The evolving role of stereotactic ablative radiotherapy in operable early stage non-small cell lung cancer

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Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer

Abstract

Background

Approximately two-thirds of patients with early-stage non-small-cell lung cancer (NSCLC) in The Netherlands currently undergo surgical resection. As an increasing number of fit patients have elected to undergo stereotactic ablative radiotherapy (SABR) in recent years, we studied outcomes after SABR in patients with potentially operable stage I NSCLC.

Methods and Materials:

In an institutional prospective database collected since 2003, 25% of lung SABR cases (n = 177 patients) were found to be potentially operable when the following patients were excluded: those with (1) synchronous lung tumors or other malignancy, (2) prior high-dose radiotherapy/pneumonectomy, (3) chronic obstructive pulmonary disease with a severity score of 3-4 according to the Global initiative for Obstructive Lung Disease classification. (4) a performance score of ≥3, and (5) other comorbidity precluding surgery. Study patients included 101 males and 76 females, with a median age of 76 years old, 60% of whom were staged as T1 and 40% of whom were T2. Median Charlson comorbidity score was 2 (range, 0–5). A SABR dose of 60 Gy was delivered using a risk-adapted scheme in 3, 5, or 8 fractions, depending on tumor size and location. Follow-up chest computed tomography scans were obtained at 3, 6, and 12 months and yearly thereafter.

Results

Median follow-up was 31.5 months; and median overall survival (OS) was 61.5 months, with 1- and 3-year survival rates of 94.7% and 84.7%, respectively. OS rates at 3 years in patients with (n = 59) and without (n = 118) histological diagnosis did not differ significantly (96% versus 81%, respectively, p = 0.39). Post-SABR 30-day mortality was 0%, while predicted 30-day mortality for a lobectomy, derived using the Thoracoscore predictive model (Falcoz PE et al. J Thorac Cardiovasc Surg 2007;133:325–332), would have been 2.6%. Local control rates at 1 and 3 years were 98% and 93%, respectively. Regional and distant failure rates at 3 years were each 9.7%. Toxicity was mild, with grade ≥3 radiation pneumonitis and rib fractures in 2% and 3%, respectively.

Conclusions

Patients with potentially operable disease who underwent primary SABR had a median OS that exceeded 5 years. This finding supports ongoing randomized clinical trials comparing surgery and SABR in cases of operable stage I NSCLC.

Introduction

An anatomical surgical resection is considered the standard of care for patients presenting with stage I non-small-cell lung cancer (NSCLC)[1]. However, approximately 1 of every 3 patients with early-stage disease will not undergo surgery[2]. In patients older than 75 years of age, even 2 of 3 patients will not undergo surgery[3]. One reason for this is that lung cancer predominantly affects elderly patients and patients with comorbidity associated with the use of tobacco, and large studies reveal that mortality associated with surgery in patients aged 70 or older range from 5.2% to 7.4%[3,4]. Besides comorbidity, which may increase surgical risk, a decision not to undergo surgery can also be due to a patient's perception of prognosis and racial factors[5].

For patients who refuse surgery, the use of conventionally fractionated radiotherapy is increasingly being replaced by stereotactic ablative radiotherapy (SABR). Using SABR, local control rates of approximately 90% for stage I NSCLC are reported in single and multicenter studies[6–10]. The excellent local control and low toxicity of SABR have challenged the assumption that surgery is the preferred treatment for patients with potentially operable stage I NSCLC[11]. However, randomized prospective trials comparing surgery with SABR (protocols NCT00840749 and NCT00687986) in patients with operable cancer have not yet been completed. Two single-arm phase II trials of SABR in patients who were fit enough to undergo surgery have been completed, and the mature results of Japan Clinical Oncology Group (JCOG) study 0403 (protocol NCT00238875) and Radiation Therapy Oncology Group (RTOG) study 0618 (protocol NCT00551369) are awaited. A recent study of Japanese patients with operable cancer who elected to undergo SABR in 14 Japanese institutions over a 9-year period reports 5-year overall survival (OS) rates of 72% and 62% for stage IA and IB subgroups, respectively[9].

The introduction of SABR in The Netherlands in 2003 led to a rapid change in treatment utilization and patterns of care in elderly patients with stage I NSCLC[3]. Another development was the increase in the number of usually elderly patients with potentially operable conditions with an elevated risk for surgical mortality, who, after discussion and in multidisciplinary tumor board meetings, were referred for SABR instead of surgery. The purpose of this study was to evaluate outcomes in a cohort of patients with potentially operable stage I NSCLC treated with SABR at a single center.

