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

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Stage I-II non-small cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): Outcomes of a propensity score-matched analysis

Abstract

Background

Video-assisted thoracoscopic surgery (VATS) lobectomy and stereotactic ablative radiotherapy (SABR) are both used for early-stage non-small-cell lung cancer. We carried out a propensity score-matched analysis to compare locoregional control (LRC).

Patients and methods

VATS lobectomy data from six hospitals were retrospectively accessed; SABR data were obtained from a single institution database. Patients were matched using propensity scores based on cTNM stage, age, gender, Charlson comorbidity score, lung function and performance score. Eighty-six VATS and 527 SABR patients were matched blinded to outcome (1:1 ratio, caliper distance 0.025). Locoregional failure was defined as recurrence in/adjacent to the planning target volume/surgical margins, ipsilateral hilum or mediastinum. Recurrences were either biopsy-confirmed or had to be PET-positive and reviewed by a tumor board.

Results

The matched cohort consisted of 64 SABR and 64 VATS patients with the median follow-up of 30 and 16 months, respectively. Post-SABR LRC rates were superior at 1 and 3 years (96.8% and 93.3% versus 86.9% and 82.6%, respectively, P = 0.04). Distant recurrences and overall survival (OS) were not significantly different.

Conclusion

This retrospective analysis found a superior LRC after SABR compared with VATS lobectomy, but OS did not differ. Our findings support the need to compare both treatments in a randomized, controlled trial.

Introduction

Lung cancer is the commonest cause of cancer-related deaths worldwide, a finding partly due to the small proportion of patients presenting with early-stage disease[1]. The recommended treatment for early-stage non-small-cell lung cancer (NSCLC) is a lobectomy, but many patients with stage I NSCLC do not undergo surgery due to comorbidities or patient preference[2,3]. Increasingly, minimally invasive video-assisted thoracoscopic surgery (VATS) has replaced open thoracotomy for early-stage tumors, as oncological outcomes may be similar, and with less morbidity and shorter hospital stays[2,4,5].

Stereotactic ablative radiotherapy (SABR) is increasingly being considered as the preferred treatment option in patients unfit for surgery or patients at high-risk for postoperative complications ('borderline operable')[3,6]. In prospective, multi-institutional studies, local control rates in excess of 90% were reported, with regional nodal recurrences observed in ~10%[7,8]. The introduction of SABR has improved population-based survivals[3,6]. In potentially operable patients, overall survival (OS) after SABR is comparable with that after surgical resection[9,10]. Similarly, a population-based matched pair comparison of SABR versus surgery in elderly patients with stage I NSCLC revealed similar OS[11].

As yet, no randomized trials comparing SABR versus VATS lobectomy have been completed and non-randomized comparisons may be hampered by imbalances in baseline characteristics between both groups. Propensity score analysis allows for matching across a broad range of baseline factors, creating two similar groups for comparison. As both SABR and VATS are routinely available to patients in the North Holland region, we carried out a propensity score-matched analysis to compare locoregional control (LRC) after both treatments for a clinical diagnosis of stage I–II NSCLC.

Materials and Methods

This retrospective study was approved by the institutional ethics board. VATS was introduced at the VU University Medical Center (VUMC) in 2007 and subsequently implemented in five regional hospitals, where each procedure was carried out jointly with an experienced VUMC surgeon. Lobectomy was carried out using the complete VATS technique, as previously described[12]. Details of patients with a clinical or pathological diagnosis of T1-3N0M0 NSCLC and treated with VATS lobectomy at all six centers were accessed through a database. All disease staging was carried out using UICC TNM-7[13]. A

diagnosis of clinical stage I–II disease was made after guideline-specified staging, including a CT scan of the thorax and upper abdomen and ^{18}FDG-PET scans. Findings suspicious of nodal metastases required confirmatory biopsy, generally using minimally invasive endoscopic techniques. A nodal dissection was routinely carried out in accordance with guidelines[14].

