

# Nodal Upstaging During Lung Cancer Resection Is Associated With Surgical Approach

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**Background.** Recent reports indicate that thoracoscopic lobectomy for lung cancer may be associated with lower rates of surgical upstaging. We queried a statewide cancer registry for differences in upstaging rates and survival by surgical approach.

**Methods.** The Kentucky Cancer Registry (KCR) collects data, including centralized pathology reporting, on cancer patients treated statewide. We performed a retrospective review from 2010 to 2012 to examine clinical and pathologic stage. We assessed rates of upstaging and whether the surgical approach, thoracotomy (THOR) versus minimally invasive techniques (video-assisted thoracic surgery; VATS), had an impact on final pathologic stage and survival.

**Results.** The KCR database from 2010 to 2012 contained information on 2830 lung cancer cases, 1964 having THOR procedure and 500 having VATS resections. Preoperatively, 36.4% of THOR were clinically stage 1a versus 47.4% VATS ( $p = 0.0002$ ). Of these, final

pathologic stage remained stage 1a in 30.5% of THOR procedures and 38.0% of VATS ( $p = 0.0002$ ). The overall nodal upstaging rate for THOR was 9.9% and 4.8% for VATS ( $p = 0.002$ ). Decreased nodal upstaging was found with VATS, independent of tumor size and extent of resection (odds ratio 0.6, 95% confidence interval [CI]: 0.387 to 0.985,  $p = 0.04$ ). However, improved survival was found with VATS compared with THOR (hazard ratio 0.733, 95% CI: 0.592 to 0.907,  $p = 0.0042$ ).

**Conclusions.** Consistent with other reports, we report a lower upstaging rate with VATS. Nevertheless, there is a survival advantage in VATS patients. Although selection bias may play a role in these observed differences, the improved quality of life measures associated with VATS may explain survival improvement despite lower surgical upstaging.

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The ideal surgical approach for the treatment of lung cancer is still a matter of debate [1]. There are clear advantages to thoracoscopy. Patients experience decreased pain, shorter length of stay, quicker return to work, and are more likely to adhere to adjuvant regimens when indicated [2–7]. However, several studies raise concerns that thoracoscopy results in lower rates of nodal upstaging than open surgical procedure [8–10].

Surgical upstaging reflects the inherent limitations of clinical staging and the sensitivity and specificity of the tools which are used [11]. In addition, it is possible that there may be disease progression during the course of workup which in some cases may be delayed for a variety of reasons [12]. Although surgical upstaging occasionally represents intraoperative findings of pleural invasion or multiple nodules (modification of T stage), intraoperative finding of lymph node involvement is the most common reason for upstaging [8–10, 13].

Kentucky has the nation's highest incidence of and mortality from lung cancer. Age-adjusted annual incidence rates are in excess of 150 in 100,000 [14]. With a population of 4.4 million and an area of 40,000 mi<sup>2</sup> many patients have to travel substantial distances to obtain care that is provided by two academic medical centers and a large number of busy community hospitals and cancer centers. The statewide Kentucky Cancer Registry (KCR) offers an opportunity to study cancer incidence, treatment, and outcomes in this diverse and real-world population.

Therefore, we sought to use these data to evaluate the primary endpoint of nodal upstaging stratified by surgical approach and to explore possible effects on survival.

## Patients and Methods

The University of Kentucky Institutional Review Board approved this retrospective review of the cancer registry. The KCR was instituted in 1986, with mandatory reporting by all state hospitals in 1991. The KCR attained National Cancer Institute Surveillance Epidemiology and End Results designation in 2000. Today, all Kentucky acute-care hospitals, outpatient facilities, and other nonhospital facilities participate in the registry. A key

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component is the cancer patient data management system that is a standardized reporting system. Statewide data are collated at KCR, and these data are used for research and participation in the national registries. The data management system includes e-path that allows for near real-time reporting of pathology data from participating laboratories throughout the state to the centralized cancer registry.

In 2010, a stratification variable was introduced which allowed for comparison of surgical approach (thoracoscopy, robot-assisted, conversion, open). We chose to examine registry data between 2010 and 2012 to allow for at least 2 years of follow-up data for survival. The KCR database was linked to external data sources, including Kentucky death certificates, the national death index, Social Security Administration, and Center for Medicaid Services.

Cancer records were stratified by surgical approach. Nodal upstaging was defined as cN0 patients being found to have either pN1 or pN2 nodes.

