Multidisciplinary Approach to Esophageal and Gastric Cancer

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Cancers of the esophagus and stomach are a worldwide problem, constituting the eighth and fourth most common malignancies respectively.1 These cancers tend to be diagnosed late and typically are advanced at presentation. Surgery traditionally has been the mainstay of treatment, although because of the high rate of locoregional and systemic recurrence with surgery alone, chemotherapy and radiation therapy have become integrated into the management of these cancers. Although exact treatment regimens may vary on a regional level, data suggest that the multimodal approach affords the best hope for improved outcomes in patients who have esophagogastric cancers.

ESOPHAGEAL CANCER

Esophageal cancer (EC) is fairly rare in the United States, with an estimated 16,500 new cases and 14,300 deaths in 2008.2 Squamous cell carcinoma (SCC) and adenocarcinoma (AC) comprise the two major histologic subtypes of EC. SCC has a predilection for the proximal and midesophagus, and is more common in endemic parts of the world. SCC is associated with smoking and alcohol abuse. AC tends to occur in the distal esophagus and gastroesophageal (GE) junction, particularly in the setting of gastroesophageal reflux disease (GERD), obesity, or Barrett’s esophagus.3–5

Clinically, patients with EC often present with dysphagia on ingestion of solids, often progressing to difficulty with liquids. Retrosternal pain may be noted. Decreased parenteral intake results, followed by weight loss. Tumor invasion into surrounding structures, such as the laryngeal nerves or tracheobronchial tree, may lead to

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hoarseness or severe coughing spells upon eating that interfere with breathing. Aspiration pneumonia can develop from fluid breathed into the lungs.

An esophagogram is usually the first diagnostic test performed in the work-up of suspected malignancy, and may help differentiate functional causes of symptoms from mass or mechanical causes, such as tumor. Alternatively, esophagogastroduodenoscopy (EGD) may be performed first. This permits direct observation of the tumor and allows for biopsy and brushings to be obtained. Additionally, evaluation of tumor depth and regional nodes can be performed with endoscopic ultrasound (EUS) to stage the tumor and help determine the next course of treatment.  

Additional work-up includes CT of the chest with positron emission tomography using radiolabeled fluorodeoxyglucose (CT-PET). This allows for detection of distant metastases with an accuracy of greater than 90%. It also may allow for the assessment of tumor response to preoperative therapy based on changes in detectable metabolic activity within the tumor. Based on radiographic and histologic studies, EC can be considered localized or metastatic, with treatment based on extent of disease.

**Surgery**

Two surgical approaches are employed commonly in the United States. The Ivor-Lewis esophagectomy (ILE) uses a right-sided thoracotomy and a laparotomy. It allows for visible dissection of the intrathoracic esophagus and surrounding nodal tissue, although it is associated with a higher rate of pulmonary complications. Moreover, because the final anastomosis is in the chest, a postoperative leak can impart a great degree of morbidity. Transhiatal esophagectomy (THE), which involves a laparotomy and a cervical incision and avoids a thoracotomy, is the other commonly used approach to esophageal resection. The esophagus is bluntly dissected from the surrounding mediastinal structures, and the anastomosis ultimately is created in the neck. The largest study on THE recently was published by Orringer and colleagues, who reported a major complication rate of less than 3% in over 2000 operated patients over a 30-year period. Comparisons between the two techniques show that outcomes are ultimately similar in experienced centers, with a direct correlation to both hospital volume and the number of esophagectomies performed annually.

Minimally invasive esophagectomy (MIE) has been proposed as an alternative to ILE or THE. Luketich and colleagues reported their experience with 222 patients who underwent the procedure using thoracoscopic mobilization of the esophagus. In their study, MIE offered results as good as or better than open operation; the authors observed a lower mortality rate (1.4%) and shorter hospital stay (7 days) than most open series. Given these results, a new intergroup trial (ECOG 2202) to assess MIE in a multicenter setting is underway.

Endoscopic mucosal resection (EMR) is a minimally invasive approach to early SCC that is used commonly in Japan. It is applicable in particular to well-differentiated or moderately differentiated SCC confined to the lamina propria. Although there are no large randomized controlled trials evaluating its use in patients who have EC, smaller studies have shown that it may have some applicability to Western populations, even in patients who have AC of the esophagus.

**Definitive, Nonsurgical Treatment**

The use of radiation therapy as definitive treatment for EC has been evaluated in older series, with varying degrees of success. Ultimately, radiation alone in EC yields few survivors. Presently, the use of radiation alone has been relegated largely to patients who are either not surgical candidates or who are in need of palliation.
Additionally, patients who have cervical esophageal tumors that would require total pharyngolaryngectomy to resect, or with extensive mediastinal involvement, may derive some benefit from radiation therapy.

