Perspective

Improving lung cancer outcomes by improving the quality of surgical care

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Abstract: Surgical resection remains the most important curative treatment modality for non-small cell lung cancer, but variations in short- and long-term surgical outcomes jeopardize the benefit of surgery for certain patients, operated on by certain types of surgeons, at certain types of institutions. We discuss current understanding of surgical quality measures, and their role in promoting understanding of the causes of outcome disparities after lung cancer surgery. We also discuss the use of minimally invasive surgical resection approaches to expand the playing field for surgery in lung cancer care, and end with a discussion of the future role of surgery in a world of alternative treatment possibilities.

Keywords: Quality improvement; surgical resection; survival; outcomes of care; comparative effectiveness

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In the US, approximately 50,000 to 60,000 patients undergo surgical resection for lung cancer annually (1). From this population, which represents 29% of all newly diagnosed patients, comes approximately 80% to 90% of 5-year survivors. Therefore, surgery is the most important curative treatment modality in the management of lung cancer. However, more than 50% of patients who undergo curative-intent resection for lung cancer die within 5 years, mostly of lung cancer (2). Therefore, expanding the appropriate use of surgery, and improving short and long-term post-operative survival are key strategies for improving the overall survival of lung cancer patients in populations.

Survival after lung cancer surgery

Surgically resected lung cancer patients encounter two main challenges: surviving the operation (avoiding post-operative mortality), and surviving the cancer (avoiding cancer-related mortality). There is significant variation in the incidence of each of these adverse results, disparities driven by patient, surgeon and institutional factors. Short-term variation in surgical outcomes is driven by patient selection factors (3), surgeon factors such as volumes of care (4), specialty training and level of experience (5-9) and institutional factors such as case-volume (10-13), teaching status (14), institutional resources and predominant payer mix (15).

Although post-operative mortality has traditionally been measured at 30 days, there is good evidence that 30-day mortality measurements significantly under-estimate the operative hazard to which lung cancer patients are exposed (4,10,11,16,17). The 60- and 90-day mortality statistics appear to be more reliable. Indeed, the 90-day mortality statistic generally doubles the 30-day mortality statistic and has been advocated as the most accurate measurement of post-operative risk (16-25). In addition, patients re-admitted within 30 days of post-operative discharge have a 6-fold increase in mortality rate (26).

Patient selection, pre-operative physiologic evaluation, intraoperative and immediate post-operative management are all major determinants of short-term post-operative risk and the quality of these processes links provider and institutional characteristics with the disparity in short-term outcomes (27,28).

While post-operative survival is a readily identifiable surgical quality measure, the quality of oncologic resection is an even more important, but less readily measured quality yardstick, given the delayed nature of the adverse event. Although delayed, the adverse impact of variation in surgical quality on long-term survival has been estimated to be approximately 2-3 fold the impact of quality variations on short term survival, in terms of the number of potentially avoidable deaths (29). Large as this impact is, it is not readily apparent because of the distribution of deaths over years, and prevailing general nihilism about the probability of surviving lung cancer. In addition, there is a relative paucity of high quality data on the determinants of good quality oncologic resection for lung cancer. Most recommendations are based on institutional experience and expert opinion, and evidence-based quality guidelines mostly rely on analysis of relatively small, retrospective, often single institutional data sets, usually without prospective validation (28,30,31).

Lung cancer oncologic quality resection criteria

Lung cancer oncologic quality resection criteria can be distilled down to recommendations for the anatomic extent of resection, the completeness of resection, and the lymphadenectomy procedure performed. Controversies remain with each of these.

Even though the prospective randomized trial of lobectomy *vs.* sublobar resection performed by the Lung Cancer Study Group (LCSG) in the 1990s revealed a higher relapse rate with sublobar resection, there remains no universal agreement that lobectomy ought to be the standard default procedure for all patients when feasible (32-34). The LCSG trial revealed no difference in overall survival, and there remain concerns that lobectomy may be too much surgery for certain subsets of patients, such as patients over 71 years old (35,36), those with limited lung function, and those with small peripheral tumors or relatively indolent-behaving lesions such as adenocarcinomas emanating from ground glass opacities (37). The latter scenarios continue to be the subject of clinical trials because advances in computerized tomography (CT) technology and the advent of CT screening are likely to increase the population of these particular lung cancer patients. Furthermore, anatomic segmental resection appears to be an oncologically equivalent procedure in patients with stage I disease (37,38).

