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Target volume definition for staple line recurrences of non-small cell lung cancer

Jan Nuzhat[1], Nitai D. Mukhopadhyay[2], Elisabeth Weiss[1]

[1]Department of Radiation Oncology, Virginia Commonwealth University Health System, Richmond, VA, United States
[2]Department of Biostatistics Virginia Commonwealth University, Richmond, VA, United States

ABSTRACT

Background: Staple line (SL) recurrences of non-small cell lung cancer (NSCLC) are commonly treated with radiotherapy (RT), but the target volume definition — whole SL versus focused on recurrence — is unclear. The aim of the study was to determine the appropriate target volume for RT of SL recurrences.

Materials and methods: Twenty-two consecutive patients (20 stage I, 2 stage II) treated with salvage RT for SL recurrences were retrospectively analyzed. Imaging features at the time of SL recurrence were evaluated to guide target volume definition.

Results:

Surgery: All patients had complete tumor resection (wedge resection in 10 (45%) and lobectomy in 12 (55%) patients). 14 (64%) patients had risk factors for recurrence, including surgical margins ≤ 2 cm, angiolymphatic and visceral pleural invasion.

Salvage RT: After a median 26 months (9–67), all 22 patients developed SL recurrence which was metabolically active on PET in all and biopsy-confirmed in 18/22 (82%) patients. All patients underwent RT targeting the location of the SL recurrence only. 13/22 (59%) patients had additional PET-negative nodular or linear SL changes that were not included in the irradiated volume.

Recurrence after RT: After a median 17 months (9–34) 10/22 (45%) patients recurred either regionally 6/10 (60%), in the lungs 4/10 (40%) or distally 3/10 (30%). No patient recurred at the SL. Two-year overall and disease-free survival rates after RT were 71% and 65%, respectively.

Conclusion: RT to SL recurrences alone results in excellent local control. Additional treatment to reduce regional and distant recurrences should be considered.

Key words: radiotherapy; staple line; non-small cell lung cancer; SABR; recurrence

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Introduction

Surgery is the recommended treatment for medically operable patients with early stage non-small cell lung cancer [1]. Despite innovations in surgical techniques and imaging in recent years, local recurrence rates still range between 4% and 20% [2–7]. Various risk factors for local tumor recurrence have been identified, including larger tumor size, sublobar resection, close resection margin, visceral pleural and lymphovascular space invasion [2, 7–11].

Salvage treatment options for tumor recurrence after initial surgery include repeated surgery, RT, systemic therapy and combinations thereof [3]. While surgery is the preferred salvage treatment option [12], it is often not feasible due to limited cardio-pul-

Address for correspondence: Elisabeth Weiss, 401 College Street, PO Box 980058, Richmond, VA 23298, USA, tel: (804) 828-7232, fax: (804) 828-6042; e-mail: elisabeth.weiss@vcuhealth.org

monary reserve or comorbid conditions. As an alternative treatment modality, salvage RT with curative intent has been recommended [13]. However, information on the outcome after salvage RT is limited. Excellent long-term local control rates of about 95% have been reported for isolated lung recurrences or oligorecurrences using SABR [14–15]. In other reports on patients with predominately stage I and II disease at the time of surgery, SABR for local and/or regional recurrences resulted in local control rates of about 85% after 2–3 years [5, 16]. Local control rates for conventionally fractionated salvage RT were in general lower than for SABR [13, 17, 18].

Staple or suture line/surgical margin recurrences (together termed "SL recurrence" in this study) are a subgroup of local recurrences that are commonly treated with RT. Target volume definition for SL recurrences is particularly challenging as, presumably, any part of the SL or surgical margin is at risk for recurrence. The question is, therefore, whether all of the SL or only the manifest recurrence need to be included in the treatment volume. Complicating the target volume definition is the finding that tissue granulation with thickening along the SL is often observed on CT imaging. For that reason, it might be challenging to exclude active tumor in these areas [19].

The aim of the present study is to analyze local control at the SL in patients irradiated for isolated SL recurrence after surgery. Recurrence pattern and clinical outcome following salvage RT are characterized. In addition, imaging features at the SL outside the manifest SL recurrence are assessed to provide information supporting target volume definition at the time of RT.

