



Application of quality metrics to wedge resection for early stage non-small cell lung cancer demonstrates differences in overall survival

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In their recent publication entitled “Surgical quality of wedge resection affects overall survival in patients with early stage non-small cell lung cancer,” Ajmani and colleagues applied established quality metrics to pulmonary wedge resection to examine trends in long-term overall survival and pathologic upstaging for patients with cT1 N0M0 and cT2N0M0 tumors (1). Specifically, they utilized the National Cancer Database (NCDB) to stratify patients who received a wedge resection according to the number of lymph nodes sampled and surgical margin status. Wedge resections were categorized into “high quality” (negative margins with >5 lymph nodes sampled), “average quality” (negative margins with ≤5 nodes sampled), and “low quality” (positive surgical margins) cohorts. In their analysis, they determined that wedge resections of differing quality had significantly different overall survival—patients who received a high quality wedge had 45% decreased risk of mortality compared to their low quality wedge counterparts.

The consideration of applying quality metrics to a pulmonary wedge resection for early stage non-small cell lung cancer (NSCLC) is novel and timely. The 1995 randomized controlled trial published by the Lung Cancer Study Group (LCSG) represents the only published level I evidence to date comparing lobectomy with sublobar resection (including wedge resection) (2). In that landmark trial, the study investigators compared 5-year overall survival and disease recurrence in patients with clinical T1 N0 tumors undergoing either lobectomy or limited resection. Patients who underwent lobectomy or sublobar resection had similar long-term survival, but patients

who had a sublobar resection had three times the risk for locoregional recurrence. Given this difference, lobectomy was deemed to be the “gold standard” of care for stage I NSCLC. However, it is important to remember that patients who underwent sublobar resection (and lobectomy) in this randomized controlled trial were compared under somewhat artificial conditions required by the study protocol. All patients were required to undergo systematic mediastinal lymph node sampling of each nodal station, have 2 cm margins, and have intraoperative frozen pathology performed to ensure negative margins—factors that are neither guaranteed nor commonly observed in real world practice.

The LCSG trial was more than 20 years ago and a lot has changed with screening, staging and surgical outcomes. More recently, in a large observational analysis of an enhanced dataset from the NCDB, we compared 5-year overall survival and locoregional recurrence in NSCLC patients undergoing lobectomy and sublobar resection as it occurs in clinical practice (3). Using these broadly generalizable data, we observed alarming trends. The median number of lymph nodes sampled in patients undergoing lobectomy was 7 nodes compared to only 1 node for patients undergoing sublobar resection. Additionally, the fraction of cases with positive pathologic margins was significantly higher in patients undergoing sublobar resection (6.8% *vs.* 2.5%, $P=0.013$). Long-term survival was similar between lobectomy and sublobar resection cohorts. However, similar to the LCSG trial, we observed a 40% increase in 5-year locoregional recurrence

in patients treated with sublobar resection.

These background data make the study by Ajmani and colleagues a timely and important contribution. Wedge resection, despite its potentially inferior oncologic quality, is occurring on a large scale in actual practice. Utilization of sublobar resection in any form is increasing. In a study of trends in the diagnosis and management of stage I NSCLC, McMurry and colleagues found that utilization of lobectomy among lung resections decreased from 2008 to 2012, while the use of sublobar resection grew significantly (11.8% to 17.4%) (4). However, a consequence of this shift to lesser resections is that numbers of lymph nodes sampled and rates of pathologic upstaging with sublobar resection remained disappointingly low.

Given the increased utilization of wedge resection, it is important for surgeons to understand the impact of quality measures on patient survival. The existence of an association of between quality measures and survival in anatomic resection has previously been demonstrated. In an analysis of 133,366 patients with clinical stage I NSCLC, Samson and colleagues utilized the NCDB to measure adherence to quality measures endorsed by organizations including the National Comprehensive Cancer Network, the American College of Surgeons Commission on Cancer, and the American College of Chest Physicians (5). These quality measures included sampling of 10 or more lymph nodes, achievement of an R0 resection, performing an anatomic resection, and providing a timely operation (within 8 weeks of diagnosis). Samson found that increasing adherence to quality measures was associated with reductions in hazard of death. Compared to patients who had no quality measures met, patients who met one quality measure had a 30% decreased risk while patients who met four quality measures had a 61% decreased risk. The findings presented by Ajmani exhibited parallel trends: adherence to quality measures in wedge resection is associated with improved survival (1). Compared to patients who received an “average quality” wedge resection, those with a “high quality” wedge had a 25% reduced hazard of mortality (HR: 0.75, 95% CI: 0.68–0.82). Compared to “low quality” wedge resections, patients in the “high quality” group faced a hazard of mortality of less than half (HR: 0.45, 95% CI: 0.39–0.52) after adjusting for other acknowledged covariates.

