Neoadjuvant Therapy for Cancer of the Esophagus

Robert J. Green, MD, and Daniel G. Haller, MD

Neoadjuvant chemoradiation for cancer of the esophagus is promising but, as yet, of unproven value.

Background: The standard of care for esophageal cancer has historically been surgical resection. However, survival following surgical treatment of esophageal cancer remains poor. In inoperable patients, both radiation therapy and chemotherapy alone and in combination have been used with some success. Consequently, these therapies have been utilized in the neoadjuvant setting to improve palliation and prolong survival.

Methods: The author reviewed the literature regarding clinical trials that employed neoadjuvant chemotherapy and radiation therapy in the treatment of squamous cell carcinoma and adenocarcinoma of the esophagus.

Results: In most patients, surgery alone is noncurative therapy, even when performed with curative intent. Most phase III trials of neoadjuvant therapy have not been designed with adequate statistical power to detect clinically relevant improvement. The available data are insufficient to determine a benefit to preoperative radiation therapy alone. Preoperative chemotherapy with 5-FU plus cisplatin followed by surgery probably offers little or no improvement over surgery alone. Trials of combined preoperative chemoradiation therapy have yielded promising but not definitive results.

Conclusions: Outside of a clinical trial, neoadjuvant therapy for esophageal cancer should be reserved for only a select group of patients. Future clinical trials may determine a role for neoadjuvant chemoradiation and identify more active chemotherapeutic agents and populations most likely to benefit.

Introduction

Esophageal cancers are diverse tumors that exhibit great variations in geographic distribution and incidence rates. A striking recent development has been the increase in the incidence of adenocarcinoma of the esophagus, whereas the incidence of squamous cell carcinomas has been declining. The changing proportion of adenocarcinomas to squamous cell carcinomas is clearly reflected in the steadily increasing proportion of patients with adenocarcinomas entered into clinical trials over the past two decades. The grouping together of both of these distinct tumor subtypes in clinical trials has made interpretation of treatment results somewhat difficult.

Squamous cell tumors of the esophagus occur more often in blacks than whites and are clearly associated with a number of predisposing risk factors including achalasia, caustic injury, and tobacco use, particularly when associated with ethanol intake. Patients with squamous cell carcinoma generally are of a lower socioeconomic status and tend to have a long duration of symptoms consisting of dysphagia and weight loss. Because of their high incidence of tobacco abuse, these patients often present with concurrent or subsequent tumors of the upper aerodigestive tract such as lung cancer or head and neck cancers.

For unclear reasons, adenocarcinomas of the esophagus have been increasing in incidence over the last several decades. While these tumors may arise from normal glandular epithelium of the distal esophagus, they more typically arise in the setting of Barrett’s esophagus. The prevalence of adenocarcinoma in patients with known Barrett’s esophagus may be in excess of 25%. Duration of symptoms is most often brief, there is usually relatively little weight loss, the incidence of disease is higher in men than women, and patients tend to be of a higher socioeconomic status than those with squamous cell carcinoma.

Treatment Overview

The standard of care for esophageal cancer has historically been -- and remains -- surgical resection. The two most common surgical approaches are the total thoracic esophagectomy, in which both the abdomen and chest are entered, and the transhiatal esophagectomy, in which the esophagus is bluntly dissected through the thoracic inlet and the diaphragmatic opening, with the gastroesophageal anastomosis performed in the neck. These two procedures have similar morbidity and mortality. Esophageal resection, however, remains a quite morbid procedure. Because of this, it is reserved for those patients with potentially curable disease and is infrequently used for palliation alone.

Despite improvements in surgical techniques and reductions in procedure-related mortality, survival following treatment of esophageal cancer remains poor. Though five-year survival has improved slightly over the past several decades, it remains less than 15%. For the two thirds of patients with clinically localized disease at presentation, esophagectomy with curative intent is the treatment of choice. However, even for those patients with localized disease, less than 25% are alive at five years.