Materials and methods

Twenty-two consecutive patients with non-small cell lung cancer treated with definitive RT for SL recurrences were identified from our institutional database and included in this IRB-approved retrospective study. The analysis is based on electronic chart review and image evaluation. All patients initially underwent surgery for de novo lung cancer followed by salvage RT between 2007 and 2015. Patients with previous RT to the chest were excluded. Repeated surgery at the time of SL recurrence was discussed for all patients, but was declined by thoracic surgeons or multidisciplinary tumor board due to limited pulmonary function and underlying comorbidities restricting medical operability. All radiation treatment plans were generated based on 4D CT of the chest with 3 mm slice thickness in treatment position using individualized patient positioning with vacuum bags and overhead arm positioning devices. Using reconstructed maximum intensity projection (MIP) images, iGTVs were created, and target coverage was ensured using all 10 breathing phase bins of the 4D CT. Alternatively, GTVs created on one breathing phase were deformably propagated to the other 9 bins from where the iGTV was created through summation of all per-phase GTVs. 18-Fluorodeoxyglucose (FDG) PET-CT scans were available during tumor volume delineation for visual assessment of target coverage. For SABR, typically a 5 mm iGTV-to-PTV margin was added, for conventional fractionation a 6 to 8 mm margin was added to create a CTV which was then expanded by 5 mm to generate the PTV. Whereas SABR treatments were performed every other day, conventional treatments were performed with 5 fractions per week. For both techniques, image guidance was used for each fraction. For SABR, cone beam CTs (CBCT) were performed, whereas for conventional fractionation, daily kilovoltage planar imaging and weekly CBCTs were obtained. All alignments were to the target volume.

Routine follow-up exams after both surgery and RT included routine chest CT every 3 months for 2 years, then every 6 months up to 5 years, followed by annual scans. PET scans were obtained as clinically indicated for equivocal findings on CT imaging. Biopsies for suspected recurrences were performed as deemed medically safe following multidisciplinary tumor board evaluation. The time to SL recurrences after surgery, and the location and time to any recurrences following salvage RT were recorded. In addition, demographic, clinical and treatment specific information, such as type of surgery, pathologic risk factors, and type and dose of RT were collected. Post RT toxicities were graded according to common terminology criteria for adverse events (CTCAE) v5.0.

Imaging features at the time of SL recurrence were analyzed including size of SL recurrence, metabolic activity on PET scans, and peripheral versus central location. Central SL recurrences in this study were defined as being located in direct connection to the bronchus stump, hilum and central

airways, whereas peripheral SL recurrences were surrounded by the lung tissue, close to the chest wall or the mediastinal visceral pleura outside the central area. In addition, the presence, shape and thickness of additional CT imaging changes along the SL were assessed.

Statistical analysis

Overall and disease-free survival as well as recurrence rates were calculated with the Kaplan-Meier method. Log-rank tests were used to assess significant differences ($p < 0.05$) in the recurrence rates associated with various clinical, radiological and pathologic factors in statistical software R v3.6.1.

Results

Initial surgery

The 22 study patients with a median age of 73 years and Karnofsky performance status between 70 and 100% had stage I (20 patients, 91%) and II (2 patients, 9%) non-small cell lung cancers (pT1–3 N0 M0, AJCC 8th edition). All patients underwent surgery as primary tumor treatment consisting in either lobectomy (12 patients, 55%) or wedge resection (10 patients, 45%). Median tumor size at surgery was 17 mm (range 8–60 mm). Six patients underwent lymph node dissection, but no lymph node involvement was found either radiographically or on pathology review in any patient. Preoperative PET scans were obtained in 6 patients with a median SUV of 7.4 (2–10). Adenocarcinoma and squamous cell carcinoma were the most common pathologies, see Table 1 for further patient characteristics. Review of pathological specimen revealed risk factors of tumor recurrence in 14 patients. All patients had negative resection margins, but 10 patients had resection margins ≤ 2 cm. Six patients had angiolymphatic and seven patients visceral pleural invasion. Following surgery, two patients received chemotherapy: one patient for a new diagnosis of non-Hodgkin's lymphoma, the other patient with 0.1 cm to the parenchymal margin received adjuvant chemotherapy after surgery.

Salvage RT

The median time to recurrence after surgery was 26 months (range 9–67 months). 20 of 22 patients (91%) developed isolated SL recurrences (see examples in Fig. 1). One additional patient also had a simultaneous contralateral new secondary lung tumor that was treated with SABR following treatment of the SL recurrence. Another patient was diagnosed with oligometastatic bone metastasis in one rib at the time of SL recurrence and underwent chemotherapy. While the bone metastasis responded without recurring throughout the patient's lifetime, the local recurrence in the SL progressed and RT was initiated. Two patients had chemotherapy prior to RT for management of the SL recurrence, but were offered RT at the time of local progression.

