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Archives of Cancer Biology and Therapy Commentary

Surgery Versus Radiation Therapy for Early-Stage Lung Cancer: Patient Selection is Crucial

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Lung cancer remains the leading cause of cancer related death in the United States with mortality rates surpassing breast, prostate, brain, and colorectal cancers combined [1,2]. Recent data shows that susceptibility for both men and women for developing invasive lung and bronchogenic carcinoma peak after the age of 70 years [2]. As the generation of baby boomers age, those older than 65 years will nearly double and the number of elderly population older than 85 years will triple from 2020 to 2050 [3]. These shifting demographics are an early sign of the improvements and advancements in overall care of the elderly population. It therefore remains imperative that lung cancer treatment and selection criteria evolves accordingly in elderly and high-risk population. Some of the challenges facing the elderly and high-risk population relates to comorbidities, limited cardiac and pulmonary function reserve, decreased decision-making capacity, quality of life issues and lack of social support among others [4,5].

Currently, the standard of care for early-stage non-small cell lung cancer (NSCLC) includes an anatomic pulmonary resection with sampling or dissection of mediastinal and hilar lymph nodes amongst appropriate surgical candidates [6]. However, the use of Stereotactic Body Radiotherapy (SBRT), or Stereotactic Ablative Radiotherapy (SAbR), has been increasing over time and has surpassed lobectomy for treatment of Stage I NSCLC in octogenarians [7]. At the same time, researchers in the Netherlands saw a dramatic increase in SBRT in just 9 years from 26% to 42% of patients 75 years or older receiving SBRT for Stage 1 NSCLC [8].

SBRT greatly impacted the capability of offering definitive ablative treatment for early-stage NSCLC in high-risk patients [9]. With its arrival, patients who refused surgery or were medically inoperable with early-stage NSCLC were given a definitive alternate treatment therapy that had a low toxicity profile and could be conducted in a relatively short amount of time [10]. Given the success of SBRT in early-stage lung cancer amongst populations unfit for surgery, its utility in high-risk populations has been investigated in various trials, but early studies struggled to enroll patients [10].

In a meta-analysis by Cao et al., when compared to SBRT in patients with early-stage NSCLC, both lobectomy and sublobar resection were associated with better overall survival (OR 1.71 95% CI: 1.52-1.93 $p<0.001$) [11]. Importantly, periprocedural mortality was 0% in SBRT and as high as 8% in those undergoing surgery [11]. It is important to note that those receiving SBRT disproportionately comprised of patients who were not good surgical candidates or refused surgery, so conclusions regarding differences between lobectomy vs SBRT amongst true surgical candidates cannot be made from this analysis [11]. Of note, patients undergoing surgery frequently reported more severe postoperative morbidities including pneumonia, pulmonary embolism, or myocardial infraction compared to less severe complications such as fatigue and chest pain seen in SBRT patients [11]. Surgery carries a perioperative risk for patients, both in mortality and in major morbidity, that was and is still not seen in SBRT. When compared to the perioperative risks associated with surgery, the relative low toxicity profile and overall better tolerance of SBRT makes this an attractive option for elderly and high-risk populations.

Gulack et al. set out to establish an objective risk

classification to aid in determining the appropriate selection of operative technique for resection of early-stage NSCLC [12]. Using the American College of Surgeons National Surgical Quality Improvement Program database, the authors determined that a risk score >5 conferred a statistically higher perioperative mortality rate in patients receiving lobectomy (4.9%) vs segmentectomy (3.6%) or wedge resection (0.8%, p<0.01) [12]. Among patient characteristics used for the calculation of the risk score, patients >80 years of age and patients 65-80 years of age automatically received scores of 5 and 3 respectively [12]. Additionally, dependent functional status was also weighed at a 3 and favored mortality only second to age >80 years [12]. This is critical in understanding the necessity in choosing appropriate surgical candidates, since age alone did not confer an increase in perioperative mortality. For all patients >80 years of age, just one more risk characteristic, such as COPD or smoking within the last year, pushes them over the threshold that raises their perioperative mortality. Additionally, a 65-year-old patient with a dependent functional status would also surpass the threshold leaving patients at an increased risk of perioperative mortality after lobectomy. Further assessments of the Society of Thoracic Surgeons General Thoracic Surgery Database determined Zubrod score, and American Society of Anesthesiologists score to consistently confer the highest likelihoods of major morbidity or mortality after lung cancer resection [13].