Chemoradiotherapy without surgery has the ability to cure a percentage of patients who have EC, although these tend to be patients who have SCC rather than AC. The landmark RTOG 85-01 study compared radiation alone (64 Gy) versus chemoradiotherapy (50 Gy given with concurrent and adjuvant cisplatin and fluorouracil [5-FU]) in patients who had T1-3N0-1M0 EC. Eighty-two percent of patients had SCC carcinoma; the remainder had AC. Combined modality treatment yielded 5- and 8-year overall survival rates of 26% and 22% respectively; there were no survivors at 5 years in the radiation-alone arm. Distant metastases were reduced from 30% to 16% at 5 years with combined modality treatment. Of note, locally persistent or recurrent disease was the most common cause of treatment failure in both groups, and was seen in 38% of the combined modality arm. In the EST-1282 trial, another study comparing radiation alone with radiation plus chemotherapy, investigators demonstrated an improvement in median survival for those patients receiving both radiation and chemotherapy (14.8 versus 9.2 months). Pattern of recurrence was not reported in this study.

Given the low overall survival and high local recurrence rate even in patients treated with chemoradiation, efforts have been made to increase the radiation dose or intensity of chemotherapy, with the goal of improving rates of local recurrence and distant metastases. Intergroup 0122 increased the radiation dose and added neoadjuvant chemotherapy to concurrent chemoradiation, but was unsuccessful because of treatment toxicity. Intergroup 0123 used the same chemotherapy as the RTOG 85-01 trial, but increased the radiation dose from 50.4 Gy to 64.8 Gy. There was no difference outcome, and there were more treatment related deaths in the high-dose arm. At this time, for patients who have inoperable tumors or in tumors of the cervical esophagus, definitive chemoradiotherapy is administered as per RTOG 85-01, until further studies show improvement in patient outcomes.

**Combined Approaches Including Surgery**

Because EC is characterized by locoregional and systemic recurrence even after resection, investigators have concentrated on treating EC with a bi- or trimodal approach, employing chemotherapy or chemoradiotherapy in addition to surgery, either before or after esophagectomy.

Induction chemotherapy followed by surgery has been compared with surgery alone in the treatment of EC. The American Intergroup 0113 trial was a multi-institutional randomized trial comparing 213 patients who received preoperative chemotherapy followed by surgery with 227 patients who underwent surgery alone for local and operable EC. Preoperative chemotherapy included three cycles of cisplatin and 5-FU. Surgery was performed within 4 weeks after completion of the third cycle. Patients also received two additional cycles of chemotherapy after the operation. Patients assigned to surgery alone underwent the same operations as those patients who received preoperative chemotherapy. After a median follow-up of 55.4 months, there were no significant differences between the two groups in median survival: 14.9 months for the patients who received preoperative chemotherapy and 16.1 months for those who underwent immediate surgery (P = .53). The lack of a significant difference between treatment arms continued for the 2 years after initiation of treatment. With the addition of chemotherapy, there was no change in the rate of recurrence at locoregional or distant sites. A recent update on these patients has showed that while there was no difference in overall survival between patients...
receiving perioperative chemotherapy compared with the surgery-only group, a few patients who underwent a complete (R0) resection and who had objective tumor regression after preoperative chemotherapy did have improved survival.30

Another randomized controlled study on preoperative chemotherapy in patients who had EC was conducted by the Medical Research Council (MRC).31 In contrast to the Intergroup 0113 study, overall survival was better in patients who received two cycles of preoperative cisplatin and 5-FU compared with those who had surgery alone (P = .004). Median survival was 16.8 months in the former group compared with 13.3 months in the surgery-alone group, with 2-year survival rates of 43% and 34%, respectively. Another trial conducted by the MRC used perioperative epirubicin, cisplatin, and 5-FU for patients who had resectable esophagogastric cancers (MRC Adjuvant Gastric Cancer Infusional Therapy/MAGIC trial).32 Patients who had resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus were assigned to receive either perioperative chemotherapy and surgery or surgery alone. After a median follow-up of 4 years, the perioperative chemotherapy group had a higher likelihood of overall survival (P = .009), with a 5-year survival rate of 36% versus 23% in the surgery-alone group. Additionally, resected patients who received the perioperative regimen were found to have a decrease in both tumor size and stage. Although these results suggest that preoperative chemotherapy had some benefit with regards to overall survival, only 15% of patients in this study had true lower esophageal tumors.

