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Salvage surgery for local recurrence after stereotactic body radiotherapy for early stage non-small cell lung cancer: a systematic review

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Abstract

Introduction: Stereotactic body (or ablative) radiotherapy (SBRT/SABR) is now a guideline-recommended treatment for medically inoperable patients with peripherally-located, stage I non-small cell lung cancer (NSCLC), and for medically operable patients who decline surgery. The 5-year local failure rate after SBRT is about 10% and in highly selected patients, surgery has been used as a salvage therapy. We performed a systematic review to address the feasibility, safety, and outcome of salvage surgery for locally recurrent early stage NSCLC after SBRT.

Methods: A systematic literature search was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. *PubMed, Embase* and *Cochrane databases* were searched and two authors independently assessed the articles. A total of seven eligible articles were identified.

Results: All seven articles were retrospective case series, representing a total of 47 patients. Surgery was completed in all patients. Where reported in sufficient detail, morbidity (four studies) was between 29 and 50% (series of two patients) and 90-day mortality (six studies) was between 0% (four studies) and 11% ($n = 1$, disease progression). Median ($n = 5$)/mean ($n = 1$) reported or calculated follow ups were 7–54.5/17.3 months. Median overall survival was reported in three studies and ranged between 13.6–82.7 months. Crude survival in three others was 2–35 months.

Conclusion: Limited, low-level evidence prevents firm conclusions, but based on the existing data, salvage surgery after local recurrence of NSCLC following SBRT appears technically feasible, with acceptable morbidity and mortality in appropriately selected and counselled patients who are fit enough and who accept the risks (level of evidence 4, strength of recommendation C).

Keywords: Non-small cell lung cancer (NSCLC), salvage, stereotactic ablative radiotherapy (SABR), stereotactic body radiotherapy (SBRT), surgery

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Introduction

Lung cancer is the most common cause of cancer-related death.[1] The majority of patients (>80%) have non-small cell lung cancer (NSCLC) and about 20% present with localized disease.[2] The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for early stage (I and II) disease state that 'The cornerstone of treatment of potentially resectable lung cancer is surgical removal of the tumour'.[3] The therapy recommended for patients with stage I NSCLC (up to 5 cm in diameter) who are inoperable due to

comorbidity or for other reasons, or who do not accept the risks of surgery, is stereotactic body (or ablative) radiotherapy (SBRT/SABR).[3] Local control rates of about 90% at 5 years can be expected with SBRT.[3]

The use of SBRT for NSCLC has increased substantially in the last decade and has been associated with gains in population-based survival.[4] From a technical perspective, the high-dose region, which is most damaging to normal tissues, is concentrated on the tumour region with a small margin around it and the intermediate-low dose area spreads out around this.[5] This helps to limit the toxicity, which is usually mild, even in elderly patients and those with severe chronic obstructive pulmonary disease (COPD) and limited lung function.[6–8]

The efficacy and favourable toxicity profile of SBRT in medically inoperable patients has led to interest in its use in medically operable patients.[9,10] Although there have so far been no successfully completed randomized trials comparing surgery and SBRT in operable patients, a small pooled analysis of the STARS and ROSEL studies concluded that it could be an option for treating operable stage I NSCLC.[11] The use of SBRT in operable patients highlights the needs for effective detection of local failure and the availability of effective salvage options. Curative-intent salvage treatment options include surgery, which is supported by current guidelines.[3] We performed a systematic review to assess the available literature regarding salvage surgery for local recurrence after SBRT with a particular focus on feasibility and safety.

Methods

Study selection

A literature search was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[12] Publications about recurrent NSCLC following stereotactic radiotherapy, were identified in the bibliographic databases *PubMed* (Supplementary Table 1), *EMBASE.com* (Supplementary Table 2), and the *Cochrane Library* (via Wiley) (Supplementary Table 3) from inception to 7 November 2017. Search terms included controlled terms (MeSH in *PubMed* and Emtree in *Embase*) as well as free text terms. Free text terms only were used in the *Cochrane Library*. Searches focused on NSCLC, stereotactic radiotherapy, SBRT, SABR, radiosurgery, recurrence and salvage. Only English language papers were included in the review.

Following the removal of duplicates, articles were initially screened by title and abstract to exclude nonrelevant reports, and the remaining articles were accessed in full and further screened to identify those meeting the inclusion criteria: any type of original English language report (reviews and editorials were excluded) concerning surgery for local recurrence after stereotactic radiotherapy for NSCLC. Finally, the reference lists of relevant articles were searched. Debate over article selection was resolved with consensus. The full search strategies for all databases can be found in supplementary Appendix 1.

