A propensity-matched analysis of surgery and stereotactic body radiotherapy for early stage non-small cell lung cancer in the elderly

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Abstract
Elderly patients with early stage non-small cell lung cancer (NSCLC) who undergo surgical resection are at a high risk of treatment-related complications. Stereotactic body radiation therapy (SBRT) is considered an alternative treatment option with a favorable safety profile. Given that prospective comparative data on SBRT and surgical treatments are limited, we compared the 2 treatments for early stage NSCLC in the elderly.

We retrospectively collected information from the database at our geriatric institution on patients with clinical stage IA/B NSCLC who were treated with surgery or SBRT. The patients were matched using a propensity score based on gender, age, T stage, tumor location, pulmonary function (forced expiratory volume in 1 second [FEV1]% and FEV1), Charlson comorbidity score, and World Health Organization performance score. We compared locoregional control rate, recurrence-free survival (RFS), overall survival (OS), and cancer-specific survival (CSS) between the 2 treatment cohorts before and after propensity score matching.

A total of 106 patients underwent surgery, and 74 received SBRT. Surgical patients were significantly younger (72.6 ± 7.9 vs 82.6 ± 4.1 years, P = 0.000), with a significantly higher rate of adenocarcinoma (P = 0.000), better Eastern Cooperative Oncology Group performance scores (P = 0.039), and better pulmonary function test results (P = 0.034 for predicted FEV1 and P = 0.032 for FEV1). In an unmatched comparison, there were significant differences in locoregional control (P = 0.0012) and RFS (P < 0.001). The 5-year OS was 69% in patients who underwent surgery and 44.6% in patients who underwent SBRT (P = 0.0007). The 5-year CSS was 73.9% in the surgery group and 57.5% in the SBRT group (P = 0.0029). Thirty-five inoperable or marginally operable surgical patients and 36 patients who underwent SBRT were matched to their outcomes in a blinded manner (1:1 ratio, caliper distance = 0.25). In this matched comparison, the follow-up period of this subgroup ranged from 4.2 to 138.1 months, with a median of 58.7 months. Surgery was associated with significantly better locoregional control (P = 0.0191) and RFS (P = 0.0178), whereas no significant differences were found in OS (5-year OS, 67.8% for surgery vs 47.4% for SBRT, P = 0.07) or CSS (67.8% for surgery vs 58.2% for SBRT, P = 0.1816).

This retrospective analysis found superior locoregional control rates and RFS after surgery compared with SBRT, but there were no differences in OS or CSS. SBRT is an alternative treatment option to surgery in elderly NSCLC patients who cannot tolerate surgical resection because of medical comorbidities. Our findings support the need to compare the 2 treatments in randomized controlled trials.

Abbreviations: CSS = cancer-specific survival, CT = computed tomography, FEV1 = forced expiratory volume in 1 second, ITV = internal target volume, LCR = locoregional control rate, MDT = multidisciplinary team, NSCLC = non-small cell lung cancer, OS = overall survival, PSM = propensity score matching, RFS = recurrence-free survival, SBRT = stereotactic body radiation therapy.

Keywords: geriatric, non-small cell lung cancer, stereotactic body radiotherapy, surgery

1. Introduction
More than one-quarter of cancer deaths are caused by lung cancer,[1,2] partially due to the small number of patients who present with early stage carcinoma.[3] The gold standard treatment for patients with early stage non-small cell lung cancer (NSCLC) who can tolerate surgery is lobectomy. However, this treatment may be contraindicated in patients with many comorbidities, potential postoperative complications, or individual unwillingness.[4] As a result, patients who do not receive curative-intent treatment have poor survival outcomes.[5] Unfortunately, lung cancer has become a geriatric disease; the number of elderly patients with lung cancer has increased, and the median age at diagnosis is 70 years. For elderly NSCLC patients, a decline in circulatory or respiratory function and other comorbidities limit the use of surgery, and the proportion of patients who refuse surgery is high.
Radiotherapy has conventionally been considered the next-best treatment option for lung cancer patients who are unfit for or refuse surgery. Both the National Comprehensive Cancer Network Clinical Practice Guidelines and European Society for Medical Oncology Consensus\cite{6} recommend stereotactic body radiotherapy (SBRT) as the nonsurgical treatment choice for stage I NSCLC. Some studies have revealed similar or better rates of local recurrence, disease-specific survival, and overall survival (OS) in patients treated with SBRT compared with those treated with surgery.\cite{7,8} Furthermore, several studies have indicated that SBRT has significant advantages in elderly patients. However, given that late recurrence is not uncommon, the relatively short follow-up periods in these studies may not be ideal for a comparison of outcomes.