Malthaner and colleagues33 published a meta-analysis of patients with potentially resectable carcinomas of the esophagus who were randomized to having either chemotherapy or no chemotherapy before surgery, with the primary outcome being survival. Eight trials, including a total of 1729 patients, were included in the meta-analysis. There was some evidence to suggest that preoperative chemotherapy improves survival. Interestingly, there was no evidence that tumor recurrence differed in patients who received preoperative chemotherapy compared with surgery alone. The authors concluded that preoperative chemotherapy plus surgery may offer a survival advantage compared with surgery alone for resectable EC.

Historically, surgical resection has been the primary form of treatment for patients who have EC, with a 3-year overall survival rate after surgery alone ranging from 6% to 37%.34–37 In patients undergoing R0 resection, 3-year overall survival remains only 39%,30 with up to 29% of patients experiencing locoregional failure.30 Distant metastases occur in up to 50% of patients undergoing curative resection.29 Preoperative radiation alone has not been shown to significantly improve survival.38 Several studies have evaluated the role of a brief course of concurrent chemoradiation followed by resection, to help achieve a more adequate surgical resection and sterilize micrometastatic disease. A selection of studies on neoadjuvant therapy in EC is presented in Table 1. Three trials studied patients with SCC only, and none showed a benefit to neoadjuvant therapy.34,39,40 Two of these studies used sequential chemotherapy and radiation, which may be inferior to concurrent therapy; moreover, the radiation dose and fractionation in these studies were not considered standard in the United States.34,39 The Chinese University Research Group for Esophageal Cancer (CURE) trial used more standard chemotherapy and radiation dose, but had very short median follow-up at 16.9 months.40

The remainder of the studies in Table 1 includes both SCC and AC, with the exception of Walsh and colleagues.36 Probably the most widely quoted study for neoadjuvant therapy, the study used preoperative radiation to 40 Gy with 5-FU and cisplatin during weeks 1 and 6, followed by surgery, compared with surgery alone. The authors found a difference in 3-year overall survival of 32% with preoperative
## Table 1
Randomized trials of surgery with or without neoadjuvant chemotherapy and radiation in esophageal cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Histology</th>
<th>CRT Arm</th>
<th>3-Year Overall Survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le Prise</td>
<td>1994</td>
<td>86</td>
<td>Squamous</td>
<td>Sequential to 20 Gy</td>
<td>14</td>
<td>19 Sequential low RT dose (20 Gy), underpowered</td>
</tr>
<tr>
<td>Walsh</td>
<td>1996</td>
<td>113</td>
<td>Adenocarcinoma</td>
<td>CTRT to 40Gy</td>
<td>6</td>
<td>32&lt;sup&gt;d&lt;/sup&gt; Lower than expected OS in surgery alone arm</td>
</tr>
<tr>
<td>Bosset</td>
<td>1997</td>
<td>297</td>
<td>Squamous</td>
<td>Sequential to 37 Gy</td>
<td>37</td>
<td>39 Sequential, altered RT fractionation</td>
</tr>
<tr>
<td>Urba</td>
<td>2001</td>
<td>100</td>
<td>75% adenocarcinoma</td>
<td>CTRT to 45 Gy</td>
<td>16</td>
<td>30 Underpowered</td>
</tr>
<tr>
<td>Burmeister</td>
<td>2005</td>
<td>256</td>
<td>62% adenocarcinoma</td>
<td>CTRT to 35 Gy</td>
<td>19.3 mo</td>
<td>22.2 mo&lt;sup&gt;a&lt;/sup&gt; One cycle of chemotherapy, low RT dose</td>
</tr>
<tr>
<td>Chiu</td>
<td>2005</td>
<td>81</td>
<td>Squamous</td>
<td>CTRT to 50–60Gy</td>
<td>54.5</td>
<td>58.3&lt;sup&gt;b&lt;/sup&gt; Limited follow-up (16.9 months)</td>
</tr>
<tr>
<td>Tepper</td>
<td>2008</td>
<td>56</td>
<td>75% adenocarcinoma</td>
<td>CTRT to 50.4 Gy</td>
<td>16</td>
<td>39&lt;sup&gt;c,e&lt;/sup&gt; Closed early due to slow accrual</td>
</tr>
</tbody>
</table>

**Abbreviations:** CRT, chemotherapy and radiation; CTRT, chemoradiation; RT, radiation therapy.

<sup>a</sup> Median survival.

<sup>b</sup> 2-year overall survival.

<sup>c</sup> 5-year overall survival.

<sup>d</sup> Statistically significant.

