last follow-up	Grade 3+ toxicity in 10 CRT patients (n=3 esophagitis, n=1 pneumonitis, n=4 hematologic); 4 chemotherapy only patients; 1 RT only patients

*Includes only studies of salvage after SABR, not salvage after mixed conventionally-fractionated radiotherapy and SABR.

**32 lesions

Abbreviations: SABR, stereotactic ablative radiotherapy; re-SABR, repeat stereotactic ablative radiotherapy; iLR, isolated local recurrence; NSCLC, non-small cell lung cancer; Gy, Gray; LC, local control; iRR, isolated regional recurrence; CFRT, conventionally fractionated radiation therapy; LRC, locoregional control; CRT, chemoradiotherapy