Management of Esophageal Cancer

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The standard approaches of surgery or radiotherapy cure only a minority of patients with esophageal cancer. Because of these poor results and the frequent systemic pattern of recurrences, combined-modality therapy

**Introduction**

In 1995, 12,100 new cases of esophageal cancer were diagnosed in the United States, and the vast majority, 10,900 patients, will die of the disease.[1] Esophageal cancer represents 2% of American cancer deaths and 9% of deaths due to gastrointestinal cancer.[1] In Western countries, there is a clear association between the development of squamous cell carcinoma of the esophagus and the abuse of tobacco and alcohol.[2] Although esophageal squamous cell cancer remains relatively uncommon in the United States, it is a leading worldwide cause of cancer, with a particularly high incidence observed in northern China, the Caspian Littoral, and the Transkei province of South Africa.

Adenocarcinoma of the esophagus, which in the past represented only a small proportion of cases of esophageal cancer, is rapidly overtaking squamous cell carcinoma as the predominant disease histology in the United States and currently represents half of newly diagnosed cases. Indeed, esophageal adenocarcinoma poses a potentially daunting health care problem, with cases increasing at an annual rate exceeding that of any other malignancy, including malignant melanoma.[3] Although Barrett's esophagus is one established premalignant precursor of esophageal adenocarcinoma, the factors responsible for the rapid rise in the incidence of adenocarcinoma have yet to be determined. Recent epidemiologic studies have implicated obesity[4] and tobacco abuse[5] as potential risk factors for the development of adenocarcinoma of the esophagus. The epidemiologic factors responsible for the geographic variability in the incidence of esophageal squamous cell cancer, including potential dietary and environmental carcinogens, also remain indeterminate.

**Surgical Management**

The prognosis for patients with esophageal cancer treated with the standard approaches of surgery or radiation therapy is poor. The poor prognosis for patients with locally advanced esophageal carcinoma is compounded by poor patient tolerance of therapy, given the comorbid cardiac, hepatic, and pulmonary diseases that accompany long-standing alcohol and tobacco abuse. The largest retrospective series of patients treated with either surgery alone or radiotherapy alone, reviewed by Earlam and Cunha-Melo, reported equally poor 5-year survival rates of 4% for surgery alone and 6% for radiotherapy alone.[6,7] In this early surgical review, the operative mortality for patients treated surgically was a sobering 29%. This significant operative mortality has fueled an ongoing debate regarding the relative efficacy of surgery and radiation therapy for treating local disease, although more recent surgical series from single institutions have reported an operative mortality of 5% to 15% for esophagectomy, with Muller et al citing an overall rate of 12.5% in a review of the surgical literature.[8]

**Optimal Surgical Approach**

The optimal surgical approach in the local management of esophageal cancer has been vigorously debated. Of all esophageal surgical procedures, a laparotomy is performed first, to mobilize the stomach or colon to reconstitute the upper gastrointestinal tract. One standard approach, the Ivor Lewis esophagectomy, employs a separate right thoracotomy for resection of the esophageal tumor, dissection of regional lymph nodes, and intrathoracic gastroesophageal reanastomosis. The use of thoracotomy in surgery for esophageal cancer has been advocated because it allows direct visualization of the mediastinal contents. Another approach, transhiatal esophagectomy, avoids thoracotomy and employs an abdominal approach to resect the esophageal tumor and to dissect mediastinal lymph nodes; it achieves gastroesophageal reanastomosis via a cervical incision.
Proponents of transthiatal esophagectomy argue that this approach reduces operative morbidity and mortality. Surgical series, however, have indicated comparable operative morbidity and mortality whether or not a thoracotomy is performed, and critics of the transthiatal approach argue that an adequate mediastinal dissection cannot be performed without a thoracotomy, particularly for proximal or mid-thoracic esophageal lesions.\[9\]

At the other end of the spectrum, even more radical surgical approaches have been advocated, involving either en bloc resection of the mediastinal contents\[10\] or a three-field lymph node dissection involving resection of the cervical and abdominal lymph nodes in addition to the traditional mediastinal lymph node dissection.\[11\] Although proponents of more radical surgical approaches contend that greater local control may lead to an improvement in survival, this is achieved at the potential cost of higher surgical morbidity and mortality.\[12\] The optimal surgical management of a locally advanced esophageal lesion remains to be established. However, regardless of the approach taken, ultimately, the majority of patients treated with surgery are destined to die of recurrent disease.

Causes of Treatment Failure

The failure of standard surgical or radiation-based therapy, even in patients with disease clinically limited to the locoregional area prior to treatment, is due to both locoregional failure and early systemic dissemination of disease. Autopsy series verify the frequent systemic nature of squamous cell carcinoma, even at or shortly after the initial presentation.\[13\] Despite the brief duration of illness for these patients, the majority were found to have evidence of distant metastatic disease, often in association with locally recurrent or persistent disease, at autopsy. Adenocarcinoma of the distal esophagus or gastroesophageal junction appears to have a natural history of disease similar to that of squamous cell esophageal carcinoma, with equally poor survival after surgical therapy due to a combination of local and systemic disease recurrence.\[14\] The clear need to address the early systemic spread of esophageal carcinoma with systemic treatment has led to the incorporation of chemotherapy into combined-modality therapy employing surgery and radiation therapy.