All SL recurrences were diagnosed on routine follow up CT scans. The median size of the recurrent tumor on CT scan was 21 mm (range 7–50 mm). PET-CT scans at the time of recurrence showed metabolic activity in the location of recurrence with a median SUV_{max} of 4.7 (range 2–16).

Table 1. Patient characteristics

Characteristics	Number of patients (%) unless specified differently
Race	
AA	12 (55)
Caucasian	10 (45)
Gender	
Female	12 (55)
Male	10 (45)
Age (median (range) [years]	73 (53–93)
BMI [median (range)] [kg/m^2]	23 (13–52)
Pack year smoking [median (range)]	58 (30–135)
Tumor site	
UL and ML	17 (77)
LL	5 (23)
Surgery	
Lobectomy	12 (55)
Wedge resection	10 (45)
Pathology	
Adenocarcinoma	12 (55)
SCC	7 (32)
Other	3 (13)
Tumor size[a] (median (range) [mm]	17 (8–60)
Stage at surgery	
I	20 (91)
II	2 (9)
Tumor size[b] (median (range) [mm]	21 (7–50)
PET SUV_{max}[b] (median (range))	4.7 (2.2–16)

AA — African American; BMI — body mass index; LL — lower lobe; ML — middle lobe; PET — positron emission tomography; RT — radiotherapy; SCC — squamous cell carcinoma; SUV_{max} — maximum standard uptake; UL — upper lobe; [a]at the time of surgery; [b]at the time of radiotherapy