All final studies were independently reviewed by three authors to extract relevant information, including article type, number of patients, radiotherapy details, time between radiotherapy and surgery, type of surgery, morbidity, mortality, follow up and survival.

Data analysis

We planned to conduct a quantitative data analysis (meta-analysis) if the data reporting was sufficiently homogenous [with respect to such parameters as time of follow up, morbidity and overall survival (OS)]. However, due to the small sample sizes and heterogeneity in the aforementioned study characteristics, pooling of data was not appropriate. Therefore, taking the level of evidence into account, we chose to perform a qualitative overview of the current publications, summarizing the important outcome measures.

Results

The initial search resulted in a total of 2847 records: 670 from *PubMed*, 2146 from *Embase* and 31 from the *Cochrane Library*. After removal of duplicates ($n = 619$), and screening all titles and abstracts, 2204 records were excluded. The remaining 24 articles were accessed in full (Figure 1). From these, two were excluded from further assessment as they reported on salvage surgery for both early stage NSCLC and metastatic lung disease. Overall, one study reported results for NSCLC and metastases separately and was included.[13] There were two author groups that published more than one paper or abstract on this topic. To prevent possible double counting of patients, these papers and abstracts

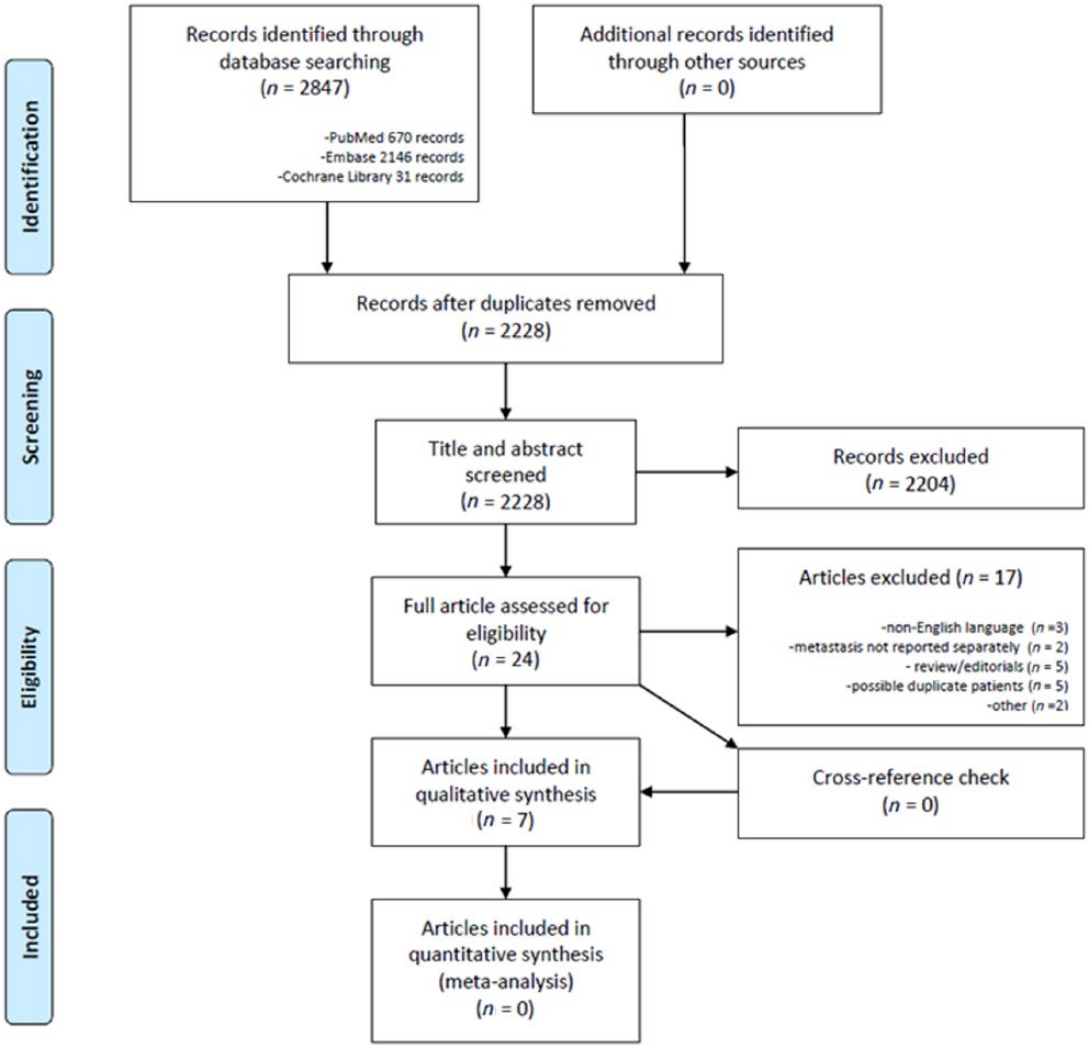

Figure 1. Flowchart depicting study selection criteria.

were checked and possible duplicates were excluded ($n = 5$). Other reasons for exclusion were results not in the English language ($n = 3$), reviews/editorials ($n = 5$), or other reasons not meeting the inclusion criteria ($n = 2$). Cross-checking the references of relevant studies did not yield any additional articles. Finally, seven suitable articles remained, representing 47 patients.[13–19] The key data are summarized in Table 1. All were retrospective case series. The reasons that the patients were not operated on, and instead received SBRT, are summarized in Table 2. The most common was patient preference (25/44 patients for whom the reason was reported).

All articles described the radiotherapy that had been delivered as 'stereotactic'. They reported a range of different dose-fractionation schedules (Table 1) in varying levels of detail. Based on the available data, it would seem that all, or nearly all, of the patients received a biological effective dose to the tumour (BED_{10}) of at least 100 Gy (i.e. assuming an α/β ratio for tumour of 10). This has been considered to be the desirable BED to achieve a sufficiently high probability of tumour ablation/control.[3]