Baseline characteristics included age, sex, clinical staging (c stage, cT, cN, cM and tumor size). Operative characteristics included surgical approach, extent of resection, pathologic data (p stage, pT, pN, pM), and histology. Measurements also included analysis of survival data and extent of resection categorized as anatomic (lobectomy, bilobectomy, pneumonectomy), extended anatomic (when additional structures such as chest wall, diaphragm, pericardium were involved), segmentectomy, and nonanatomic resections.

Descriptive statistics included mean and standard deviation for normally distributed continuous variables, median and interquartile range for non-normally distributed continuous variables, and counts and percentages for categorical variables. Univariate comparisons used Student *t* test, analysis of variance,  $\chi^2$ , and Fisher exact test as appropriate.

Logistic regression was used to measure the association between the occurrence of nodal upstaging and the other measured variables. Significant variables were entered into a final logistic model to estimate multivariable odds ratios (ORs) that reflected the risk of nodal upstaging.

Survival analysis was initially conducted with the standard Kaplan-Meier method. This was stratified by stage of surgical approach. The individual association of each variable with survival was estimated with univariate Cox regression, and significant factors were entered into a final multivariable Cox regression model.

Analyses were performed in SAS 9.3 (SAS Institute, Cary, NC).

## Results

During the study period of 2010 to 2012, 2830 lung cancer resections were performed in the state of Kentucky. Of these, 1,964 (69%) were performed open. An additional 134 (5%) began as a minimally invasive approach and were converted. The remaining cases were completed either using conventional thoracoscopy (18%) or robot-assisted approaches (8%).

Baseline characteristics are given in Table 1. Overall the cases were similarly distributed in terms of age, sex, race, and smoking history. Patients who underwent open resections had slightly larger tumors (median, 25 mm versus 20 mm,  $p < 0.001$ ) when comparing open with minimally invasive patients.

Operative approach was in the form of an anatomic resection in most patients; however, in the thoracoscopy group there were 31% (149) nonanatomic resections compared with 19% (365) in the open group (Table 1).

The prevalence of nodal upstaging overall was 8.8%. This represented the finding of pN1 in 5.5% and pN2 in 3.3%. Nodal upstaging in the thoracoscopy group was only 4.8%, compared with 8.6% in the robot-assisted group, and 9.9% in the open group ( $p = 0.002$ ) (Table 2).

Because there were significantly more wedge resections in the video-assisted thoracic surgery (VATS) group, we performed an additional stratified subgroup analysis that excluded wedge resections and extended anatomic resections (chest wall) and was limited to clinical stage 1 only. Thoracoscopy had a nodal upstaging rate of 9.1% compared with 13.9% for thoracotomy in clinical stage I (Table 3).

Multivariate logistic regression analysis confirmed the findings of the univariate and stratified analyses. Thoracoscopy was associated with decreased nodal upstaging, independent of tumor size and extent of resection (OR 0.6, 95% CI: 0.387 to 0.985,  $p = 0.04$ ). Anatomic resection compared with other approaches was also independently associated with nodal upstaging (OR 2.6, 95% CI: 1.473 to 4.533,  $p = 0.0009$ ) (Table 4).

Kaplan-Meier stratified analysis found a survival advantage to thoracoscopy in pathologic stage 1 tumors (Fig 1).

Multivariable Cox regression found that thoracoscopic approach was independently associated with improved survival (hazard ratio [HR] 0.733, 95% CI: 0.592 to 0.907,  $p = 0.0042$ ) while controlling for extent of resection, nodal upstaging, and pathologic stage. Although nodal upstaging did not affect survival, anatomic resection was associated with improved survival compared with nonanatomic (HR 0.687, 95% CI: 0.575 to 0.821,  $p \leq 0.0001$ ) (Table 5).

## Comment

Nodal upstaging is a function of both preoperative clinical workup and the intraoperative detection of occult nodal disease [9, 11, 13, 17]. Our study finds that thoracoscopy is independently associated with lower rates of nodal upstaging. A retrospective study such as this cannot infer causality but rather further highlights the association of decreased nodal upstaging that has been reported in other studies.

Two scenarios exist. First, decreased rates of upstaging may not be reflective of surgical technique. The difference may represent selection bias because surgeon preference for thoracoscopy may favor smaller tumors that are more likely to indeed be node negative. We lack sufficient detail in the database to determine the clinical staging

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