Neoadjuvant Chemotherapy

Clinical trials of systemic chemotherapy administered preoperatively for esophageal cancer, also termed neoadjuvant or primary chemotherapy, have been undertaken largely because of the poor results achieved with conventional surgery or radiation therapy and the frequent systemic pattern of disease recurrence. Such combined-modality trials employing chemotherapy have taken one of three different approaches: chemotherapy followed by a planned surgical procedure, chemotherapy given concurrently with radiation therapy followed by surgery, and chemotherapy and radiation therapy without subsequent surgical intervention. The rationale, both preclinical and clinical, for neoadjuvant chemotherapy has been reviewed.\[15\]

For patients with esophageal cancer, the approach of preoperative chemotherapy offers several potential clinical benefits, including enhancing resectability by downstaging the primary tumor. Another potential advantage is the assessment of the response to preoperative chemotherapy directly in the primary tumor, making the end point of adjuvant therapy more precise by identifying patients who respond to chemotherapy and who might therefore benefit from further chemotherapy postoperatively. Administering chemotherapy early in the course of disease also has the advantage of treating subclinical but established micrometastatic disease, when chemotherapy is likely to have its greatest impact, given the limited effectiveness of systemic therapy for clinically apparent metastatic disease. A disadvantage of preoperative chemotherapy is the delay in achieving local control of disease.

The rationale for concomitant chemotherapy and radiation has also been reviewed.\[16\] Concurrent chemoradiotherapy potentially allows for the achievement of enhanced local tumor control, as well as the simultaneous treatment of systemic micrometastases.

Although a neoadjuvant, combined-modality approach to esophageal cancer should be reserved for patients at high risk of death due to disease recurrence, most US patients present with high-risk transmural (T3) or lymph node-positive (N1) disease and are therefore candidates for neoadjuvant therapy. Use of the recently available technique of endoscopic ultrasonography may provide greater ability to stage locoregional disease in the esophagus, particularly the degree of local tumor extension by T-stage and the detection of regional node involvement.\[17\] Evaluation by endoscopic ultrasonography is increasingly being used in clinical trials for staging and evaluating response, but assessing response by endoscopic ultrasonography should still be considered investigational.

Preoperative Chemotherapy Followed by Surgery
The use of preoperative chemotherapy for locally advanced esophageal carcinoma has been the subject of numerous clinical trials. Most studies have been single-arm, phase II trials evaluating preoperative chemotherapy in one to up to six cycles followed by a definitive surgical procedure. In early trials, patients with T3 or node-positive disease went on to undergo postoperative radiotherapy. However, in more recent trials, radiotherapy has not been added preoperatively or postoperatively, because randomized clinical trials have failed to show a survival benefit resulting from the addition of radiotherapy to surgery (discussed below). Also, in these more recent trials, chemotherapy has been performed both preoperatively and postoperatively. The results of selected phase II trials of preoperative chemotherapy for esophageal cancer are summarized in Table 1.

### Phase II Trials

Virtually all preoperative chemotherapy trials for esophageal cancer have employed cisplatin (Platinol)-based combination chemotherapy. Although earlier trials treated squamous cell carcinoma, with the increased incidence of adenocarcinoma, both histologies have been treated on preoperative protocols. Early trials combined bleomycin (Blenoxane) with cisplatin and other agents, but the pulmonary toxicity associated with bleomycin and the marginal antitumor activity observed with the combination of bleomycin and cisplatin in preoperative therapy prompted trials of other cisplatin-based combinations. In these trials, major antitumor responses were seen in up to 50% to 60% of patients, with pathologic complete responses in up to 11% of patients. Most patients were operable after preoperative chemotherapy, with an operative mortality ranging from 0% to 24%. Median survival ranged from only 8 to 28 months.

Kelsen et al.[18] reported long-term follow-up of a single trial of 34 patients with squamous cell carcinoma treated preoperatively with the combination of cisplatin, vindesine, and bleomycin. In this study, survival was encouraging, with 18% of patients alive and free of disease at 5 years and no recurrences occurring after 3.5 years, representing a doubling of survival compared with historic surgical controls.[18]

The combination of cisplatin and 5-fluorouracil (5-FU), given by continuous infusion for 4 to 5 days, has also been extensively studied in preoperative chemotherapy trials. Major responses have been observed in 40% to 60% of patients, with pathologic complete responses in up to 11% of patients; the majority of patients had resectable disease after preoperative treatment, with an acceptable operative mortality. Subsequent trials for both esophageal squamous cell cancer and adenocarcinoma combining cisplatin with etoposide (VePesid) and 5-FU, leucovorin and 5-FU, or doxorubicin and etoposide have noted similar response proportions, rates of resectability, operative mortality, and survival comparable to those of 5-FU and cisplatin alone.[19-21] Toxicity in these trials, mainly mucositis, myelosuppression, and nephrotoxicity, has been substantial but tolerable.