Lobectomy was the most commonly described surgical procedure. Both minimally invasive and open procedures were performed. When reported, nearly all resections were radical (29/30) and vital tumour was found on pathological examination in 41/44 patients. In the 39 patients with known post-operative pathological staging, it can be summarized as: 30/39 N0 [pT1/mic ×8; pT2 ×16; pT3 ×4; pT4 ×2 (one M1)], 2/39 N1 (pT2), 7/39 N2

Table 1. Summary of all studies included in qualitative synthesis.

Author	Year of publication	Study	Number of patients[a]	Gy / fractions	Time between SBRT and surgery in months (range)	Type of lung resection	Radical resection	Vital tumor on pathology	Morbidity	Mortality	Follow up in months (range)	Overall survival (months)
Antonoff[b,13]	2017	Case series	15	48–70 / 4–15[e]	16.2 median[e] (6.4–71.5)	L, BL, S, W, P[e]	15/15	15/15	28.6%[e,f]	4.8% (90 day)[e]	17.3 mean[e]	Median 13.6 3-yr 43.1%
Neri[c,14]	2010	Case series	2	48 /4	8 and 19	L, S	n.r.	2/2	50%	0%	17 median (2–32)	Both alive at 2/32 months
Hamaji[15]	2015	Case series	12	48–60 / 4–8	17.5 median (8.6–105)[g]	L, S, W	n.r.	12/12	25%	0%	54.5 median (3–86)	Median 82.7 5-yr 79.5%
Taira[16]	2014	Case series	2	48 /n.r.	36 and 38[h]	W	n.r.	0/2	n.r	n.r.	n.r.	n.r.
Allibhai[17]	2012	Case series	4	48–60 / 3–8	15.4 mean (10–25)	L	3/3	3/4	[d]	0%	30.5 median (14–35)	All alive at 14–35 months
Verstegen[18]	2017	Case series	9	55–60 / 3–8	22 median[i] (10–35)	L, SL, P, W	8/9	9/9	33%[j]	11% (90 day)[k]	19 median	Median 26
Yamasaki[19]	2017	Case series (abstract)	3	48 / 4	21 mean (14–30)	n.r.	n.r.	n.r.	n.r.	0% (90 day)[l]	7 median (3.3–8)	1 alive 8 months

BL, bilobectomy; CT, computed tomography; L, lobectomy; MDACC, MD Anderson Clinic; n.r., not recorded; NSCLC, non-small cell lung cancer; P, pneumonectomy; S, segmentectomy; SL, sleeve-lobectomy; W, wedge resection.
[a]Only patients with NSCLC were included.
[b]Only patients from MDACC were included.
[c]Abstract excluded from same group.
[d]'No significant intra-operative or postoperative complications'.
[e]Data for all patients, not only NSCLC.
[f]Rate for 'any complication'.
[g]These values are for disease-free intervals from Table 1, lower limit of range 10 m in Table 2 of the reference.
[h]Interval to CT scan prior to operation.
[i]Time to local recurrence.
[j]Grade ⩾2.
[k]Disease progression.
[l]One patient died of respiratory failure 103 days postoperatively.