<sup>e</sup> Significance of 3-year overall survival not reported.
therapy versus 6% with surgery alone. Despite the results, however, the study has been criticized because of the very low survival rates of patients in the surgery-alone arm compared with other contemporary series.

Urba and colleagues included both SCC and AC in a study using preoperative 5-FU and cisplatin with 45 Gy of concurrent radiation and found a difference in 3-year overall survival of 30% with neoadjuvant therapy versus 16% with surgery alone. Unfortunately, this study was not powered to detect this difference, and thus the finding, while promising, was not statistically significant. More recently, investigators in the Cancer And Leukemia Group B (CALGB) attempted a study of neoadjuvant 5-FU and cisplatin with radiation to 50.4 Gy, the regimen found to be effective in RTOG 85-01, and compared this with surgery alone. The study closed prematurely because of slow accrual however, because practitioners were unwilling to randomize to a surgery alone at the time the study was performed. Only 56 of 475 planned patients were enrolled. Results were presented after 6 years of follow-up in 2008, with the median survival of patients in the neoadjuvant arm 4.5 years, compared with 1.8 years in the surgery-alone group.

Although a consistent benefit to neoadjuvant chemoradiation has not been demonstrated repeatedly in individual trials, several meta-analyses point to an improvement in survival. Gebski and colleagues found an absolute survival difference of 13% at 2 years, favoring preoperative chemoradiation. In another meta-analysis, Fiorica and colleagues calculated an odds ratio for mortality at 3 years after treatment of 0.53, favoring chemoradiation. In most of these studies involving neoadjuvant chemoradiation, pathologic response has been found to be an important endpoint, because patients found to have a complete response at the time of surgery consistently have shown an improved progression-free and overall survival.

Given the findings of the previously mentioned studies, neoadjuvant chemotherapy and radiation followed by surgical resection are preferred treatments for EC in the United States. 5-FU and cisplatin, given concurrently with 45-50 Gy as in the CALGB study, is preferred over a shortened radiation course or altered fractionation, as these techniques may increase operative mortality or long-term morbidity.

Is Surgery Required After Chemoradiation?

The results of definitive chemoradiation in RTOG 85-01 rival those studies of trimodality therapy. Subsequently, determining which patients actually will benefit from surgery following neoadjuvant treatment has emerged as an important issue. Two recent studies compared definitive chemoradiation to neoadjuvant therapy followed by surgery. A French study evaluated 444 patients with T3N0-1 tumors, 89% of whom had SCC of the esophagus. All patients underwent initial therapy with two cycles of 5-FU and cisplatin given concurrently with 46 Gy of radiation. If patients responded to therapy, they randomly were assigned to surgical resection or to definitive chemoradiation. There was no significant difference in median survival (17.7 months with surgery versus 19.3 months with continued chemoradiation) or 2-year overall survival (34% with surgery versus 40% with continued chemoradiation). The surgery arm had fewer locoregional recurrences, but also experienced significantly higher 3-month mortality.

Stahl and colleagues studied patients who had T3-4N0-1 SCC. Patients were randomized up front to neoadjuvant chemotherapy with 5-FU, leucovorin, etoposide, and cisplatin for three cycles followed by definitive chemoradiation with cisplatin and etoposide to 60 to 65 Gy, versus the same induction chemotherapy, then chemoradiation to 40 Gy, followed by surgery. Thirty-four percent of patients randomized to the surgery arm did not undergo resection, either because of patient refusal or development...
of metastatic disease. Of those patients who had surgery, 82% had complete tumor resection, and 35% had complete pathologic response. Overall survival at 2 years was similar, at 40% with surgery and 36% with continued chemoradiation. Median survival was also equivalent at 16.4 months in the surgery arm and 14.9 months with continued chemoradiation. Local progression-free survival was higher in the surgery arm, but treatment-related mortality was also significantly higher in the surgery group. On subgroup analysis of patients who responded to induction chemotherapy, 55% to 58% were alive at 3 years, while conversely, those who did not respond did poorly. In patients who responded poorly to induction chemotherapy who underwent R0 resec- tion after chemoradiation, survival at 3 years was 32%, while the 3-year overall survival in the surgery arm for all nonresponders was 18%. Although numbers in this latter group were low, the results nevertheless suggest some benefit from surgery in patients who have minimal response to neoadjuvant therapy.

