

Treatment Outcomes in Stage I Lung Cancer

A Comparison of Surgery and Stereotactic Body Radiation Therapy

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Introduction: The relative roles of surgery and stereotactic body radiation therapy in stage I non–small-cell lung cancer (NSCLC) are evolving particularly for marginally operable patients. Because there is limited prospective comparative data for these treatment modalities, we evaluated their relative use and outcomes at the population level using a national database.

Methods: Patient variables and treatment-related outcomes were abstracted for patients with clinical stage I NSCLC from the National Cancer Database. Patients receiving surgery were compared with those undergoing stereotactic body radiation therapy (SBRT) in exploratory unmatched and subsequent propensity matched analyses.

Results: Between 1998 and 2010, 117,618 patients underwent surgery or SBRT for clinical stage I NSCLC. Of these, 111,731 (95%) received surgery, whereas 5887 (5%) underwent SBRT. Patients in the surgery group were younger, more likely to be males, and had higher Charlson comorbidity scores. SBRT patients were more likely to have T1 (versus T2) tumors and receive treatment at academic centers. Thirty-day surgical mortality was 2596 of 109,485 (2.4%). Median overall survival favored the surgery group in both unmatched (68.4 versus 33.3 months, $p < 0.001$) and matched analysis based on patient characteristics (62.3 versus 33.1 months, $p < 0.001$). Disease-specific survival was unavailable from the data set.

Conclusion: In a propensity matched comparison, patients selected for surgery have improved survival compared with SBRT. In the absence of information on cause of death and with limited variables to characterize comorbidity, it is not possible to assess the relative contribution of patient selection or better cancer control toward the

improved survival. Rigorous prospective studies are needed to optimize patient selection for SBRT in the high-risk surgical population.

Key Words: Non–small-cell lung cancer, Surgery, Stereotactic body radiation therapy, Outcomes.

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Surgical resection has been traditionally considered the standard procedure in patients with clinical stage I non–small-cell lung cancer (NSCLC). Stereotactic body radiation therapy (SBRT) was introduced over a decade ago as an alternative to conventionally fractionated radiation therapy in patients considered medically inoperable. Since then, the application of SBRT has expanded, and it is often considered in patients who may be surgical candidates but face a potentially higher risk of perioperative morbidity or mortality. Several retrospective institutional studies have compared early and intermediate-term outcomes after these two treatment modalities^{1–9} yet high-quality prospective trial data remain elusive.

Most comparative studies have generally found patients undergoing surgery to have longer overall survival (OS) when compared with SBRT patients^{3,7,10} particularly when the operation performed is a lobectomy. However, studies comparing local/regional recurrence and disease-free survival (DFS) after surgery or SBRT have shown mixed results.^{1,3,8,9} A part of the problem comparing locoregional control is the lack of uniformity between treating specialties (surgeons and radiation oncologists) and individual studies in definitions of local and regional recurrence as well as the varying schedules of follow-up imaging studies employed after surgery or SBRT. In addition, both treatment modalities have evolved with the widespread use of thoracoscopic techniques in surgery and the improvement of radiation doses and fractions in SBRT.

The literature contrasting SBRT and surgery has largely come from major academic centers with leading radiation oncology and thoracic surgery programs. Another criticism of the institutional studies has been the relatively short follow-up in the SBRT cohorts. Recent claims database analyses have studied surgery and SBRT for lung cancer in the elderly population.^{11,12}

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The National Cancer Data Base (NCDB), a joint program of the Commission on Cancer of the American College of Surgeons and the American Cancer Society, is a nationwide oncology outcomes database for more than 1500 commission-accredited cancer programs. About 70% of all newly diagnosed cases of cancer in the United States are captured at the institutional level and reported to the NCDB.^{13,14} We aimed to study the actual practice patterns of treatment for stage I NSCLC in the United States and understand the relative efficacy of surgical resection and SBRT in this population using the NCDB.

PATIENTS AND METHODS

Using deidentified patient information from the NCDB participant user file, we abstracted information on patients with clinical stage I NSCLC who received treatment between 1998 and 2010 with either surgical resection (surgery) or SBRT. Patients who did not receive either one of these two treatment plans (surgery or SBRT) were excluded. Specifically, the surgical cohort began in 1998, whereas the first SBRT case was from 2003. Patients who received only palliative treatment (as coded in the database) were also excluded from the analysis. For both the surgery and SBRT arms, patients with tumors greater than 5 cm in size, clinical T2b disease or clinical N1/2/unknown or clinical M1/unknown status were excluded. In addition, surgical patients who received any neoadjuvant therapy (chemotherapy or radiation) were excluded. Patients who were eventually pathologically upstaged or received adjuvant therapy after surgery or SBRT were included. The study was exempted by the institutional review board.