Defining the completeness of resection in lung cancer has not been straightforward. There has been controversy about the definition of "positive margin". For example, it has been posited that carcinoma *in-situ* at the resection margin may not have any prognostic significance (39). Others have attempted to include the lymph node dissection and location of mediastinal nodal metastasis in the definition of completeness of resection (40). Even the fundamental question of the implications of resection with positive margins has been the subject of much debate for decades, with relatively small, predominantly single institutional studies suggesting this to be, or not to be, a prognostic determinant (41-46). This controversy has recently been laid to rest by large database analyses in the US, which clearly demonstrate that resection with positive margins causes the equivalent of at least a single aggregate stage deterioration in survival (47,48).

Finally, the optimal extent of mediastinal lymphadenectomy remains somewhat contentious. Even though the American College of Surgeons Oncology Group Z0030 trial revealed no difference in survival between pN0/non-hilar pN1 patients who received either a thorough systematic sampling or mediastinal lymph node dissection procedure, the reality of clinical practice remains that majority of lung cancer resections in the western world do not meet the control standard systematic sampling procedure in this trial (49-56). In addition, the applicability of these results to resections performed for more advanced lung cancer, such as those with hilar nodal metastasis, is very much open to question (57). Therefore, even the few prospective randomized clinical trials of lung cancer surgery have often left more questions than they answered.

It is therefore not surprising that observational studies and expert opinion have attempted to fill the void. This has led to variations in the delineation of quality parameters. For example, the National Comprehensive Cancer Network (NCCN) recommends the combination of lobectomy, negative margins, and sampling of lymph nodes from a minimum of three mediastinal nodal stations as minimum requirements (58). The American College of Surgeons Commission on Cancer (CoC) has set a quality surveillance standard requiring examination of ten or more lymph nodes in resections for stage IA to IIB non-small cell lung cancer, without stipulating where the lymph nodes should be retrieved from (59). These recommendations, although based on various retrospective studies that have shown the association between the number of lymph nodes (or lymph node stations) examined and survival, have never been prospectively validated. A recent effort to validate these recommendations using a large regional database, revealed significant improvement in survival in patients whose resection met the NCCN minimum recommendations. It also revealed that of the four components, the recommendation for examination of a minimum of three mediastinal lymph nodes was the most impactful on prognosis (60). A similar examination of the CoC criteria revealed them to be of weak prognostic value, but imposition of a stipulation for examination of at least one mediastinal lymph node significantly improved the prognostic value of this quality measure (61).

These quality measures, once validated, can be used for rigorous intra-institutional quality improvement work. It is clear that the incidence of sub-optimal resection (however defined) is higher in certain types of institutions, with certain types of surgeons, than others. Rigorous definition of quality will enable health services researchers to better evaluate the human and organizational factors contributing to these quality variances, raising the possibility of testing hypotheses on the transferability of high quality practices. The major questions are: what key practices or processes separate institutions or surgeons with excellent outcomes from those with less-than-excellent outcomes? Can these practices be transferred to less high performing environments? If so, how?

The role of pathologists

Because lung cancer survival and the use of post-operative adjuvant therapy depends on pathologic stage, especially nodal stage, the quality of oncologic surgical resection and long-term patient survival are also reliant on the quality of the pathologic examination. High risk patients benefit from postoperative adjuvant therapy and there are numerous ongoing trials of novel post-operative adjuvant therapy agents in lung cancer. Successful execution of these trials and, even trial results, can be significantly impaired by poor quality surgery or pathology examination (62). This relatively under-recognized problem is extensively discussed in this special issue (63).

Expanding the role of surgery using minimally-invasive approaches in lung cancer

The surgical approach in the management of patients with thoracic malignancies continues to evolve and improve. While conventional open surgical approaches (including standard posterolateral thoracotomy, muscle-sparing thoracotomy, trans-sternal thoracotomy, and median sternotomy) remain viable options for some patients, minimally invasive procedures are being used for an increasing number of patients with lung cancer, esophagus cancer, and thymic malignancy, to minimize operative morbidity without sacrificing oncologic efficacy.