Results of studies evaluating definitive chemoradiation and neoadjuvant therapy followed by resection have produced surprisingly consistent results, with 3-year overall survival averaging 30% to 35%. Patients treated with chemoradiation alone still experience a high rate of locoregional recurrence, suggesting that surgery may be of benefit in these patients. Local recurrence in EC has profound effects on quality of life; thus surgery may be warranted even if overall survival is not prolonged. Patients who respond to neoadjuvant chemotherapy or chemoradiation fare particularly well, and may represent a subset of patients who may not benefit from surgery. Most patients in large studies of neoadjuvant chemoradiation followed by surgery versus definitive chemoradiation had SCC; conclusions regarding outcome of patients who have AC require further study. Regardless of tumor type, the difficulty in such studies lies in determining preoperatively whether a patient has a complete response to therapy, and therefore can avoid an operation. PET-CT has emerged as a potential indicator of response to induction therapy in EC, and study of response-directed therapy in EC is warranted. The RTOG is evaluating a nonoperative regimen, adding cetuximab to paclitaxel, cisplatin, and radiation therapy, and this study is accruing.

GASTRIC CANCER

Gastric cancer (GC) is a fairly uncommon cancer in the United States, with 21,500 new cases and roughly 11,000 deaths expected in 2008. Nevertheless, it is a serious health problem, as it is usually at an advanced stage at diagnosis. In Western countries, 5-year survival averages 20%. In Japan, where intense screening for GC is standard, tumors are found at an earlier stage, contributing to better overall survival. Risk factors include Helicobacter pylori infection, high intake of salty or smoked foods, increased intake of nitrates, pernicious anemia, and smoking. Surgery is the mainstay of treatment, although because patients can recur both locally and distally, chemotherapy, radiation therapy, or combinations thereof have been used to help increase chance for cure.

Histologically, tumors are classified as intestinal-type or diffuse-type using the Lauren classification system. Intestinal-type tumors often originate as metaplastic cells, which devolve into carcinoma. Diffuse-type tumors do not necessarily develop along a dysplastic pathway but can present because of genetic mutation, often appearing in younger patients. E-cadherin mutations are observed in roughly 25% of families who have predisposition to diffuse-type cancers, with an autosomal dominant inheritance pattern.

Patients who have GC commonly present with epigastric pain, weight loss, and early satiety. Anemia caused by gastrointestinal bleeding may also be seen. Upper
endoscopy is used to evaluate symptoms and obtain biopsies to confirm the diagnosis. Staging is done with a CT scan of the abdomen and pelvis, although diagnostic laparoscopy often is employed to help assess the possibility and extent of peritoneal involvement, given that small peritoneal nodules may be undetectable by CT scan. Treatment strategy is based on whether disease is found to be localized versus systemic.

**Surgery**

Although it is clear that surgery remains the primary treatment modality for GC, the actual extent of resection has been debated. Comparison between total and subtotal gastrectomy suggests that survival rates are comparable, with better quality of life and nutritional status in subtotal gastrectomy patients. Extent of lymph node dissection is also a matter of controversy when evaluating studies on GC. The Japanese Research Society for the Study of Gastric Cancer has created a classification of lymph nodes based on location. N1 nodes are perigastric lymph nodes along the lesser curvature (stations 1, 3, and 5) and greater curvature (stations 2, 4, and 6). N2 nodes are those found along the left gastric artery (station 7), common hepatic artery (station 8), celiac artery (station 9), and splenic artery (stations 10 and 11).

Classification of lymph node dissection is based on these stations. A D0 node dissection involves failure to remove N1 lymph nodes. A D1 dissection involves gastrectomy with the greater and lesser omenta along with N1 nodes. A D2 dissection involves gastrectomy along with removal of the omenta, the front leaf of the transverse mesocolon, and N2 nodes. Splenectomy and distal pancreatectomy are employed to allow removal of stations 10 and 11 for proximal tumors.

In Japan, D2 dissection has been advocated as the treatment of choice for patients who have GC. Western investigators have attempted to perform extended lymphadenectomy in patients who have GC, but without significantly affecting overall survival. In a prospective study conducted by the MRC, 400 patients were randomized followed a staging laparotomy to undergo D1 or D2 resection. After a median follow-up of 6.5 years, the 5-year survival rates were 35% for D1 resection and 33% for D2 resection. There was no difference in the overall 5-year survival between the two arms. Survival based on death from GC was similar in the D1 and D2 groups, as was recurrence-free survival. In a multivariate analysis, clinical stages 2 and 3, old age, male sex, and removal of spleen and pancreas were independently associated with poor survival. The MRC concluded that D2 resection offered no survival advantage over D1 surgery.