Because of these poor outcomes and the high rate of both local and distant recurrence, and also because many patients may be poor candidates for a primary surgical procedure, other treatment modalities have been employed for esophageal cancer. Radiation therapy and chemotherapy have been used as individual treatments in patients who never undergo surgery, as single modalities in the neoadjuvant and adjuvant settings, and as combined therapy in the neoadjuvant and adjuvant settings. We focus our discussion on the neoadjuvant uses of chemotherapy and radiation therapy in esophageal carcinoma.

Radiation Therapy

Both squamous cell carcinomas and adenocarcinomas of the esophagus are radiosensitive tumors. Radiation therapy by itself can provide tumor shrinkage and palliation in some patients. Nonrandomized studies have provided conflicting information about the benefit of radiation therapy both for palliation in inoperable patients and as a neoadjuvant treatment.
Five randomized trials compared surgery alone to preoperative radiation followed by surgery.3-7 As seen in Table 1, the results of these trials are somewhat inconclusive, and none show a clear survival benefit. Three of these trials included only patients with squamous cell carcinoma,1,6 one included both adenocarcinoma and squamous cell carcinoma,7 and one did not report pathology type.3

<table>
<thead>
<tr>
<th>Trial</th>
<th>Tumor Type</th>
<th>Power Calculations</th>
<th>Study Arm</th>
<th>Number of Patients</th>
<th>Radiation</th>
<th>Survival Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arno et al8</td>
<td>Squamous + adenocarcinoma</td>
<td>Not reported</td>
<td>Surgery</td>
<td>68</td>
<td>None</td>
<td>8 yr, 57% combined therapy vs 44% surgery alone (uncrit)</td>
</tr>
<tr>
<td>Gignoux et al4</td>
<td>Squamous</td>
<td>Not reported</td>
<td>Surgery</td>
<td>100</td>
<td>None</td>
<td>5 yr, 22% (approaches both arms)</td>
</tr>
<tr>
<td>Laurens et al7</td>
<td>Squamous</td>
<td>Not reported</td>
<td>Surgery</td>
<td>102</td>
<td>None</td>
<td>5 yr, 10% (approx. 50% vs 40%)</td>
</tr>
<tr>
<td>Mei et al9</td>
<td>Unknown</td>
<td>Not reported</td>
<td>Surgery</td>
<td>102</td>
<td>None</td>
<td>5 yr, 95% (combined therapy vs 70% surgery alone (P=0.08))</td>
</tr>
<tr>
<td>Nygaard et al6</td>
<td>Squamous</td>
<td>Not reported</td>
<td>Surgery</td>
<td>41</td>
<td>None</td>
<td>10 yr (survival rate data not available)</td>
</tr>
</tbody>
</table>

*All trials that included radiation therapy vs all arms that did not.*

The two largest trials each included approximately 200 patients. In 1987, Gignoux and colleagues4 from the European Organization for Research on Treatment of Cancer (EORTC) compared surgery alone to 33 Gy of preoperative radiation therapy followed by surgery. While there was improved local control, there was no difference in survival or resectability of tumors. In 1989, Mei et al1 compared surgery alone with 40 Gy of preoperative radiation therapy. They found a five-year survival of 35% in the combined-modality arm compared to 30% in the surgery-alone arm. This difference, however, did not achieve statistical significance. No conclusions can be made regarding local control because the causes of failure were unknown in almost 25% of patients.

Launois et al5 compared 39 to 45 Gy of neoadjuvant radiation therapy to surgery alone and found no difference in five-year survival. Median survivals were not reported. Very little information about patient characteristics was reported, making this trial difficult to interpret. A Scottish study7 using low-dose radiation therapy (20 Gy) found the neoadjuvant therapy to have no effect on any outcome variable.

Nygaard et al6 compared surgery alone to three different neoadjuvant approaches: chemotherapy, radiation therapy, and combined chemoradiation therapy. There was a trend towards improved survival in the radiation plus surgery arm compared to surgery alone (five-year survival was 21% vs 9%, respectively, P=0.08). A combined analysis of all patients receiving radiation compared to all patients not receiving radiation yielded a five-year survival of 19% vs 6%, respectively (P=0.009). This information, however, must be interpreted cautiously, as it was a post hoc analysis.

