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Modeling the COVID Pandemic: Do Delays in Surgery Justify Using Stereotactic Radiation to Treat Low-Risk Early Stage Non–Small Cell Lung Cancer?

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Introduction: It was suggested that stereotactic radiation (SBRT) is an “alternative if no surgical capacity is available” for non–small cell lung cancer (NSCLC) care during the COVID-19 pandemic. The purpose of this study was to compare the oncologic outcomes of delayed surgical resection and early SBRT among operable patients with early stage lung cancer.

Methods: The National Cancer Database was queried for patients with cT1aN0M0 NSCLC who underwent surgery or SBRT (2010-2016) with no comorbidity. Patients with any comorbidities or age >80 were excluded. The outcome of interest was overall survival. Delays in surgical care were modeled using different times from diagnosis to surgery. A 1:1 propensity match was performed and survival was analyzed using multivariable Cox regression.

Results: Of 6720 healthy cT1aN0M0 NSCLC patients, 6008 (89.4%) received surgery and 712 (10.6%) received SBRT. Among surgery patients, time to surgery >30 d was associated with inferior survival (HR > 1.4, P < 0.013) compared with patients receiving surgery ≤14 d. Relative to SBRT, surgery demonstrated superior survival at all time points evaluated: 0-30 d, 31-60 d, 61-90 d, and >90 d (all P < 0.001). Among a propensity-matched cohort of 256 pairs of patients, delayed surgery (>90 d) remained association with better overall survival relative to early SBRT (5-year survival 76.9% versus 32.3%, HR = 0.266, P < 0.001).

Conclusions: Although longer time to surgery is associated with inferior survival among surgery patients, delayed surgery is superior to early SBRT. Surgical resection should
**Introduction**

In the last century, lung cancer has progressed from an uncommon and obscure disease to one of the most common cancers in the world, and the most common cause of death from cancer. It occurred in approximately 2.1 million patients in 2018 and caused an estimated 1.7 million deaths worldwide. In the United States, there are over 235,000 new cases of lung cancer and 131,000 deaths annually. Current guidelines suggest that the preferred treatment for early stage lung cancer is surgical resection.

Coronavirus disease 2019 (COVID-19) is the illness caused by the novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The COVID-19 pandemic has brought unprecedented challenges to the cancer care. To preserve health care resources and reduce the risk of exposure to SARS-CoV-2, nonurgent health care was suspended. Surgical procedures were among the most commonly reported delays during the pandemic, about 15% of all delays were surgeries. It was reported an average of 28.6 days of procedure delays was caused by COVID-19.

Deciding whether to offer, postpone, or even cancel treatments to patients has become a crucial recurrent dilemma for lung cancer specialists in the pandemic era. The European Society for Medical Oncology (ESMO) guidelines for operable non–small cell lung cancer (NSCLC) T1aN0M0 during the COVID-19 pandemic suggests that stereotactic radiation (SBRT) is an “alternative if no surgical capacity is available”. Although SBRT has been compared to surgery in high risk patients, study on comparisons among medically operable patients is limited. Therefore, the utility of SBRT in low-risk patients with lung cancer during the pandemic is not well-defined yet.

The purpose of this study was to compare the oncologic outcomes of delayed surgical resection and early SBRT among patients with early-stage lung cancer and limited comorbidities to model possible changes in resource allocation during the COVID pandemic. As the COVID-19 situation is rapidly evolving, these data may help to guide clinicians to adopt actions which could guarantee the best patients’ treatment while protecting and respecting their rights, safety, and well-being. We hypothesized that stereotactic radiation would be associated with inferior survival.

**Methods**

**Data collection and data elements**

A retrospective cohort study of the National Cancer Database (NCDB) was performed. Jointly sponsored by the American College of Surgeons and the American Society, NCDB is a clinical oncology database sourced from hospital registry data representing more than 70% of newly diagnosed cancer cases nationwide. The database covers more than 1500 Commission on Cancer (CoC)-accredited facilities. Definitions of the database variables are available from the dictionary of NCDB Participant Use Data File (http://ncdbpuf.facs.org). The CoC’s NCDB and the hospitals participating in the CoC NCDB are the source of the deidentified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

**Patient cohort and data analysis**

The NCDB was queried to analyze patients underwent surgery or SBRT from 2010 to 2016. Clinical staging data for the cohort was based on TNM classification in the American Joint Committee on Cancer (AJCC) 7th edition. Patients were excluded if they were age >80 or Charlson Comorbidity Score >0 or if they were missing critical study information (e.g., follow-up data). Patients who received SBRT due to surgery not being recommended were also excluded.