A Dutch group also evaluated the effect of extended lymph node dissection on GC patients. Seven hundred eleven patients who had potentially curative resections were evaluated. In an effort to ensure quality control, a Japanese GC surgeon trained the participant surgeons in the study, with numbers and locations of lymph nodes detected at pathologic investigation graded in accordance to the guidelines of the Japanese Research Society for the Study of Gastric Cancer. Protocol adherence during the course of the trial and its impact on complications, hospital mortality, and survival were evaluated. Major noncompliance was noted in 15.3% of D1 and 25.9% of D2 patients. Intensification of quality control resulted in only a marginal improvement in protocol adherence and in the number of lymph nodes detected. The 5-year survival reported was 45% for D1 dissections and 47% for D2 dissections, suggesting that nonadherence to the protocol did not lead to increased hospital morbidity and mortality, but also had no impact on long-term survival. A follow-up after 11 years showed no difference in overall survival (30% and 35% for D1 and D2 dissections, respectively). Risk for morbidity and mortality was higher in patients older
than 70 years who underwent D2 dissections. Of all subgroups analyzed in the follow-up study, only patients who had metastases in 7 to 15 regional lymph nodes were found to have potential benefit from a D2 dissection, although the study admitted that it was difficult to preoperatively identify those patients who had that extent of disease.

**Combined Approaches**

Surgery alone leads to long-term survival of 77% to 90% for early, lymph node-negative lesions.\(^51,54\) Because most of these patients recur locoregionally, and a significant portion develop distant metastases,\(^55\) investigators have focused on developing pre- or postoperative therapies to improve outcome.

In the MAGIC study recently reported by Cunningham and colleagues at the MRC, the effects of perioperative epirubicin, cisplatin, and 5-FU (ECF) on patient outcome were compared with surgery alone in 503 patients who had resectable AC of the lower esophagus, GE junction, and stomach.\(^52\) The primary endpoint was overall survival. In previous studies, ECF had been shown to achieve response rates in up to 56% of patients who received it,\(^56,57\) and also had been shown to improve survival among patients who had incurable locally advanced or metastatic gastric adenocarcinoma.\(^56,58\)

Patients who had resectable tumors randomly were assigned to receive either perioperative chemotherapy and surgery or surgery alone. ECF was given as three preoperative and three postoperative cycles of intravenous epirubicin and cisplatin on day 1, and a continuous intravenous infusion of 5-FU for 21 days. Morbidity and mortality rates were similar between groups. The resected tumors were significantly smaller and less advanced in the patients who received perioperative ECF. Five-year survival rates for patients who received ECF versus those who did not were 36% and 23%, respectively. The perioperative chemotherapy group had a higher likelihood of overall \((P = .009)\) and of progression-free survival \((P < .001)\).

An Italian group recently reported the results after a 7-year follow-up of a study aimed at evaluating a different perioperative chemotherapy protocol in a group of patients who had locally advanced GC.\(^59\) Twenty-four patients who had locally advanced GC underwent D2 gastrectomy after three preoperative cycles of chemotherapy (epidoxorubicin, etoposide, cisplatin). Three further cycles were planned after surgery. Of the 24 patients, 17 (71%) received postoperative treatment. Curative resection (R0) was achieved in 83.3% of patients. No pathologic complete responses were documented, but tumor downstaging was obtained in 10 of 24 patients (41.7%). Overall median survival was 40 months, and the 7-year survival rate was 46%. After univariate and multivariate analysis, R0 resection and tumor diameter were the most important prognostic factors. In this study, there was a clear benefit for patients treated by perioperative chemotherapy and D2-gastrectomy when compared with previously studied controls who had surgery with postoperative chemotherapy alone.

RTOG 99-04 is a phase 2 study that evaluated a neoadjuvant regimen of up to two cycles of 5-FU, cisplatin, and leucovorin followed by chemoradiation with 5-FU and weekly paclitaxel.\(^60\) Forty nine patients who had stage 1b to 3 gastric cancer were entered. The R0 resection rate was 77%, and a complete pathologic response rate of 26% was observed. More patients who had a complete pathologic response were alive at 1 year than those with less response (82% versus 69%). The authors recommend further evaluation in a larger randomized trial, and this approach remains investigational.

Neoadjuvant chemoradiation may provide the benefit of tumor downstaging before surgery. Additionally, by administration before surgery, induction therapy increases the likelihood that patients receive a complete course of chemotherapy, given that
some patients who are scheduled to receive therapy in the postoperative setting may not receive it because of postoperative complications. The risks of this strategy are that the tumor may progress during neoadjuvant therapy. Alternatively, surgery may be delayed or even abandoned because of treatment toxicity from chemotherapy or radiation, eliminating an opportunity for curative resection.

