Salvage Stereotactic Ablative Irradiation for Isolated Postsurgical Local Recurrence of Lung Cancer

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Background. For isolated postsurgical local recurrences (IPSLR) of lung cancer, salvage resection is often unfeasible due to a high risk of morbidity and death. Stereotactic ablative body radiotherapy (SABR) provides excellent therapeutic effects, with mild toxicities, for patients with medically inoperable lung cancer. However, the outcomes of SABR for IPSLR have not been reported.

Methods. Patients with IPSLR who were treated with SABR between 2005 and 2012 were retrospectively identified. The prescribed doses were 40 to 60 Gy per 5 to 10 fractions. Treatment outcomes and toxicities were evaluated.

Results. We identified 23 patients with IPSLR, including 21 with bronchial stump or staple line recurrences and 2 with chest wall recurrences. During follow-up, IPSLR occurred at a median of 36.7 months (range, 5.0 to 190 months) after resection. All patients were N0 M0, and the T stages at recurrence were T1a, T1b, T2a, and T4 in 6, 5, 3, and 9 patients, respectively. The initial pathologic diagnoses were adenocarcinoma in 17 patients and squamous cell carcinoma in 6. At a median follow-up duration of 17.0 months (range, 6.0 to 89.6 months) after SABR, there were 2 local recurrences. Local control and overall survival rates at 1 and 2 years were 94.7% and 86.8% and 84.0% and 76.4%, respectively. Grade 3 to 5 radiation pneumonitis occurred in 1 patient each. Grade 3 temporary but repeated obstructive pneumonia occurred in 2 patients.

Conclusions. SABR for IPSLR achieved high local control with limited toxicities. SABR may lead to a potential cure and should be considered as a salvage treatment option for IPSLR.


Recurrent non-small cell lung cancer (NSCLC) has been regarded as almost always fatal [1]. It is often associated with significant distress that requires substantial supportive treatment. Recurrence leads ultimately to a significant decrease in patient quality of life, limiting further interventions. Patterns of recurrence can be broadly divided into local, regional, and distant [2, 3]. They may occur alone or in combination.

The National Comprehensive Cancer Network (NCCN) guideline for NSCLC states that salvage resection is preferred for resectable local recurrences and that external beam radiotherapy (EBRT) or stereotactic ablative body radiotherapy (SABR) should be treatment options as well [4]. However, salvage resection is often unfeasible [5, 6]. The median survival time after EBRT was reported to be approximately 30 months for bronchial stump recurrence of NSCLC in a review derived from reports of small numbers of patients [7]. However, outcomes of SABR for isolated postsurgical local recurrences (IPSLR) have not been reported.

SABR enables accurate delivery of high doses of radiation to a small pulmonary nodule while sparing the surrounding normal lung and has a short treatment period. It has excellent efficacy and mild toxicity in early-stage NSCLC [8] and has been widely accepted as a therapeutic option for inoperable tumors [9]. However, SABR should be used with caution in patients with tumors located near the hilum or central airways because excessive toxicities could occur [10]. In our institution, we have proactively and carefully treated patients with IPSLR using SABR. In this study, we retrospectively investigated the outcomes of radical salvage SABR for IPSLR.

Patients and Methods

The Ofuna Chuo Hospital Review Board approved this retrospective study. All patients provided written informed consent.

Patients

Between April 2005 and July 2012, 360 patients were treated with curative SABR in our institution. We retrospectively identified patients with IPSLR of NSCLC with a performance status of 0 to 2, according to World Health...
Organization guidelines, who were treated with a total dose of 40 to 50 Gy per 5 to 10 fractions. We defined IPSLR as isolated bronchial stump recurrence, staple line recurrence, or thoracic wall recurrence [2, 3] with no regional lymph node involvement or distant metastasis. IPSLR were diagnosed by pathologic confirmation or defined as an increase of more than 25% in the cross-sectional tumor size on successive computed tomography (CT) scans at least three times during a 6-month period. Starting in 2007, 2-deoxy-2-[18F]-fluoro-D-glucose ([18F-FDG] positron-emission tomography (PET)/CT scans were added for restaging starting in 2007.

Treatment

We described our SABR methods previously [11]. Briefly, long scan-time CT was used to visualize the internal target volume (ITV) directly, after the patient was immobilized with a vacuum pillow. The planning target volume (PTV) was determined by adding a margin of 6 to 8 mm to the ITV. We used dynamic conformal multileaf therapy with 8 arcs and additional static ports. The prescribed dose was defined as the 80% isodose of the maximum doses between 2001 and 2011 and shifted to the 60% isodose starting in 2012.