In early 2016, four prospective randomized trials were reported to compare outcomes in operable stage I NSCLC undergoing SBRT vs surgical resection (Table 1) [10]. Of those, a trial in the United Kingdom, SABRTooth, was abandoned after a feasibility study showed difficulty recruiting patients into the surgery group [14]. VALOR, the Veterans Affairs Lung cancer surgery or stereotactic Radiotherapy, was the next referenced listed and is currently in the recruitment phase and most recent updates predict a completion date of September 2027 [15]. The POSTLIV trial is currently active, however it is no longer recruiting patients and lists a total of 44 patients enrolled with a completion date estimated at the beginning of 2026 [16]. Lastly, most recent updates posted for STABLE-MATES poses a glimmer of hope with patient recruitment still occurring and an enrollment of 272 patients so far [17]. The ROSEL and STAR trials would go on to combine their study populations for a total of 58 patients. With the authors themselves citing insufficient follow-up and small sample size, this analysis offers the only literature depicting favorable outcomes of SBRT vs surgery in randomized patients deemed surgical candidates with Stage I NSCLC [18]. Overall, 3-year survival was 95% (95% CI 85-100) in the SAbR group and 79% (95% CI 64-97%) in the surgery group proving to be statistically significant (log-rank p=0.037, HR 0.14 95% CI 0.017-1.190) [18].

So where have we arrived? There is evidence showing that surgery is inherently risky, and that risk only increases with age and those with poor functional status [11-13,19,20]. Yet, four recent meta-analysis have shown surgical resection for early-stage NSCLC to have superior overall survival than SBRT [11,21-23]. The superior merit of surgery lies in the capability of establishing true pathological staging by virtue of adequate lymph node

Study (Clinical Trial Number)	Status	Treatment Arms	Description
STARS (NCT00840749)	Closed	CyberKnife vs Lobectomy	Abandoned after poor recruitment
ROSEL (NCT00687986)	Closed	SBRT vs Lobectomy	Abandoned after poor recruitment
ACOSOG Z4099/RTOG 1021 (NCT01336894)	Closed	SAbR vs Sublobar Resection	Abandoned after poor recruitment
SABRTooth (NCT02629458)	Closed	SAbR vs Surgery	Abandoned after a feasibility study showed large proportions of those randomized to the surgery arm refused and chose SABR
VALOR (NCT02984761)	Open	SBRT vs Surgery	Randomized trial with the primary aim of measuring overall survival up to 10 years. Estimated recruitment is to include 670 participants with an estimated completion by September 2027
POSTLIV (NCT01753414)	Open	SBRT vs Surgery	Small phase II trial aimed at measuring efficacy of local-regional control of T1N0 NSCLC
STABLE-MATES (NCT02468024)	Open	SAbR vs Sublobar Resection	Randomized trial comparing overall survival in high-risk operable Stage I NSCLC after treatment with either SAbR or Sublobar Resection

Table 1: Ongoing and previous randomized trials comparing SBRT and surgical resection.

dissection and negative margins. Consequently, accurate tumor staging affords patients the opportunity for systemic treatment when unsuspected micrometastatic disease is found in the lymph nodes. Additional factors that may continue to improve postoperative outcomes and overall survival after lung cancer surgery includes, but not limiting to, appropriate patient selection after risk stratification, adaptation of minimally invasive techniques, high volume centers and centers of excellence and Enhanced Recovery After Surgery (ERAS) protocols [24-27].

Other trials have come into the fold, providing a glimpse of innovative ways to enhance the potential effectiveness of SBRT. RAXSIA is currently underway in Canada with the primary aim to compare disease free 5-year survival between SBRT and surgery in patients with T1a or T1b NSCLC [28]. Over the last few years, innovations in immunotherapies have shown promise within the realm of cancer therapy. Recently, trials have been developed to combine immunotherapies such as atezolizumab and durvalumab with SBRT for NSCLC [29,30]. If these treatment combinations are proven effective, we could see expansion of these trials to include patients with early-stage NSCLC that might otherwise undergo surgical resection.

In conclusion, surgery remains the standard of care for early-stage lung cancer while SBRT provides a viable treatment alternative for patients who are not suitable candidates for surgery. It therefore remains imperative that thoracic surgeons carefully evaluate and select patients with potentially curable lung cancer, especially when alternate treatment options such as SBRT are being considered.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Author Contribution

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