Historically, postoperative chemotherapy has yielded variable although mostly favorable effects on patient outcome, and it is considered standard therapy at most North American institutions. Liu and colleagues recently published a meta-analysis on adjuvant chemotherapy for GC patients. Twenty-three trials including 4919 patients (2441 in the adjuvant chemotherapy arm, 2478 in the surgery-alone arm) were included. Nineteen studies reported survival rates at the end of follow-up; 60.6% were alive among 2286 patients in the adjuvant chemotherapy arm, while 53.4% were alive among 2313 patients in the surgery-alone arm. Additionally, the surgery-alone arm also had a shorter disease-free survival, and the adjuvant chemotherapy arm had a lower recurrence rate.

Other studies have not found such benefit to postoperative chemotherapy in GC patients. An Italian group conducted a randomized phase 3 trial on patients who had AC of the stomach (stages 1b, 2, 3a and b, or 4 [T4N2M0]) treated with potentially curative surgery, with half of patients randomly assigned to follow-up alone or to treatment with of 5-FU, epidoxorubicin, leucovorin, and cisplatin (PELF regimen). After a median follow-up of 72.8 months, 49.6% of patients experienced recurrence, and 53.9% were dead of disease. Adjuvant chemotherapy did not increase disease-free survival or overall survival in this study. Another Italian group investigated the use of a weekly PELF as adjuvant treatment for high-risk radically resected GC patients. Four hundred GC patients at high risk for recurrence (pT3 N0, or pT2/pT3 N1, N2, or N3) were enrolled. Two hundred one patients randomly were assigned to receive the PELF regimen, and 196 patients were assigned to a regimen consisting 5-FU and leucovorin. The 5-year survival rates were 52% in the PELF arm and 50% in the 5-FU/leukovorin arm. Compared with the 5-FU/leukovorin regimen, the PELF regimen did not reduce the risk of death or relapse. Moreover, only 9.4% of patients were able to complete the treatment in the PELF arm, while 43% of patients completed the treatment in the 5-FU/leukovorin arm, underscoring the unfavorable effect that treatment toxicity from an intensive weekly regimen had on patients' ability to receive treatment.

A Japanese study using adjuvant S-1 therapy after curatively resected GC was published recently. S-1 is an oral fluoropyrimidine compound, comprised of the agents tegafur, 5-chloro-2,4-dihydroxypyridine, and oxonic acid. Patients with stage 2 or 3 gastric cancer who underwent gastrectomy with D2 lymph-node dissection randomly were assigned to undergo surgery followed by adjuvant therapy with S-1 or to undergo surgery alone. In the S-1 group, administration of S-1 was started within 6 weeks after surgery and continued for 1 year. There were 529 patients in the S-1 group and 530 patients in the surgery-alone group. The trial was stopped on the recommendation of the independent data and safety monitoring committee, because it was found that the S-1 group had a higher rate of overall survival than the surgery-only group at the 1-year interim analysis ($P = .002$). At 3 years after treatment, the overall survival rate was 80.1% in the S-1 group and 70.1% in the surgery-alone group. Another Japanese study showed that S-1 may have some applicability in GC patients initially deemed unresectable. Patients receiving S-1 with cisplatin who showed a good clinical response underwent curative gastrectomy. A microscopically detailed examination of surgically obtained specimens showed the complete disappearance of malignant cells. These results are promising, although the study was small. The applicability of S-1 to a Western population remains uncertain, however.
Hallissey and colleagues\textsuperscript{66} studied the use of postoperative radiation therapy alone in the treatment of patients who had GC. Their data, which failed to demonstrate an improvement in overall survival, did show a benefit toward reducing locoregional recurrence in patients who received radiation postoperatively. Given the persistence of distant relapse and potential benefit of chemotherapy, however, a trial evaluating radiation alone likely will not be repeated.

Intergroup 0116 evaluated the use of postoperative chemoradiation, and essentially changed the standard of care for gastric cancer in the United States.\textsuperscript{67} In this study, 556 patients who had stage 1\textsubscript{b} to 4 M\textsubscript{0} adenocarcinoma of the stomach or GE junction were randomized to surgery alone or to surgery followed by one cycle of 5FU/leucovorin, then chemoradiation with 5FU/leucovorin and radiation to 45 Gy, then a final two cycles of 5FU/leucovorin. Three-year overall survival rates were 50\% and 41\%, favoring adjuvant therapy. The median overall survival was 35 months with adjuvant therapy versus 26 months with surgery alone. Intergroup 0116 has been criticized because of its poor compliance rate with the recommended extent of lymph node dissection. Only 10\% of patients underwent the recommended D\textsubscript{2} dissection, with 36\% having a D\textsubscript{1} and 54\% have a D\textsubscript{0} dissection. The authors evaluated outcome according to dissection type, and all subsets seemed to benefit from adjuvant therapy. Intergroup 0116 was updated in 2004 after more than 6 years of follow-up.\textsuperscript{68} Chemoradiation reduced the frequency of first relapse locally, but distant relapse remained a problem, emphasizing the need for more efficacious systemic therapy.