Minimally invasive procedures, using operative telescopes and video technology, are referred to synonymously as thoracoscopic procedures or video-assisted thoracic surgery (VATS). For clarity, the term VATS and thoracoscopic refer to totally thoracoscopic approaches, where visualization depends on video monitors, and rib spreading is avoided. Thoracoscopic lobectomy is defined as the anatomic resection of an entire lobe of the lung, using a videoscope and an access incision, without the use of a mechanical retractor and without rib spreading; various approaches using either one, two or three incisions are considered acceptable (64). The anatomic resection includes individual dissection and stapling of the involved pulmonary vein, pulmonary artery, and bronchus and appropriate management of the mediastinal lymph nodes, as would be performed with thoracotomy. In selected patients, thoracoscopic anatomic segmentectomy may be performed, adhering to the same oncologic principles that guide resection at thoracotomy (65).

The indications for thoracoscopic lobectomy are similar to those for lobectomy using the open approach (66). Thus, the procedure is applied to patients with known or suspected lung cancer if the disease appears amenable to complete resection by lobectomy. Preoperative staging and patient selection for thoracoscopic lobectomy should be conducted as for conventional thoracotomy (67). Tumor size may preclude the option of thoracoscopic lobectomy in some patients, as some large specimens may not be amenable to removal without rib spreading; however, no absolute size criteria are used. Although it is controversial, some have also argued that the thoracoscopic approach may allow recruitment and resection of some patients considered medically inoperable, who could not undergo conventional thoracotomy, such as the elderly and those with poor pulmonary function (68,69).

Absolute contraindications to thoracoscopic lobectomy include the inability to achieve complete resection with lobectomy, T4 tumors, active N2 or N3 disease, and inability to achieve single-lung ventilation (70). Relative contraindications include tumors visualized in the lobar orifice at bronchoscopy [although successful thoracoscopic sleeve resection has been reported (71)], the presence of complex, calcified benign hilar lymphadenopathy that would complicate vascular dissection, and prior thoracic irradiation. Prior thoracic surgery, central tumors, T3 tumors that involve the pericardium, mediastinal pleura, or diaphragm, incomplete or absent fissures, and benign noncalcified mediastinal adenopathy should not be considered contraindications (72,73). Increasing experience has allowed successful thoracoscopic lobectomy after induction therapy, including for patients with stage IIIA (N2) disease (74) and patients requiring pneumonectomy (75). Finally, chest wall involvement would obviate thoracoscopic resection for most patients, but successful en bloc resection via VATS has been reported (76).

Proved advantages to minimally invasive resection include decreased postoperative pain, shorter chest tube duration, shorter length of stay, preserved pulmonary function, superior compliance with adjuvant chemotherapy and fewer complications (77-81). These advantages are achieved with equal or perhaps superior oncologic effectiveness (82). In fact, a recent meta-analysis of series comparing thoracoscopic to open lobectomy including both propensity- matched and unmatched patients demonstrated that thoracoscopic lobectomy was associated with a lower relative risk of perioperative morbidity and a lower relative risk of all-cause mortality (83).

In summary, thoracoscopic lobectomy may be employed in the majority of patients with clinical stage I or II lung cancer, and in selected patients with locally advanced disease and after the use of induction therapy. While various specific approaches are acceptable, the avoidance of thoracotomy is associated with improved quality of life, improved morbidity, and perhaps improved long-term survival. This has now enabled extension of surgery to subsets of patients who might have been regarded as medically inoperable.

The future of lung cancer surgery

Surgery is likely to remain the most important curative treatment modality for lung cancer, especially with increased identification of patients with early stage, asymptomatic non-small cell lung cancer in the age of lung cancer screening. Pathologic staging, obtained at surgical resection, remains the most accurate means of determining patient prognosis. The comparative efficacy of surgical resection or stereotactic body radiation for relatively infirm patients with early stage non-small cell lung cancer is an ongoing area of inquiry, with dueling reports from multiple observational studies arguing the case for one side or the other (84-91). These questions will only be resolved by prospective randomized clinical trials in which outcomes in equivalent patient populations can be directly compared. Multiple attempts to conduct such trials have failed to recruit adequate numbers of patients (92). However, two new trials, Veterans Affairs Lung cancer surgery or stereotactic Radiotherapy (VALOR) in the US, and SABRTooth [a multicenter study of Stereotactic Ablative Radiation (SABR) *vs.* surgery in high surgical risk patients with peripheral stage I non-small cell lung cancer] in the UK, are reportedly now afoot (92). There is now sufficient equipoise in the existing evidence to ethically justify enrolling patients into such clinical trials (91,93).

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Footnote

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

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