Impact of Patient Selection, Disease Progression, and Adverse Events on Esophageal Cancer Outcomes After Trimodality Therapy

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Background. Neoadjuvant chemoradiation followed by surgery (NeoCRT) has been advocated as standard therapy for resectable esophageal cancer. Our objective was to compare oncologic outcomes between NeoCRT and upfront surgical resection (SURG).

Methods. We conducted a single-institution, retrospective review of all potentially resectable esophageal cancer patients treated with NeoCRT or SURG.

Results. From 2003 to 2010, 151 patients had NeoCRT (n = 48; 31.8%) or SURG (n = 103; 68.1%). Histology was mostly adenocarcinoma (77.5%) or squamous carcinoma (19.2%). Mean radiation dose was 44 ± 1 Gy, and 80.8% received platinum-based doublet chemotherapy. There were more women in the SURG group (23.3% vs 4.2%; p < 0.01) and more cardiovascular comorbidity in the NeoCRT group (23.3% vs 4.2%; p < 0.01) and more cardiovascular comorbidity in the NeoCRT group (23.3% vs 4.2%; p < 0.01). There was no difference in age, histology, R0 resection rate, and treatment-related mortality (NeoCRT = 4.2%; SURG = 3.9%; p = 0.15). Failure to undergo resection after NeoCRT (n = 11; 22.9%) was mainly due to disease progression (n = 6) or treatment-related mortality (n = 4). Resection could not be performed in 4 SURG patients (3.9%; p < 0.001; unresectable = 2; occult metastases = 2). NeoCRT did not improve median survival (NeoCRT = 29 ± 6; SURG = 26 ± 3 months; p = 0.376) or recurrence-free interval (NeoCRT = 25.8 ± 5; SURG = 19.4 ± 2 months; p = 0.19). Complete pathologic response (n = 8; 21.6%) was not associated with improved survival. If we exclude from analysis NeoCRT patients who did not undergo surgery, survival was significantly improved after NeoCRT (NeoCRT = 41 ± 15; SURG = 24 ± 8 months; p = 0.0082).

Conclusions. Patient selection and early assessment of treatment response may be key factors in identifying the best candidates for trimodality therapy.


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The incidence of esophageal carcinoma is on the rise and despite advances in medical and surgical care, the prognosis for long-term survival (ie, 5 years) remains dismal [1]. Over the past 3 decades, several prospective trials comparing neoadjuvant chemotherapy or chemoradiotherapy to upfront surgical resection have been completed. Although individually, few trials have demonstrated a statistically significant survival advantage, meta-analysis of pooled data has shown that overall survival may be improved after neoadjuvant chemoradiation [2]. More recent results from a large, European trial of trimodality therapy also lend support to this strategy [3]. The investigators stated that their treatment regimen should be considered “standard care” for esophageal cancer patients who are potential candidates for surgery.

Based on published literature and discussion amongst the members of our multidisciplinary care team, we have treated an increasing number of patients using a neoadjuvant strategy [2–7] (Fig 1). The objective of this study was to compare oncologic outcomes of esophageal cancer patients treated with neoadjuvant chemoradiation to those who underwent upfront surgical resection. Our hypothesis was that neoadjuvant therapy would be associated with an improvement in overall survival.

Material and Methods

After approval from the institutional research ethics board, a single-institution retrospective review of all consecutive esophageal cancer patients who were deemed candidates for surgical resection between January 2003 and December 2010 was performed. Patients were identified through multiple sources including the regional cancer center database, the hospital medical records, and our thoracic surgery quality monitoring system. Patients who received neoadjuvant chemotherapy alone or neoadjuvant radiation alone were excluded. The remaining patients were divided into
two groups: the first received neoadjuvant chemoradiation (NeoCRT) before planned surgical resection, and the second was treated with upfront surgery with or without adjuvant therapy (SURG). Patient characteristics, diagnostic and staging workup, treatment details, histopathology, and follow-up data were extracted from available medical records, de-identified, and stored in a password-protected relational database.