Overall, preoperative treatment with cisplatin-based combination chemotherapy achieves a major response in 50% of patients, with occasional pathologic complete responses. The use of preoperative chemotherapy appears to be safe, with no demonstrable adverse effect on surgical outcome. However, the overall survival of patients treated with preoperative chemotherapy has been disappointing, with a median survival ranging from 10 to 28 months in larger series, although a trend toward improved survival has been suggested in these trials.

The duration of chemotherapy delivered in preoperative chemotherapy trials has also undergone evolution. Although earlier trials administered only one to two cycles of chemotherapy preoperatively without subsequent postoperative therapy, more recent trials have given up to three or more cycles of preoperative therapy and two or three cycles of postoperative chemotherapy. The treatment outcome of earlier and more recent trials may not be directly comparable, particularly with regard to the impact of additional cycles of systemic therapy on systemic recurrence.

### Phase III Trials

The role of preoperative chemotherapy in the treatment of locoregional esophageal carcinoma can be clearly defined only in the context of random-assignment trials with a surgery-only control arm. Four small, randomized trials comparing surgery alone with preoperative chemotherapy followed by surgery have been published, and a fifth trial compared preoperative chemotherapy with preoperative radiotherapy (Table 1). Roth et al.[22] randomized patients to receive preoperative chemotherapy with cisplatin, bleomycin, and vindesine vs surgery alone. Reporting in abstract form only, Schlag[23] randomly assigned patients to undergo surgery alone or to receive three cycles of preoperative chemotherapy with 5-FU and cisplatin. Nygaard et al.[24] randomized patients to receive surgery alone, preoperative chemotherapy with cisplatin and bleomycin, preoperative radiotherapy, or preoperative treatment with sequential chemotherapy and radiotherapy. LePrise et al compared surgery alone with sequential preoperative chemotherapy as well as cisplatin and 5-FU and radiotherapy to a dose of 6,000 cGy, given in two split courses.[25] None of these small, randomized trials demonstrated a survival advantage for preoperative
In the study by Roth et al,[22] the subgroup of patients who responded to chemotherapy showed a trend toward improved survival, compared with surgical controls, that nearly reached statistical significance. A prognostic factor analysis identified percentage of weight loss prior to diagnosis and objective response to chemotherapy as predictive of long-term survival. No survival benefit was conveyed by preoperative chemotherapy in the study by Nygaard et al[24] and the patients with the poorest survival at 3 years (3%) received preoperative chemotherapy. Kelsen et al[18] randomly assigned 96 patients to receive treatment with either preoperative high-dose radiotherapy, 5,500 cGy delivered over 5.5 to 6.0 weeks by a multifield technique, or preoperative chemotherapy with cisplatin, vindesine, and bleomycin. In this trial, a survival comparison between the two treatment groups could not be made because the trial design permitted a postoperative crossover to the other treatment modality, and most patients received both chemotherapy and radiation therapy. The actuarial survival rate observed for all patients was 20% at 5 years, which was superior to that of historic controls, with the subgroup of responders to either chemotherapy or radiotherapy showing a trend toward improved survival.

At present, for patients treated surgically, surgery alone remains the standard of care, and the use of preoperative chemotherapy outside an investigational setting cannot be recommended. A conclusive evaluation of preoperative chemotherapy using the best currently available combination chemotherapy regimen awaits the completion of ongoing, random-assignment clinical trials. A national intergroup trial (Intergroup Trial 113) randomizing patients to receive three preoperative and two postoperative chemotherapy cycles with cisplatin and 5-FU vs surgery alone has now been completed, and data analysis of this trial is under way.

**Chemoradiotherapy Followed by Surgery**

The intensification of radiotherapy with concurrent chemotherapy used as a radiation sensitizer, either in the preoperative setting or as definitive local therapy, has been the subject of many single-arm, phase II studies. Recently completed phase III trials have better defined the role of concurrent chemotherapy and radiation in the management of locally advanced esophageal cancer. Preoperative radiotherapy alone, without radiosensitizing chemotherapy, has been the subject of three randomized trials, which compared this approach with surgery alone. None of the trials has demonstrated a survival benefit for preoperative radiotherapy, compared with surgery alone, although one of these trials did show a reduction in local disease recurrence with radiotherapy, which did not result in an improvement in survival.[26-28] Trials of concurrent chemotherapy and radiation prior to esophagectomy have employed cisplatin or mitomycin (Mutamycin) in combination with 5-FU by continuous infusion. The results of selected phase II and phase III trials are outlined in Table 2.