The cohort was categorized as receiving SBRT or surgery. SBRT was defined by “rad Regional rx_modality”, when treatment delivered using stereotactic radiosurgery delivered with a linear accelerator, or using a Gamma Knife machine or type not specified. The surgical cohort was defined by receiving lobectomy or sublobar resection. Delay was measured by time of definitive surgical procedure (days from diagnosis). The effect of surgical “delay” was modeled with patients’ procedures which occurred <30 d, 31-60 d, 61-90 d, and >90 d from diagnosis. Time to SBRT was measured by the number of days between the date of diagnosis and the data on which SBRT was started. The primary outcome was overall survival (OS). Overall survival was measured as the number of days from date of diagnosis to date of death or date of last follow-up.

Analysis included univariate comparison of patient factors associated with receipt of surgery (versus SBRT). To compare the two groups, Wilcoxon rank-sum test was utilized for continuous variables and chi-square for categorical data. Difference in OS between the groups was analyzed using Kaplan–Meier survival estimates and compared through log-rank test. To control for confounding effects, cox proportional hazard analysis was also performed. To further account for differences between patient cohorts receiving delayed surgical treatment (<90 d) versus early SBRT treatment (≤90 d), a 1:1 propensity match with replacement was performed, correcting for age, gender, race, private insurance and academic facility. The propensity match dropped observations of patients underwent surgical treatment (>90 d delay) whose propensity score as higher than the maximum or less than the minimum score of the controls (early SBRT treatment). Nearest neighbor matching with replacement was used, with the caliper set to 0.01. Standardized differences before and after matching were reported and graphed during the analysis of propensity matching. Differences in survival among the remain the standard of care to treat operable early stage lung cancer despite delays imposed by the COVID-19 pandemic.
matched pairs were analyzed using a stratified log-rank test and Cox proportional hazard regression analysis using a clustered “sandwich” robust variance estimator to account for clustering within the matched pairs.

All statistical analysis was performed using STATA/MP, version 16.0 (Stata Corp LLC, College Station, TX). Institutional Review Board (IRB) approval was exempted by the University Hospitals Cleveland Medical Center IRB as all data is deidentified.

Results

The final analytic cohort included 6720 patients with a primary diagnosis of T1aN0M0 NSCLC (Table 1). 6008 (89.4%) underwent surgery, and 712 (10.6%) were treated with SBRT. SBRT patients were more likely to be male (41.7% versus 36.9%, \( P = 0.001 \)), have nonprivate insurance (82.6% versus 61.9%, \( P < 0.001 \)), and be older (median age 71 versus 66, \( P < 0.001 \)). There was no difference in race distribution or facility type. Among surgery patients, 7.3% (423/5810) also received chemotherapy (all chemotherapy) and 89.6% (5071/5660) had lymph nodes sampled at the time of surgery. The median time to receipt of SBRT was 61 d and the median time to surgery was 25 d.

Among the surgery patients, the effect of surgical “delay” was modeled using cox proportional hazard analysis by comparing procedures which occurred 0-14 d, 15-30 d, 31-60 d, 61-90 d, and >90 d from diagnosis and is shown in Table 2. Relative to surgery performed within 14 d of diagnosis, delays in receipt of surgery was associated with inferior survival at 31-60 d (hazard ratio [HR] = 1.4, \( P < 0.001 \)), 61-90 d (HR = 1.419, \( P = 0.013 \)), and >90 d (HR = 1.534, \( P = 0.005 \)).

We next compared patients receiving SBRT to the different surgery time points. Using the Kaplan–Meier estimate, overall survival was superior if surgery occurred at all time points evaluated \( (P < 0.001, \text{Fig. 1}) \). Multivariate Cox regression also showed that surgery was associated with prolonged survival regardless of the extent of delay (surgery 0-30 d, HR = 0.352, \( P < 0.001 \); surgery 31-60 d, HR = 0.439, \( P < 0.001 \); surgery 61-90 d, HR = 0.463, \( P < 0.001 \); surgery >90 d, HR = 0.468, \( P < 0.001 \). Table 3). Further, to analyze the possible effect of different surgery type, both sublobar resection (HR = 0.507, \( P < 0.001 \)) and lobectomy (HR = 0.355, \( P < 0.001 \)) provided superior survival benefit over SBRT (supplemental Table 1).