Clinical staging was derived primarily from esophagoscopy, computed tomography (CT) scan, or positron-emission tomography (PET)/CT scan data. CT scan measurement of esophageal wall thickness was used to determine T status as follows: less than or equal to 5 mm for T1, 5 to 15 mm for T2, and more than 15 mm for T3. Clinical T4 was defined as invasion of adjacent mediastinal structures characterized by obliteration of normal anatomic tissue planes. Lymph nodes in the regional drainage of the esophagus and gastroesophageal junction were deemed positive if the short-axis diameter exceeded 10 mm or the standard uptake value was reported as abnormally elevated. Selection criteria for neoadjuvant chemoradiation included: 1) clinical stage T2-3 N0-3, biopsy-proven, potentially resectable esophageal or esophagogastric carcinoma; and 2) patient deemed to be a surgical candidate after thoracic surgery evaluation. Pathological N status in the NeoCRT group was obtained from the surgical resection specimens (ie, ypN status). The primary outcome was overall survival which was defined as the interval from the start of treatment (ie, surgery or neoadjuvant chemoradiation) to either death or loss to follow-up. The secondary outcome was recurrence-free (or disease-free) interval which represents the period between the start of treatment and the identification of radiologic recurrence. Recurrences were classified as local, regional, or distant. Recurrent cancer within the residual proximal esophagus or the esophageal replacement conduit was defined as local. Recurrences were labeled regional if they occurred within the regional lymphatic drainage of the esophagus and gastroesophageal junction including the cervical, thoracic, and celiac axis lymph node basins. All other recurrences were considered to be distant. Pathologic confirmation of recurrence was not mandatory. Operation types included transhiatal esophagectomy, and either two-field or three-field transthoracic esophagectomy. R0 refers to a complete surgical resection with histologically negative proximal, distal, and radial margins. Complete response to neoadjuvant therapy implies no histological evidence of invasive, viable tumor cells within the surgical resection specimen. Surgical complications were classified and graded in severity according to a modified Clavien-Dindo surgical complication scale developed at our institution [8, 9]. Postoperative mortality was defined as death from any cause within 30 days of surgery.

**Statistical Analysis**

Survival analysis was performed using the Kaplan-Meier method [10]. Statistical significance was assessed by log rank test. Hazard ratios and confidence intervals were obtained at 95% significance. Cox regression analysis was used to develop univariate and multivariate models [11]. These models describe the association of independent variables with overall survival. Independent variables analyzed included: age, sex, tumor location, tumor histology and grade, radiologic and pathologic nodal status, treatment, completeness of resection (R status), and complete pathologic response to chemoradiation. $\chi^2$ statistic was obtained to assess statistical heterogeneity.

Using the propensity score matching method, the groups were examined for heterogeneity with regards to patient and tumor attributes that could potentially have a significant impact of overall survival by univariate analysis. Variables included in the model were: age, gender, histology, histologic grade, pathologic T stage, pathologic N stage, and R status. Variables were included in a logistic regression model which calculated the predicted probability of group membership [12]. The resultant model had a c-statistic of 0.78, indicating good concordance between treatment groups. The model was subse-
quently used to calculate the propensity scores. A one-to-one and a two-to-one neoadjuvant therapy to upfront surgery, case-control match were performed using the propensity scores for the variables included in the model. Matching was accomplished using a “greedy algorithm” where the most compatible matches were made first [11]. The McNemar test was then used to test the differences between paired proportions of the baseline characteristics included in the model. All statistical tests were performed in SAS 9.3 (SAS Institute Inc, Cary, NC). A p value < 0.05 was considered statistically significant.

Patient and Tumor Characteristics
Surgical resection was planned for a total of 174 patients over the 8-year review period. Of these, 151 were treated with either neoadjuvant chemoradiation (48/151; 31.8%) or upfront esophagectomy (103/151; 68.2%) with or without adjuvant therapy. The remainder received neoadjuvant chemotherapy (22/174) or neoadjuvant radiation alone (1/174), and were therefore excluded from the study (Fig 2). The majority of patients were male (126/151; 83.4%) and the median age was 68 ± 10.6 years (range, 37–90). Table 1 outlines patient and tumor characteristics. The most common histologic subtypes were adenocarcinoma (78.1%) and squamous cell carcinoma (17.3%). There were significantly more women in the upfront surgery group (23.3% vs 4.2%; p = 0.005). More patients in the neoadjuvant group presented with any cardiovascular comorbidities (77.1 vs 68.2%; p = 0.0027). There were no significant differences in age and histology. After resection, pathology findings indicated that the rate of complete resection was similar in both groups. At final pathologic examination, patients treated with neoadjuvant chemoradiation had tumors which were significantly smaller and of lower grade (Table 2). The NeoCRT group was also significantly less likely to have 1 or more pathologically positive lymph nodes in the surgical specimen (p = 0.015).

