Editorial

# Moving beyond disease-focused decision making: understanding competing risks to personalize lung cancer treatment for older adults

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Every year in the United States alone over 500,000 adults age 65 years and older undergo high-risk surgery. For many of these procedures, including lung resection, annual volume is increasing (1). This trend is driven in part by shifting demographics on a global scale. Cases of tracheal, bronchus and lung cancer worldwide have grown by nearly 30% since 2005, 18% of which may be attributed to aging of the population (2). Furthermore, recognition of the efficacy of screening with low-dose computed tomography is expected to spur ongoing detection of early-stage malignancy which can be managed surgically (3-5).

Rising hospital volume has been associated with superior patient outcomes (1). For pulmonary resection, the postoperative mortality rate has declined to 1.4% (6) and overall survival has improved for older patients with stage I non-small cell lung cancer (NSCLC) treated surgically (7). Safer surgery stems from a myriad of sources including advances in minimally invasive techniques as well as multidisciplinary management and sub-specialty care offered at high-volume centers. These improvements allow us to challenge conventional boundaries when determining which patients may be considered operative candidates.

Surgery offers great potential to both prolong life and improve quality of life for older adults. For early-stage lung cancer patients, resection also affords an opportunity for cure. However, the focus of traditional clinical decision making on achieving a disease-specific—or cancer-specific—outcome may be too narrow to account for potential competing events in medically complex older patients (8).

Association between the burden of comorbid disease and serious postoperative complications has been established for a variety of oncologic and cardiovascular procedures (1,9). While consensus on the precise definition of "high risk" patients for pulmonary resection remains elusive (10), risk models for 30-day mortality and postoperative morbidity demonstrate the importance of patient-dependent variables as harbingers of poor outcomes (6,11,12). However, traditional risk calculators do not facilitate comparison of cancer and noncancer specific mortality. As over 50% of older adults have one or more chronic condition (13), the chance of a competing event such as death due to a comorbid disease is real. Weighing this risk against the potential benefit of invasive cancer treatments is essential to informed preoperative decision making (14).

In a recent edition of the *Journal of Clinical Oncology*, Eguchi and colleagues (15) present the results of a retrospective analysis of 2,186 patients who underwent curative-intent resection for pathologic stage I primary NSCLC. The authors sought to analyze short and long term cause-specific outcomes using a competing risk analysis to evaluate the association between preoperative characteristics and the risk of lung cancer-specific and noncancer-specific death. Study subjects represent all patients who received either lobectomy or sublobar

resection at a single institution in the United States between 2000 and 2011; those who underwent a pneumonectomy or bilobectomy were excluded from analysis. Patients with a history of lung cancer within 2 years, prior lung resection, histologies other than NSCLC or who received induction therapy were also excluded.

Study end points included severe morbidity, lung cancer-specific mortality, noncancer-specific mortality and overall survival. Lung cancer-specific mortality was defined as death due to recurrent disease at the time of last documented follow up. In concordance with epidemiologic data, 70.1% of the cohort was age 65 years or older and nearly 85% were current or former smokers. Over 70% of patients were diagnosed with stage IA disease and 51.9% had at least one comorbid condition as determined by the Charlson comorbidity index. Mortality rates at 30 days, 90 days, 1 year, and 5 years were 0.7%, 1.2%, 4.1%, and 19.9%, respectively. The leading cause of death at time points up until and including 1 year postoperatively was noncancer specific, with cardiorespiratory disease accounting for the majority of deaths at 30 and 90 days. However, by 5 years post-resection the leading cause of death was lung cancer specific.

This study contributes important new knowledge on the impact of competing outcomes for older adults with early-stage lung cancer. The authors demonstrate that noncancer-specific mortality is a significant competing event that becomes more influential with increasing patient age. When stratified by age, 5-year lung cancer-specific cumulative incidence of death (CID) was 7.5% for those patients <65 years, 10.7% for age 65–74 years, and 13.2% for patients ≥75 years old. However, noncancer-specific CID increased more than 4-fold from 1.8% in patients <65 to 9% in patients ≥75 years old. When considering the overall cohort, noncancer-specific CID exceeded lung cancer-specific CID for 1.5 years after resection. This finding was even more pronounced in older patients such that for those age ≥75 years noncancer-specific mortality dominated for up to 2.5 years postoperatively. Notably, this trend did not hold for the cohort of patients <65 years old in whom lung cancer-specific mortality was predominant throughout the postoperative period.

Multivariable models were developed to assess the impact of patient characteristics on morbidity and cause-specific mortality. The authors used a comprehensive set of variables known to predict postoperative outcomes for patients with NSCLC including patient demographics, age-related comorbidities, pulmonary function measures and cancer-specific characteristics. They report lower postoperative predicted DLCO (ppo DLCO), history of COPD, elevated serum creatinine and receipt of lobectomy as opposed to sublobar resection were significantly associated with severe postoperative morbidity. Interestingly, low ppo DLCO was found to be an independent predictor of noncancer-specific mortality while low ppo forced expiratory volume in 1 second (FEV1) was significantly associated with lung cancer-specific mortality. However, both ppo DLCO and ppo FEV1 were predictive of overall survival.