**Phase III Trials**--Wayne State University piloted two regimens for patients with squamous cell cancer: 5-FU/mitomycin and 5-FU/cisplatin, administered for two cycles with 3,000 cGy of radiotherapy in 15 fractions of 200 cGy given concurrently with the first cycle of chemotherapy and followed by esophagectomy.[29,30] Patients with residual tumor in the resected esophagus went on to receive an additional 2,000 cGy of radiotherapy postoperatively. Of a total of 51 patients treated in these trials, 71% to 76% of patients tumors were resectable after treatment, with a substantial operative mortality of 13% to 27%. Pathologic complete responses to chemoradiotherapy were seen in 20% to 24% of patients, and the median survival in both studies was 18 months. Long-term follow-up was reported on patients with a pathologic complete response to treatment with 5-FU, cisplatin, and concurrent radiotherapy, who indeed were the only patients to survive longer than 3 years. All patients eventually succumbed to metastatic disease without evidence of local tumor recurrence in the esophagus,[31] questioning whether esophagectomy contributed to survival. Evaluation of preoperative 5-FU/cisplatin chemoradiotherapy in a cooperative group setting was subsequently performed by SWOG and RTOG. Median survival of all patients was a disappointing 12 to 13 months, and poor 3-year survival ranging from 8% to 16% was achieved.

Forastiere and colleagues at the University of Michigan piloted an intensive, 21-day preoperative trial in which patients with both squamous cell carcinoma and adenocarcinoma were entered on the same protocol.[32] Chemotherapy consisted of 5-FU given by 21-day continuous intravenous infusion, cisplatin given by continuous intravenous infusion on days 1 through 5 and 14 through 19, and vinblastine (Velban) given on days 1 through 4 and 17 through 20. Radiotherapy (3,750 to 4,500 cGy) was administered concurrently over the 21-day treatment program in single- or twice-daily fractionation. After preoperative chemoradiation, patients underwent transhiatal esophagectomy. Curative resection was performed in 84% of patients, with a pathologic complete response rate of 24%.

In a subsequent report of long-term follow-up of these patients, at a median follow-up of 6.5 years,
the median survival was 29 months, with a 5-year survival of 34% (comparable for squamous cell carcinoma and adenocarcinoma).[33] Patients with a partial response to preoperative chemoradiotherapy (with residual viable tumor resected at esophagectomy) also achieved a significant 5-year survival of 32%, suggesting that esophagectomy contributed to long-term survival in these patients. In this trial, in which radiotherapy overlapped with all chemotherapy delivered, toxicity was severe and more common than in earlier trials, in which radiotherapy overlapped with only the first of two chemotherapy cycles. Nutritional support was required in 79% of patients. Subsequent pilot trials have been performed for squamous cell carcinoma and adenocarcinoma, using continuous infusion of 5-FU in combination with cisplatin, mitomycin, and other agents, with radiotherapy doses given up to 6,000 cGy. Comparable rates of resectability, complete response, and survival were observed, but with substantial treatment-related toxicity.[34-37] Overall, in the trials employing preoperative concurrent chemoradiotherapy, major antitumor responses have been reported in 40% to 80% of patients, and consistently pathologic complete responses have been seen at esophagectomy in 25% of patients. Overall median survival in these series has been disappointing, ranging from 11 to 29 months. The contribution of esophagectomy in these trials remains unclear. In the Wayne State University trials, long-term survivors were patients with a complete response to chemoradiotherapy with no local failure, but they died of distant metastatic disease, arguing against the use of esophagectomy. Forastiere and colleagues,[33] on the other hand, observed that after intensive preoperative chemoradiation therapy, significant 5-year survival was observed in both patients with a pathologic complete response and patients with viable tumor resected, indicating that esophagectomy salvaged partial responders to preoperative chemoradiotherapy.

The reason for the divergent results for the Wayne State University and the University of Michigan trials employing preoperative chemoradiation therapy is unclear. Differences in trial designs included a higher dose of radiotherapy, which overlapped with all chemotherapy in the University of Michigan trial, as well as a different schedule of 5-FU infusion, with the University of Michigan trial employing a prolonged, 21-day continuous infusion of 5-FU, rather than two interrupted infusions of 5-FU reported in the Wayne State University series. However, an increase in radiotherapy from 3,000 cGy to between 5,000 and 6,000 cGy and the overlapping of radiotherapy with all cycles of chemotherapy, failed to increase the rate of pathologic complete response in reported preoperative trials. In some trials with cisplatin-based chemotherapy, a high dose of radiotherapy appeared to increase treatment-related toxicity substantially.

Phase III Trials--Based on the high rate of pathologic complete response and the encouraging survival results in these phase II studies, a random-assignment trial comparing surgery alone with preoperative chemoradiation therapy followed by surgery was performed at the University of Michigan and was recently reported in abstract form[38] (Table 2). The chemotherapy regimen of prolonged, 21-day continuous infusion 5-FU combined with cisplatin and vinblastine piloted by Forastiere et al was used, with radiotherapy given in 150-cGy fractions twice daily, to a total dose of 4,500 cGy. At short-term follow-up, no improvement was observed for preoperative chemoradiotherapy, compared with surgery alone, in either time to disease recurrence (0.79 years for surgery alone vs 0.67 years for preoperative chemoradiotherapy) or 2-year survival (36% vs 41%). The trial was designed to detect a relatively large (2-fold) improvement in survival for combined-modality therapy, compared with surgery alone, and only a small sample size (50 patients per treatment arm) was used. A second, small randomized trial comparing surgery alone with preoperative sequential chemotherapy and radiotherapy reported by LePrise et al [25] also failed to show an improvement in survival for combined-modality therapy, compared with surgery alone. Currently, a national intergroup trial comparing preoperative chemoradiotherapy with surgery alone is planned, employing a larger sample size than in earlier trials to detect a more modest difference in survival. Given the potential morbidity associated with preoperative concurrent chemoradiotherapy, and the current absence of a proven benefit for such therapy, this approach remains investigational and cannot be recommended outside the setting of a clinical trial.