In the present single-center retrospective analysis, we report the 5-year survival outcome of elderly patients with early stage NSCLC who were treated with SBRT or surgery in our geriatric center.

2. Materials and methods

This retrospective study was approved by the Ethics Committee. Clinical information was obtained from the Chinese People’s Liberation Army General Hospital electronic file database. The NSCLC patients were treated from January 1, 2002, to May 1, 2010, in the geriatric ward. Patients were eligible for inclusion in the study if they had cytologically/histologically or clinically confirmed NSCLC and were older than 60 years of age. Clinically confirmed NSCLC was defined as a primary suspicious solid, part-solid, or ground-glass opacity nodule with spiculated or smooth margins on computed tomography (CT) images that persisted for at least 3 months and showed an increase in its longest axis or a maximal standardized uptake value on fluorodeoxyglucose (FDG)-positron emission tomography >5 at 3 months. A diagnosis of clinical stage I disease was performed after guideline-specific staging, including thoracic/abdominal CT scans and brain MRI or CT scans. Suspicion of nodal metastases required a confirmatory biopsy using endoscopic techniques. All disease staging was carried out using Union for International Cancer Control TNM-7. Patients with a past history of lung cancer were excluded from the study. Patients with previous pulmonary surgery or radiotherapy and those who received adjuvant chemotherapy were also excluded. The treatment strategies for all patients were discussed, and the final decisions were made by a multidisciplinary team (MDT) that included an oncologist, thoracic surgeon, radiologist, radiation oncologist, and anesthetist. All multidisciplinary consultations were recorded in detail.

SBRT can be administered as an outpatient or inpatient treatment based on risk-adapted fractionation schemes. The internal target volume (ITV) was determined using CT with a 5-mm margin. Irradiation was performed with 6-MV x-ray beams from a linear accelerator in multiple non-coplanar static ports. The dose of SBRT was prescribed to the highest isodose line that was required to cover 100% of the ITV and >95% of the planning target volume. In the surgery patients, performance of a lobectomy, sublobectomy, thoracotomy, or video-assisted thoracic surgery was discussed within the MDT prior to the procedure.

Locoregional recurrence was defined as a recurrence in or adjacent to the primary target lesion (for SBRT patients), resection margins (for surgery patients), and the ipsilateral hilum or mediastinum on CT that persisted for at least 6 months; a maximal standardized uptake value on FDG-positron emission tomography >5 at 6 months; or occasionally through biopsy confirmation. We calculated the time to local recurrence as the date of treatment to the date of first locoregional failure. Recurrence-free survival (RFS) was defined as the date of treatment to the date of first recurrence, including locoregional failure or distant metastasis. For patients who did not have a recurrence but died, we calculated RFS from the date of treatment to the date of death. OS was defined as the date of treatment to the date of death or the cutoff date. Cancer-specific survival (CSS) was defined as the date of treatment to the date of death from recurrence of the treated NSCLC or the last follow-up.

2.1. Compliance with ethical standards

All procedures in this study were performed in accordance with the ethical standards of the institutional and/or national research committee, the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

2.2. Statistical analysis

Clinical characteristics were analyzed using Fisher exact test. Descriptive statistics are presented as the mean ± standard deviation. Independent samples t tests and 1-way analysis of variance were used to compare the continuous variables. The Kaplan–Meier method was used to analyze the time to locoregional recurrence, RFS, OS, and CSS, and differences were compared using the log-rank test. Cases were censored when death occurred. All statistical tests were 2-sided with a threshold of \( P \leq 0.05 \) for statistical significance and were carried out using Statistical Package for Social Sciences, version 22.0.