Methods and Materials

Between April 2003 and December 2010, 706 patients who underwent SABR at the VU University medical center for a stage IA-IB NSCLC were entered into a prospective institutional database. Patients with double lung tumors (N = 55), a second primary tumor after prior high-dose (chemo-)radiotherapy or pneumonectomy (N = 23), and patients with a concurrent second malignancy (N = 50) were excluded from this analysis. Patients whose cancers were potentially operable were identified retrospectively by excluding patients with (a) chronic obstructive pulmonary disease (COPD) severity according to the global initiative for obstructive lung disease (GOLD) of grade 3-4 (forced expiratoiry volume in 1 second (FEV1) <50% of predicted) or diffusing capacity of the lung for carbon monoxide (DLCO) of <50% of predicted; (b) a World Health Organization (WHO) performance score of ≥3 (N = 23); (c) a serious cardiovascular comorbidity precluding surgery (N = 94); and (d) other major comorbidities precluding surgery, such as recent cardiovascular accidents or renal failure (N = 68). A prior (bi)lobectomy was not considered an absolute contraindication for surgery, nor was advanced age.

Criteria for staging of patients' lung cancer during the study period were in accordance with Dutch practice guidelines developed by multidisciplinary teams and available online (www.oncoline.nl). All patients were seen by a pulmonary physician at diagnosis, and their cases were discussed in their local multidisciplinary tumor boards with thoracic surgeons and radiation oncologists before referral to our center for SABR. In accordance with Dutch national radiotherapy guidelines, patients without pathology were also accepted for SABR if they had all of the following: (a) a new or growing lesion on CT scans with characteristics of malignancy; (b) a high clinical risk for developing lung cancer based on age and smoking history; and (c) a fluorodeoxyglucose-positron emission tomography (FDG-PET)-positive lesion. Previous Dutch publications revealed a likelihood of benign disease in patients who underwent surgery for a diagnosis of lung cancer based upon CT- and FDG-PET scans of 1% to 4.3%[12–14]. When a differential diagnosis of infection was considered, patients were treated with broad spectrum antibiotics before imaging was repeated.

SABR was delivered on an outpatient basis using a risk-adapted fractionation scheme depending on tumor size and location as previously described[8], using either 3 (35% of patients), 5 (46% of patients), or 8 (19% of patients) fractions. Patients with peripheral T1 tumors without broad contact with the chest wall were treated with three fractions of 20 Gy each; patients with T1 tumors that had broad contact with the chest wall and T2 tumors were treated with five fractions of 12 Gy each. Patients with centrally located

tumors were treated with eight fractions of 7.5 Gy each. All fractionation schemes used were prescribed to the encompassing 80% isodose and had a biologically effective dose calculated for early responding tissues and tumors of >100 Gy_{10}. SABR was generally delivered within an overall treatment time of 2 weeks. Treatment planning was performed using individualized margins that encompassed all motion observed on four-dimensional CT scans[15]. No active motion management or respiratory gating was performed for any patient. Treatment plans were optimized to limit high-dose radiation to regions adjacent to organs at risk, such as the chest wall, hilum, mediastinum or heart.

Patients underwent follow-up at 3 months, 6 months, 1 year, and annually thereafter. Follow-up CT scans were performed at each visit but [18F]FDG-PET scans were repeated only in the event of suspected disease relapse in patients who were sufficiently fit to receive further therapy. Any growing lesion on sequential follow-up scans that could not be clearly attributed to fibrosis was labeled a local recurrence. In patients who were unable or unwilling to attend follow-up at our center, the referring lung physician or general practitioner was contacted. In addition, the Dutch civil death records, which cover the entire Dutch population, were used to ensure complete survival data for patients lost to follow-up.

We compared 30-day post-SABR mortality with an estimated surgical 30-day mortality by using the Thoracoscore model[16]. The Thoracoscore is a validated prognostic model derived from an analysis of 10,122 patients undergoing thoracic surgery, which estimates early mortality based on age, gender, American Society of Anesthesiologists score, WHO performance score, dyspnea score, priority of surgery, procedure class (pneumonectomy vs. lesser resection), diagnosis group (malignant vs. benign), and Charlson comorbidity score[16]. We calculated the predicted risk of 30-day mortality for each of our patients and assumed that a lobectomy was performed for all cases.