All patients underwent CT scanning of the chest, abdomen, and pelvis, and preoperative esophagoscopy. Bone scan was obtained in 40.4% (61/151), PET/CT scan in 14.6% (22/151), magnetic resonance imaging of the abdomen and pelvis in 6% (9/151), and CT of the brain in 2.6% (4/151). Endoscopic ultrasound (EUS) was performed in 2% (3/151). CT scan imaging data was not available for review in 20 (19.4%) SURG patients. The difference observed in the clinical N status and the overall clinical stage between the groups may be explained by the patient selection criteria for neoadjuvant therapy which excluded stage I patients. The differences may also be due to the low accuracy of CT and PET/CT in determining lymph node status based on size criteria or FDG activity [13]. Given that more advanced tumors were selected for inclusion in the NeoCRT group, clinical nodal status in these patients may reflect pathologic nodal status more accurately since abnormally enlarged regional lymph nodes are more likely to be positive for cancer. The median follow up was 19.5 ± 16.4 months in the neoadjuvant group and 21.1 ± 16.2 months in the upfront surgery group (p = 0.11).

Results
Neoadjuvant Chemoradiation
In patients who received neoadjuvant therapy, the mean radiation dose delivered was slightly lower than the planned treatment dose, but the difference was not statistically significant (4463 ± 132 cGy vs 4705 ± 36.6 cGy; p = 0.08). Most patients (40/48; 83.3%) received concurrent chemotherapy using two agents in one of the
following combinations: 5-fluorouracil (5-FU) combined with cis-platinum (29/40; 67.5%) or carboplatin (2/40; 5%), or cis-platinum in conjunction with irinotecan (11/40; 27.5%). Epirubicin was added as a third agent in 10.6% (n/H11005 5). Two patients (6.7%) who initially received 5-FU with cis-platinum had to discontinue cis-platinum because of toxicity. According to the pathologic tumor regression grade information available in 73% (27/37) of resected NeoCRT patients, 55.6% (15/27) had a moderate response and 14.8% (4/27) had minimal response to chemoradiation. A complete pathologic response was observed in 21.6% (8/37) of NeoCRT patients who underwent esophagectomy. Of the patients who underwent esophagectomy, 37.8% (14/37) received additional chemotherapy during the follow-up period.

### Surgery

Surgical approaches for esophagectomy included open (76.2%), transhiatal (8.7%), and minimally invasive with thoracic anastomosis (11.9%). A total of 136 patients (90.1%) underwent successful resection of their primary tumor. Failure to undergo resection after neoadjuvant therapy (11/48; 22.9%) was due to disease progression (6/48; 12.5%), treatment-related mortality (2/48; 4.2%), unresectable tumor (1/48; 2.1%), or death not related to treatment (2/48; 4.2%). Resection failures were significantly lower in the upfront surgery group (3.9%; 4/103; p < 0.001) and were due to unresectable primary tumor (2/103; 1.9%) or occult metastases discovered at the time of surgery (2/103; 3.9%). Among the 99 upfront surgery patients who had a resectable tumor, 79.7% (78/99) had a complete (R0) resection compared to 89% (33/37) in the neoadjuvant group (p < 0.001). Incomplete resection was due to a microscopically positive radial margin in 10.8% (4/37) in the neoadjuvant group and 12.1% (12/99) in the upfront surgery group (p = 0.83). The proportion of patients in the upfront surgery group who received subsequent therapy after resection was 30% (30/99). Radiation alone was used in 2% (2/99), chemotherapy alone in 5% (5/99), and combination chemoradiation in 23% (23/99). Postoperative mortality was 2.2% (2/99) in the upfront surgery group and none of the NeoCRT patients died within 30 days of surgery. The treatment-related mortality in the surgery group was lower than the NeoCRT group, but the difference was not statistically significant (p = 0.15).

### Recurrences

The prevalence of local, regional, and distant recurrences at the end of follow-up is outlined in Table 3. Some patients were diagnosed with recurrence at more than one site.
one site. The median recurrence-free interval was slightly longer in the neoadjuvant group, but this difference was not statistically significant (NeoCRT/H11005 25.8/H11006 25; SURG/H11005 19.4/H11006 2 months; p/H11005 0.19) (Fig 3).