Table 1 – Differences in patient characteristics of T1aN0M0 NSCLC treated with SBRT versus surgery.*

| Characteristics                  | SBRT (n = 6008) | Surgery (n = 712) | P-value |
|----------------------------------|-----------------|------------------|---------|
| Median time of receipt treatment (days) | 61 (53-80) | 25 (31-80) | <0.001  |
| Age (years)                      | 71 (53-80) | 66 (53-80) | 0.011   |
| Male (versus female)             | 297 (41.7%) | 2214 (36.9%) | 0.589   |
| Caucasian                        | 603 (84.7%) | 5041 (83.9%) | 0.328   |
| Private insurance                | 124 (17.4%) | 2289 (38.1%) | <0.001  |
| Academic program                 | 329 (46.2%) | 2623 (45.0%) | 0.528   |
| Chemotherapy                     | 11 (1.6%)   | 423 (7.3%)   | <0.001  |
| Immunotherapy                    | 1 (0.1%)    | 4 (0.07%)    | 0.496   |

Lymph nodes removed

|                 | SBRT (n = 712) | Surgery (n = 712) | P-value |
|-----------------|----------------|------------------|---------|
| None            | 675 (100%)     | 589 (10.4%)      | <0.001  |
| <10             | 0 (0%)         | 3088 (54.6%)     |         |
| ≥10             | 0 (0%)         | 1983 (35.0%)     |         |
| Total           | 675            | 5660             |         |

* Data presented as median (IQR) or n (%). Comparison of continuous variables using Wilcoxon Rank-Sum Test and comparison of categorical variables using Pearson chi-square test.

Table 2 – Cox proportional hazard regression for overall survival of surgery patients with different level of delays \( (N = 5976) \).

| Time from diagnosis to definitive surgery (days) | Hazard ratio | 95% conf. int. | P-value |
|------------------------------------------------|--------------|----------------|---------|
| 0-14 (40.0%) | Reference    | 1.000          | 1.000          | 1.000   |
| 15-30 (17.2%) | 1.144 | 0.910 | 1.438 | 0.249 |
| 31-60 (26.8%) | 1.408 | 1.162 | 1.706 | <0.001 |
| 61-90 (9.0%) | 1.419 | 1.076 | 1.871 | 0.013 |
| ≥91 (6.9%)   | 1.534 | 1.136 | 2.073 | 0.005 |
To further compare patients who received delayed surgery (>90 d) to early SBRT (≤90 d) we performed a propensity matched analysis. This generated 256 “paired” patients with similar characteristics in the delayed surgery and early SBRT group. Propensity matching effectively reduced bias between the groups (supplemental Fig. 1, supplemental Table 2). In the matched cohort, delayed surgery (>90 d) continued to be associated with superior overall survival (median follow up time 38 mo delayed surgery versus 28 mo early SBRT, 3-year survival 86.0% delayed surgery versus 69.8% early SBRT, 5-year survival 76.0% delayed surgery versus 57.6% early SBRT, P < 0.001, Fig. 2). A Cox-proportional hazard analysis among the matched cohort, confirmed that delayed surgery (>90 d) was associated with better overall survival than early SBRT (HR = 0.355, P < 0.001. Table 4).

Discussion

Ideally patients with lung cancer would receive expedited treatment. Unfortunately, delays in treatment can occur. The COVID pandemic introduced one of these delays, leading some to suggest that SBRT should be performed if surgery was unavailable. Our study demonstrated that relative to SBRT, surgical resection is associated with superior survival among patients less than 80 y old without significant comorbidity in Clinical T1aN0M0 NSCLC.

Delayed receipt of appropriate treatment has been associated with decreased overall survival in international studies if patients presented with symptoms suggestive of advanced lung cancer. [13] Among surgery patients, delayed resection of clinical stage-I NSCLC was shown to be independently associated with increased rates of upstaging and decreased median survival. [14] Patients receiving delayed resection for early-stage NSCLC have higher comorbidity scores that may affect ability to perform the surgical procedure and result in higher perioperative mortality; thus, strategies to minimize delay while medically optimizing higher risk patients are needed. [14]

This study also showed the harm of surgical delay among stage I lung cancer patients with delays >30 d associated with inferior survival. However, the detrimental effect of surgical delay has not previously been compared to other treatments. In this study, we modeled this comparison of SBRT to surgery to model possible treatment decisions during the COVID-19 pandemic. In this analysis delayed surgery (>90 d) is associated with superior survival relative to SBRT among healthy patients. These finding contradict ESMO guidelines and suggest that surgery should remain the preferred treatment even when availability is delayed more than 90 d. Even when surgical resources are diverted during the pandemic, we believe that most patients can safely wait for the surgery to “reopen” rather than receiving inferior SBRT, medical optimizing treatment may provide to these patients during the waiting period if necessary.