Because treatment selection is likely to be influenced by a patient’s clinical characteristics, we used propensity score matching (PSM) to further compare the treatment cohorts. PSM reduces bias due to confounding factors by matching patients on numerous baseline variables using a multivariable logistic regression model. Patient data were anonymized before PSM using the covariates gender, age, T stage, tumor location, pulmonary function (forced expiratory volume in 1 second % and forced expiratory volume in 1 second), Charlson comorbidity score, and World Health Organization performance score. Matching was carried out at a ratio of 1:1 and a caliper distance of 0.25 without replacement using a semiautomated method in the Matching package (version 4.8.3.4) for R (version 3.0.1).

3. Results

From January 1, 2002, to May 1, 2010, a total of 180 NSCLC patients were collected from the geriatric ward of the Chinese People’s Liberation Army General Hospital, and the patients were histologically/cytologically or clinically confirmed to have stage I NSCLC. The baseline characteristics of the patients before PSM are listed in Table 1. The mean age of patients in the surgery and SBRT groups was 72.6 and 82.6 years, respectively. Eastern Cooperative Oncology Group performance scores (PS), histology, and pulmonary function test results were not balanced between the 2 treatment cohorts, and patients in the SBRT group were more likely to be in a worse clinical condition than those in...
the surgery group. Pretreatment pathological confirmation was available for 4 (3.8%) surgery patients (percutaneous lung biopsy) and 34 (45.9%) SBRT patients; this difference was significant ($P = 0.001$). Among the 34 pathology-confirmed SBRT patients, the pretreatment confirmation process included percutaneous lung biopsy under CT guidance ($n = 20$), bronchoscope biopsy ($n = 12$), or pleural effusion cytological examination ($n = 2$). At the final analysis, the pathological type in 10 patients remained unclear. In the other 30 SBRT patients, pathology was confirmed during or after therapy.

Of the 106 (58.9%) patients in the surgery group, 64 (60.4%) underwent a lobectomy, and 42 (39.6%) underwent a sublobectomy. Video-assisted thoracic surgery and thoracotomy were performed in 54 (50.9%) and 52 (49.1%) patients, respectively. A total of 8 cases of cT1a tumors were upstaged after surgery. For the 74 patients who underwent SBRT, 67 received 60 Gy in 3 fractions ($n = 18$ patients), 5 fractions ($n = 43$), or 8 fractions ($n = 6$), and 7 received 34 Gy in 3 fractions. In addition, 60 (81.1%) radiotherapy patients were considered medically unfit for surgery based on MDT discussions, whereas the remaining 14 patients were considered marginally operable at high risk but refused surgery.

### 3.1. Recurrence and survival results before PSM

The cutoff date for the final analysis was April 4, 2015, which is when the last selected patient completed the 5-year follow-up. The median follow-up was 61.9 months, and all patients had a complete follow-up. A total of 106 cases ($52 (49.1\%)$ in the surgery group and $54 (73.0\%)$ in the SBRT group) developed disease recurrence before the final analysis. Among these patients, the outcome of locoregional recurrence was significantly better after surgery than after SBRT. The 1-, 3-, and 5-year locoregional control rates (LCRs) were 89.3%, 82.5%, and 78.7%, respectively, after surgery and 76.3%, 68.8%, and 52.1%, respectively, after SBRT. The difference in LCR between the 2 treatment groups was significant ($P = 0.0012$; Fig. 1A).

An overview of all patients with disease recurrence (locoregional or distant recurrence) showed significant differences in RFS between the 2 groups. The 1-, 3-, and 5-year any-recurrence control rates were 85.6%, 63.7%, and 57.9%, respectively, after surgery and 58.3%, 43.7%, and 27.1%, respectively, after SBRT. The median RFS time was 73.6 months in the surgery group and 18.7 months in the SBRT group ($P < 0.0001$; Fig. 1B).