The prescribed doses for peripheral tumors were 50 Gy per 5 fractions between 2005 and 2011 and 60 Gy per 5 fractions starting in 2012. Doses for tumors located centrally or adjacent to critical organs were 50 Gy per 10 fractions in 2005 and 40 Gy per 5 fractions starting in 2006.

Follow-Up

Follow-up CT scans were performed 1 and 3 months after SABR and at 3-month intervals during the first 2 years. Subsequently, follow-up CT scans were obtained at 4- to 6-month intervals. [18F-FDG-PET/CT was performed approximately 1 year after SABR and when recurrences were highly suspected. Local recurrences after salvage SABR were defined as regrowth of IPSLR, which were often seen as consolidation including them and were diagnosed by an increase of more than 25% in the cross-sectional tumor size on successive CT scans during a 3-month period. Regional and distant recurrence was defined as the new appearance of a positive hilar lymph node or mediastinal lymph node and distant metastatic lesions, or both. New appearances of disease in the same or the ipsilateral different lobe were regarded as distant metastasis. Acute and chronic toxicities were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

The local control and survival rates were calculated with Kaplan-Meier methods. Data were analyzed with SPSS 20.0 software (IBM Corp, Armonk, NY).

Results

We identified 23 patients with IPSLR of NSCLC who were treated with SABR. Patient and tumor characteristics are reported in Table 1. No patients received adjuvant radiotherapy. Two patients were treated with gefitinib after SABR. The median interval from initial treatment to SABR for IPSLR was 36.7 months (range, 5.0 to 190 months). The median maximum diameter of recurrent tumors was 2.3 cm (range, 1.2 to 4.7 cm). Figures 1 and 2 show staple line recurrences located in the central region and invading the aortic arch.

For the 23 patients with IPSLR, the median follow-up duration after the start of SABR for survivors was 17.0 months (range, 6.0 to 89.6 months). No patient was lost to follow-up. There were 2 patients with local recurrences, 3 with regional recurrences, and 4 with distant metastases. The 1- and 2-year local control rates from the start of SABR for IPSLR were 94.7% and 86.8%, respectively (Fig 3A). At 1 and 2 years, the disease-free survival rates were 89.5% and 62.5%, respectively, and the overall survival rates were 84.0% and 76.4%, respectively (Fig 3B).

All patients completed the course of SABR on schedule. During and within 1 month after SABR, no other toxicities occurred. At 1 month after SABR, radiation pneumonitis at grades 0 to 1, 2, 3, and 5 occurred in 18, 3, 1, and 1 patient, respectively. Grade 5 radiation pneumonitis developed in patient 18, with peripheral IPSLR. His medical history was NSCLC (T1 N0 M0), treated with right lower lobectomy in 2006 and a second primary lung cancer at right segment 1, treated with a first SABR in 2011. No interstitial changes occurred except for fibrosis after the first SABR. He was treated with a second SABR for IPSLR in 2012. At 1 month after the second SABR, he was diagnosed with grade 1 radiation pneumonitis, which gradually became more severe. Prednisolone was administered at 30 mg/d; however, we had to reduce the steroid dose because steroid-induced psychosomatic. The pneumonitis then exacerbated, and he died of respiratory failure 5.3 months after SABR.

With regard to chronic toxicity, transient chest pain (grade 1) was observed in 1 patient. Bronchial stenosis occurred within the PTV in 2 patients, which induced pneumonia 7.9 and 28.6 months after SABR (grade 3; Fig 4). These cases resolved, and the patients remain alive, with no recurrence or decrease in quality of life. No other toxicities, including bronchofistula, were observed during follow-up.

Comment

Although the outcomes of treatment of NSCLC have improved, local control is still a challenging issue. In large series of follow-up after resection of NSCLC, locoregional recurrence was identified in 9% to 14% of patients, with local failure alone in 3% [12, 13]. Local recurrence alone increased the risk of death. In addition, local control of IPSLR will be of greater importance as systemic therapy improves [14, 15]. Therefore, salvage therapy for local recurrence alone may be an important issue [12]. Analysis revealed that local recurrence increased the risk of death.