Treatment outcomes were evaluated using Kaplan-Meier analysis of OS, local, regional, and distant control in SPSS version 15.0 software (SPSS Inc. Chigago, Il.). Multivariate analysis was performed with Cox regression analysis to investigate the prognostic value of age, gender, tumor stage, fractionation scheme, GOLD COPD classification, WHO performance score, pathological conformation of malignancy, histology, Charlson comorbidity score, tumor location, history of malignancy, and history of lung cancer.

Results

Relevant characteristics of all 177 patients with potentially operable cancer are summarized in Table. Characteristics include 101 males (57%) and 76 females (43%) with a median age of 76 years old. All but 2 patients underwent staging [18F]FDG-PET scans; however, pathological confirmation of malignancy was obtained in both cases, in 1 patient at pretreatment and in the other patient based on a regional recurrence after SABR. In another 2 patients, the baseline [18F]FDG-PET scans were negative. Both patients were heavy smokers and had suspicious lesions. Transthoracic biopsy showed atypical cells consistent with a bronchoalveolar carcinoma in one of these patients. In the second patient, the lesion was not visible on a CT scan years before SABR, and this lesion showed growth on a subsequent CT scan despite treatment with broad spectrum antibiotics.

Sixty percent of patients' cancers were radiologically staged as T1N0M0 and 40% of cancers as T2N0M0. A histopathological confirmation of malignancy was obtained in 33% of patients. In patients without histology results, the mean calculated probability of malignancy was 90% (95% confidence interval [CI], 88%–92%), using an approach previously validated in the Dutch population (Figure 1)[13]. Only a single patient with a growing lesion on subsequent CT scans had a probability of less than 60%, as the lesion was PET negative. In 2 other patients, PET scans were not performed, and the likelihood of malignancy could not be calculated in those patients. The median comorbidity score according to the Charlson classification was 2 (range, 0–5)[17]

Figure 1: *Distribution of the likelihood of malignancy in patients without pathological verification of malignancy is shown. Likelihood calculations are based on a combination of clinical, radiological and FDG-PET findings*[13]

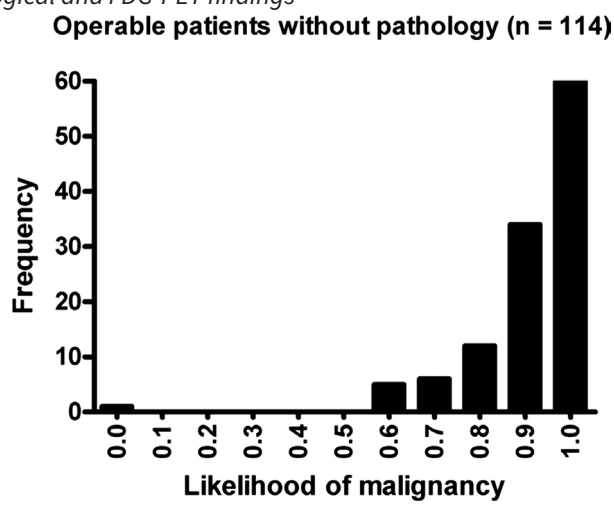
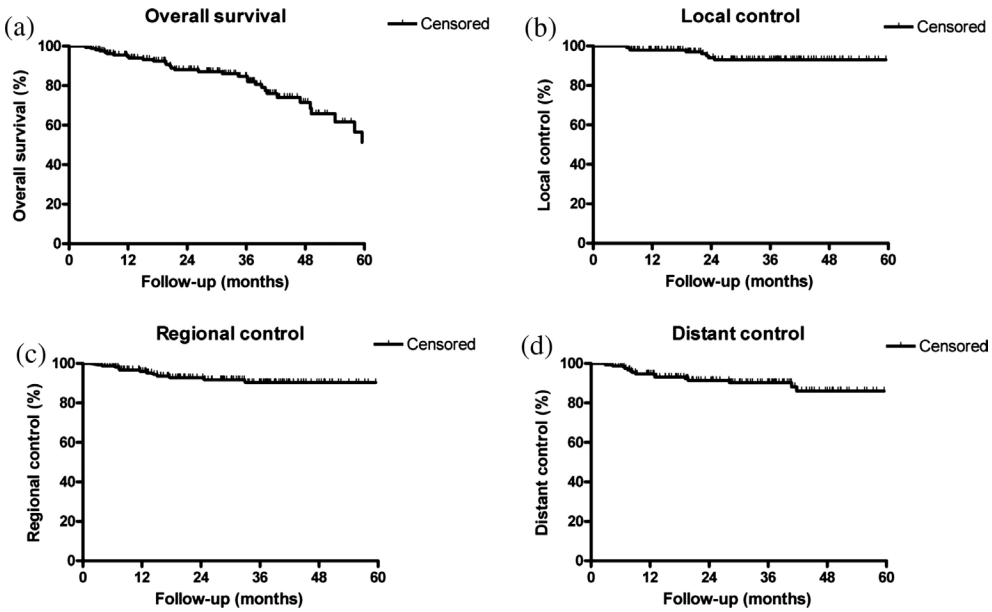