Details of all patients treated with SABR at the VUMC since November 2003 were collected in a prospective institutional database. SABR was delivered in an outpatient setting, using risk-adapted fractionation schemes, as previously described, using more fractions and a lower dose per fraction for larger tumors and those adjacent to critical normal organs[15]. Fractionation schemes had a biologically effective dose of >100 Gy10, with the scheme of 12 fractions of 5 Gy being the sole exception. Individualized target volumes encompassing all motion on four-dimensional CT scans were used for treatment planning and no active motion management, including respiratory gating, was used. Treatment plans were optimized to limit high-dose regions to organs at risk[15].

Patients were excluded from the matching procedure if they had any of the following: synchronous lung tumor, previous lung malignancy or severe COPD as defined by GOLD class 4[16]. Propensity score matching reduces bias and confounding by matching patients on numerous baseline variables, using a multivariable logistic regression model. A total of 86 VATS and 527 SABR patients were eligible for matching, which was carried out by investigators blinded to treatment outcome. Patient data were anonymized and outcome data removed before propensity score matching using the following covariates: gender, age, clinical tumor stage, tumor diameter, location of the tumor, pretreatment tumor histology, lung function (FEV1%), Charlson comorbidity score and WHO performance score. Matching was carried out using a ratio of 1:1, and a caliper distance of 0.025, without replacement.
The probability of malignancy in matched patients without a pretreatment pathological diagnosis was calculated using a combination of clinical, radiological and 18FDG-PET findings, as described previously for a Dutch population[17].

Post-treatment follow-up generally consisted of a contrast-enhanced CT scan of the thorax and abdomen carried out at 2 to 3 months, 6-monthly for 2 years, and annually thereafter. 18FDG-PET scans were only repeated in case of suspected relapse in patients who were considered fit enough to receive therapy. For patients who were unable or unwilling to attend the follow-up at the treating hospital, the general practitioner or lung physician was contacted for follow-up.

For SABR patients, locoregional failure was defined as a recurrence in, or adjacent to, the planning target volume and/or in the ipsilateral hilum or mediastinum. Locoregional failure following VATS was considered present when recurrences arose at, or adjacent to, surgical resection margins and/or in the ipsilateral hilum or mediastinum. Freedom from progression (FFP) was defined as freedom from any tumor recurrence. Every recurrence had to be either biopsy-confirmed or PET-positive and discussed in a multidisciplinary team. SABR patients suspected of local recurrence, but in whom no tissue diagnosis was available, were scored as having a recurrence.

Time-to-event outcomes were analyzed using the Kaplan–Meier method and the median follow-up was calculated using the reverse Kaplan–Meier method. Cases were censored when death was observed. In order to compare time-to-event outcomes between VATS and SABR groups, P-values were calculated using the Cox regression stratified by matched pairs[18]. Toxicity was scored according to Common Terminology Criteria for Adverse Events version 4.0[19]. The chi-square test was used to compare toxicity, and the Student t-test was used to compare the likelihood of malignancy between groups. All statistical analyses were two-sided, with $P \leq 0.05$ indicative of statistical significance, and carried out using SAS version 9.2 or the Statistical Package for Social Sciences (SPSS), version 15.0.

Results

The matching process resulted in a final cohort of 128 patients (64 SABR and 64 VATS patients) eligible for further analysis. Patient characteristics are summarized in Table 1. The mean ages of the SABR and VATS cohorts were 71 and 68 years, respectively, and the median follow-up was 30 and 16 months, respectively. Pretreatment histological confirmation of stage I NSCLC was available in 53% of SABR patients and 50% of VATS patients. The median Charlson comorbidity score was 1 in both cohorts. Using criteria previously published, 54% of SABR patients were considered medically inoperable[10]. The mean likelihood of malignancy for SABR patients who did not have a pathological diagnosis was 89.8% [95% confidence interval (95% CI) 86.7%– 92.9%], as opposed to a corresponding mean likelihood of malignancy in VATS patients without pretreatment pathological confirmation of 83.4% (95% CI 79.2%–87.7%). This difference is statistically significant ($P = 0.02$).