In summary, there is no conclusive evidence that preoperative radiation therapy improves outcome over surgery alone. However, the doses of radiation used in these studies varied widely, including relatively low and possibly subtherapeutic doses of radiation therapy (20 Gy, 33 Gy, and 40 Gy). In spite of this, it is interesting to note that three of the studies (Mei et al,9 Nygaard et al,6 and Arno et al8) show a trend towards improved survival. None of these studies reported the power calculations that were used in the design of the study, and all were relatively small. They were, therefore, all likely to be underpowered to detect a clinically significant survival difference with a high likelihood of type II error. We therefore find it difficult to conclude with confidence that preoperative radiation therapy is ineffective; rather, the question remains unanswered.

Chemotherapy

Because many patients die of distant disease from early dissemination, which is reflected in continued poor survival despite complete surgical resection with curative attempt, chemotherapy has been used in the neoadjuvant setting to increase cure rates. However, results to date have been disappointing. While various combinations of chemotherapy—typically fluorouracil (5-FU) combined with cisplatin or mitomycin—have shown clinical response rates in excess of 50% in primary tumors, such responses are partial and of brief duration. Nonrandomized studies of chemotherapy followed by surgery have shown pathologic complete response rates from 0% to 10%.2

Three randomized trials compared neoadjuvant chemotherapy with surgery alone (Table 2)6,8,9 and failed to demonstrate a statistically significant increase in survival; however, these studies were small (none with more than 50 patients per study arm) and almost certainly underpowered to detect any clinically important differences. In response to the uncertainty as to the value of preoperative chemotherapy, the Intergroup 0113 trial accrued 467 patients with adenocarcinoma or squamous cell carcinoma of the esophagus.10 Patients were randomly assigned to surgery alone or surgery with preoperative and postoperative 5-FU and cisplatin. This study had a power of 90% to detect an increase in median survival from 12.5 to 17.3 months -- a 38% improvement. The recently published results show no difference in survival, with a median survival of approximately 16 months and two-year survival of approximately 36% in both groups. Therefore, the question as to whether preoperative or postoperative chemotherapy with 5-FU and cisplatin is of benefit has probably been answered. However, the issue is complicated by the fact that newer agents, including the taxanes, have shown good response rates in esophageal cancer and may therefore provide better results when incorporated into the neoadjuvant setting. Furthermore, because cisplatin may be less effective against adenocarcinomas, with higher distant recurrence in adenocarcinomas,11 the mixing of histologic subtypes may be diluting a potential beneficial effect.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Tumor Type</th>
<th>Power Calculations</th>
<th>Study Arm</th>
<th>Number of Patients</th>
<th>Chemotherapy</th>
<th>Median Survival</th>
<th>% Survival Compared to Chemotherapy + Surgery vs Surgery Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feyereisen et al6</td>
<td>Squamous</td>
<td>Not reported</td>
<td>Surgery</td>
<td>41</td>
<td>None</td>
<td>Median survival, not reported</td>
<td>3 yr or 5% vs 0% (Post hoc)</td>
</tr>
<tr>
<td>Shive et al8</td>
<td>Squamous</td>
<td>Not reported</td>
<td>Surgery</td>
<td>59</td>
<td>None</td>
<td>Median survival, not reported</td>
<td>3 yr or 5% vs 0% (Post hoc)</td>
</tr>
<tr>
<td>Stok et al9</td>
<td>Squamous</td>
<td>Not reported</td>
<td>Surgery + chemotherapy</td>
<td>19</td>
<td>None</td>
<td>Median survival, not reported</td>
<td>3 yr or 5% vs 0% (Post hoc)</td>
</tr>
</tbody>
</table>
Chemoradiation as a Single Modality

