Carcinoma of the Esophagus Part 2: Adjuvant Therapy

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The two general approaches are used to treat esophageal cancer: primary treatment (surgical or nonsurgical) and adjuvant treatment (preoperative or postoperative). Due to differences in the patient populations selected for surgical or nonsurgical therapies, which may bias the results against nonsurgical therapy, it is difficult to determine the best treatment approach for this disease. The standard of care is either surgery alone or primary combined-modality therapy. Based on a nonrandomized comparison of the data from recent intergroup trials, the results of these two approaches are similar. For patients treated without surgery, the intergroup INT 0123 trial will determine whether higher doses of radiation are of benefit. No clear survival advantage has been seen with preoperative or postoperative adjuvant radiation therapy alone or chemotherapy alone. The randomized trials comparing preoperative combined-modality therapy vs surgery alone reveal encouraging results for the combination approach but need further confirmation. For patients treated with combined-modality therapy, the ideal regimen remains to be determined. Part 1 of this two-part review, which appeared in last month’s issue, centered on primary therapy for esophageal carcinoma. This part explores the rationale for and results of adjuvant therapy. [ONCOLOGY 13(10):1415-1427, 1999]

Introduction

Two general approaches are used to treat esophageal cancer: primary treatment (surgical or nonsurgical) and adjuvant treatment (preoperative or postoperative). Primary treatments include surgery alone, radiation therapy alone, and radiation therapy plus chemotherapy (combined-modality therapy). Adjuvant therapies include preoperative or postoperative radiation therapy, preoperative chemotherapy, and preoperative combined-modality therapy. The first part of this two-part review, which appeared in last month’s issue, focused on primary therapy for esophageal cancer. This second part examines the rationale for and results of adjuvant therapy.

Adjuvant Radiation Therapy Without Chemotherapy

The rationale for using adjuvant radiation therapy is based on the patterns of failure following potentially curative surgery in patients with clinically resectable esophageal cancer. Unfortunately, few surgical series have reported these data.

The rates of local failure in the surgical control arms from the preoperative radiation therapy randomized trials of Mei et al[50] and Gignoux et al[51] were 12% and 67%, respectively. Local failure rates in the surgical control arm from the postoperative radiation therapy randomized trial of Teniere et al[52] were 35% for patients with negative locoregional lymph nodes and 38% for patients with positive nodes.

The surgical control arm of the intergroup INT 0113 trial provides a modern, more relevant baseline for the results of surgery alone. As discussed in part 1 of this article, the rate of local failure was 31% in patients with an R0 resection, and the total rate of local failure (including the additional 30% of patients with persistent disease) was 61%.

In summary, although the majority of patients with esophageal cancer die of distant metastasis, the incidence of local failure following surgery alone is high enough to examine the use of adjuvant radiation therapy.

Preoperative Radiation Therapy

Six randomized trials have assessed the value of preoperative radiation therapy in patients with

Overall, preoperative radiation therapy did not increase the resectability rate. Only two series reported local failure rates. Although Mei and colleagues[50] found no difference in local failure, Gignoux et al[51] did report a significant decrease in local failure (46% vs 67%) in patients who received preoperative radiation therapy compared with those treated with surgery alone.

Two series showed an improvement in survival. The study by Nygaard and associates was a four-arm trial in which patients were randomized to chemotherapy (cisplatin (Platinol)/bleomycin (Blenoxane) × 2 cycles), radiation therapy, combined-modality therapy, or surgery alone.[16] Patients who received preoperative radiation therapy (with or without chemotherapy) demonstrated a significant improvement in overall 3-year survival rate compared with those who did not receive radiation (18% vs 5%; P = .009). Of the 48 patients given preoperative radiation therapy without chemotherapy, 20% were alive at 3 years; however, this benefit did not reach statistical significance. Therefore, this was not a pure radiation study, and the benefit may have been due, in part, to the chemotherapy.

Huang et al reported a similar improvement in survival in patients who received preoperative radiation therapy vs those who did not undergo such therapy (46% vs 25%); however, a statistical analysis was not performed.[55] A recent meta-analysis from the Oesophageal Cancer Collaborative Group also showed no clear evidence of a survival advantage with preoperative radiation.[56]

There have been many criticisms of the randomized trials of preoperative radiation therapy. For example, conventional doses of radiation therapy were not used. Also, none of these trials allowed an adequate interval between the completion of radiation therapy and surgery. In general, a 4- to 6-week interval is recommended. The use of these unconventional techniques precludes a meaningful analysis of radiation-related morbidity from being performed.