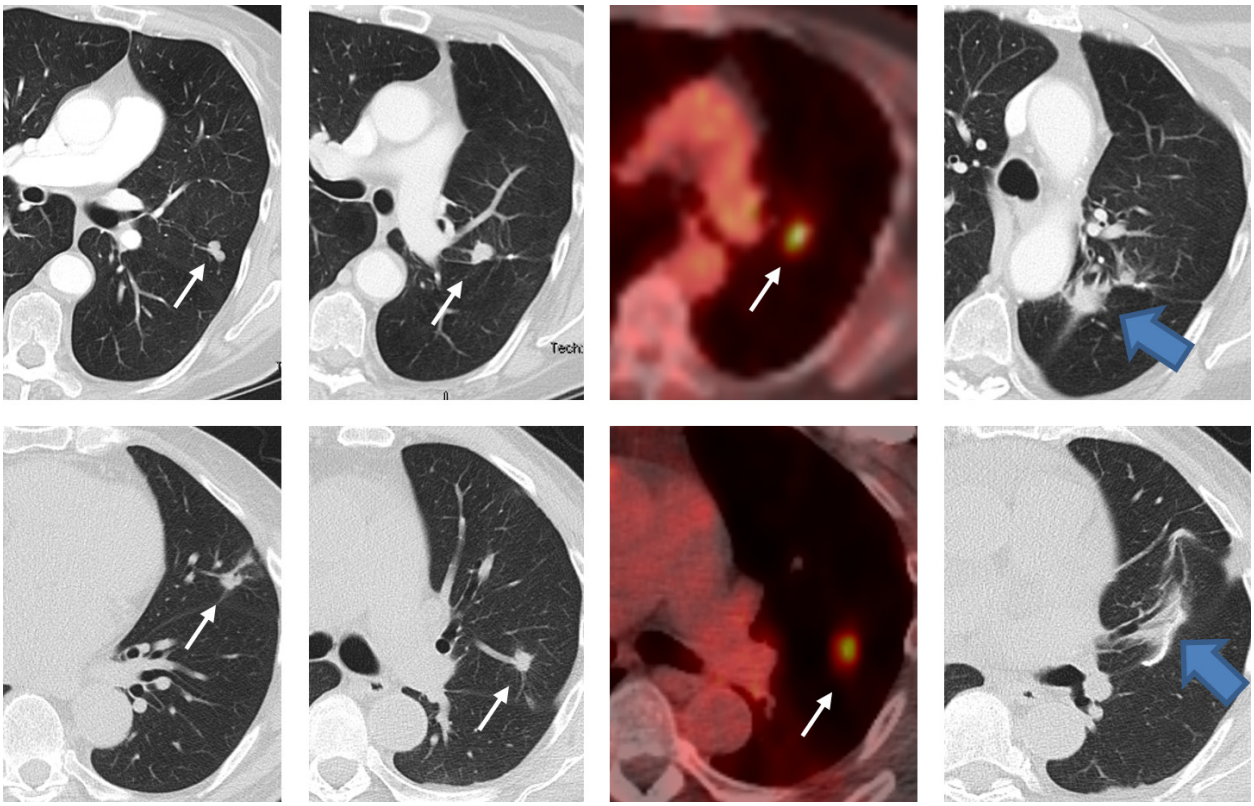

Figure 1. Examples of recurrences after wedge resection. Two examples of staple line (SL) recurrences in the left upper lobes following wedge resection. Small white arrows indicate tumor manifestations prior to surgery (1st column) and SL recurrences prior to SBRT (2nd and 3rd column). The last column in the upper row shows PET-negative nodular changes, the lower row linear SL changes outside the PET positive area (blue arrows). Radiotherapy targeted only the metabolically active tumor (shown in the 2nd and 3rd column)

Recurrences were confirmed by biopsy in 18 (82%) patients and were mostly central following lobectomy, and peripheral after wedge resection. On CT, all recurrences appeared either completely or partially dense, were bulging and had a predominantly round shape with spiculations. Overall, 13/22 (59%) patients had additional SL changes ≥ 2 mm that were nodular in 4 and predominantly linear in 9 patients. These changes were observed mostly in patients with wedge resection and were not metabolically active on PET scans (Tab. 2).

All patients underwent definitive RT with the target volume limited to the recurrent tumor volume only as defined on CT and PET scan, excluding areas of additional linear or nodular thickening. 14 (64%) patients received SABR with biologically effective doses (BED) ≥ 100 Gy. The fractionation was 48 Gy/4 fractions in 12, 45 Gy/3 in one, and 50 Gy/5 in one patient. Eight (36%) patients with tumor location near the central airways or brachial plexus underwent conventionally fractionated or hypofractionated RT. The fractionation in these patients was 45 Gy/15 in two and 60–66 Gy/30–33 in six patients. Three patients received concurrent radiochemotherapy with carboplatin and paclitaxel. All patients tolerated RT well. None of the patients experienced RT-related side effects grade ≥ 2, likely due to small treatment volumes avoiding mediastinal structures.

Recurrence after RT

Median follow up after RT was 23 months (range 1–87 months). Ten (45%) patients recurred after a median interval of 17 months (range 9–34 months). Recurrences were confirmed by biopsy in four of ten (40%) patients. Four (40%) patients developed recurrences in the lungs of which one was in the same lobe and three in the contralateral lung; three (30%) had bone metastases; six (60%) developed regional lymph node recurrences. None of the patients recurred at the SL either within or outside the radiation fields, see Table 3 for details on recur-

Table 2. Characteristics of staple line changes

Type of surgery	N	Location of staple line recurrence		Additional staple line changes			
		Peripheral	Central	Nodular ≥ 2 mm		Linear ≥ 2 mm	
		N	N	N	Median (range)	N	Median (range)
Wedge resection	10	10	–	4	4 mm (3–5 mm)	7	5 mm (4–8 mm)
Lobectomy	12	2*	11	–		2	

*One patient had both a peripheral and central recurrence after right middle lobe resection

Table 3. Characteristics of patients with recurrence after radiotherapy

	Surgery	Path	Tumor size[a] [mm]	Margin ≤ 2 cm	Visceral pleura invasion	AL invasion	Tumor size[b] [mm]	SUV_{max} [b]	Dose (Gy)/ /fractions	Site of recurrence after RT	Time to recurrence[+] [months]
1	Wedge	Adeno squam	8	x		x	7	3.9	48/4	Lung, LN	13
2	Lobe	SCC	25	x			24	12.5	48/4	LN	9
3	Lobe	NSCLC	15				15	2.4	48/4	Bone	29
4	Lobe	Adeno	18		x	x	8	5	48/4	Lung, LN, Bone	33
5	Lobe	Adeno	12	x	x		40	10.7	66/33	Bone	15
6	Wedge	Adeno	32		x	x	13	4.4	50/5	LN	18
7	Lobe	SCC	40			x	36	1.2	45/15	Lung	17
8	Wedge	SCC	45				30	12.6	45/3	Lung	34
9	Lobe	Adeno	60		x		49	4.7	66/33	LN	30
10	Wedge	Adeno	17				50	3.7	66/33	LN	14