Overall Survival
Neoadjuvant therapy did not improve median survival when compared to upfront surgical resection. The median survival for the NeoCRT group was 29.6 months compared to 26 ± 3 months for the upfront surgery group (hazard ratio, 0.79; 95% confidence interval, 0.48–1.32; p = 0.376) (Fig 4). A complete response to chemoradiation was not associated with significantly improved overall survival; however, the sample size available for analysis was small (n = 8; p = 0.36). A subset analysis was performed excluding the 11 neoadjuvant therapy patients who failed to undergo surgery. In the resulting subgroup of patients who successfully underwent surgical resection after chemoradiation (37/48), there was a significant improvement of 17 months in overall survival compared to patients treated with upfront surgery (NeoCRT/H11005 41 ± 15; SURG/H11005 24 ± 8 months; p = 0.0082).

Age over 65 (p = 0.013), positive clinical nodal status (p < 0.001), incomplete resection (p = 0.046), advanced pathologic stage (p < 0.001), pathologic T3-4 status (p = 0.011), and N1 or above pathologic nodal status (p = 0.026) were found to have a significant negative impact on overall survival. In the multivariate model, age over 65 (p < 0.001), positive clinical nodal status (p = 0.003), advanced pathologic stage (p = 0.04), and G3-4 histologic grade (p = 0.043) were significant predictors of poor survival. Neoadjuvant therapy was not a significant predictor of improved survival on both univariate and multivariate analyses. After 1:1 propensity score matching according to patient and tumor factors shown to have a significant impact on survival, 22 matched pairs were created with good concordance (c = 0.78). In this propensity matched cohort, patients who received neoadjuvant chemoradiation were also found to have a similar overall survival as those who underwent upfront surgical resection. Since the propensity-matched subgroup analysis yielded similar results, we decided to use a sample size of 151 in the final analysis despite the discrepancy in the number of patients between the two treatment groups (n = 48 vs n = 103).

Comment
In reviewing our clinical experience with esophageal cancer therapy, we included all patients for whom the initial treatment plan consisted of trimodality therapy and compared them to a cohort of patients who underwent upfront surgical resection. This approach to data analysis differs from the majority (~75%) of previously published retrospective studies which excluded patients who were unable to undergo surgery after chemoradiation from the study population [14]. Series reporting on all neoadjuvant therapy patients, regardless of outcome, differ substantially from this study by either focusing primarily on squamous cell carcinoma, or not providing data on patients treated with surgery alone for comparison. In the absence of effective means to predict treatment response or adverse events from neoadjuvant chemoradiation, we think that analyzing outcomes for all

![Fig 3. Recurrence-free survival for patients treated with neoadjuvant chemoradiotherapy (NeoCRT) (dashed red line) or upfront surgical resection (blue line) (p = 0.19).](image-url)
patients according to initial treatment intent is more reflective of clinical practice. Of our patients who received chemoradiation, 22.9% did not have surgical resection primarily as a result of disease progression or chemoradiation-related mortality (ie, grade 5 toxicity). This proportion is slightly higher than the published average (16.4%) and could explain, at least in part, why no survival benefit was observed in the neoadjuvant group as a whole [14]. This hypothesis is supported by the results of our subset analysis which included only patients who were able to successfully undergo trimodality therapy. In the latter subgroup of 37 patients, neoadjuvant chemoradiation was associated with a significant survival advantage of 17 months over upfront surgical resection. Further analysis of the neoadjuvant patients did not reveal any statistically significant factors that could reliably identify patients who would eventually not undergo resection after trimodality therapy. In the near future, PET/CT may become a viable alternative to pretreatment selection and allow early identification of non-responders. Several small case series and a few reviews have emphasized the correlation between the change in standard uptake value of the primary tumor and a positive response to neoadjuvant therapy [15–19]. At this point in time, questions remain with regards to the optimal timing of repeat PET/CT, and the criteria that should be used to define positive treatment response. With evolving technology and increasing availability, the role of PET/CT in esophageal cancer is likely to expand beyond pretreatment staging.