The combination of chemotherapy and radiation therapy for esophageal carcinoma was initially developed for patients in whom surgery was not an option. Several phase II studies have evaluated the effect of combined chemoradiation therapy without surgery. The chemotherapeutic agent typically used has been 5-FU, usually combined with either cisplatin or mitomycin C. Herskovic and colleagues treated 22 patients with squamous cell carcinoma with cisplatin and 5-FU followed by mitomycin C and bleomycin, given concurrently with a total of 50 Gy of radiation. Median survival was 22 months with a three-year survival of 28%. Coia et al at the Fox Chase Cancer Center treated 57 patients with stage I and II esophageal cancer (both adenocarcinomas and squamous cell) with 60 Gy of radiation over six weeks given with 5-FU and mitomycin C. Three-year survival was 29%. Using sequential therapy (5-FU and cisplatin with a total of 60 Gy sandwiched between chemoradiation cycles), Le Prise and colleagues treated 50 patients with squamous cell carcinoma and found a median survival of 13 months with a two-year survival of 36%.

Non-operative Radiation Therapy vs Chemoradiation

The question of which non-operative therapy -- radiation alone or chemoradiation -- is superior has been tested in three randomized studies comparing these two modalities. A Brazilian group compared radiation therapy alone to combined chemotherapy (5-FU, mitomycin C, and bleomycin) and radiation therapy in 59 patients with squamous cell carcinoma. They found no statistically significant difference. However, the sample sizes were far too small to make any definitive conclusions.

The Eastern Cooperative Oncology Group (ECOG) compared 119 patients with squamous cell carcinoma randomized to 40 Gy of radiotherapy alone or radiotherapy plus 5-FU and mitomycin C. Following therapy, patients had an option for surgical evaluation; those not undergoing surgery received an additional 20 to 26 Gy of radiotherapy. The number of patients undergoing surgery was evenly distributed in both arms. Median survival favored the chemoradiation arm (14.8 months vs 9.2 months, P=0.03) independent of whether or not surgery was performed. Overall survival at two years was 27% in the chemoradiation arm compared with 12% in the radiation alone arm; however, this difference had narrowed to 9% vs 7% at five years.

The largest study addressing the question of which is the best non-operative approach to esophageal cancer was conducted by the Radiation Therapy Oncology Group (RTOG). Most of the patients had squamous cell carcinoma. An early interim analysis found a clear survival benefit to combined-modality therapy, and the randomization process was closed. However, the study remained open to accrue more patients in the combined-modality arm. An updated report was recently published. A total of 123 patients were randomized to receive either 64 Gy of radiation therapy alone or two concurrent cycles of cisplatin 75 mg/m² and 5-FU 1000 mg/m² per day on days 1 to 4 every four weeks with 50 Gy of radiation therapy followed by two identical cycles of chemotherapy every three weeks following radiation therapy. With minimum follow-up time of five years, both median survival (14.1 months vs 9.3 months) and five-year survival (27% vs 0%, P<0.0001) were superior in the combination-modality arm. The additional 69 patients who were not randomized but received chemotherapy and radiation therapy had similar outcomes to the corresponding randomized arm. The data from this trial regarding the development of distant metastases also support the superiority of combined-modality therapy. The rate of distant metastases at two years was 37% for radiation therapy only patients and 21% for combined radiation chemoradiation patients (P=0.0327 unadjusted, P=0.0017 adjusted).

In an attempt to improve on the efficacy of non-operative therapy demonstrated in the RTOG trial, the Intergroup designed a phase II study of chemoradiation followed by concurrent chemotherapy and high-dose radiation for squamous cell carcinoma. Preliminary results were published in 1996. Thirty-seven patients were treated with three-month cycles of 5-FU and cisplatin followed by the combination of 5-FU and cisplatin plus concurrent 64.8 Gy of radiation therapy, a higher dose than administered with chemotherapy in the RTOG trial. Median survival was 20 months, not appreciably better than prior studies. More importantly, toxicity was unacceptably high with six treatment-related deaths. This regimen had originally been intended as the experimental arm of a new Intergroup trial but was abandoned because of this excessive toxicity.