It is difficult to resect IPSLR safely and effectively. Only a small number of retrospective analyses for treatment of IPSLR have been published. Besides, these analyses
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Adeno = adenocarcinoma; Adj = adjuvant chemotherapy; Ao = aortic invasion; AWD = alive with disease; D = maximal tumor diameter; DOD = death of disease; DOOD = death of other causes; Dose/Fr = dose per fraction; Duration 1 = duration between initial operation and stereotactic ablative body radiotherapy; Duration 2 = follow-up duration from stereotactic ablative body radiotherapy; F = female; Lob = lobectomy; Loc = local recurrence; M = male; Med = mediastinal invasion; ND = mediastinal nodal dissection; NED = no evidence of disease; PA = pulmonary artery invasion; Periph = peripheral; Pt = patient; PTV = planning target volume; rT = recurrent T stage; SABR = stereotactic ablative body radiotherapy; Seg = segmentectomy; SUVmax = the maximum standardized uptake value; Wedge = wedge resection.
included selection biases such as size and location of IPSLR, postoperative pulmonary function, and performance status. In addition, discriminating nodal disease from a central recurrence is often very difficult; therefore, the results were limited. Salvage curative resection for local recurrence in early studies was as low as 1.1% to 1.7% [16–18], and the results, such as a 2-year survival of 23%, were mostly discouraging [19].

IPSLRs are often regarded as inoperable or are treated with pneumonectomy, which often causes lethal toxicity. In fact, among 16 patients with stump recurrence, 5 were resected, including 4 with pneumonectomy, and 2 patients died after pneumonectomy [5]. In another report of 14 patients with stump recurrence, salvage resection was attempted in 2 patients only [6]. In contrast, in patients with recurrent stage I disease, higher local control and overall survival rates could be achieved by completion pneumonectomy, with a 5-year survival of 51% [20]. Salvage curative resection might result in better outcomes if diagnosed at earlier stages of recurrence. Therefore, more intensive follow-up procedures are needed. Routine bronchoscopy 1 year after the operation was justified in patients at high risk for local recurrence [21].

On the basis of the limited results, the NCCN guideline states that salvage resection is preferred for resectable local recurrences [4]. In a multivariate analysis [5], candidates for salvage resection survived longer than

Fig 1. Staple line recurrence adjacent to the right pulmonary artery and superior vena cava. (A) Pretreatment axial computed tomography images show dose distribution curve. The bold isodose lines from outer to inner represent 10, 20, 30, 40, and 50 Gy, respectively. For the planning target volume surface, a total dose of 40 Gy per 5 fractions (60% isodose) was administered. (B) Axial computed tomography images 1 year after stereotactic ablative body radiotherapy show that the recurrent lesion was vanishing and became a scar-like shadow. (C) 2-Dexoy-2-18F-fluoro-D-glucose–positron-emission tomography/computed tomography image 1 year after stereotactic ablative body radiotherapy shows that the maximum standardized uptake value decreased from 3.4 at the pretreatment study to 2.2.

Fig 2. Staple line recurrence invading into the aortic arch. Pretreatment (A) coronal and (B) axial computed tomography images show the dose distribution curve. The bold isodose lines from outer to inner represent 12.5, 25, 37.5, 50, and 62.5 Gy, respectively. For the planning target volume surface, a total dose of 50 Gy per 10 fractions (80% isodose) was administered. (C) Axial computed tomography image 3 years after stereotactic ablative body radiotherapy clearly shows that the recurrence disappeared.
those treated with chemotherapy or radiotherapy, or both, and those with no treatment.

The NCCN guideline indicates EBRT is also a treatment option for local recurrence [4]. In a review of six retrospective studies including 54 patients with local recurrence, high-dose EBRT appeared to be an effective treatment modality for recurrent NSCLC confined to the bronchial stump after curative resection, with a 5-year survival of approximately 30% [7]. There was a dose–response effect [7, 22]. However, these results were derived from conventional fractionated radiotherapy.

In addition, SABR has excellent therapeutic effects, with mild toxicities for early-stage NSCLC. A computational study using a linear-quadratic model demonstrated that hypofractionated SABR is a better regimen than conventional fractionated EBRT in NSCLC [23]. In fact, SABR reduced local failure by nearly three times compared with EBRT (12% vs 34%) in stage I inoperable NSCLC [24]. Therefore, SABR is expected to be a better regimen for IPSLR as well.

Patients with IPSLR should be treated carefully with SABR, because IPSLR is often located in the central region. SABR for central tumors was reported to cause excessive late toxicities [10, 25]. The most serious late toxicity is bronchial stricture and secondary obstructive pneumonia. In a series of 9 patients with centrally located...
tumors treated with 40 to 60 Gy in 3 to 5 fractions, 3 patients experienced grade 3 to 5 pulmonary toxicities, and partial or complete bronchial stricture developed in 8, with a median duration of 20.5 months [25]. Other toxicities specific for central tumors included tracheal necrosis, bronchial occlusion, fatal bronchial necrosis, fatal esophageal ulcer, and pulmonary artery hemorrhage [26]. In this study, bronchial stricture occurred in 2 of 8 patients (25%) who were followed up for more than 20 months. We should monitor patients for a longer time to ascertain the frequency and severity of late toxicities after SABR for IPSLR.