For lung cancer patients, the presence of competing risks may obscure interpretation of the effect of treatment. The standard approach to prognostic analysis is based on statistical models that harness preoperative variables to characterize a patient's risk of a composite endpoint, such as all-cause 1-year mortality, disease-free survival or overall survival. Use of a composite primary outcome facilitates sample size calculations and maximizes statistical power in clinical trials. While elegant in its simplicity, this strategy is only effective when we can presume that the variables have a similar impact on each individual event that comprises the aggregate endpoint (16). In the setting of cancer, this assumption is often flawed as the predictors of cancer recurrence or mortality may differ from those associated with death from noncancer causes.

Competing risk analysis has emerged as a promising technique to facilitate greater precision in preoperative patient stratification and prognostication. Recent work by Carmona and colleagues (17) compared a novel generalized competing event model to the traditional Cox proportional hazards regression model for elderly patients with nonmetastatic head and neck, prostate or breast cancer. By measuring the impact of preoperative characteristics on cause-specific outcomes, the competing event model enhanced the ability to stratify patients based on their risk of death from cancer as compared to overall mortality.

Despite recognition of the importance of preoperative risk assessment, there is ongoing debate as to specific criteria necessary to designate a patient as "high risk" for pulmonary resection (10,18). Multicenter clinical trials conducted by the American College of Surgery Oncology Group (ACOSOG) to evaluate lung cancer therapies in high-risk surgical candidates used expert consensus to define FEV1 ≤50% predicted or DLCO ≤50% predicted as major criteria for study enrollment (19). However, the ability of these parameters to forecast poor clinical outcomes has been challenged (10,18).

The field of cardiothoracic surgery is fortunate to have

 

a high quality clinical registry in the Society of Thoracic Surgeons (STS) National Database. The STS General Thoracic Surgery Database (GTSD) component of the national registry was formally established in 2002. Generation of risk models for lung cancer resection from the GTSD (6,20,21) enable thoracic surgeons to quantify the risk of operative mortality and major morbidity based on patient characteristics. While surgeons can use this information for clinical decision making and preoperative patient counseling, STS risk models are limited to 30-day outcomes. Similarly, models using European databases focus on predictors of short-term events such as in-hospital mortality (11,12). Recent work by Fernandez and colleagues (7) linked the GTSD to Centers for Medicare and Medicaid Services data (22) to allow longitudinal follow up of over 37,000 lung cancer operations performed on patients age 65 years and older in the United States between 2002 and 2012. The authors report the median survival following resection for patients with pathologic stage I disease was 6.7 years. However, this study used an aggregate endpoint of overall survival.

Analysis of competing events has potential to augment existing risk stratification tools. A major strength of the study by Eguchi and colleagues (15) is the use of all cancer and noncancer related preoperative variables known to impact postoperative outcomes. Analysis of cause-specific outcomes beyond 30 days using such a comprehensive set of variables is a unique contribution to the literature. In particular, the authors report a heterogeneous effect of pulmonary function measures in that ppo DLCO was strongly associated with noncancer-specific mortality while ppo FEV1 was predictive of lung cancer-specific mortality. Although the GTSD is well-respected for its quality and completeness, DLCO was excluded as a covariate in the STS risk adjustment models due to a significant proportion of missing values for this measurement in the database. However, other studies demonstrating an association between DLCO and composite measures of postoperative survival advocate for its use in determining treatment benefit (23,24). As such, this differential impact of pulmonary parameters on cause-specific outcomes highlights a need for further investigation.

With advancing age, many patients reap diminishing benefits from invasive procedures. Understanding outcomes beyond 30-day mortality is essential for older patients to engage in shared decision making to select treatments that align with their preferences. However, by focusing on the treatment outcomes for a specific disease such as lung cancer, it is easy to interpret a subsequent event such as a myocardial infarction as a consequence of cancer treatment rather than a competing event due to the patient's underlying coronary disease (25). In a qualitative analysis of focus groups with older adults with multiple comorbid conditions, Fried and colleagues (8) found that patients can understand the concept of competing outcomes. When asked about potential interaction between their illnesses, many study participants were unaware that having multiple comorbidities placed them at risk for negative outcomes and focused on benefits of treatments in relation to specific diseases. However, when prompted to prioritize from a variety of outcomes, participants were able to broaden the scope of their thinking to acknowledge the impact of treatments in more general terms rather than specific to an individual disease.

Delivery of personalized medicine goes beyond genomic analysis and development of targeted immunotherapeutic agents. While advanced age is often a surrogate for frailty and poor overall health, age alone should not be the determining factor in the decision to offer surgery. The ability to stratify patients based on their risk of competing events offers significant opportunity to refine patient selection. Identifying older surgical candidates with greater risk for early noncancer mortality gives thoracic surgeons valuable information by which to judge the appropriateness of sublobar resection versus lobectomy or determine which patients may benefit most from non-operative modalities. Furthermore, the findings of Eguchi and colleagues (15) offer data on longer-term cancer and noncancer-specific outcomes to use in conjunction with surgical risk models to personalize preoperative discussions. Although we have yet to find a precise definition of the "high risk" patient, attention to competing risks gets us closer to optimizing treatment for older adults.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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