In summary, since only two of the six series of preoperative radiation therapy have reported local failure rates, it is difficult to draw firm conclusions regarding the influence of this therapy on local control. Two series have reported an improvement in survival; in one of these studies, half of the patients received chemotherapy, and the other series did not perform a statistical analysis. Four of the six series found no advantage of preoperative radiation with respect to overall survival. Nonrandomized trials from Yadava et al[57] and Sugimachi and associates[58] also report no survival benefit.

Thus, based on the available randomized, albeit limited, trials, preoperative radiation therapy does not appear to significantly decrease local failure or improve survival.

Postoperative Radiation Therapy

Nonrandomized trials have reported encouraging results with postoperative radiation therapy. For example, in a study by Kasai et al, patients with lymph node-negative disease had a 5-year survival rate of 88%.[59] Yamamoto et al reported a 2-year local control rate of 94% in node-positive patients.[60]

Only two randomized trials have been published that were limited to patients treated in the adjuvant setting. Teniere and colleagues[52] reported 221 patients with squamous cell esophageal carcinoma randomized to surgery alone or surgery plus postoperative radiation therapy (4,500 to 5,500 cGy at 180 cGy/fraction). With a minimum follow-up of 3 years, postoperative radiation had no significant impact on survival.

The second randomized trial, by Fok et al,[61] included patients with squamous cell carcinoma and adenocarcinoma. It should be emphasized that patients with both curative and palliative resections were included in this series. Although the total dose of radiation was conventional, the dose per fraction (350 cGy/fraction) was not. The addition of postoperative radiation therapy did not significantly decrease local or distant failure or improve median survival.
Postoperative radiation therapy is sometimes recommended for patients with positive locoregional lymph nodes. Although the data from Teniere et al[52] support the use of postoperative radiation therapy for decreasing local failure, the benefit was limited to patients with negative lymph nodes. In this subset of patients, postoperative radiation therapy decreased the local failure rate from 35% to 10%. There was no significant effect of postoperative radiation in patients with positive nodes.

In summary, although the limited available data suggest that adjuvant postoperative radiation therapy may decrease local failure in node-negative patients, it has no impact on overall survival. The only established role for postoperative radiation therapy is in patients with positive margins. In patients selected for treatment with postoperative radiation, based on the positive survival results from combined-modality therapy trials, such as Radiation Therapy Oncology Group (RTOG) 85-01, it is reasonable to combine systemic chemotherapy with radiation.[5,6]

**Preoperative Chemotherapy**

Given the advantage in local control and survival when systemic chemotherapy is added to radiation therapy, two randomized trials were designed to examine the role of preoperative chemotherapy compared with surgery alone in patients with clinically resectable disease. In the Dutch trial, patients who received two cycles of preoperative cisplatin and etoposide experienced a significant increase in median survival over those treated with surgery alone (19 vs 11 months; P = .002).[46]

These results contrasted with those of the INT 0113 trial (RTOG 89-11), which randomized patients who underwent an R0 resection to receive two cycles of preoperative fluorouracil (5-FU)/cisplatin or surgery alone. This trial found no differences between the two groups with respect to median survival (15 vs 16 months), overall survival at 2 years (35% vs 37%) or 5 years (20% vs 20%), incidence of postoperative death (7% vs 6%), or local failure (32% vs 31%).[47]

In summary, preoperative chemotherapy as delivered in the above randomized trials, shows no survival benefit. At present, therefore, preoperative chemotherapy remains investigational.

**Preoperative Combined-Modality Therapy**

Given the limited success of radiation therapy when used as either a single modality or in the adjuvant setting (preoperatively or postoperatively), a number of investigators have explored the use of systemic chemotherapy in conjunction with preoperative radiation therapy. There is a strong rationale for this combination—the objective response rate of 40% to 60% in patients with metastatic disease, the observation that the majority of patients with esophageal cancer die of distant metastasis, and the fact that many of the active agents in esophageal cancer (ie, 5-FU, cisplatin, mitomycin [Mutamycin], and paclitaxel [Taxol]) are radiation sensitizers.