A total of 56 ($52.8\%)$ and 46 ($62.2\%)$ deaths were recorded in the surgery and SBRT groups, respectively. The 30-day mortality was 1.9% in the surgery group (1 patient died of an acute pulmonary embolism, and another died of pulmonary infection—induced disseminated intravascular coagulation) and 0% in the SBRT group. Patients who underwent surgery achieved better OS outcomes than those in the SBRT group. The 1-, 3-, and 5-year OS was 95.2% versus 90.2%, 77.5% versus 54.9%, and 69.0% versus 44.6% after surgery and SBRT, respectively. The median OS was significantly longer in the surgery group ($89.5$ months) than in the SBRT group ($48.0$ months) ($P = 0.0007$; Fig. 1C).

A total of 64 patients died of lung cancer ($32 (30.2\%)$ in the surgery group and $32 (43.2\%)$ in the SBRT group). The causes of death for the other 38 patients are detailed in Table 2. The 1-, 3-, and 5-year CSS was 98.0%, 81.4%, and 73.9%, respectively, after surgery and 92.9%, 70.7%, and 57.5%, respectively, after SBRT; the difference between treatment groups was significant ($P = 0.0029$). The median CSS was 108.5 months for the surgery group and 87.1 months for the SBRT group (Fig. 1D).

### 3.2. Recurrence and survival results after PSM

PSM between the surgery and SBRT groups yielded 35 matched pairs. These pairs were comparable in age, gender, T stage, Eastern Cooperative Oncology Group PS score, histology, lesion location, Charlson comorbidity score, and pulmonary function test results (Table 3). The follow-up period of these 2 cohorts ranged from 4.2 to 138.1 months, with a median follow-up period of 58.7 months. In the propensity-matched comparison, there was significantly less locoregional recurrence after surgery than after SBRT; the 1-, 3-, and 5-year LCRs were 91.3%, 85.6%, and 78.7%, respectively, after surgery and 76.3%, 68.8%, and 52.1%, respectively, after SBRT. The difference in LCR between the 2 treatment groups was significant ($P = 0.0191$; Fig. 2A). The median RFS for the matched patients receiving surgery or SBRT was 63.9 and 20.4 months, respectively ($P = 0.0178$; Fig. 2B). The 1-, 3-, and 5-year any-recurrence control

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### Table 1

Patient characteristics, comparing patients undergoing surgery and patients undergoing SBRT, before propensity score matching.

| Characteristics          | Surgery (n = 106) | SBRT (n = 74) | $P$   |
|--------------------------|------------------|--------------|------|
| Mean age ± SD            | 72.6 ± 7.9       | 82.6 ± 4.1   | 0.000|
| Range                    | 60–86            | 70–90        |      |
| Age >75 yr               |                  |              |      |
| Yes                      | 50 (47.2)        | 50 (67.6)    | 0.007|
| No                       | 56 (52.8)        | 24 (32.4)    |      |
| Gender                   |                  |              |      |
| Male                     | 98 (92.5)        | 65 (87.8)    | 0.298|
| Female                   | 8 (7.5)          | 9 (12.2)     |      |
| T stage *                |                  |              |      |
| La                       | 56 (52.8)        | 44 (59.5)    | 0.378|
| Ib                       | 50 (47.2)        | 30 (40.5)    |      |
| ECOG PS *                |                  |              |      |
| 0                        | 31 (29.3)        | 10 (13.5)    | 0.039|
| 1                        | 70 (66.0)        | 58 (78.4)    |      |
| 2                        | 5 (4.7)          | 6 (8.1)      |      |
| Pathology pretreatment   |                  |              |      |
| Yes                      | 4 (3.8)          | 34 (45.9)    | 0.001|
| No                       | 102 (96.2)       | 40 (54.1)    |      |
| Histology                |                  |              |      |
| Adenocarcinoma           | 78 (73.6)        | 28 (37.8)    | 0.000|
| Squamous cell carcinoma  | 24 (22.6)        | 34 (45.9)    |      |
| Other                    | 4 (3.8)          | 4 (5.4)      |      |
| Unknown                  | 0                | 10 (13.5)    |      |
| Location                 |                  |              |      |
| Left lower               | 16 (15.1)        | 14 (18.9)    | 0.885|
| Left upper               | 28 (26.4)        | 18 (24.3)    |      |
| Right lower              | 18 (17.0)        | 14 (18.9)    |      |
| Right middle             | 4 (3.8)          | 4 (5.4)      |      |
| Right upper              | 40 (37.7)        | 24 (32.4)    |      |
| Charlson comorbidity score * |              |            |      |
| 1                        | 42 (39.6)        | 29 (39.2)    | 0.148|
| 2                        | 30 (28.3)        | 22 (29.7)    |      |
| 3                        | 24 (22.6)        | 10 (13.5)    |      |
| 4                        | 7 (6.6)          | 8 (10.8)     |      |
| 5                        | 1 (0.9)          | 4 (5.4)      |      |
| 6                        | 0 (0.0)          | 1 (1.4)      |      |
| Pulmonary function test * |                |              |      |
| Percentage predicted     | 92.78 ± 24.12    | 85.69 ± 20.11| 0.034|
| FEV1, mean ± SD          | 1.82 ± 0.81      | 1.57 ± 0.69  | 0.032|