Table 2. Reason for SBRT as the primary treatment.

Author	Number of patients	Reason not to consider surgery as the initial treatment
Antonoff[13]	15	**Inoperable (n = 5)**: FEV_1 or DLCO less than 40% (*n* = 4), considered inoperable in other hospital (*n* = 1) **Operable but high risk (n = 10):** refused surgery (*n* = 4), additional malignancy (*n* = 3), previous lobectomy + anticoagulation (*n* = 1), previous lobectomy + borderline spirometry + coronary arterial disease (*n* = 1), previous chemoradiotherapy for N2 disease without a known primary, with subsequent discovery of the primary nodule (*n* = 1)
Neri[14]	2	**Operable but refused surgery (n = 2)**
Hamaji[15]	12	**Operable but refused surgery (n = 9) Inoperable (n = 3):** ipsilateral thoracotomy (*n* = 1), previous stage IV NSCLC under chemotherapy (*n* = 1), multiple organ failures (*n* = 1)
Taira[16]	2	**Operable but refused surgery (n = 1) Operable but high risk (n = 1):** COPD (*n* = 1)
Allibhai[17]	4	**Inoperable (n = 4):** recent stroke + aortic stenosis (*n* = 1), recent cardiac event + poorly controlled diabetes (*n* = 1), recent acute coronary event + prolonged air leak following biopsy (*n* = 1), severe COPD (*n* = 1)
Verstegen[18]	9	**Operable but refused surgery (n = 9)**
Yamasaki[19]	3	Not reported

COPD, chronic obstructive pulmonary disease; DLCO, diffusion capacity; FEV_1, forced expiratory volume in 1 second; NSCLC, non-small cell lung cancer.

(pT1 ×2; pT2 ×4; pT3 ×1). The high proportion of pT2+ tumours after surgery contrasts with cT1 staging in 33 patients prior to SBRT.

Reported morbidity varied widely but reporting was not standardized and was not reported in all studies. Mortality was reported in six papers, with a 90-day mortality of 11% being the highest reported.[18] This represented one patient who died of disease progression. OS reporting also varied between studies. The median reported/calculated follow up in six studies was 17–54.5 months. Median OS was reported in three studies, and ranged 13.6–82.7 months. Crude survival in three others was 2–35 months. One study reported a 3-year OS of 43.1%,[13] and one a 5-year OS of 79.5%.[15]

Adhesions attributed to the radiation were reported to a various extent in four studies: 16.7%,[15] 56%,[18] 97.3% (MD Anderson and non-MD Anderson patients, including patients undergoing salvage after SBRT for metastasis),[13] and 100%.[17] Overall, one study reported 'no severe adhesions'.[19] In two studies, it was reported that adhesions necessitated conversion in one patient each from minimally invasive to open surgery,[15,17] and in one study a patient required a partial chest wall resection due to adhesions.[17] Where described, prolonged air leak was reported in: 9.5% (MD Anderson patients, including patients undergoing salvage after SBRT for metastasis),[13] 11%,[18] and 25% of patients.[15] In total, one patient was reported to have had a postoperative pulmonary fistula.[14] There was one patient that was reported to have died from postoperative complications (acute respiratory distress syndrome and multiple organ failure) after bilobectomy with pulmonary arterial patch angioplasty,[13] and one patient died of respiratory failure, 103 days postsurgery.[19]

Discussion

This systematic review identified seven studies, representing 47 patients treated with surgery for local recurrence after SBRT for early stage NSCLC. To the best of our knowledge this is the most complete review performed so far on this topic. All studies were retrospective case series representing a low level of evidence (level 4, any

recommendation is therefore level 'C') according to the Oxford Centre for Evidence-Based Medicine.[20] In addition, the amount of detail and the description of complications and outcomes was, as expected, variable in whether and how they were described. This prevented an individual patient meta-analysis. Nonetheless, the available results show that salvage surgery for local recurrence ± regional recurrence, is technically feasible and that it can be performed with acceptable morbidity and mortality, even in patients previously considered medically inoperable or at high surgical risk prior to SBRT. It is important to note however, that the numbers of patients are small, and they are likely to have been highly selected. Therefore, any conclusions are tentative.