Thus, two important conclusions can be made from these data. First, combined-modality therapy is superior to radiation alone when surgery is not an option. Second, when surgery is not an option, chemoradiation therapy alone appears to result in survival rates similar to the best surgery-alone series. However, the question as to whether non-operative therapy is equal to or better than surgery alone or surgery combined with other modalities may never be answered. There has never been an adequate randomized study comparing patients treated with surgery vs patients treated with non-operative approaches. Retrospective studies have attempted to compare surgical and nonsurgical approaches; however, these all suffer from the selection bias that occurs whenever one attempts to compare groups of patients whose treatment assignment is strongly related to other prognostic factors that influence outcome.

Neoadjuvant chemoradiation

There are many potential advantages to utilization of a multimodality approach to esophageal carcinoma that includes surgery, radiation therapy, and chemotherapy. As noted above, the combination of chemotherapy and radiation therapy in the absence of surgery results in better outcomes compared with radiation therapy alone, most likely as a result of a reduction of distant metastases and perhaps because of radiosensitizing effects. There is a sound rationale for combining chemoradiation and surgery. Following chemoradiation, the likelihood of residual disease in the esophagus is high. Surgical resection, therefore, may contribute to overall treatment outcome by removing residual tumor, and preoperative chemoradiation may improve the poor disease-free and overall survival observed after surgery alone.

Numerous nonrandomized studies evaluated chemoradiation followed by surgery in both squamous cell and adenocarcinomas (Table 3). Most of these used either 5-FU plus cisplatin or 5-FU plus mitomycin C. Radiation doses were generally in the 30 Gy to 60 Gy range. Median survivals generally ranged from 12 to 24 months but were occasionally longer. Most patients were able to undergo resection following their neoadjuvant therapy. Pathologic complete response rates were found in only approximately 25% of patients, thus supporting the potential value of surgical consolidation after initial chemoradiation.

<p>| Table 3. Nonrandomized Prospective Trials of Preoperative Chemoradiation Therapy Plus Surgery |
| --- | --- | --- | --- |</p>
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Number of Patients</th>
<th>Radiation</th>
<th>Chemotherapy</th>
<th>Median Survival (mo)</th>
<th>% Survival (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell</td>
<td>123</td>
<td>64 Gy</td>
<td>Cisplatin, Bleomycin</td>
<td>14.1</td>
<td>27%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>119</td>
<td>40 Gy</td>
<td>5-FU, Mitomycin C</td>
<td>14.3</td>
<td>27%</td>
</tr>
</tbody>
</table>

*Chemoradiation given both preoperatively and postoperatively.
The two most recent nonrandomized studies come from The Johns Hopkins Oncology Center and the University of Pittsburgh. Forastiere and colleagues treated 50 patients with cisplatin (26 mg/m² per day continuous infusion on days 1-5 and 26-30) and 5-FU (300 mg/m² per day continuous infusion on days 1-30) concurrently with 44 Gy (2 Gy/fx in 22 daily fractions) followed by esophagectomy. A total of 94% of patients underwent esophagectomy, and 40% had a pathologic complete response. Toxicity was significant with grade 3 or 4 neutropenia in 60% of patients, with one septic death occurring during chemoradiation. They showed, as have most similar studies, that patients with pathologic complete responses do better than those without. Their overall median survival rate of 31.3 months (two-year survival, 58%) is superior to that seen in most trials and awaits confirmation in larger randomized trials.

Posner et al treated 44 patients with potentially resectable esophageal/gastroesophageal junction adenocarcinoma or squamous cell carcinoma with 5-FU (300 mg/m² per day on days 1-28), cisplatin (20 mg/m² per day on days 1-5 and 24-28), and interferon alfa (3 million units/m² intravenously on days 1-5 and 24-28 and subcutaneous QOD on days 6-23) concurrently with 40 to 45 Gy of radiation therapy. Median survival was 27 months, and toxicity was considered to be tolerable. The authors concluded that their regimen appeared effective but that the value of interferon alfa remained uncertain.