Combined-modality therapy has been used both in the preoperative setting and as a primary, nonsurgical treatment. In the preoperative trials, patients had clinically resectable disease, whereas in the nonsurgical trials, most patients had clinically unresectable disease. This selection bias precludes a meaningful comparison of the two approaches.

Furthermore, many of the preoperative combined-modality regimens have employed accelerated courses of radiation (either twice-daily administration or large fraction sizes [> 200 cGy]) plus a short but intensive course of systemic chemotherapy. Some programs have used more conventional fractionation (180 to 200 cGy/d) and moderate total doses of radiation (4,000 to 5,000 cGy).

In contrast, the nonsurgical combined-modality regimens have commonly used conventional fractionation and moderate to high doses of radiation (5,000 to 6,480 cGy) plus longer but less intensive chemotherapy regimens. Some of these regimens have included neoadjuvant chemotherapy prior to the start of the combined-modality therapy.[12,22,62]

**Nonrandomized Trials**
In general, the nonrandomized series of preoperative combined-modality therapy have used two treatment approaches. Patients either undergo a planned operation (Table 1) or, for a variety of reasons, are selected for an operation (Table 2). The results of these two approaches must be analyzed separately since the selection factors for surgery may have an impact on the results.

This discussion will focus on series that are limited to patients with clinically resectable disease and will exclude series including patients with metastatic disease.[63] Most of the trials use 5-FU/cisplatin-based chemotherapy. Recent trials have used taxane-based chemotherapy[23,64-66]; these studies will be discussed as well. Posner and colleagues have added interferon to the regimen,[67] and Nesbitt et al deliver neoadjuvant paclitaxel prior to the start of preoperative combined-modality therapy.[65]

The results of selected phase II series in which patients underwent preoperative combined-modality therapy followed by a planned operation are summarized in Table 1. The seminal trial, performed by Leichman and colleagues at Wayne State University, focused on 21 patients with squamous cell carcinomas.[68] Patients received 3,000 cGy of radiation therapy at 200 cGy/d plus two cycles of concurrent 5-FU and cisplatin. If residual tumor was noted at surgery, an additional 2,000 cGy was delivered postoperatively.

In the 19 patients who underwent an operation, the pathologic complete response rate was 37%, and median survival was 18 months. In addition to an operative mortality of 27%, 48% of patients required hyperalimentation during preoperative therapy.

This pilot trial was expanded by the Southwest Oncology Group (SWOG 80-37) to include 113 patients with squamous cell carcinoma.[69] Of these patients, only 71 underwent an operation. The pathologic complete response rate was 16% and operative mortality was 11%. Despite a 3-year actuarial survival rate of 16%, all patients were dead of disease within 4 years.

Since those initial reports, a variety of treatment approaches have been developed. Most of these have achieved pathologic complete response rates of approximately 25%.

An intensive combined-modality regimen employing hyperfractionated radiation was described by Urba et al and Forastiere and associates[70-72] at the University of Michigan, as well as by Shahab and colleagues at Ellis Fischel Cancer[73] and Adelstein et al at the Cleveland Clinic.[74] Some of these more intensive regimens achieve higher pathologic complete response and survival rates, usually with a corresponding increase in acute toxicity.

For example, Raoul et al reported a 56% complete pathologic response rate and a 52% 3-year survival rate but a 63% incidence of grade 3+ acute toxicity. In the series of Adelstein et al, patients received preoperative accelerated fractionation (150 cGy twice daily to 4,500 cGy) plus 5-FU/cisplatin.[75] The complete response rate (27%) and 3-year survival rate (44%) were comparable with the results of other studies using conventional fractionation; however, the surgical mortality of 18% was higher.

In addition to the different treatment schedules, there are also variations in surgical techniques among the trials. The University of Michigan investigators use transhiatal esophagectomy, whereas most others advocate the Ivor-Lewis approach. Transhiatal esophagectomy is a more conservative approach compared with the Ivor-Lewis procedure since the thorax is not entered in the former. There is much debate in the surgical literature as to the relative benefits and risks of these two approaches; an analysis of this controversy is beyond the scope of this review.