ECOG = Eastern Cooperative Oncology Group, FEV1 = forced expiratory volume in 1 second, SBRT = stereotactic body radiation therapy, SD = standard deviation.

*Variable used to compute propensity scores.
rates for the matched patients receiving surgery or SBRT were 88.6% versus 61.8%, 65.4% versus 46.2%, and 57.9% versus 28.6%, respectively. The difference in OS in the matched pairs became insignificant after PSM (\(P=0.07\); Fig. 2C). The median OS in the surgery and SBRT groups was 71.3 and 53.8 months, respectively, and the 1-, 3-, and 5-year OS was 97.1% versus 94.0%, 79.5% versus 58.4%, and 67.8 versus 47.4% in the surgery and SBRT groups, respectively. Cause-specific survival was also similar between the 2 cohorts (67.8% vs 58.2% at 5 years), with a median value of 104.1 versus 89.8 months (\(P=0.1816\); Fig. 2D).

4. Discussion

The widespread adoption of CT screening for lung cancer is thought to be responsible for the increasing incidence of NSCLC in China. With the development of CT technology and increased resolution, a growing number of individuals are diagnosed with having early stage lung cancer. Surgical resection remains the gold standard treatment option for early stage NSCLC. However, elderly patients often have severe comorbid conditions that make surgery prohibitive. SBRT may be a reasonable alternative to surgical treatment for inoperable early stage NSCLC in the elderly.\(^9\)

In this retrospective study, we performed a propensity-matched comparative analysis of elderly patients with NSCLC who underwent surgery or SBRT. Patients were well matched for key variables. Our data indicate that the patients selected to undergo surgery had similar survival outcomes compared to those treated with SBRT.

### Table 2
The cause of death for non-small cell lung cancer.

|                      | Surgery (n=24) | Radiotherapy (n=14) |
|----------------------|---------------|--------------------|
| Second primary cancer| 12            | 6                  |
| Pneumonia or respiratory failure | 8   | 4                  |
| Acute myocardial infarction | 3   | 4                  |
| Acute pulmonary embolism   | 1   | 0                  |

### Table 3
Patient characteristics, comparing patients undergoing surgery and patients undergoing SBRT, after propensity score matching.