Concurrent Chemoradiation Without Surgery

Concurrent chemoradiation as definitive therapy without esophagectomy has also been the subject of several phase II and phase III trials, with selected studies outlined in Table 3. The Wayne State University group piloted a nonoperative trial of 20 patients with squamous cell carcinoma of the esophagus. Esophagectomy after chemoradiotherapy was not planned, based on the operative...
mortality in prior Wayne State University trials and because the pattern of systemic failure in prior trials questioned the contribution of esophagectomy to long-term survival.[31] Patients were treated with 5-FU and cisplatin for two cycles concurrently, with 3,000 cGy of radiotherapy delivered over 3 weeks. Two additional cycles of chemotherapy with mitomycin-C and infusional bleomycin were planned after completion of chemoradiotherapy. An additional boost of radiotherapy (to 2,000 cGy) was administered on completion of chemotherapy. In this series, median survival was 22 months. Nine patients (45%) had persistence of locoregional tumor after treatment. Pulmonary toxicity was prohibitive in this study, leading to the early withdrawal of bleomycin therapy.

Coia et al reported a 10-year experience with squamous cell carcinoma and adenocarcinoma of the esophagus in 57 patients treated with continuous infusion 5-FU and mitomycin, administered for two cycles concurrently with higher dose radiotherapy (6,000 cGy) over 6 to 7 weeks.[39] Median survival was 18 months, with a disease-free survival of 18% at 5 years for patients with clinical stage I to II disease; survival for adenocarcinoma and squamous cell carcinoma was comparable in this series. Local control was reportedly achieved in 70% of patients. Of the 29 patients with recurrence in this series, local failure occurred in 48% of patients, and some component of distant failure occurred in 72% of patients. Severe toxicities were uncommon in this series, but there were two treatment-related fatalities.

Other trials using concurrent radiotherapy in doses ranging from 4,000 to 6,000 cGy, given together with cisplatin or mitomycin in combination with 5-FU, have yielded comparable responses to treatment and survival.[40-44] In addition to trials of definitive chemoradiotherapy for locoregional esophageal cancer, this approach has been studied in patients with unresectable disease. Two randomized trials comparing radiotherapy alone with concurrent radiotherapy and single-agent methotrexate or cisplatin failed to show an improvement in survival for combined chemoradiotherapy vs radiotherapy alone for unresectable disease,[45,46] although the latter trial reported a reduction in local recurrence with chemoradiation vs radiation therapy alone. Evaluation of the combination of 5-FU and cisplatin and concurrent radiotherapy for unresectable disease, compared with radiotherapy alone, continues in an ongoing trial in Europe, sponsored by the EORTC.

**Chemoradiotherapy vs Radiotherapy Alone**

Given the promising results with definitive chemoradiation therapy without a planned esophagectomy for locoregional disease, a nonsurgical, random-assignment trial for locoregional esophageal carcinoma comparing radiation therapy alone with radiation and concurrent 5-FU and cisplatin was conducted by the RTOG. The results were recently published by Herskovic et al.[47] (Table 3). In this study, 60 patients were randomly assigned to receive treatment with radiation therapy alone, and 61 patients were assigned to receive radiation and concurrent 5-FU and cisplatin. Patients with both squamous cell carcinoma and adenocarcinoma were enrolled, although the majority of patients had squamous cell carcinoma. Patients receiving radiotherapy alone were treated with 5,000 cGy, with a boost of 1,400 cGy, to a total dose of 6,400 cGy delivered over 7 weeks in 200-cGy fractions. Patients undergoing concurrent chemotherapy and radiation received 3,000 cGy of radiation, with a boost of 2,000 cGy, for a total dose of 5,000 cGy delivered over 5 weeks. Chemotherapy consisted of 5-FU given by continuous IV infusion for 4 consecutive days on weeks 1, 5, 8, and 11, with cisplatin given on day 1 of each 5-FU treatment course. Radiation therapy, delivered in 200-cGy fractions, overlapped with the first two chemotherapy cycles. The chemotherapy design employed two additional cycles of systemic chemotherapy after chemoradiotherapy was completed.

With a median follow-up of 18 months, a significant median survival benefit was observed for chemoradiation vs radiotherapy alone (12.5 vs 8.9 months). More important, 1- and 2-year survival rates were significantly longer for the combined-modality arm (50% and 38%, respectively) than for the radiotherapy alone group (33% and 10%, respectively). The results strongly indicate that the combination of chemotherapy and radiation is superior to radiation therapy alone.