There are several studies which support SBRT in patients with early stage lung cancer. Timmerman et al. reported that patients with early stage but inoperable NSCLC had a survival rate of 55.8% at 3 y, high rates of local tumor control and moderate treatment-related morbidity. [15] Compared with conventional radiation therapy or radiofrequency ablation or best supportive care, SBRT has been shown to be able to improve overall survival for nonoperable patients in
both large retrospective analyses and prospective clinical trials. However, in medical-operable patients, due to lack of level A evidence, SBRT only appears as a viable treatment option in the situation when lobectomy is refused by the patients. Patients or providers may prefer SBRT: noninvasive, outpatient-basis, and short overall treatment time of 1-2 wk; these are all attractive factors of SBRT. Surgical risk is significant and may influence the decision to pursue SBRT which is often seen as having less “upfront” risk. In this analysis of the NCDB, there are limited data regarding why these young and reportedly healthy patients underwent SBRT. The database suggests that surgery was not performed because surgery was “not part of the planned first course treatment” in the majority of 67.9% patients, followed by contradictions due to patients’ risk factors (25.8%) and 6.0% of noncompliance to the physician’s recommendations on surgery (data not shown).

Despite using a large sample size, our study has numerous limitations. The NCDB does not provide granular data on why a certain type of treatment was selected (i.e., surgeon preference, hospital resources, patient factors such as pulmonary function test etc.) which therefore cannot be factored into analyses. There may be conditions or situations (such as previous lung resection) which would favor SBRT, although patients with comorbidities were excluded from the analytic cohort. SBRT patients were not truly “healthy”. There were significant differences in median age and private insurance which could suggest unobserved differences in factors contributing to need or option for SBRT, these conditions will all confound analysis of long-term survival. In this setting, we continue to believe that surgical resection should be preferred as the decreased survival associated with surgical delay is quite modest (compared with surgery performed on day 0-14, surgery 31-60 d, HR = 1.408, \( P < 0.001 \); surgery 61-90 d, HR = 1.419, \( P = 0.013 \); surgery >91 d, HR = 1.534, \( P = 0.005 \)), and are still superior to SBRT (compared with SBRT, delayed surgery HR > 0.352, \( P < 0.001 \)). Finally, the NCDB only received data from Commission on Cancer-accredited hospitals, so these findings may not be applicable to other centers in the United States, where the relative benefit of surgery may vary.

Table 3 – Cox proportional hazard regression for overall survival of clinical T1aN0M0 NSCLC patients treated with SBRT or surgery at different time points (\( N = 4359 \)).

| Cofactor                                | Hazard ratio \(^{a}\) | 95% conf. int. | \( P \)-value |
|-----------------------------------------|-----------------------|----------------|---------------|
| Age                                     | 1.025                 | 1.014          | 1.036         | <0.001        |
| Male                                    | 1.395                 | 1.196          | 1.628         | <0.001        |
| Caucasian                               | 1.375                 | 1.079          | 1.752         | 0.010         |
| Private insurance                       | 0.851                 | 0.699          | 1.036         | 0.107         |
| Academic facility                       | 0.748                 | 0.637          | 0.878         | <0.001        |
| Tumor size                              | 1.000                 | 0.996          | 1.003         | 0.925         |
| Grade                                   |                       |                |               |
| Well-differentiated                     |                       |                |               |
| Moderately differentiated               | 2.274                 | 1.795          | 2.882         | <0.001        |
| Poorly differentiated                   | 2.777                 | 2.143          | 3.599         | <0.001        |
| Undifferentiated                        | 2.656                 | 1.228          | 5.743         | 0.013         |
| Laterality (left versus right)          | 1.076                 | 0.919          | 1.260         | 0.361         |
| Histology                               |                       |                |               |
| Adenocarcinoma                          |                       |                |               |
| Squamous carcinoma                      | 1.277                 | 1.064          | 1.534         | 0.009         |
| Non–small cell lung cancer              | 1.642                 | 1.110          | 2.430         | 0.013         |
| NOS                                      | 1.139                 | 0.850          | 1.527         | 0.383         |
| Location                                |                       |                |               |
| Upper lobe                              |                       |                |               |
| Middle lobe                             | 1.301                 | 0.950          | 1.781         | 0.1           |
| Lower lobe                              | 1.053                 | 0.887          | 1.250         | 0.554         |
| Overlapping lesions                     | 3.937                 | 1.255          | 12.345        | 0.019         |
| NOS                                      | 1.388                 | 0.778          | 2.479         | 0.267         |
| SBRT versus surgery                     |                       |                |               |
| SBRT                                    | Reference             |                |               |
| Surgery (0-30 d)                         | 0.352                 | 0.275          | 0.452         | <0.001        |
| Surgery (31-60 d)                        | 0.439                 | 0.336          | 0.572         | <0.001        |
| Surgery (61-90 d)                        | 0.463                 | 0.331          | 0.649         | <0.001        |
| Surgery (>90 d)                          | 0.468                 | 0.322          | 0.680         | <0.001        |