Randomized Studies of Chemoradiation Plus Surgery vs Surgery Alone

Five randomized trials compared neoadjuvant chemoradiation plus surgery with surgery alone (Table 4). Only three of these trials reported power calculations that were used to determine their sample sizes. The largest of these studies did not reach its target sample size and thus had less power than intended.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arm</th>
<th>Median Survival vs Surgery Alone</th>
<th>% Survival Calculations</th>
<th>Power Calculations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forastiere</td>
<td>Chemoradiation + surgery</td>
<td>31 months</td>
<td>90%</td>
<td>0.80</td>
</tr>
<tr>
<td>Le Prise</td>
<td>Chemoradiation + surgery</td>
<td>27 months</td>
<td>80%</td>
<td>0.60</td>
</tr>
<tr>
<td>University of Michigan</td>
<td>Chemoradiation + surgery</td>
<td>30 months</td>
<td>75%</td>
<td>0.75</td>
</tr>
</tbody>
</table>

The French study by Le Prise and colleagues randomized 86 patients with squamous cell carcinoma of the esophagus to surgery alone or preoperative 5-FU (600 mg/m² per day continuous infusion on days 2-5 and 20-25), cisplatin (100 mg/m² intravenously on day 1 and 21), and radiation (20 Gy in 10 fractions over 12 days). Three-year actuarial survival was 19% for the chemoradiation group vs 14% for the surgery-alone group but was not statistically significant. A sample size of 150 patients was originally planned and would have given a 90% power to detect a statistically improvement in two-year survival from 10% to 30%. However, the study was stopped early, leaving only an estimated 70% power to detect the originally planned difference.

The Nygaard study discussed earlier was a four-armed study comparing various combinations of preoperative therapy. The comparison between the chemoradiation plus surgery arm with the surgery-alone arm showed a statistically insignificant improvement in three-year disease-free survival from 9% to 17% (P=0.3). Power calculations were not reported, but these two arms had fewer than 50 patients each. Thus this study was far too small to rule in or out an important treatment effect. In addition, this trial also had a low rate of curative resection when compared with similar trials.

The University of Michigan study, which included patients with both squamous cell carcinoma (25%) and adenocarcinoma (75%), has been reported only in abstract form and has not yet been published in full. The results from this study are encouraging, but further research is needed to confirm these findings.
abstract form. A total of 100 patients were randomized to surgery alone (transhiatal esophagectomy) or preoperative cisplatin (20 mg/m² on days 1-5 and 17-21), vinblastine (1 mg/m² on days 1-4 and 17-20), 5-FU (300 mg/m² on days 1-21), and radiation therapy (1.5 Gy BID on days 1-5, 8-12, and 15-19). Median survival was approximately 17 months in both groups; three-year survival was improved in the combined-modality arm (32% vs 15%) but of borderline statistical significance. Additionally, the group that received combined modality therapy had a reduced risk of locoregional failure. Site of first disease recurrence was locoregional for 19% of the combined-modality arm compared to 39% of the surgery-alone arm (P=0.039).

The two most recent fully reported studies regarding the value of neoadjuvant chemoradiation provide conflicting information. The study of Walsh et al 34 compared surgery alone with preoperative 5-FU (15 mg/kg on days 1-5) and cisplatin (75 mg/m² on day 7) administered concurrently with radiation therapy (40 Gy administered in 15 fractions over three weeks in patients with adenocarcinoma). Of 113 randomized patients, 11 were withdrawn due to protocol violations. Ten of these 11 withdrawals had been assigned to the combined-modality arm. Median survival (16 months vs 11 months, P<0.01) and three-year survival (32% vs 6%, P<0.01) favored the combined-modality group. However, the interpretability of this study is limited by several weaknesses, including small numbers, short follow-up, variable surgical procedures used, incomplete preoperative staging, premature termination based on unplanned early analysis, and large number of withdrawals on the experimental arm. Longer follow-up is required before concluding from this study that neoadjuvant chemoradiation therapy is superior to surgery alone.