The results of this study also illustrate some of the potential pitfalls of relying almost exclusively on radiologic investigations for staging before neoadjuvant therapy. Over the past years, our approach to pretreatment staging has been a reflection of the methodology used in most prospective trials of neoadjuvant chemoradiation for esophageal cancer. Of 10 published randomized studies enrolling over 1000 patients, 4 required routine CT scan staging and only 2 of these used endoscopic ultrasound [5, 20–22]. The shortcomings of inadequate pre-treatment staging have already been addressed in detail in meta-analyses [2, 7]. It is clear that, from the patient's standpoint, noninvasive staging is more appealing. However, with staging accuracy ranging between 50 to 60%, CT and PET/CT scans currently cannot provide a clinically reliable estimate of T or N stage [19, 23–26]. Nevertheless, we think that PET/CT still plays an important role in evaluating esophageal cancer patients, especially for distant disease. Our current practice with regard to PET/CT scanning is underestimated in this study. Because of health care system constraints, PET/CT was approved for esophageal cancer patients only over the last 16 months of the study period. Since then, it has been performed in all potentially resectable esophageal cancer patients. It is possible that the staging strategy which prevailed throughout most of the study period had an impact on the overall outcome of the neoadjuvant group. For instance, with laparoscopic staging, small peritoneal metastases may be detected and resectability of advanced gastroesophageal junction tumors can be assessed. As a result, patients may be offered definitive chemoradiation instead of trimodality therapy. Up to 4 neoadjuvant patients who did not undergo resection could have been eliminated from the study population if more extensive staging had been performed.

In meta-analyses, neoadjuvant chemoradiation has been associated with a significant survival advantage in esophageal cancer [7, 27]. When considered individually, 3 out of 6 published prospective trials which included adenocarcinomas showed no significant survival benefit to neoadjuvant chemoradiation. The difference between our results and the earliest positive trial of adenocarcinoma by Walsh and colleagues could be explained by the relatively low 3-year survival after upfront surgery (6% vs 42.5% in this study) [28]. We find the results of the second positive trial (CALGB 9781) difficult to interpret and compare since accrual was only 12% of the planned sample size [5]. The third and latest positive trial (CROSS...
trial) also included mostly adenocarcinoma patients, but the chemotherapy regimen used was different (ie, paclitaxel and carboplatin). In addition, when compared to our cohort, the proportion of patients who completed trimodality therapy was higher (90% vs 77%), the complete response rate was better (32% vs 21.6%), and the complete resection rate was lower for the surgery alone group (67% vs 78.8%) [3]. This combination of factors (ie, different chemotherapy, low treatment failures, high response rate, low R0 resection rate after upfront surgery) could explain why the results of the CROSS trial are different from the current study.

We interpret the study results with caution given the inherent biases associated with retrospective study designs, and the discrepancy in sample size between the treatment groups. As a whole, the neoadjuvant chemoradiation group did not experience a significant survival advantage over the upfront surgery patients. Our treatment failure rate was higher (22.9% vs 16.4%), and the rate of complete response to chemoradiation was lower (21.6% vs 26%) than the average from the published literature [14]. Also, the potential survival benefit typically associated with a complete pathologic response may have been negated by adverse outcomes from neoadjuvant therapy. In the subgroup analysis, patients who successfully completed trimodality therapy had a significant survival advantage. This finding raises questions regarding patient selection for trimodality therapy. Identifying reliable predictors or early indicators of neoadjuvant treatment failure remains a clinical challenge in the multimodality treatment of esophageal cancer. Until this objective is achieved, more diligent pretreatment staging may improve patient selection and allow for more accurate stage-based comparisons between treatment groups. Continued efforts are needed to identify esophageal cancer patients who are most likely to benefit from multimodality therapy.

References

DISCUSSION

DR MARK J. KRASNA (Neptune, NJ): I enjoyed the presentation. I have two questions. I think it's pretty much standard now, not only in the United States but throughout the world, that in order to stage patients before getting neoadjuvant therapy for esophageal cancer, full staging, including esophageal ultrasound, not only should be done to assess the T stage but also can be used to assess the lymph node stage, with an increasing number of patients giving you accuracy in EUS-guided fine needle aspiration (FNA). I noticed in that one graph that you showed us, obviously there was a huge disparity there between the T stage among the two groups and the N. My first question is did you use EUS or have you now since begun using EUS, and along with that, if you're not using EUS-FNA, are you trying something like laparoscopic staging for the adenocarcinomas, for instance?