The articles reported varying rates of adhesions, however, even when present these did not preclude surgery, although they could require conversion from a minimally invasive to an open procedure or necessitate a more extensive resection. Whether there was a correlation between the location of the recurrence in the previously irradiated area and the grade of adhesions, could not be extracted from these studies. A study reported on the distance between tumour surface and pleura, as a measure of how central of peripheral the recurrence was located in the lung.[14] It could be of interest for future investigations to study whether the tumour location correlates with the amount and severity of adhesion formation by SBRT, and whether this should be taken into account during surgical planning [e.g. whether to opt for open or video-assisted thoracoscopic surgery (VATS)].

Prolonged air leak was one of the most common reported complications but was manageable. Although the number of patients was limited, 90-day mortality rates were low (0% in 4/7 studies, although in one of these a patient died at 103 days postsurgery) and in the study reporting a 90-day mortality of 11% this was due to disease progression.[18] These results compare favourably with those for primary lung cancer resection.[21] Although it relates to a different treatment scenario (neoadjuvant lung SBRT followed by planned surgical resection), the MISSILE-NSCLC study has reported interim acute toxicity results in 10 patients: the rate of grade 3–4 toxicity was 10% and the 30- and 90-day mortality was 0%.[22] Even though salvage surgery is typically performed after a considerably longer interval, which may allow the development of adhesions, the results compare favourably with early surgical resection.

Another interesting finding is the good OS reported in several of the studies, which was up to almost 80% at 5 years in one series.[16] Brooks and colleagues have also reported in abstract that patients with isolated local recurrence (LR) and regional recurrence (RR) after SBRT for NSCLC can have good outcomes with salvage therapy (surgery, re-irradiation, radiofrequency ablation, chemotherapy and chemoradiotherapy), 5-year OS 45.2% for LR and 42.9% for RR, comparable with patients with no recurrence (53.5%, $n = 569$).[23] These results are especially important because there is a gradual shift towards offering medically operable patients SBRT as first-line treatment for early stage NSCLC. If this continues, then multidisciplinary tumour boards can expect to encounter more patients with post-SBRT LRs, who are eligible for salvage surgery. It is worth noting that certain tumour locations (lower lobe) and histology (squamous cell histology) may be associated with an increased risk of local failure after SBRT.[24–25]

A lower BED may also increase the risk of LR and therefore the likelihood of requiring salvage surgery.[26]

While some of the patients underwent SBRT because they declined surgery, others had been considered to be medically inoperable, or to have too high a risk for primary surgery. This systematic review highlights that the perception and acceptance of risk may change once recurrence has occurred. Or that perhaps patient's medical status may change over time, and so the option of surgical salvage should not be dismissed too quickly. Patients being considered for salvage surgery should be discussed in an experienced lung cancer tumour board and operated on by a sufficiently experienced surgical team.

Salvage surgery will of course not be suitable for patients who cannot undergo surgery. For some of these patients (e.g. with peripheral tumours), salvage with repeat SBRT may be an option.[27,28] For those patients in whom salvage surgery and repeat SBRT are not an option, the possibilities may include chemo/targeted/immune therapy and occasionally attempted salvage with other local therapies.[29]

An important question to be addressed is how tumour recurrence can be diagnosed early, preferably before nodal spread has occurred. Standard computed tomography (CT) thorax imaging after SBRT is prone to inter-observer variability in

interpretation and distinguishing between post-SBRT changes and recurrent tumours can be challenging, even with the use of fluorodeoxyglucose-positron emission tomography/CT.[30–32] The difficulty in identifying tumour recurrence and distinguishing it from postradiotherapy changes in previously irradiated lung tissue, may also account, at least in part, for the high proportion (where specified) of pT2+ tumours after surgery (when the majority were cT1 prior to SBRT). Among other strategies, improved interpretation of imaging data and circulating tumour cells merit investigation.[30,33] However, at the present time, the potential risks of surgery mean that in general, cytology or histology-proven recurrence is preferable prior to surgical salvage.

Conclusion

This systematic review represents a comprehensive summary of English language reports of salvage surgery after LR of NSCLC following SBRT for early stage NSCLC. From the available data it seems that salvage surgery may be performed with reasonable mortality and morbidity rates, in appropriately selected and counselled patients. However, because there are limited data available, and the quality is variable, appropriate care and caution is needed with interpretation and in drawing conclusions.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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