More conventional doses and techniques of chemotherapy and radiation therapy have been recommended by Stahl et al,[76] Jones et al,[77] Forastiere et al,[78] and Bates et al.[79] Bates and associates also addressed two additional issues: (1) Does surgical resection improve overall survival? (2) Can preoperative endoscopy and biopsy accurately identify those patients who are likely to have a pathologic complete response? The 3-year survival rate was 65% in patients who achieved a pathologic complete response, as opposed to 25% in those who did not respond completely. Regarding the issue of preoperative staging, preoperative
endoscopy and biopsy had a false-negative rate of 41%. Therefore, this technique was not helpful in determining the need for further therapy. The nonrandomized study of Bates et al suggested that, with preoperative regimens (which use modified, as opposed to full, doses of chemotherapy and radiation), surgery is an important component of therapy.

In some trials, patients were selected for surgery based on their overall medical status and response to preoperative therapy (Table 2). Gill and colleagues attempted to determine whether the addition of surgery following combined-modality therapy was beneficial. In their series, patients received two cycles of 5-FU, cisplatin, and radiation therapy.[41] Patients who were treated either palliatively or were medically inoperable were excluded from having surgery; therefore, patients selected for surgery had more favorable prognostic features. Although the differences were not statistically significant, the local and distant failure rates were higher in the patients who underwent surgery than in those who did not have surgery.

Using a similar approach of limiting surgery to patients who responded to preoperative therapy and delivering higher radiation doses to nonresponders, Kavanagh and associates reported that patients who underwent surgery had a lower local failure rate than those who were not treated surgically (24% vs 44%). However, there were no differences in distant failure or median survival.[80]

The 1992-1994 Patterns of Care Study reported a significant improvement in survival in patients selected to receive preoperative combined-modality therapy, compared with those treated with combined-modality therapy alone.[81]

Randomized Trials

Three randomized trials have compared preoperative combined-modality therapy with surgery alone in patients with clinically resectable disease (Table 3).[82-84] Urba and associates at the University of Michigan randomized 100 patients (75% with adenocarcinoma) to either (1) preoperative cisplatin (20 mg/m² on days 1 to 5 and days 17 to 21), vinblastine (1 mg/m² on days 1 to 4 and days 17 to 20), 5-FU (300 mg/m²/24 h on days 1 to 21) and concurrent radiation therapy (150 cGy twice daily to 4,500 cGy), followed, on day 42, by a transhiatal esophagectomy; or (2) surgery alone.[82] With a median follow-up of 1.82 years in surviving patients, the preliminary report revealed no benefit of preoperative combined-modality therapy over surgery alone with respect to median survival (1.46 vs 1.48 years) or estimated 2-year survival (41% vs 36%).[82]

These results have recently been updated in abstract form.[84] With a median follow-up of 5.2 years in the 19 living patients, preoperative combined-modality therapy did not improve median survival (1.41 vs 1.46 years). However, univariate analysis showed a n improvement in 3-year survival in patients given preoperative therapy (32% vs 15%; P = .07), which was of borderline statistical significance. By multivariate analysis, this survival benefit reached statistical significance (P = .04). Preoperative combined-modality therapy also significantly decreased the rate of local recurrence (19% vs 39%; P = .04).

In the series from Dublin, Walsh et al also reported a significant survival benefit with preoperative combined-modality therapy. In this trial, 113 patients with adenocarcinoma of the middle or distal esophagus (including the cardia) were randomized to undergo surgery preceded by two cycles (weeks 1 and 6) of 5-FU (15 mg/kg/24 h on days 1 to 5), cisplatin (75 mg/m² on day 7) plus concurrent preoperative radiation therapy (267 cGy/d to 4,000 cGy) or to treatment with surgery alone.[83] Surgery was performed 8 weeks from the start of chemotherapy, and a variety of operations were allowed.

Combined-modality therapy was well tolerated, with a 15% incidence of acute grade 3+ toxicity. Operative mortality in patients treated with combined-modality therapy was 9%, as compared with 4% in patients undergoing surgery alone. With a median follow-up of 18 months in surviving patients, there was a significant improvement in both median survival (16 vs 11 months; P = .01) and 3-year survival rate (32% vs 6%; P = .01) with preoperative therapy compared with surgery alone.

The major criticisms of this trial are the high operative mortality (9%) in the combined-modality arm.
and the low 3-year survival rate (6%) in the surgical control arm. In the surgical control arm of INT 0113 (RTOG 89-11), the 3-year survival was 25% and operative mortality was 6%; these figures are more consistent with most other modern reports of surgery alone.