What does this finding mean for the thoracic surgical community? Surgeons choosing to omit anatomic resection in favor of a wedge resection are still duty-bound to adhere to quality measures. If a quality procedure isn't accomplished, patients who receive a low quality wedge

resection may already have multiple strikes against them, even before leaving the operating room. As demonstrated by Ajmani and colleagues, adherence to quality metrics in wedge resection is regrettably low. Of all wedge patients, only 17% were observed to have >5 nodes sampled, and only 16.7% of patient were assigned to the high quality wedge group (1). This low nodal sampling raises the question of how many patients who would have been pathologically upstaged had the targeted number of lymph nodes been resected. The authors did note that N1 upstaging rate increased from 1.6% for patients with 1 to 5 nodes examined, to 4.2% for patients >10 nodes collected. Clearly, there remains ample room for improvement.

Ajmani and colleagues provided an additional analysis of factors associated with the likelihood of receiving high quality wedge resections, an endeavor which could shed light into underlying trends in disparities of care (1). They identified several patient-related factors including age, comorbidity burden, tumor location, and hospital type (academic *vs.* non-academic) as factors associated with likelihood of receiving a high-quality wedge. However, there may be important features related to the individual surgeon effort and the process of harvesting and examining lymph nodes that may be at play. We need a better understanding of how surgeon-specific factors (including specialty, case volume, and propensity to perform anatomic or wedge resections) affect adherence to quality measures. Further study may unmask additional factors that influence the collection of lymph nodes beyond traditional patient and hospital factors captured in existing databases. This task will likely require multicenter prospective study to effectively capture detailed and pertinent information to trigger much needed quality improvement.

Another interesting aim of Ajmani's study introduced a propensity-matched comparison between stereotactic body radiation therapy (SBRT) and wedge resections. The authors compared SBRT to wedge resection, and stratified by the quality of wedge resection. This analysis is crucial, because it is clear that the utilization of SBRT has risen substantially. In a published analysis of trends in surgical treatment using the NCDB, McMurry and colleagues showed that the use of SBRT for patients with clinical stage I NSCLC rose from 0% in 1998 to 6.6% in 2012, a shift that was accompanied by a decrease in lobectomy from 55% to 49.5% over the same time period (4). Given the rapid improvements in technology and the increasing experience with SBRT, this estimate of the preference shift toward SBRT six years ago is likely to be an underestimate

of the facts today. SBRT represents a real and beneficial alternative for many patients deemed to be high-risk surgical candidates. However, the answer to important question of “should this patient undergo a wedge resection or SBRT,” has remained elusive.

Many voices in the lung cancer community have touted randomized controlled trials comparing SBRT to sublobar resection as the ultimate source of high quality evidence that will steer patients and providers towards one therapy or the other. However, many of these trials (including ACOSOG 4099/RTOG1021, ROSEL, and STARS) suffered poor patient recruitment and early closure (6). To fill the void, an unplanned pooled analysis of 58 patients collected from the terminated ROSEL and STARS trials was published (6). The authors of the pooled analysis concluded that SBRT was a viable option for many patients based on patchwork data from two failed trials. However, there were several limitations associated with this strategy. First, the compared cohorts were small and unbalanced leading to possible instability of results (7,8). Additionally, there were extremely few deaths (events) over a short and variable period of patient follow-up (7,8). Significant caution is warranted about accepting any conclusions from such a study, given the extremely small sample size and risk of type I error.