DR GILBERT: Thank you very much for your question, Dr Krasna. I am, as I believe you are, a proponent of minimally invasive staging of esophageal cancer before starting neoadjuvant treatment. The data presented here spans over several years during which pretreatment staging, beyond imaging and regular esophagogastrscopy, was not routinely performed. Since I began working at our institution, I have been emphasizing the potential usefulness of minimally invasive staging in decision making with regards to neoadjuvant therapy. Even if a given institution's approach to esophageal cancer includes neoadjuvant therapy for all but the earliest stage patients, minimally invasive staging can still provide a basis for more objective and accurate quantification of treatment effect, and better stage-matched comparisons of outcomes. As thoracic surgeons, we may be in an ideal position to acquire staging information in a single procedure as an increasing number of us can safely perform endobronchial ultrasound, EUS, and laparoscopy. Changes to our pretreatment staging protocol are not reflected in this review because it is still relatively recent. In my opinion, it is important to make an effort to obtain the most accurate baseline stage as possible, especially in patients who will be treated with neoadjuvant therapy. This would help reverse the trend seen in most of the past esophageal cancer trials where a minority of patients, usually around 20%, underwent pretreatment staging other than CT scanning. We also have to take into account that some of these trials date back to the 1980s, and that access to the technology necessary for minimally invasive staging was limited or nonexistent. However, in today's clinical environment, these staging modalities are readily available and should become part of the routine assessment of esophageal cancer patients.

DR KRASNA: And because you did show us your subset analysis, and, again, the numbers may be small because you only had 22% responders, but have you looked at the responders and looked at their survival? My guess is, even though there were only 22%, when you look at the 22% responders, you do have a difference in survival there.

DR GILBERT: We did a Kaplan-Meier survival analysis looking at subgroups of patients receiving neoadjuvant chemoradiation, one subgroup being the complete responders and the other subgroup being the partial or nonresponders. There was no statistical difference in survival. For that analysis, we excluded patients who started chemoradiation but did not undergo successful resection due to either disease progression, or toxicity. In the pathologic T stage and N stage, there was a significant shift towards lower pathologic T and N stage in the neoadjuvant chemoradiation group. It is not possible to determine with certainly whether or not this difference is due to treatment effect or if it is due to selection bias. Since 2007, we started treating almost every patient with neoadjuvant chemoradiation. This should have helped decrease the potential for selection bias but we cannot confirm nor deny this using the current dataset.

DR ROSS BREMNER (Phoenix, AZ): Can you comment on your attempt to do a full lymph node dissection? I was struck by two numbers there. One was your limited yield of lymph nodes even though you are doing a transthoracic approach, and, secondly, a fairly high incidence of locoregional recurrence in the surgical arm.

DR GILBERT: Thank you very much for this pertinent question. The actual operative techniques have probably not changed significantly over the span of this study. When I began working at our institution, my lymph node yield was dismal. According to the pathology report, I was supposedly retrieving 5 or 6 lymph nodes per esophagectomy specimen. The clinical relevance of resecting and analyzing a minimum number of lymph nodes has been recently emphasized by the World Esophageal Cancer Consortium. After discussion with our Head of GI pathology, the specimen processing was modified in a way that is similar to the processing of colonic resection specimens. In my understanding, it basically involves enzymatic digestion of the lymph node bearing adipose tissue and dye staining of individual lymph nodes. Lymph node yield subsequently increased exponentially leading us to conclude that the relatively low lymph node yield after transthoracic open esophagectomy may have been artefactual.

DR BREMNER: I'm sure we are all aware of some of the pathology aspects of the lymph node yield, but are you attempting to do a full lymph node dissection or, I hazard to use the term, an en bloc resection?

DR GILBERT: Well, my colleagues and I do not perform a radical en bloc lymphadenectomy as advocated by Drs Altorki and Lerut. The abdominal lymphadenectomy is a modification of the technique described to perform a D2 lymphadenectomy for gastric cancer. Specifically, I leave behind the splenic hilum and peripancreatic lymph node bearing tissue. I think the risks of lymphadenectomy in these anatomic areas exceed the potential benefits in terms of lymph node yield. In the chest, we typically resect all visible lymph nodes up to the tracheobronchial angles. We do not routinely dissect lymph nodes along the recurrent laryngeal nerves or cervical lymph nodes, unless they are clinically positive.