\(^{a}\) adjusted Hazard Ratio.
Fig. 2 — Overall survival of clinical T1aN0M0 NSCLC patients in the propensity matched cohort of delayed surgery (> 90 d) and early SBRT (< 90 d). The overall survival was superior for patients underwent delayed surgery versus early SBRT (< 90 d) (P < 0.001): 3-year survival (86.0 % delayed surgery versus 69.8% early SBRT) and 5-year survival (76.0% delayed surgery versus 57.6% early SBRT).

Table 4 — Cox proportional hazard regression for overall survival among a propensity matched cohort of patients with Clinical T1aN0M0 NSCLC (N = 512).

| Cofactor                                      | Hazard ratio | 95% conf. int. | P-value |
|-----------------------------------------------|--------------|----------------|---------|
| Delayed surgery (>90 d) versus early SBRT (<90 d) | 0.355        | 0.233 0.540 | 0.000   |
| Age                                           | 1.010        | 0.984 1.036 | 0.454   |
| Male                                          | 1.013        | 0.699 1.469 | 0.944   |
| Caucasian                                     | 2.245        | 1.328 3.795 | 0.003   |
| Private insurance                             | 1.333        | 0.825 2.154 | 0.240   |
| Academic facility                             | 1.035        | 0.685 1.563 | 0.871   |
| Tumor size                                     | 1.055        | 1.022 1.088 | 0.001   |
| Grade                                         |              |               |         |
| Well-differentiated                           | Reference    |               |         |
| Moderately differentiated                     | 1.978        | 1.228 3.185 | 0.005   |
| Poorly differentiated                         | 1.684        | 0.900 3.150 | 0.103   |
| Undifferentiated                              | 1.011        | 0.092 11.136| 0.993   |
| Laterality (left versus right)                | 1.900        | 1.246 2.899 | 0.003   |
| Histology                                     |              |               |         |
| Adenocarcinoma                                | Reference    |               |         |
| Squamous carcinoma                            | 1.297        | 0.834 2.015 | 0.248   |
| Non–small cell lung cancer                    | 2.083        | 0.463 9.375 | 0.339   |
| NOS                                           | 1.712        | 0.805 3.644 | 0.163   |
| Location                                      |              |               |         |
| Upper lobe                                    | Reference    |               |         |
| Middle lobe                                   | 1.821        | 0.803 4.131 | 0.152   |
| Lower lobe                                    | 0.625        | 0.407 0.961 | 0.032   |
| NOS                                           | 1.850        | 0.398 8.587 | 0.432   |
Despite these limitations, these data suggest that surgical resection should remain the standard of care to treat early stage lung cancer in medically operable patients despite delays imposed by the COVID-19 pandemic.

Conclusions

Despite the delays imposed by the COVID-19 pandemic, surgical resection should remain the standard of care to treat operable early stage lung cancer. SBRT could be an alternative only if surgical capacity is not available and inferior overall survival of SBRT is clearly communicated with the patients. Surgery is preferred.

Supplementary Materials

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jss.2022.10.081.

Author Contributions

Cao, L. and Towe C.W. contributed to the conception or design of the work; Cao, L. and Towe, C.W. contributed to the acquisition, analysis and interpretation of data for the work; Cao, L. Drafted the work; Cao, L., Linden P.A., Biswas T., Worrell S.G., Sinopoli, J.N., Miller, M.E., Shenk, R, Montero, A.J. and Towe, C.W. revised it critically for important intellectual content; Cao, L., Linden P.A., Biswas T., Worrell S.G., Sinopoli, J.N., Miller, M.E., Shenk, R, Montero, A.J. and Towe, C.W. approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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