Table 1: *Characteristics of all propensity-matched patients*

Characteristic	SABR (n = 64)	VATS (n = 64)	P-value
*Age (mean ± SD)	70.53 ± 9.91	67.95 ± 8.84	0.123
*Sex - N(%) - Male - Female	 37 (57.8) 27 (42.2)	 36 (56.3) 28 (43.8)	0.858
Inoperable - Yes - No	 29 (45.3) 35 (54.7)	 -- --	 --
*cTNM - N(%) - T1 - T2 - T3	 39 (60.9) 25 (39.1) --	 39 (60.9) 24 (37.5) 1 (1.6)	1.00
*Tumor diameter (mm) (mean ± SD)	28.83 ± 12.87	28.63 ± 12.41	0.928
*Location - N(%) - Right upper lobe (RUL) - Left lower lobe (LUL) - Right lower lobe (RLL) - Left lower lobe (LLL - Right middle lobe (RML)	 26 (40.6) 14 (21.9) 11 (17.2) 10 (15.6) 3 (4.7)	 23 (35.9) 17 (26.6) 12 (18.8) 10 (15.6) 2 (3.1)	0.949
*Pathology pre-treatment - N(%) - Yes - No	 34 (53.1) 30 (46.9)	 32 (50.0) 32 (50.0)	0.724
*Histology pre-treatment - N(%) - No - Adenocarcinoma - NSCLC - Squamous	 30 (46.9) 15 (23.4) 10 (15.6) 9 (14.1)	 32 (50.0) 19 (29.7) 6 (9.4) 7 (10.9)	0.618
*FEV1‡ (%), mean ± SD	92.66 ± 27.59	86.84 ± 18.52	0.165
FEV1 (L), mean ± SD	2.34 ± 0.85	2.32 ± 0.67	0.894
*WHO - N(%) - 0 - 1 - 2	 12 (18.8) 51 (79.7) 1 (1.6)	 14 (21.9) 49 (76.6) 1 (1.6)	0.912
*Charlson co-morbidity score - N(%) - 0 - 1 - 2 - 3 - 4 - 5	 12 (18.8) 23 (35.9) 12 (18.8) 13 (20.3) 3 (4.7) 1 (1.6)	 12 (18.8) 23 (35.9) 10 (15.6) 14 (21.9) 4 (6.3) 1 (1.6)	0.995
* Variable used to compute propensity scores. ‡ Forced expiratory volume 1 second			