In a recent update of the survival of patients in this study, 31% of patients treated with chemoradiation were alive at 3 years, compared with 0% of patients treated with radiotherapy alone.[48] A statistically significant reduction in both local and distant recurrence of disease was also noted, favoring combined chemoradiation and radiotherapy. Nonetheless, a high percentage of patients treated with combined chemotherapy and radiation, 44%, had either persistence or recurrence of local disease at 12 months.

The morbidity of chemoradiotherapy was also significantly higher than that of radiotherapy alone, with 64% of patients treated with chemoradiotherapy vs 28% of patients treated with radiotherapy experiencing severe or life-threatening toxicity (mainly mucositis and myelosuppression). One patient treated with chemoradiotherapy died of treatment-related toxicity (1.6%), and there were no
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deaths in the radiotherapy arm. Because of toxicity, only 50% of patients treated with combined-modality therapy received the final planned two cycles of systemic therapy. Supportive evidence of an improvement in median survival for concurrent chemotherapy and radiation compared with radiotherapy alone also comes from a preliminary report of a trial conducted by ECOG comparing radiotherapy alone with radiotherapy and concurrent 5-FU and mitomycin.[49] Furthermore, a small, random-assignment trial by Araujo et al reported a survival advantage for chemoradiation with 5-FU, mitomycin, and bleomycin, compared with radiotherapy alone, for patients with squamous cell carcinoma, which, however, did not reach statistical significance.[50]

Concurrent chemotherapy and radiotherapy as definitive, nonsurgical therapy is curative for squamous cell carcinoma and adenocarcinoma of the esophagus. Although no trial has directly compared chemoradiation with surgery for management of locally advanced esophageal cancer, chemoradiation represents an alternative to surgical management of locally advanced esophageal carcinoma, particularly in patients with T3 or node-positive disease, for whom the prognosis is particularly poor with surgical management. Chemoradiation is clearly superior to radiotherapy alone and is now considered standard care in the nonsurgical setting. The question of whether or not esophagectomy is an obligate part of local disease control after combined chemotheraphy and radiation therapy must ultimately be answered in the context of a random-assignment trial comparing treatment of locoregional disease with surgery or chemoradiation.

Further study of chemoradiotherapy continues for locally advanced esophageal cancer. A recent pilot trial for locally advanced squamous cell carcinoma intensified the treatment by increasing the number of chemotherapy cycles of 5-FU/cisplatin from four to five, with three cycles administered as induction chemotherapy followed by concurrent chemoradiotherapy during the last two cycles. The radiotherapy dose was also increased from 5,040 to 6,480 cGy. Significant treatment-related morbidity and mortality were observed in this trial, and further study of this treatment design using induction chemotherapy was not recommended.[51] A follow-up intergroup trial (INT 123) is currently under way; it compares an escalated radiotherapy dose (6,480 cGy) with the more conventional dose of 5,040 cGy, given together with two cycles of 5-FU/cisplatin during radiotherapy and two cycles of chemotherapy after radiotherapy. The trial is addressing the issue of whether an increase in radiotherapy dose will lead to an improvement in local disease control.

Chemotherapy for Metastatic Disease

Metastatic esophageal carcinoma, which is the clinical presentation at diagnosis in 50% to 60% of patients, is an incurable disease, with a median survival of 5 to 8 months. Squamous cell carcinoma of the esophagus is relatively sensitive to chemotherapy, as shown in trials conducted over the past 20 years (Table 4). Although the majority of studies have evaluated patients with squamous cell carcinoma, recent trials have evaluated patients with both squamous cell carcinoma and adenocarcinoma.

Single Agents

Modest antitumor activity for a broad range of chemotherapy drugs has been seen in patients with esophageal carcinoma, but the duration of response to single-agent chemotherapy is generally brief, on the order of 4 to 6 months. Early chemotherapy trials were performed on small numbers of patients, often in the context of broad, phase I and phase II trials for diverse solid tumors. Such trials also included patients who had undergone prior, often extensive, chemotherapy treatment. More recent trials, however, have been large phase II trials and have generally limited new drug evaluation to patients without prior chemotherapy exposure. In addition, recent studies have employed a population size large enough to quantify a major antitumor response with some degree of statistical significance. Modest antitumor responses, on the order of 10% to 25%, have been observed for the commonly used single agents 5-FU, mitomycin, and cisplatin.