| Characteristics | Surgery (n=35) | SBRT (n=35) | \(P\)  |
|-----------------|---------------|-------------|-------|
| Mean age ± SD   | 74.8 ± 6.6    | 77.1 ± 5.2  | 0.110 |
| Range           | 66–82         | 70–85       |       |
| Age >75y Yes    | 15 (42.9)     | 12 (34.3)   | 0.461 |
| No              | 20 (57.1)     | 23 (65.7)   |       |
| Gender Male     | 33 (94.3)     | 33 (94.3)   | 1     |
| Female          | 2 (5.7)       | 2 (5.7)     |       |
| T stage Ia      | 18 (51.4)     | 21 (60.0)   | 0.470 |
| Ib              | 17 (48.6)     | 14 (40.0)   |       |
| ECOG PS 0       | 5 (14.3)      | 4 (11.4)    |       |
| 1               | 28 (80.0)     | 28 (80.0)   | 0.856 |
| 2               | 2 (5.7)       | 3 (8.6)     |       |
| Histology       |               |             |       |
| Adenocarcinoma  | 18 (51.4)     | 17 (48.6)   | 0.255 |
| Squamous cell carcinoma | 15 (42.9) | 16 (45.7)   |
| Other           | 2 (5.7)       | 0 (0)       |       |
| Unknown         | 0 (0)         | 2 (5.7)     |       |
| Location        |               |             |       |
| Left lower      | 6 (17.1)      | 7 (20.0)    |       |
| Left upper      | 9 (25.7)      | 9 (25.7)    |       |
| Right lower     | 8 (22.9)      | 6 (17.1)    | 0.952 |
| Right middle    | 1 (2.9)       | 2 (5.7)     |       |
| Right upper     | 11 (31.4)     | 11 (31.4)   |       |
| Charlson comorbidity score | 13 (37.1) | 11 (31.4)   | 0.967 |
| 2               | 9 (25.7)      | 11 (31.4)   |       |
| 3               | 9 (25.7)      | 8 (22.9)    |       |
| 4               | 3 (8.6)       | 4 (11.4)    |       |
| 5               | 1 (2.9)       | 1 (2.9)     |       |

ECOG = Eastern Cooperative Oncology Group, FEV1 = forced expiratory volume in 1 second, SBRT = stereotactic body radiation therapy, SD = standard deviation.
surgery had significantly better LCRs and RFS than those who underwent SBRT in both the unmatched and PSM comparisons. A number of retrospective PSM studies have compared surgery and SBRT for early stage NSCLC. One study showed that surgery or SBRT did not influence OS ($P = 0.73$), although SBRT significantly increased locoregional recurrences ($P = 0.028$).\[10\] In contrast, Verstegen et al found that SBRT resulted in a higher LCR than surgery (96.8% vs 86.9% and 93.8% vs 82.6% at 1 and 3 years, respectively, $P = 0.04$).\[7\] Moreover, Grills et al found no significant difference in regional recurrence or freedom from any failure between the 2 treatment groups at 30 months.\[11\] Although these study designs are similar, the different results may be due to different SBRT plans, SBRT dosage delivery, or baseline patient characteristics. Several studies have indicated that inconsistent definitions of locoregional failure between the 2 arms may lead to different outcomes. Two analyses using uniform definitions of locoregional failure reported better local control rates with surgery; however, the regional control rates seemed to be similar.\[12,13\]

Both before and after PSM, our results indicate that the patients who underwent surgery had significantly longer RFS and higher control rates than the SBRT patients. One possible explanation for this finding may include the lack of invasive mediastinal and hilar staging in the SBRT patients, which suggests that this cohort may have been understaged. Some studies support the hypothesis that 1 advantage of SBRT is the ability of radiation to improve immune function, which is mediated by T-cell regulation.\[14\] High doses of SBRT may result in low-dose spillage to regional nodes, which possibly eliminates microscopic disease.\[15\]