There are current randomized trials that aim to compare wedge resection and SBRT and show greater promise of fulfilling recruitment goals. The STABLE-MATES trial, which compares sublobar resection and SBRT in high risk, stage I NSCLC patients is currently underway. The SABRTooth trial, which compares SBRT with surgical resection in high-risk stage I NSCLC patients with peripheral tumors, has completed study recruitment. “High-risk” has been surprisingly difficult to define in RCT enrollment criteria in a way that is meaningful and accurate (8). Puri and colleagues examined post-resection outcomes for clinical stage IA patients labeled “high-risk” by American College of Surgeons Oncology Group (ACOSOG) trial criteria (which includes pulmonary function tests, age, and cardiopulmonary function) (9). On examination of 1,066 patients who underwent lung resection in routine clinical practice, they found that 194 patients (18%) met “high-risk” criteria that had been previously defined for enrollment in multiple ACOSOG clinical trials. Compared to normal-risk patients, these “high-risk” patients were older but otherwise had no substantial difference in the prevalence of comorbidities including hypertension, coronary artery disease, and diabetes. Despite

being labeled “high-risk”, roughly 60% of these patients underwent an anatomic resection (lobectomy). Thus, it is possible that patients enrolled in trials by similar risk-defining criteria may not be “sick-enough” to really reflect the population of interest where the question of wedge resection *vs.* SBRT is concerned. Patients labeled “high-risk” by traditional enrollment criteria and subsequently randomized to surgery may actually have lower preoperative-risk than expected, and could potentially lead to surgery demonstrating artificially superior outcomes. Despite the fact that of the label “high risk” is widely used as a part of inclusion-exclusion criteria of many relevant trials, it is likely not a consistent or homogeneous description and may not be representative of true surgical risk from the clinician perspective.

Ajmani and colleagues utilized robust and broadly generalizable data to address an important area of inquiry where previous randomized trials have failed. Their study represents a thought-provoking approach to studying the important question of wedge resection *vs.* SBRT. They documented important trends in demographics and baseline clinical characteristics of patients receiving each therapy. For example, the authors noted that prior to propensity-score matching, patients receiving SBRT were older and less likely to have private insurance, but interestingly had significantly reduced comorbidity burden (1). With propensity-score matching, they were able to create comparable study cohorts. Using these cohorts, they found that wedge resection overall was significantly associated with decreased risk-adjusted hazard of death compared to SBRT (HR: 0.66; 95% CI: 0.61–0.71). On further analysis, they noted a greater survival benefit for wedge resection patients who had more lymph nodes collected with an R0 resection (>5 nodes and negative margin: HR: 0.50, 95% CI: 0.43–0.58; ≤5 nodes and negative margin: HR: 0.65; 95% CI: 0.60–0.70) compared to SBRT. However, wedge resection patients with positive margins had similar survival to patients receiving SBRT.

There are limitations to their analysis that should be noted, mainly with respect to the limitations imposed by the dataset. For example, the NCDB does not collect data on pulmonary function, individual comorbidities, or functional status—factors that likely contribute to treatment assignment. Not knowing these patient attributes makes it impossible to adjust for them. A more detailed, prospective registry could better capture patient and tumor characteristics that are likely to influence treatment assignment. However, one true advantage of the findings

published by Ajmani is high external validity. The NCDB captures 70% of incident lung cancers in the United States, making the results broadly representative of community practice (10). Like the 1995 LCSG trial, any RCT published on wedge *vs.* SBRT will likely artificially inflate adherence to quality measures of R0 resection and adequate lymph node sampling because of the surgical requirements of the study protocol. However, as Ajmani and colleagues observed, adherence to quality in routine clinical practice is low—only 17% of patients in their study had a high quality wedge. Thus, when results from ongoing randomized trials are published, how do we interpret the conclusions when the care provided in trials may be representative of fewer than 20% of wedge resections in the United States? Additionally, Ajmani provided a thorough analysis of the impact of adherence to quality measures in wedge resection on survival compared to SBRT. However, how do we characterize the quality of SBRT delivered? Development and widespread use of quality metrics for SBRT could provide an interesting and more nuanced comparison between limited resection and SBRT.

Ajmani's findings have several important lessons for surgeons who engage in wedge resection for NSCLC. First, adherence to quality measures is not a trivial matter—there are real survival advantages at stake. There are certainly times when wedge resection might be clinically indicated, and the utilization of sublobar resection is on the rise. Thus, it is imperative that surgeons think carefully about whether or not they can carry out these important quality metrics prior to offering a wedge resection to patients. A higher number of sampled lymph nodes was associated with improved overall survival, possibly due to greater upstaging of disease and providing the patient an opportunity to receive adjuvant therapy. Additionally, patients who did not have an R0 resection had similar survival to patients receiving SBRT. Thus, surgeons are not doing their patients any favors by performing a low quality wedge resection, since a less invasive and risky alternative (SBRT) is likely to produce similar results. While surgical resection may be better than non-surgical alternatives in many cases, it seems clear that “no surgery” may be as good or better than low quality surgery.

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Footnote

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