Table 1: *Patient characteristics (N=177)*

Characteristics	No. of patients (% of total)
Gender - Male - Female	 101 (57) 76 (43)
Median age	76 years (range 50-91 years)
Stage - Ia - Ib	 106 (60) 71 (40)
Median tumor diameter	26 mm (range 10-70)
Fractionation scheme: - 3x20Gy (3x18Gy as of 2008) - 5x12Gy (5x11Gy as of 2008) - 8x7.5Gy	 61 (34) 82 (46) 34 (19)
Smoking - Current of former - Never smoked	 168 (95) 9 (5)
GOLD class - No COPD - Class I - Class II	 65 (37) 37 (21) 75 (42)
Charlson co-morbidity score - 0 - 1 - 2 - 3 - 4 - 5	 18 (10) 59 (33) 38 (22) 39 (22) 16 (9) 7 (4)
Pathological confirmation - Yes - No	 60 (33) 117 (66)
Histology (n = 60 patients) - Adenocarcinoma - Squamous cell carcinoma - Undifferentiated NSCLC	 20 (33) 16 (27) 24 (38)
GOLD = Global initiative for chronic Lung Disease; COPD = chronic obstructive pulmonary disease	

Figure 2: *Actuarial curves show OS (a), local control (b), regional control (c), and distant control (d).*



Overall survival and patterns of relapse

The median follow-up of the entire patient cohort, calculated according to the inverse Kaplan-Meier method[18], was 31.5 months. The median OS for all patients was 61.5 months, with OS rates at 1 and 3 years of 94.7% and 84.7%, respectively (Figure 2a). The OS rate at 5 years after SABR was 51.3%, although it must be noted that only 10 patients were still at risk at that time point. On multivariate analysis, female gender was a favorable variable for OS ($p = 0.02$); all other investigated factors were not significant. The 3-year OS rate for patients without pathological verification of malignancy was lower than for those with pathological verification (81% vs. 96%, respectively), but this difference was not statistically significant ($p = 0.39$).

Local relapses were observed in 8 patients at a median follow-up duration of 20 months, and actuarial local control rates at 1 and 3 years were 98% and 93%, respectively (Figure 2b). Any growing lesion on sequential follow-up scans that could not be clearly attributed to fibrosis was labeled a local recurrence. Local recurrences were confirmed by histology in 1 patient and were established in others by using a combination of CT and FDG-PET findings. Both the regional and the distant control rates at 3 years were 90.3% (Figure 2c–d). In total, a relapse at any location (local, regional, or distant) was observed in 25

patients (14.1%) and was locoregional in 9 patients. Three of those 9 patients underwent lobectomy as salvage treatment, and another 2 patients received high-dose radiotherapy. Four patients received no salvage treatment. Freedom from any progression at 3 years was 81% both for patients with and without pathological verification.

A total of 34 patients have died, and the cause of death could be determined in 85% of cases (n = 29). Of those patients, 14 patients died from disseminated lung cancer, and 6 patients from cardiovascular events, 4 patients from other primary malignancies diagnosed after SABR, and 2 patients from renal failure. Two patients died of pulmonary hemorrhage. The first patient underwent SABR for a pathology confirmed NSCLC and died 16 months after treatment from a hemorrhage associated with Aspergillus infection in the contralateral lung. The second patient had a history of pulmonary bleeding prior to SABR, and no cause could be found for the fatal bleeding in that case. A single patient with a pretreatment FEV1 of 52% of predicted volume died from progressive respiratory failure 3 years after treatment.