In both cohorts, the RFS was within the range previously reported for both treatments.\[16\] Despite the decreased RFS in the SBRT group, the OS and CSS were similar between the 2 cohorts, and the outcomes were in line with those reported in previous studies.\[7,17,18\] Palma et al performed a comparison of SBRT and surgery in elderly population-based, matched-pair patients with stage I NSCLC and found that the 1- and 3-year OS rates after SBRT were 87% and 42%, respectively, which were comparable with the rates for those who underwent surgery (75% and 60%, respectively) ($P = 0.22$).\[17\] Shirvani et al retrospectively analyzed 10,923 elderly patients ≥66 years of age from the SEER database and reported that the OS and CSS were similar for the patients who underwent SBRT and those who underwent surgery, with hazard ratios of 0.82 ($P = 0.38$) for OS and 2.14 ($P = 0.10$) for CSS.\[19\] A Japanese study found that the difference in OS was not significant between matched pairs (40.4% and 55.6% at 5 years with SBRT and surgery, respectively; $P = 0.124$), and CSS was comparable between the groups (35.3% and 30.3% at 5 years with SBRT and surgery, respectively, $P = 0.427$).\[18\]

Our study showed better OS and CSS rates than some of the published literature.\[7,8,17,18\] One possible reason for this difference may be the complicated clinical background of our patients. Some of the patients in the SBRT cohort were medically regarded as marginally operable but personally unwilling to undergo surgery. Currently, few randomized studies have compared SBRT and surgery in operable patients. Two single-arm prospective studies investigated the outcomes of operable patients who underwent SBRT and found that the 3-year OS was 84.7%\[20\] and 76% in elderly patients.\[21\] Conversely, a total of 59 medically inoperable patients who underwent SBRT were evaluated in a prospective phase II study. The 3-year OS was 55.8%, and the median OS was 48.1 months.\[22\] According to figures from these studies, inoperable is undoubtedly inferior to operable. In our study, 13 of 14 marginally operable patients requested SBRT in the PSM comparison, which potentially improved their survival because the prognosis of these patients was better than that of those with inoperable NSCLC. Another explanation for the difference between our study and previous studies may be differences in treatment methods. In the current study, the majority of the patients received a lobectomy rather than a sublobectomy. Although there have been several attempts to utilize sublobar resection over lobectomy in elderly patients,\[23,24\] lobectomy unfortunately remains the optimal surgical procedure.\[9\]
The lack of a significant difference in OS and CSS between the 2 cohorts after PSM may be explained by the fact that 28.6% of the patients died due to secondary cancers in the surgery group, compared with 11.4% in the SBRT group. The results from a meta-analysis that included 6 phase II studies comparing surgery with SBRT showed that the only advantage of surgery was in the 3-year survival, whereas CSS was not significantly changed.25 We believe that early stage patients tend to have a longer life expectancy, and the possibility of a non–cancer-related death would therefore be higher. A second explanation may be the different subsequent treatments. Before the IPASS study was published, the relationship between tyrosine kinase inhibitor (TKIs) and epidermal growth factor receptor (EGFR) mutation was not clear.26 Despite the matching procedure, the SBRT patients were in a worse condition than the surgery patients when the disease recurred, necessitating TKI treatment, whereas the surgery patients who experienced disease recurrence were in relatively good condition and thus received traditional chemotherapy. Based on the current literature, TKIs are notably superior to chemotherapy with regard to RFS and quality of life among the subgroup of patients with EGFR mutations. Few surgery patients had the opportunity to receive second-line TKI therapy when chemotherapy failed because of their deteriorating condition. In contrast, more than half of the SBRT patients received second-line treatment. Although there was no significant difference in OS between the matched patients, the absolute difference in OS between the 2 cohorts was 17.5 months (71.3 vs 53.8 months), which deserves further discussion. One of the reasons for these results may be the poorer clinical condition of the patients within the SBRT cohort, even after PSM. Because the medically inoperable patients were physically weak, they were more likely to die of lung cancer–related infections and treatment-related complications. Another reason is that the sample size was too small after PSM, which decreased the statistical power.

Our study used PSM to minimize bias between the 2 cohorts. Nevertheless, a number of limitations inherent to a retrospective analysis must be kept in mind. One limitation is that the data were collected from a single treatment center. Therefore, the treatments and final outcomes may not be widely representative. The sample size is another limitation. Several key variables, which may complicate the analysis, must be balanced using PSM methods; therefore, many patients were excluded. In addition, the lack of preoperative invasive staging in the SBRT group is another important limitation. The SBRT cohort had more central lesions, which could have predisposed the patients to increased nodal involvement.