The new antimicrotubular agent paclitaxel (Taxol), a drug with significant activity for breast and ovarian cancer, has recently been studied for squamous cell carcinoma and adenocarcinoma of the esophagus. First identified by Wani et al,[52] paclitaxel is the first organic compound with a taxane ring to have significant clinical cytotoxic activity. Unlike the vinca alkaloids vincristine (Oncovin) and vinblastine, which inhibit microtubular assembly, paclitaxel promotes and stabilizes microtubular assembly. In the first study of paclitaxel for esophageal cancer, Ajani et al reported the results of a joint M. D. Anderson Cancer Center-Memorial Sloan-Kettering Cancer Center trial of paclitaxel, administered at a dose of 250 mg/m² by 24-hour infusion and recycled every 21 days, and granulocyte
colony-stimulating factor (G-CSF [Neupogen]). Fifty-one patients with unresectable or metastatic esophageal cancer were evaluable for response. Paclitaxel had significant antitumor activity, with 16 major responses seen (32%), including a single complete response (2%). Comparable activity was seen for adenocarcinoma and squamous cell carcinoma.

Another alkaloid, the semisynthetic vinca alkaloid vinorelbine tartrate (Navelbine), has also recently been reported to have significant single-agent activity for squamous cell cancer,[54] with responses seen in 25% of previously untreated patients.

Combination Chemotherapy
With modest activity demonstrated for several single chemotherapy agents, combination chemotherapy has also been extensively studied (Table 4). In earlier trials, patients with both locoregional and metastatic disease were treated on the same protocols, with patients with locoregional disease usually undergoing subsequent definitive surgery or radiation therapy.

Cisplatin-Based Combinations—Virtually all studies shared cisplatin as a common agent. Cisplatin-based combination chemotherapy has yielded antitumor activity for metastatic squamous cell carcinoma of the esophagus in the range of 25% to 35%; the response proportion observed for locoregional disease has been consistently higher, on the order of 45% to 75%. Despite higher response rates seen with combination therapy than single-agent chemotherapy, the response duration to combination therapy has been relatively brief, on the order of 4 to 6 months.

The combination of cisplatin and 5-FU (given by continuous infusion for 4 to 5 days) has been studied extensively, based primarily on activity of this regimen for squamous cell carcinoma of the head and neck and because of waning interest in the use of bleomycin-containing regimens due to pulmonary toxicity observed in surgical and radiation therapy protocols. Response is seen in 50% of patients treated preoperatively with 5-FU/cisplatin, whereas for metastatic or unresectable disease, the response is lower, ranging from 35% to 40%. The addition of doxorubicin[57] or doxorubicin and etoposide to 5-FU and cisplatin has also been reported in small series of patients, with the 95% confidence limits of the response proportions comparable to those of 5-FU and cisplatin alone. Despite the increasingly common use of 5-FU plus cisplatin for the treatment of esophageal carcinoma, only a single trial has directly addressed the issue of the comparative efficacy of single-agent cisplatin vs the combination of 5-FU and cisplatin, published only in abstract form.[55] Of 89 patients with unresectable or metastatic squamous cell carcinoma randomly assigned to receive cisplatin alone or the combination of cisplatin and 5-FU, a higher response rate was observed for the combination group (36% vs 11%). However, the higher response rate did not result in any significant difference in survival.

Overall, cisplatin-based combination chemotherapy has significant antitumor activity for esophageal cancer. Response rates are consistently lower for metastatic disease than for locoregional disease (in the context of preoperative trials). Although most trials have evaluated patients with squamous cell carcinoma, more recent trials have evaluated patients with adenocarcinoma. Response rates for adenocarcinoma appear to be comparable to those of squamous cell carcinoma (Tables 1 and 4).

Paclitaxel in Combination Regimens—The significant antitumor response seen with single-agent paclitaxel for squamous cell carcinoma and adenocarcinoma has prompted further trials of the combination of paclitaxel and cisplatin/5-FU. We have observed promising antitumor activity for paclitaxel combination chemotherapy, in particular the suggestion of a substantial complete response rate in preoperative therapy and as treatment of metastatic disease.[58,59] Because of the encouraging results of these studies, further trials evaluating paclitaxel in combination therapy for metastatic disease and preoperative therapy, and as a radiosensitizer in the radiation-based treatment of locally advanced esophageal carcinoma, are under way.

Palliative Treatment

Systemic Chemotherapy
Whereas systemic chemotherapy may offer palliative benefit for metastatic esophageal cancer, the palliation of locally advanced esophageal tumors poses a particular challenge to medical and surgical oncologists, regardless of the presence or absence of metastatic disease. Given the dysphagia and odynophagia to solid foods, and often to semisolids or liquids, patients are nutritionally at risk and may be unable to maintain oral maintenance fluids. If local tumors cause esophageal obstruction patients must cope with intractable nausea and vomiting and are at risk for aspiration. In the setting of metastatic disease and moderate dysphagia, systemic chemotherapy may serve to palliate local disease and to treat metastases, if a response is seen. Although adding concurrent radiotherapy to chemotherapy may increase local control, given the cost and toxicity of
combined-modality therapy, its use is generally reserved for locally advanced tumors in the absence of metastatic disease.

Local Treatment Options

Although a trial of systemic chemotherapy may be appropriate for some patients, patients with more severe dysphagia and limited oral intake may not be able to tolerate the toxicity of chemotherapy or to maintain adequate oral intake over the several weeks to months needed to achieve a response to systemic chemotherapy. Fortunately, a number of local treatment options are available to palliate locally advanced esophageal carcinoma.