Bosset et al 32 reported on 282 patients with squamous cell carcinoma randomized to surgery alone or preoperative cisplatin (80 mg/m² on days 0-2 prior to each course of radiation) and radiation (37 Gy divided into two one-week courses separated by two weeks). The study was designed with a power of 80% to detect an improvement in five-year survival from 15% to 25%, and planned accrual was for 320 patients. Recruitment was stopped early because of a higher than anticipated rate of postoperative mortality in the combined modality group. Median survival was identical (18.6 months) in both groups, as was three-year survival. However, disease-free survival was significantly longer in the combined treatment group (P=0.003). The high incidence of postoperative deaths in the combined-treatment group may partially explain why overall survival was not superior. Additionally, only a single chemotherapy drug was administered, and the radiation dose and schedule were somewhat atypical. Thus, while this trial did not show a conclusive survival benefit, it certainly does not rule one out. As its authors conclude, "preoperative chemoradiotherapy merits consideration as an adjuvant treatment for squamous-cell esophageal cancer."

Conclusions

How are we to interpret the data regarding neoadjuvant treatment for esophageal carcinoma? In interpreting any of these results, one must be aware that while often grouped together, squamous-cell carcinoma and adenocarcinoma are different diseases that occur in patients with markedly different comorbidities.

The data support several conclusions. First, surgery alone, in most patients, is not curative therapy, even when performed with curative intent. Second, both chemotherapy and radiation show activity against esophageal cancer. Third, combined chemoradiation therapy when used in the non-operative setting appears to be superior to radiation therapy alone and can be delivered with tolerable toxicity. Fourth, adequate studies have not been done to rule in or out a benefit to preoperative radiation therapy alone. Fifth, preoperative chemotherapy with 5-FU plus cisplatin followed by surgery probably offers little or no improvement over surgery alone, although new drug combinations may prove to be more effective.

However, we are still left with the question of whether combined-modality preoperative chemoradiation and surgery is superior to surgery alone. How can we interpret the randomized trials that address this question? Those that show no benefit either are underpowered or suffer from other weaknesses that do not allow them to conclusively rule out a benefit. The Walsh trial, which provides evidence of benefit, suffers flaws, particularly short follow-up. Clearly, further trials will be required before recommending neoadjuvant therapy as standard treatment for all patients with operable esophageal cancer.

What are the relevant endpoints that should be tested? We would consider an absolute increase of approximately 10% or greater in overall survival to be a clinically important and achievable difference. Certainly, in other tumors such as breast and colon cancer, similar or smaller absolute survival benefits have been considered important and achievable. A recent activated trial will hopefully provide more definitive answers to the questions raised by smaller studies of neoadjuvant chemoradiotherapy. In 1997, the Cancer and Leukemia Group B (CALGB) initiated a study to assess the value of neoadjuvant chemoradiation (cisplatin and 5-FU with concomitant radiation therapy) plus surgery vs surgery alone in esophageal adenocarcinoma and squamous-cell carcinoma. The trial was planned with a power of 90% to detect an increase in five-year survival from 20% to 32%. Planned accrual is for 500 patients and should take five years to complete.

Unfortunately, this trial does not directly address quality-of-life issues. We would argue that measurements of quality of life are important in the assessment of treatments for esophageal cancer and should be prospectively assessed in any study comparing treatment modalities. Clearly, in a situation where both the disease and its therapy can cause significant morbidities, quality of life should be factored into any decision about which treatment to pursue.

We are thus left with more questions than answers. Until more definitive information becomes available, we believe that the role of chemoradiation therapy, outside of a clinical trial, should be reserved for two groups of patients: those in whom primary surgery is technically not possible but who may be resectable following chemoradiation, and those who are not operable candidates.

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