In conclusion, SBRT and surgery resulted in comparable OS and CSS in the PSM cohort. SBRT is an alternative treatment option to surgery in high-risk elderly patients who cannot tolerate surgery or in marginally operable patients who are unwilling to undergo surgery. Rigorous prospective studies are urgently needed to accurately define the elderly patients who are at high surgical risk and to optimize patient selection for SBRT in this population.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
[2] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115–32.
[3] Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
[4] Owonikoko TK, Ragin CC, Belani CP, et al. Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. J Clin Oncol 2007;25:5570–7.
[5] Deterbeck FC, Gibson CJ. Turning gray: the natural history of lung cancer over time. J Thorac Oncol 2008;3:781–92.
[6] Vansteenkiste J, Crino L, Dooms C, et al. 2nd ESMO consensus conference on lung cancer: early-stage non-small cell lung cancer consensus on diagnosis, treatment and follow-up. Ann Oncol 2014;25:1462–74.
[7] Verstegen NE, Oosterhuis JW, Palma DA, et al. 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. Ann Oncol 2013;24:1543–8.
[8] Crabtree TD, Denlinger CE, Meyers BE, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2010;140:377–86.
[9] Shuvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. JAMA Surg 2014;149:1244–53.
[10] van den Berg LL, Klinkenberg TJ, Groen HJ, et al. Patterns of recurrence and survival after surgery or stereotactic radiotherapy for early stage NSCLC. J Thorac Oncol 2015;10:826–31.
[11] Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol 2010;28:928–35.
[12] Robinson CG, DeWees TA, El Naqa IM, et al. Patterns of failure after stereotactic body radiation therapy or lobar resection for clinical stage I non-small-cell lung cancer. J Thorac Oncol 2011;6:192–201.
[13] Crabtree TD, Pun V, Robinson C, et al. Analysis of first recurrence and survival in patients with stage I non-small cell lung cancer treated with surgical resection or stereotactic radiation therapy. J Thorac Cardiovasc Surg 2014;147:1183–92.e10.
[14] Lee Y, Auh SL, Wang Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8(+) T cells: changing strategies for cancer treatment. Blood 2009;114:589–95.
[15] Timmerman R, Bastasch M, Sahi D, et al. Optimizing dose and fractionation for stereotactic body radiation therapy. Normal tissue and tumor control effects with large dose per fraction. Front Radiat Oncol 2007;40:332–65.
[16] Hamaji M, Chen F, Matsuo Y, et al. Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer. Ann Thorac Surg 2015;99:1122–9.
[17] Palma D, Visser O, Lagerwaard FJ, et al. Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery. Radiat Oncol 2011;10:240–4.
[18] Matsuo Y, Chen F, Hamaji M, et al. Comparison of long-term survival outcomes between stereotactic body radiotherapy and sublobar resection for stage I non-small-cell lung cancer in patients at high risk for lobectomy: a propensity score matching analysis. Eur J Cancer 2014;50:2932–8.
[19] Shrivani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. Int J Radiat Oncol Biol Phys 2012;84:1060–70.
[20] Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:348–53.
[21] Nagata Y, Takayama K, Matsuo Y, et al. Clinical outcomes of a phase III study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys 2005;63:1427–31.
[22] Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070–7.
[23] Donington JS. Point: are limited resections appropriate in non-small cell lung cancer? Yes. Chest 2012;141:588–90.
[24] Chamogeorgakis T, Ieromonachos C, Georgiannakis E, et al. Does lobectomy achieve better survival and recurrence rates than limited pulmonary resection for T1N0M0 non-small cell lung cancer patients? Interact Cardiovasc Thorac Surg 2009;8:564–72.
[25] Zhang B, Zhu F, Ma X, et al. Matched-pair comparisons of stereotactic body radiotherapy (SBRT) versus surgery for the treatment of early stage non-small cell lung cancer: a systematic review and meta-analysis. Radiology 2014;212:350–5.
[26] Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–57.