Traditionally, radiotherapy (given via a simple two-field technique to a total dose of 3,000 cGy) has been used to palliate the primary esophageal tumor. The delivery of radiotherapy, however, takes several weeks, and a response to therapy may not be seen immediately. Palliation of the local tumor via endoscopy may provide more immediate relief of dysphagia, and frequently used endoscopic techniques include dilatation, endoscopic placement of an esophageal plastic prosthesis or stent, endoscopic laser ablation, and the recently developed technique of endoscopic photodynamic therapy, in which patients receive an IV photosensitizer and then undergo endoscopic exposure to a light source. Palliative benefits have been reported for all these procedures, and their sequential use is generally at the discretion of treating thoracic surgeons or gastroenterologists.

A recent controlled trial compared the complications and benefits of plastic esophageal prostheses with those of the newer expansible metal stents in 39 patients with esophageal carcinoma and 3 patients with malignant esophageal extrinsic compression.[60] A lower complication rate was observed for patients with the metal stents. Palliation of dysphagia, however, was comparable with either approach.

Future Directions

Given the limitations of currently used surgical or radiation therapy-based treatment of esophageal cancer, future improvement lies in the development of better systemic therapy, both to treat metastatic disease and to enhance the effectiveness of radiotherapy by radiosensitization. Future strategies in the treatment of esophageal carcinoma will undoubtedly be based on advances in the understanding of the biochemistry and molecular biology of the disease.

Oncogenes and Tumor-Suppressor Genes

Ongoing studies indicate a potential role for oncogenes and tumor-suppressor genes (including growth factor receptors, growth factor receptor ligands, and cell cycle regulatory factors) in the mechanism of tumorigenesis; they may be important biologic prognostic factors predicting eventual clinical outcome. Laboratory studies have revealed evidence of enhanced expression and amplification of the epidermal growth factor (EGF) receptor gene[61,62] and amplification of the c-myc oncogene[62] in esophageal squamous cell carcinoma. Immunohistochemical studies of EGF and EGF-receptor protein expression in resected esophageal squamous cell cancers have shown that an increased degree of expression of EGF or EGF receptor protein correlates with a poor outcome and poor survival.[63] Increased expression of another ligand of the EGF receptor, transforming growth factor a, also correlated with a poor prognosis in patients treated with surgery.[64] In addition, a high degree of expression of the HER-2 receptor has been demonstrated for esophageal adenocarcinoma and Barrett's esophagus; like the EGF receptor, the HER-2 receptor is also a tyrosine kinase growth factor receptor.[65]

p53

The tumor-suppressor gene p53 has been studied in relation to esophageal carcinoma, with demonstration of p53 mutations in squamous cell carcinoma and adenocarcinoma and in the premalignant lesion of Barrett's epithelium.[66,67] Loss of heterozygosity of the retinoblastoma tumor suppressor gene locus in human squamous cell carcinoma and adenocarcinoma of the esophagus has also been demonstrated.[68] Furthermore, the tumor suppressor genes APC (familial polyposis) and DCC have been shown to have a loss of heterozygosity in esophageal squamous cell carcinoma and adenocarcinoma.[69]

The int-2 oncogene, the fibroblast growth factor-related proto-oncogene, has been shown to be coamplified with the locus hst-1, with the coamplification correlating with poor survival and a high incidence of eventual systemic metastasis in patients with squamous cell carcinoma of the esophagus resected for cure.[70] Finally, the gene encoding cyclin D, involved in cell-cycle regulation, has been shown to be amplified in esophageal squamous cell carcinoma.[71]

New Model for Adenocarcinoma Progression
A recent model of tumor progression for adenocarcinoma of the esophagus was proposed by Blount et al.\[72\] Thirty-two patients with Barrett's esophagus, the premalignant precursor of many esophageal adenocarcinomas, were followed with serial endoscopy and biopsy over 10 years. These patients ultimately developed adenocarcinoma, high-grade dysplasia, or both while under endoscopic surveillance. Based on serial cytogenetic and molecular genetic studies, 17p allelic loss (the locus of the p53 gene) was determined to be an early cytogenetic event, which preceded the development of aneuploidy during neoplastic progression in Barrett's esophagus. Because 17p allelic loss was also frequently associated with mutation of the remaining p53 gene, the authors proposed that loss of the p53 gene was an important early event in neoplastic progression of Barrett's esophagus, leading to genetic instability and resulting in the development of aneuploidy and ultimately invasive carcinoma. The loss of the p53 gene as a potential marker of the eventual development of adenocarcinoma in Barrett's esophagus and other potential markers (including tissue ploidy and cytogenetic abnormalities) are under continuing study and remain areas of active research.

The ultimate goal in studying potential biochemical perturbation of normal growth factor receptor and growth signal transduction pathways is the identification of novel targets for future chemotherapeutic agents. The challenge to improve the treatment of esophageal cancer lies in advancing the effectiveness of systemic therapy.

**References:**


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