Chest wall pain and rib fracture are also significant toxicities that can affect patients’ quality of life after SABR for those with lung tumors adjoining the chest wall [27]. In treating such patients, we should plan treatment carefully to reduce the dose and volume of the chest wall.

Owing to the possible severe toxicities of SABR for central tumors, the optimal dose prescription and schedule for SABR remains undetermined for tumors located near the hilum or central airways as well as peripheral ones. Timmerman and colleagues [10] claimed that 60 Gy per 3 fractions should not be used for patients with central tumors. We started SABR for IPSLR in 2005, with a routine dose regimen of 50 Gy in 5 fractions. In 2005, we preliminarily treated 1 patient with tumor invading the aortic arch with 50 Gy in 10 fractions and then changed the dose regimen to 40 Gy in 5 fractions starting in 2006 for such patients. For peripheral IPSLR and peripheral tumors, we administered 50 Gy in 5 fractions until 2011 and then changed the regimen to 60 Gy per 5 fractions after confirming the safety in a dose escalation phase I study.

Whether patients with IPSLR are treated with resection or SABR, considerable toxicities are unavoidable. In this difficult situation, we should discuss in a multidisciplinary team setting the treatment policy considering the balance between the probability of disease control and the morbidities and death of each treatment, as well as quality of life and cost-effectiveness. We should also discuss the options with patients and obtain informed consent. Quality of life seems to favor SABR. For patients with stage I NSCLC treated with SABR, quality of life was maintained, and emotional functioning improved significantly after treatment. No statistically or clinically significant worsening of any quality of life functioning or symptom scores was observed [28]. In contrast, a significant increase in negative effect on quality of life was recorded after pneumonectomy [29]. As for cost-effectiveness, SABR also appeared to be less costly than surgical intervention. Cause-specific survival was identical between the 2 groups, and the difference in overall survival was not statistically significant [30].

The candidates in this study included 9 patients with recurrent T4 disease. Although they seemed to have a poor prognosis, they had high selection biases. They had only isolated postoperative local recurrence after relatively long intervals after resection, without regional or distant metastasis. Such patients had better outcomes [5]. In addition, they were followed up routinely and their recurrences were detected relatively earlier.

To better select candidates, we should rule out regional recurrence. Endobronchial ultrasound-guided fine-needle aspiration can accurately sample mediastinal lymph nodes for thoracic malignancy staging and is also less invasive [31]. Therefore, endobronchial ultrasound-guided fine-needle aspiration should be considered for staging as well as 18F-FDG-PET/CT.

The limitations of this study are its retrospective nature, the small number of patients, especially highly selected patients, and the short follow-up. Further follow-up is needed to evaluate outcomes and toxicities of this regimen. Although the data are still preliminary, we believe that salvage SABR for IPSLR can be considered in patients who have inoperable tumors, who are at high risk for resection, or who refuse resection. However, this is the first report on the outcomes of SABR for IPSLR.

In conclusion, SABR for IPSLR achieved high local control with limited toxicities and may lead to a potential cure. SABR should be considered as a salvage treatment option for IPSLR. These patients should be monitored for a longer time to confirm the efficacy and safety of SABR for IPSLR.

References

Southern Thoracic Surgical Association: Sixtieth Annual Meeting

The Sixtieth Annual Meeting of the Southern Thoracic Surgical Association (STSA) will be held October 30–November 2, 2013 at the Hyatt Regency Scottsdale Resort & Spa at Gainey Ranch.

The meeting will feature Surgical Motion Pictures, the STSA Post Graduate Program, an Ethics Debate, a Coding Update for 2014, and the STSA Scientific Sessions—including adult cardiac, general thoracic, congenital, and transplant breakout sessions.

The President’s Invited Speaker is Doug Hanson. His talk on Friday morning titled “Distinctions of Success and Significance” will take place just prior to Robert J. Cerfolio, MD’s STSA Presidential Address titled “The Athleticism of Surgery and Life: How to be a super performer at work, home and in life.”

The Southern Thoracic Surgical Association is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. STSA designates this educational activity for a maximum of 21.25 AMA PRA Category 1 Credit(s). Physicians should only claim credit commensurate with the extent of their participation in the activity.

Review a detailed program and register online at www.stsa.org through October 7. After this date, attendees must register on-site at the Annual Meeting; there will be an additional $50 charge for attendees registering on-site.