Adeno — adenocarcinoma; Adenosquam — adenosquamous carcinoma; AL — angiolymphatic; CTRT — concurrent radiochemotherapy; Gy — gray; LLL — left lower lobe; LN — regional lymph node; LUL — left upper lobe; Path — pathology; na — not available; R — right; RLL — right lower lobe; RT — radiotherapy; SCC — squamous cell cancer; SUV_{max} [b] — maximum standard value uptake at the time of radiotherapy; [a]Tumor diameter at the time of surgery; [b]Tumor diameter at the time of radiotherapy; [+]Time to recurrence after radiotherapy

Table 4. Analysis of factors influencing recurrence rates

Characteristic	HR	95% CI	p-value
Tumor size at surgery (small *vs.* large)	0.7008	0.1955 2.5121	0.58
Tumor size at RT (small *vs.* large)	0.3738	0.1045 1.3374	0.12
Surgery type (wedge *vs.* lobectomy)	0.5758	0.1600 2.0719	0.39
RT type (SABR *vs.* conventional)	0.2363	0.0559 0.9989	0.035
SUV at RT (low *vs.* high)	0.8670	0.2481 3.0290	0.82
Surgical margin ≤ 2 cm	0.4758	0.1207 1.8762	0.28
Pleural invasion present	1.8936	0.5376 6.6697	0.31
Angiolymphatic invasion present	1.5455	0.4285 5.5747	0.5
≥ 2 pathological risk factors*	2.4198	0.6176 9.4806	0.19

HR — hazard ratio; CI — confidence interval; RT — radiotherapy; SABR — stereotactic ablative radiotherapy; *risk factors are tumor size, resection margin ≤ 2 cm, visceral pleura and angiolymphatic involvement

rences. None of the investigated factors (tumor size at surgery, tumor size at radiotherapy, SUV value, type of surgery, margin at surgery, pleural invasion, angiolymphatic invasion) was significantly associated with the recurrence risk following RT, except for the RT type, see Table 4. Patients undergoing SABR had a reduced risk of recurrence compared to conventionally fractionated RT (p = 0.035).

Two-year overall and disease-free survival after RT were 71% and 65%, respectively (Fig. 2). Further

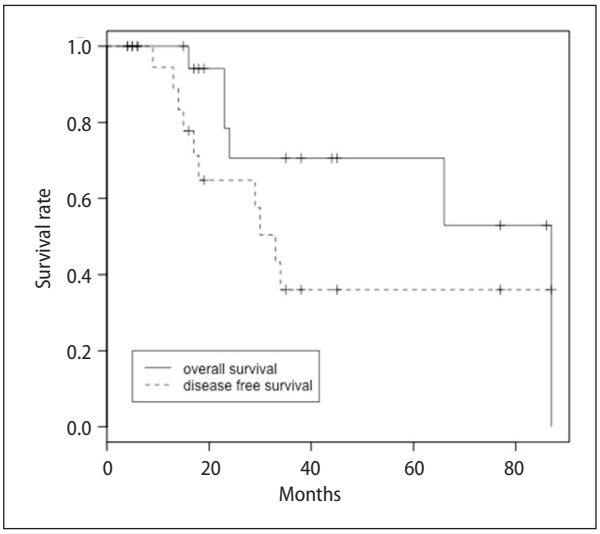

Figure 2. Survival following salvage radiotherapy for staple line recurrences. Kaplan-Meier curves for overall and disease-free survival following radiotherapy. 2-year overall survival and disease-free survival were 70.6% and 64.8%, respectively

treatment for patients with recurrence after salvage RT for SL recurrence included RT in 7/10 (70%) patients and systemic therapy in 4/10 (40%).