Side effects

All patients completed SABR, and the 30-day mortality rate observed in the SABR cohort of 177 patients was 0%. In contrast, in these patients, the calculated 30-day mortality after lobectomy would have been 2.6% (95% CI, 2.4%–2.8%) according to the Thoracoscore[16]. No early side effects were reported by 42% of patients, and Grade 1 to 2 early side effects reported were fatigue (25%), cough (14%), local chest wall pain (11%), and dyspnea (10%), with some patients reporting more than one side effect. Severe late toxicity was uncommon, with Grade ≥3 radiation pneumonitis seen in 4 patients (2%). Rib fractures developed in 5 patients (3%); for 2 patients treated with the three-fraction scheme, 1 patient was treated with the five-fraction scheme, and 2 patients were treated with the eight-fraction scheme

Discussion

SABR has rapidly replaced conventional radiotherapy for treating inoperable stage I NSCLC[3], largely due to high local control rates achieved with little toxicity or adverse effects on quality of life[19,20] and pulmonary function[21]. These considerations are important as many patients presenting with stage I NSCLC have relative contraindications for surgery, such as advanced age, cardiovascular morbidity, and COPD. In addition, Dutch pulmonologists and multidisciplinary tumor boards are increasingly considering the

option of SABR in patients with potentially operable cancer, and this patient category has now increased to nearly one-third of all referrals for SABR to our center.

The present study represents the largest cohort reported in the literature of patients with potentially operable cancers who were treated with SABR. An early report of outcomes in 29 patients with operable conditions found a 3-year OS rate of 86%[22]. A recent Japanese multicenter report of 87 patients with operable disease suggested 3-year survival rates of approximately 80% and 70% in T1 and T2 tumors, respectively[9]. Our findings of a 3-year survival of 84.7% are in line with those publications.

Our finding of a local control rate of 93% at 3 years is comparable to that reported in other studies of SABR and also surgical series[6–9,23–25]. However, our findings of no 30-day mortality following SABR contrasts with the predicted 30-day surgical mortality of 2.6% determined by using the Thoracoscore[16]. This mortality rate of 2.6% is based on the assumption that all patients would have undergone a lobectomy, which probably underestimates the actual risks, as 10% or more of Dutch patients have undergone a pneumonectomy for a stage I NSCLC in recent years[26–28].

A reliable comparison between the OS of our SABR patients and that of patients reported in the surgical literature is difficult, despite our efforts to select patients whose conditions were potentially operable. For instance, the median age of 76 years old and Charlson comorbidity score of 2.0 in our population were higher than is commonly reported in surgical series[29]. Even so, the observed 3-year survival rate of 84.7% following SABR seems to be largely comparable to that reported after surgery[23,24,30]. In a systematic review of 3,670 patients, Whitson et al. found 3-year OS rates of 87.2% and 81.6% in video-assisted thoracoscopic lobectomy (VATS) and open thoracotomy, respectively[31]. Nevertheless, we acknowledge that our selection criteria for operability were applied retrospectively based on the medical records. Whether these criteria are absolute contraindications for surgery, however, can be debated.

A frequently criticized characteristic of our SABR patient population is the lack of histopathological confirmation in 67% of patients prior to SABR. In this high-risk population containing mostly elderly (former) smokers with suspected lesions following appropriate imaging (PET-CT), the likelihood of malignancy is very high. Previous studies in patients with early-stage NSCLC in the Western European population have shown that the risk of finding benign lesions during surgery is less than 4.3%[12,14,32]. The rate of benign disease, however, may be larger in countries with a higher incidence of infections, such as

those with endemic tuberculosis and histoplasmosis. The probability of malignancy can be calculated using a combination of clinical, radiological, and [18F]FDG-PET findings[13,33]. The mean likelihood of malignancy in our SABR population without histology was 90%, and 87% of patients had a likelihood of ≥80%. In that respect, our treatment policy is consistent with American College of Chest Physicians (ACCP) guidelines, which recommend that an upfront likelihood of malignancy of >60% warrants treatment without further diagnostic procedures[34]. The final argument for our SABR acceptance policy comes from the fact that there was no difference in local control or survival between the patients with or without pathological confirmation.

Conclusions

In conclusion, SABR in patients with potentially operable stage I NSCLC results in local control and survival rates that are comparable to those reported after surgery. These findings further underscore the importance of the awaited JCOG 0403 (NCT00238875) and RTOG 0618 (NCT00551369) trials and the ongoing randomized comparative trials of surgery and SABR (NCT00840749 and NCT00687986).

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