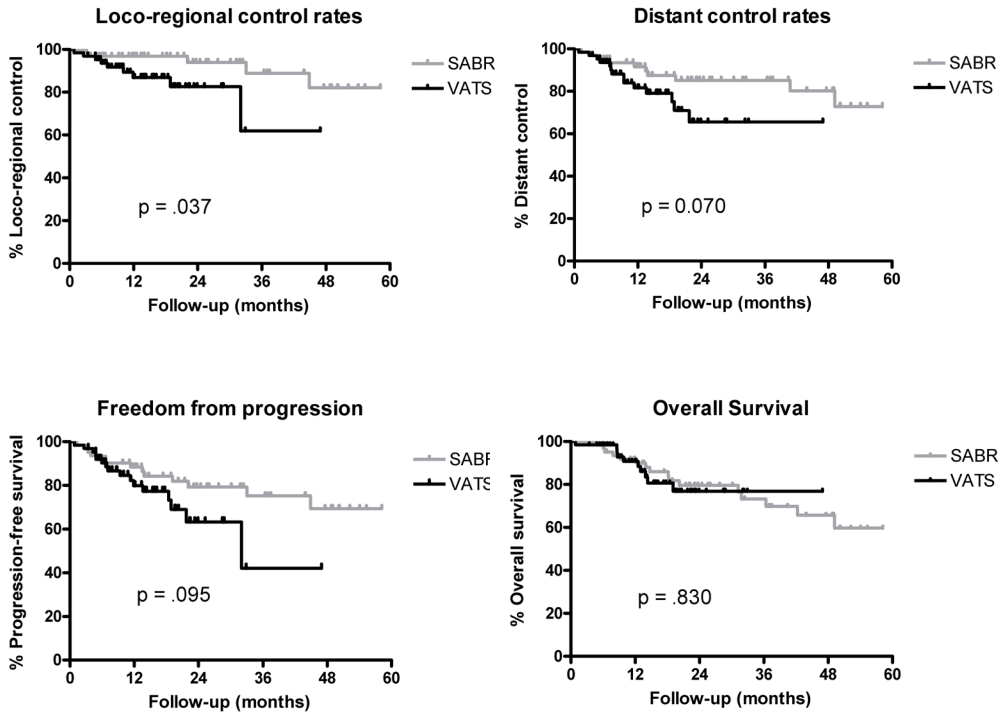
Three planned VATS resections (4.7%) were converted into an open lobectomy due to intraoperative hemorrhage. The median number of dissected lymph node stations was 4 (range 1–6), and the median number of dissected lymph nodes was 8.5 (range 1–24), with 71.9% of patients having six or more nodes dissected. Unsuspected nodal disease was detected at surgery in 12 (18.8%) patients. Of these, four patients (6.3%) had N1-disease, and eight patients (12.5%) unsuspected N2-disease. Two of eight patients with pathological N2-disease had some ^{18}FDG-PET uptake in the mediastinum before treatment, but invasive staging procedures (transbronchial biopsy, mediastinoscopy) had excluded nodal metastases. Patients upstaged at surgery were offered adjuvant treatment according to guidelines[14]. Eight of 12 cases with nodal disease received adjuvant therapy, with 7 patients receiving chemotherapy and 1 patient locoregional radiotherapy. One patient refused adjuvant chemotherapy, and three others were unfit for adjuvant treatment due to comorbidity or performance status. A final pathological diagnosis of benign disease was made in four patients (6.3%) after VATS lobectomy.

The total radiation dose delivered to SABR patients ranged from 54 to 60 Gy, delivered in 3 (36%), 5 (52%), 8 (9%) or 12 fractions (3%), all within an overall treatment time of <3.5 weeks.

Fourteen patients developed locoregional recurrences during the follow-up. LRC was significantly better after SABR, with actuarial LRC rates at 1 and 3 years after treatment of 96.8% and 93.8%, respectively. Corresponding 1- and 3-year LRC rates after VATS lobectomy were 86.9% and 82.6%, respectively (hazard ratio (HR) = 3.68; 95% CI = 1.09–12.50; P = 0.04, Figure 1A). The five SABR patients who developed a locoregional recurrence had either a local recurrence (n = 1), regional (n = 3), or both (n = 1). The eight VATS patients with locoregional recurrence had either isolated local (n = 2) or regional recurrences (n = 6). Distant recurrences occurred in 24 patients, and the incidence did not differ significantly between both groups. However, a trend was seen for improved distant control after SABR, as 1- and 3-year distant control rates were 91.6% and 85.2%, versus 81.7% and 65.5% at 1 and 3 years after VATS lobectomy (HR = 2.241; 95% CI = 0.94–5.36; P = 0.07, Figure 1B). FFP was not significantly different, with post-SABR rates at 1 and 3 years being 88.4% and 79.3%, versus post-VATS rates at 1 and 3 years being 79.9% and 63.2% (HR = 3.93; 95% CI = 0.89–4.18; P = 0.09, Figure 1C). Overall survival (OS) was similar in both groups, with post-SABR rates at 1 and 3 years of 91.8% and 79.6%, and post-VATS 1- and 3-year OS rates being 90.8% and 76.9% (HR = 1.09; 95% CI = 0.50–2.36; P = 0.83, Figure 1D).