Discussion

Salvage RT for SL recurrences resulted in excellent local control with both SABR and conventionally fractionated RT and is well tolerated similar to other studies using SABR for salvage treatment [20, 21]. SABR is well known for low local failure rates in early stage lung cancer [22–24]. The 5-year local failure rate after SABR for isolated local lung recurrence anywhere in the lung was 5.2% in a prospective phase II trial [15]. SABR for oligorecurrence after lung ca surgery resulted in a 3-year local control rate of 94.9% [14]. For patients with predominately stage I and II disease at the time of surgery, SABR for local and/or regional recurrences resulted in local control rates of about 85% after 2-3 years [5, 15]. For conventionally fractionated salvage RT of intrathoracic recurrences Kelsey et al. [13][13] reported 2-year local control rates of 68% after delivering 66 Gy with radio(chemo)therapy. The majority of patients in this study had mediastinal lymph node involvement, whereas patients in our study had local recurrence at the SL only. The incidence of SL recurrences is not well known. In one multi-institutional database the absolute rate of isolated surgical margin recurrences was only 3% following complete tumor resection and negative lymph nodes at the time of surgery and constituted 22% of all recurrences for this patient group [7]. Reports specifically targeting RT of SL recurrences are rare. Similar to our study, Takeda et al. [25] reported a cohort of 21 patients with recurrence at the SL or bronchial stump and 2 patients with chest wall recurrence treated with SABR after initial lobectomy or wedge resection for stage I and II lung cancer (one patient had stage III disease with lymph node involvement). The authors observed only 2 local recurrences compared to 100% local control in our cohort. While RT can achieve excellent local control rates, regional recurrences and, in particular, distant metastases are the predominant locations of post salvage RT recurrences [25, 26]. Regional lymph node recurrences were reported in 10–20%, distant recurrences in 20–40% [5, 15, 16], which is comparable to the recurrence rates in our study where 30% experienced regional and distant recurrences each. Given the observed re-recurrence rates, the value of adjuvant therapy after RT for SL recurrence needs to be evaluated. Depending on the pattern of re-recurrences in the individual patient, additional RT or systemic therapy are both treatment options. In our study, 70% of patients with re-recurrence underwent an additional course of RT. Survival rates after salvage RT for SL recurrences in our study (2 y OS — 71%, 2 y DFS — 65%) were in agreement with survival rates reported by Takeda et al. [25] (2 y OS — 76.4%, 2 y DFS — 62.5%). These outcomes are also at least comparable to de novo SABR for inoperable stage I NSCLC [27, 28].

Various risk factors for postoperative tumor recurrence have been identified. For example, tumor size has been found to predict local recurrence risk following wedge resection for stage I NSCLC [2]. Other factors related to local control included sublobar resection, close resection margins, visceral pleural invasion, lymphovascular space invasion, squamous cell cancer, and increased metabolic activity on PET-CT [7–11]. Lymphovascular invasion was identified also as a risk factor for distant recurrences and overall survival [7–11]. In our study, despite achieving local control after salvage RT with both SABR and conventionally fractionated RT, patients undergoing conventionally fractionated RT had a higher recurrence rate potentially related to

lower biologically effective doses and central tumor locations with higher risk of recurrence. This observation is interesting as it indicates the likely presence of tumor cells outside the SL recurrence at the time of salvage therapy, again supporting the potential benefit of adjuvant therapy following salvage RT. Liquid biopsies at the time of local recurrence might be helpful to direct additional treatments [29].

While there was a concern that localized RT to SL recurrences might result in additional SL recurrences in other areas later on, our present study indicates that local RT to the recurrence alone results in excellent in-field control and no further recurrences anywhere at the SL. In a recent investigation by Sun et al. [19] SL thickening on CT imaging was frequently observed. In this study, areas of SL thickening either remained staple or regressed in 84%. SL recurrences were diagnosed only in areas with increasing thickness of ≥ 2 mm over time. CT imaging in our cohort showed additional SL thickening in nearly 60% of patients. In comparison, actual SL recurrences were in general larger than other areas of SL thickening. Although some SL areas showed thickening of up to 8 mm, metabolic activity on PET-CT clearly identified locations with active tumor disease.

This study is limited through its retrospective nature, the rather small patient cohort and some heterogeneity in patient treatments with the common feature that all patients received definitive intent salvage RT for SL recurrence. Based on consistent follow up procedures including multimodality imaging and biopsies over a median of more than 2 years after each therapy step, important findings were made that add to the currently limited information on the effectiveness of salvage RT for lung cancer recurrence. These findings include the pattern of re-recurrence, patient outcomes after salvage RT and selection of radiation target volumes.

Conclusions

RT as a salvage treatment for SL recurrences after initial surgical resection appears to be a safe and well-tolerated treatment option in our study cohort. While survival post salvage RT is comparable to SABR for newly diagnosed early stage lung cancer, adjuvant treatment options need to be considered to improve regional and distant control either in the form of concomitant chemotherapy with normofractionated RT or adjuvant systemic treatment following SABR. Our study demonstrated excellent local control after RT to SL recurrences alone. Focusing RT to the SL recurrence alone appears therefore justified.

Conflicts of interest

There are no conflicts of interest. EW receives grant support through NIH and royalties from UpToDate.

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Data sharing

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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