The third randomized trial of preoperative combined-modality therapy was reported by Bosset et al from the European Organization for Research and Treatment of Cancer (EORTC).[85] A total of 282 patients with clinically resectable squamous cell carcinomas were randomized to preoperative combined-modality therapy plus surgery or surgery alone. The preoperative regimen included 370 cGy × 5 of radiation, followed by a 2-week rest and another 370 cGy × 5. Chemotherapy was limited to cisplatin (80 mg/m²) given 0 to 2 days prior to starting radiation therapy.

With a median follow-up of 55 months, patients who received preoperative combined-modality therapy had a significantly higher 3-year disease-free survival rate than those treated with surgery alone (40% vs 28%), as well as a significantly better local disease-free survival rate (relative risk, 0.6). However, the combined-modality group showed no improvement in median survival (19 months) or overall 3-year survival (36%) compared with the group treated with surgery alone.

It must be emphasized that this combined-modality therapy regimen was unconventional in design. Not only was the radiation administered as a split course and delivered with unusually high doses per fraction, but also the doses of chemotherapy were inadequate for systemic therapy. Thus, it is not surprising that this regimen did not improve survival.

Although two of the three randomized trials reveal a survival advantage of preoperative combined-modality therapy, since they are limited by a small number of patients and short follow-up, their results should be interpreted with caution. In order to help clarify this controversy, the Intergroup has developed a randomized trial of preoperative combined-modality therapy (Cancer and Leukemia Group B [CALGB] C9781). This is the follow-up trial to INT 0113. The preoperative regimen is based on the combined-modality arm from RTOG 85-01 and will use conventional 5-FU/cisplatin and 5,040 cGy of radiation (Figure 1). Since preoperative chemotherapy was not beneficial in INT 0113, the control arm in CALGB C9781 is surgery alone.

**Incorporating New Agents Into Combined-Modality Regimens**

Fluorouracil has been the most widely used systemic agent in the treatment of esophageal cancer. New chemotherapeutic agents are being developed and used clinically in esophageal cancer. Paclitaxel-based regimens have achieved favorable response rates in patients with advanced disease and their incorporation into preoperative combined-modality regimens has shown encouraging results.[64-66]

A concern with the use of paclitaxel-based combined-modality regimens has been an increase in acute radiation esophagitis seen in the initial reports. For example, Safran et al reported a 9% incidence of acute esophagitis with a 3-hour infusion of paclitaxel.[66] However, more protracted infusions appear to be better tolerated. For example, in the ongoing, phase I, dose-escalation trial using a 96-hour paclitaxel infusion plus cisplatin and 5,040 cGy of radiation (Figure 1), no patient has experienced grade 3+ esophagitis at the 80-mg/m² dose level of paclitaxel.[23]

As with combined-modality regimens in other gastrointestinal cancers, the development of the ideal regimens and schedules for esophageal cancer remains an active area of clinical study.

In summary, the preoperative combined-modality approach is encouraging. The most intensive regimens appear to have the greatest benefit in phase II trials but are also associated with the highest incidence of toxicity. Two of the three randomized trials indicate that preoperative combined-modality therapy confers a survival advantage. However, in the trial by Urba et al[82,84] this benefit reaches significance only by multivariate analysis, and the trial by Walsh et al[83] has an unusually low survival rate in the surgical control arm. Both trials are limited by a relatively small number of patients and short follow-up.

With further maturation of these randomized trials and the future results of the intergroup trial
CALGB C9781, the role of preoperative combined-modality therapy will be better defined. In the interim, preoperative combined-modality therapy remains a reasonable but investigational approach.

**Conclusions**

Due to selection bias inherent in the studies of nonsurgical and surgical therapies, it is difficult to determine the best treatment for patients with esophageal cancer. The standard of care is either surgery alone or primary combined-modality therapy. Based on a nonrandomized comparison of the data from the recent intergroup trials, the results of these two approaches are similar.

For patients treated with a nonsurgical approach, the INT 0123 trial will determine whether higher doses of radiation are of benefit. There is no clear survival advantage with preoperative or postoperative adjuvant radiation therapy alone or chemotherapy alone.

The randomized trials show a benefit of preoperative combined-modality therapy plus surgery over surgery alone. However, these results need further confirmation. For patients treated with preoperative combined-modality therapy, the ideal operative technique and combined-modality regimen remain to be determined.

**References:**


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