A complete overview of all patients with recurrences and their subsequent salvage therapy are summarized in supplementary Tables S1 and S2. Isolated locoregional recurrence was the first reported relapse in 10 patients (8%), with 5 each in the SABR and VATS cohorts. Distant metastases as the initial relapse occurred in 16 patients (13%), with 8 each in SABR and VATS groups. Simultaneous local and distant recurrences manifest in three VATSpatients (2%).

Figure 1: *(A) Locoregional tumor control rates after stereotactic ablative radiotherapy (SABR) and video-assisted thoracoscopic surgery (VATS) lobectomy. (B) Distant tumor control rates after SABR and VATS lobectomy. (C) Freedom from progression rates after SABR and VATS lobectomy. (D) Overall survival rates after SABR and VATS lobectomy.*



The median time to any recurrence in the SABR cohort was 11.3 months. Of the five SABR patients who developed an isolated locoregional recurrence, two patients with progression at the primary tumor site underwent a lobectomy. Another two patients underwent radical chemo-radiotherapy, and one patient with major comorbidity declined any curative treatment. Of eight SABR patients who developed distant metastasis, four underwent chemotherapy and/or radiotherapy, and the remaining four received

supportive care only.

The median time to any recurrence in patients treated with VATS lobectomy was 8.2 months. Of these 16 patients, one developing distant metastases received no active treatment. The five patients presenting with an isolated locoregional recurrence underwent radiotherapy alone (n = 2), chemotherapy alone (n = 2) and chemo-radiation (n = 1).

The 30- and 90-day mortality after VATS resection was 1.6%, with one patient dying of multi-organ failure caused by septicemia due to thoracic empyema and bronchopleural fistulae. In the VATS cohort, 39.1% experienced no treatment-related toxicity, and 23.4% (n = 15) experienced complications ≥grade 3 CTCAE toxicity. Of the latter, eight patients underwent reoperation for reasons including a thoracic empyema (n = 4), damage to other lobes (n = 2) or severe lung hemorrhage (n = 1). The median duration of hospital stay after VATS resection was 7 days (range 2–119 days).

No mortality was observed in SABR patients in 90-day period; a third (32.8%) experienced no adverse effects, and 6.3% (n = 4) experienced ≥grade 3 toxicity. Of the latter, two developed grade 3 radiation pneumonitis requiring steroids, and one each developed hemoptysis requiring embolization and chest wall pain requiring opioids. No patients treated with SABR required hospitalization. Fewer and milder toxic effects were observed after SABR compared with VATS (P = 0.03).

Discussion

We carried out a propensity score-matched pair analysis of outcomes of two potentially curative approaches for early-stage NSCLC. Early analysis revealed similar OS and 3-year FFP for SABR when compared with VATS lobectomy, but significantly higher LRC rates following SABR. Treatment-related toxicity was lower in SABR patients, with no reported 90-day mortality or admission to hospital. To the best of our knowledge, this is the first study to directly compare treatment outcomes of exclusively VATS lobectomy with SABR in patients who presented with clinical stage I– II NSCLC. Earlier reports had shown that SABR can achieve results comparable with those using non-VATS surgical techniques[9–11,20,21].

A key advantage of surgery in stage I–II NSCLC is the ability to invasively stage lymph nodes, thereby allowing adjuvant chemotherapy to be administered when patients have nodal metastasis[2]. A majority of our VATS patients had the recommended minimum number of six nodes removed[14]. Unfortunately, one-third of patients whose disease was upstaged

after surgery received no adjuvant treatment due to comorbidities or patient preference. This is consistent with findings of other studies, in which up to 40% of patients failed to receive planned chemotherapy post-surgery[22].

Surgery has the added advantage of establishing a definitive histological diagnosis. Nevertheless, current guidelines recommend treatment for suspected early-stage NSCLC without pathological confirmation if the likelihood of malignancy exceeds 60%[23]. However, 50% of patients in both arms of this study had no pretreatment histology, rates which are in accordance with previous reports on both treatments for stage I–II NSCLC[10,24,25]. Benign disease was found in 6.3% of VATS patients, all of whom were discussed preoperatively at the same tumor boards, which recommended treatment for all patients presenting with early-stage NSCLC. Similar rates of benign pathology in clinically staged patients have been observed in recent Dutch surgical literature, and analysis of recurrence rates after SABR in our region suggests that outcomes are unlikely to be significantly biased by the inclusion of benign lesions[8,26]. However, it remains our policy to obtain a pretreatment diagnosis in all patients, if possible.