For each patient, we obtained information on patient-related variables, tumor-related variables, treatment, and short-term (30-day mortality, readmission) and long-term (OS) outcomes. Using information on race and income, we formed dichotomized groups in which a patient was either Caucasian or not Caucasian and had an annual income less than or greater than \$35,000. In addition, based on the population size of the area from which a patient presented rural (regional population less than 250,000) and urban locations were defined. Comorbidity was annotated using the Charlson/Deyo score, categorized as 0, 1, or greater than or equal to 2. The NCDB combined those with scores of 2 or greater into one group as very few patients had scores greater than 2. Treatment facilities are classified as in the NCDB as community cancer programs, comprehensive community cancer programs, and academic/research centers in the NCDB, and the former two were categorized as nonacademic centers for the purpose of this analysis.

Last known vital status and the time between diagnosis and the last known follow-up date were used to determine survival. We initially contrasted patients receiving surgery to those who received SBRT in an unmatched comparison. Patients in the surgery group were then matched to those in the SBRT group using a propensity score based technique. The propensity score was the probability of receiving SBRT during the study period, estimated using a logistic regression model including age at diagnosis, gender, race, income, rural versus urban status, Charlson/Deyo score, tumor size,

T1 versus T2 status, and type of facility where treatment was administered. These variables were selected from an initial univariate analysis comparing the surgery and SBRT groups, and variables significantly different between the groups were chosen for propensity matching. Patients for whom the propensity scores matched to the fourth decimal place were matched in 1:1 fashion. Automated matching was performed using the Fuzzy extension command in SPSS (SPSS 21.0 for Windows, SPSS Inc., Chicago, IL).¹⁵ Recognizing that surgery in the form of sublobar resection (wedge resection or segmentectomy) is a closer anatomical approximation to the volume of lung parenchyma treated with SBRT and often offered to patients at higher risk from lobectomy, we performed a secondary analysis (unmatched and propensity score matched) restricting surgery patients only to those who underwent sublobar resection (Fig. 1).

All statistical analyses were performed using SPSS 21.0. Descriptive statistics were expressed as mean \pm standard deviation unless otherwise specified. Independent samples *t* tests and one-way analysis of variance were used to compare continuous variables. Chi-square tests were used to compare categorical data. OS was estimated by the Kaplan–Meier method. The log-rank test was used to determine differences in OS. All statistical tests were two-sided and a 0.05 level of significance was used.

RESULTS

Between 1998 and 2010, 230,224 patients were diagnosed with clinical stage I NSCLC at 1600 institutions. A total of 117,618 of 230,224 met study criteria (Fig. 1) and were treated with primary surgery ($n = 111,731$, 95.0%) or SBRT ($n = 5887$, 5.0%). The mean follow-up for the entire study group was 36.5 months. The median follow-up was longer for surgical patients (27.5 versus 16.6 months, $p < 0.001$).

Patients in the surgery group were younger and were more likely to be males and non-Caucasians (Table 1). Surgical patients were also more likely to be from rural areas and had higher Charlson comorbidity scores and slightly larger tumors. SBRT patients were more likely to have T1 (versus T2) tumors and receive treatment at academic centers. In the surgery cohort, lobectomy (82,749 of 111,731, 74.1%) was the most common operation, whereas the remaining patients underwent a sublobar resection (26,292 of 111,731, 23.5%) or pneumonectomy (2690 of 111,731, 2.4%). Median postoperative hospital stay was 6 days, and the 30-day surgical mortality was 2596 of 109,485 (2.4%). In surgical patients, 1-year OS was 90.0%. One-year survival after SBRT was 85.5%.

Postoperatively, 13,610 of 94,086 (14.5%) surgical patients with pathologic staging data available were found to have pathologic upstaging (final pathologic stage II or higher). Overall 9.1% of surgical patients received adjuvant chemotherapy only, 2.8% received adjuvant radiation alone, whereas 2.3% received both adjuvant chemotherapy and radiation. In the SBRT cohort, the mean radiation dose was 5383 ± 678 Gy, and 4.1% of patients received chemotherapy. Median survival for unmatched patients receiving surgery versus SBRT was 68.4 versus 33.3 months, respectively ($p < 0.001$) (Fig. 2A)

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