SABR patients manifested a higher LRC rate, despite this group undergoing only non-invasive staging of the lymph nodes. A previous matched comparison of patients with T1-2N0M0 NSCLC who underwent either sublobar resection or SABR also reported improved LRC in SABR[20]. Despite more surgical patients undergoing invasive mediastinal nodal staging, the study of Grills et al. found no significant differences in regional recurrence, locoregional recurrence, distant metastasis or freedom from any failure between the two groups at 30 months[20]. A recent propensity score-matched pair analysis comparing SABR with surgical techniques in stage I NSCLC, in which patients were matched on age, clinical stage and comorbidity, also found no significant differences in rates of local control, disease-free survival or OS[21].

Reasons postulated for the observed differences in LRC between SABR and surgery include the possible improvement of function of the immune system by radiation, mediated by T-cell regulation[27,28]. High radiation doses used in SABR may also have resulted in low-dose spillage to the regional nodes, possibly eliminating microscopic disease[29]. Surgery-induced oxidative stress may potentiate tumor growth through local release of cytokines, and growth factors may stimulate tumor growth[30].

LRC rates observed in both groups are within the range reported previously for both modalities[7,31]. Despite the worse LRC in the VATS group, OS rates were similar and also

comparable with published literature[9,11,32,33]. The lack of differences in OS could be related to the fact that 94% (15 of 16) of post-VATS recurrences received further treatment, compared with 62% (8 of 13) of post-SABR recurrences. We postulate that this finding was due to SABR patients being in a poorer condition than VATS patients, despite the matching procedure. Furthermore, the relatively short period of follow-up for VATS patients (16 months) may also account for a high proportion of patients with a recurrence being alive at the time of analysis. We recognize that differences in the duration of the follow-up between patient cohorts may contribute to differences in failure patterns, and the rapid decline in numbers of VATS patients at risk for an event in our analysis suggests that the current data should be regarded as an analysis of only early outcomes.

Some other limitations of this study have to be acknowledged. Although we believe the cohorts in this study are accurately matched, it remains a retrospective study, and factors not taken into account in the matching process may be responsible for the observed differences in outcome. An indication in support of the latter is the fact that despite matching, 50% of SABR patients were still considered medically inoperable. Furthermore, VATS resections for early-stage NSCLC were only introduced at the VUMC in November 2007, and a learning curve of up to 60 operations has been reported to be necessary for optimal performance of VATS resections[12,34]. Despite the presence of an experienced consulting surgeon during each procedure in regional hospitals, this learning curve may result in poorer outcomes than would have been the case in a single high-volume center.

High local control rates combined with a low-toxicity profile in inoperable patients after SABR for stage I NSCLC have made it a standard treatment option for patients unable to undergo surgical resection[3,7,20]. Interest has also been growing in the use of SABR for potentially operable patients, but the present study is the first to compare both treatment modalities in propensity score-matched patients, which creates two cohorts of patients with similar characteristics. The lower rate of localregional recurrences and fewer adverse effects indicate that SABR should be explored further. Our findings support the interest in randomized, controlled trials to investigate the role of SABR as a treatment option for medically operable patients with stage I NSCLC.

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Supplement 1: *Sites of first tumor recurrence and salvage therapy for SABR patients*

Site first recurrence		Time to recurrence	Treatment recurrence	Survival after recurrence
LR	Hilus	3.2	Chemoradiation	Alive 20 months after recurrence
LR	Mediastinum	3.9	Chemoradiation	Died 36 months after recurrence of distant metastasis
LR	Tumor site	22.1	Lobectomy	Alive 18 months after recurrence
LR	Mediastinum	33.1	Lobectomy + complete lymph node dissection	Alive 32 months after recurrence
LR	Tumor site + hilus	44.9	No (resection not feasible, pt refused chemotherapy or radiotherapy)	Died 4 months after recurrence of tumor progression
D	Liver	1.3	Chemotherapy	Died 8 months after recurrence of tumor progression
D	Bone	3.4	No (poor performance score)	Died 2 months after recurrence of tumor progression
D	Bone	4.9	Radiotherapy	Died 9 months after recurrence of unknown cause
D	Brain	6.7	No (reason no therapy unknown)	Died 1 month after recurrence of tumor progression
D	Brain	11.3	Stereotactic radiotherapy	Died 3 months after recurrence of tumor progression
D	Lung + Adrenal gland	13.5	No (poor performance score)	Died 5 months after recurrence of tumor progression
D	Bone	13.8	Chemotherapy + radiotherapy	Died 4 months after recurrence of tumor progression
D	Bilateral lung	19.2	No (poor performance score + high age)	Died 12 months after recurrence of unknown cause
Median time to any recurrence: 11.3 months				

Supplement 2: *Sites of first tumor recurrence and salvage therapy for VATS patients*

Site first recurrence		Time to recurrence	Treatment recurrence	Survival after recurrence
LR	Hilus + mediastinum	2.6	Chemotherapy	Died 11 months after recurrence of distant metastasis
LR	Hilus + mediastinum	4.9	Chemotherapy	Died 8 months after recurrence of distant metastasis
LR	Bronchus stump	5.9	Radiotherapy	Died 3 months after recurrence of distant metastasis
LR	Mediastinum	11.9	Chemoradiation	Alive 11 months after recurrence
LR	Bronchus stump	32.0	Radiotherapy	Alive 1 month after recurrence
D	Brain	4.3	Resection + radiotherapy	Alive 6 months after recurrence
D	Bone	4.8	Radiotherapy	Died 5 months after recurrence of tumor progression
D	Thoracic wall	6.7	Radiotherapy	Alive 2 months after recurrence
D	Lung + rib	9.4	Radiotherapy + chemotherapy	Died 1 month after recurrence of tumor progression
D	Pleura + rib	11.3	Stereotactic radiotherapy	Alive 9 months after recurrence
D	Brain	13.6	Resection + radiotherapy	Died 6 months after recurrence of cerebrovascular accident
D	Lung + rib	18.5	Chemotherapy	Alive 14 months after recurrence
D	Brain	21.7	No	Alive 2 months after recurrence
LR +D	Hilus + mediastinum + lung	0.8	Chemotherapy	Died 8 months after recurrence of tumor progression
LR +D	Mediastinum + Adrenal gland	7.1	Radiotherapy	Alive 7 months after recurrence
LR +D	Hilus + Mediastinum + liver + lung + rib	18.9	Chemotherapy	Alive 4 months after recurrence
Median time to any recurrence: 8.3 months				

Corrigendum

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The authors of the above article recently performed an update of all patient data, and the senior surgical author reviewed all the surgical case notes of study patients. This process uncovered some discrepancies in the data on lymph node staging as listed below.

- The median number of lymph nodes dissected in the patients who underwent VATS was 9 (range 1-26), instead of 8.5 (range 1-24) as was reported in the article.
- The median number of dissected lymph node stations should read 4 (range 1-7), instead of 4 (range 1-6).
- A total of 76.6% of VATS patients had 6 or more lymph nodes dissected, instead of 71.9% of VATS patients, as was reported in the article.
- Another important omission was that one additional patient had lymph node metastasis detected during surgery, thereby leading to a total of 13 patients who were upstaged during surgery (20.3%). This patient with N2-disease was subsequently treated with chemoradiation.

These findings do not in any way alter the conclusions of the study, but do reflect the fact that the surgical intra-operative staging was somewhat better than was previously reported.

The authors apologize for the errors.