Intraperitoneal chemotherapy (IPC) has been used to treat appendiceal, colonic, peritoneal mesothelial, and ovarian cancers with varying degrees of success.\textsuperscript{69–72} Some investigators have shown that the technique may have applicability to patients who have GC also.\textsuperscript{73} A recent meta-analysis by Yan and colleagues\textsuperscript{74} investigated the effectiveness and safety of adjuvant IPC for patients who had locally advanced resectable GC. Ten reports fit selection criteria and were included in the meta-analysis. A significant improvement in survival was associated with hyperthermic intraoperative intraperitoneal chemotherapy (HIIPC) alone or HIIPC combined with early postoperative IPC. There was a trend toward survival improvement with normothermic intraoperative IPC, but this was not significant with either early postoperative IPC alone or delayed postoperative IPC. IPC also was associated with higher risks of intra-abdominal abscess and neutropenia, confirming that the technique is not without risk.

### Treatment for Advanced Malignancy of the Esophagus and Stomach

Numerous patients with EC or GC have unresectable, recurrent, or metastatic disease at diagnosis. Alternatively, there are patients with advanced but resectable EC or GC who would not tolerate surgery. Although surgery in such cases may not be possible, palliative interventions have an important role in managing these patients. The availability of newer cytotoxic agents has provided hope that current outcomes can be improved; indeed, several combinations have been shown to be effective and therefore good candidates for patients who have advanced disease.

The National Cancer Research Institute in the United Kingdom conducted a study of chemotherapy in 1002 patients who had advanced EC and GC.\textsuperscript{75} The Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) Study evaluated capecitabine (an oral fluoropyrimidine) and oxaliplatin (a platinum compound) as alternatives to infused 5-FU and cisplatin, respectively, for untreated advanced esophagogastric cancer. Patients received triplet therapy with epirubicin and cisplatin plus either 5-FU (ECF) or capecitabine (ECX) or triplet therapy with epirubicin and oxaliplatin plus either 5-FU (EOF) or capecitabine (EOX). The primary endpoint was noninferiority in overall survival for the triplet therapies containing...
capecitabine as compared with 5-FU and for those containing oxaliplatin as compared with cisplatin. Median survival times in the ECF, ECX, EOF, and EOX groups ranged from 9 to 11 months, while survival rates at 1 year ranged from 38% to 47%. Progression-free survival and response rates did not differ significantly among the regimens. Compared with the regimens containing cisplatin, the regimens containing oxaliplatin were associated with a lower incidence of alopecia and renal toxicity. Other studies have confirmed an acceptable toxicity profile in oxaliplatin-containing regimens.76–78 Additionally, alternative regimens containing other cytotoxic agents such as irinotecan may prove efficacious for patients who have advanced disease.79,80

The use of S-1 in conjunction with other chemotherapeutic agents is being studied. Japanese investigators have found some benefit to S-1 combined with cisplatin in patients who have advanced GC, with acceptable toxicity profiles.81,82 Another group has initiated a prospective, multicenter, multinational, nonblinded, randomized phase 3 trial comparing S-1 alone versus an S-1/docetaxel combination (JACCRO GC-03 Study).83 Six hundred twenty-eight patients who have advanced or recurrent gastric cancer (314 in each treatment arm) will be enrolled. The final results of this study are expected in 2010.

A randomized controlled trial has started in Japan and Korea to evaluate the role of gastrectomy for managing incurable advanced gastric cancer.84 Patients diagnosed as having a single noncurable factor and who otherwise would tolerate surgery will be randomized to gastrectomy plus chemotherapy or chemotherapy alone. Three hundred thirty patients are to be recruited into the study. The primary endpoint will be overall survival, with secondary endpoints being progression-free survival and adverse events associated with either gastrectomy or chemotherapy.

**New Treatment Approaches**

Increased understanding of the molecular basis of cancer has led to the investigation of other treatments, often using biologic therapies to target malignancy. The addition of new agents to existing chemotherapeutic regimens has the potential to improve outcomes in patients who have malignancies of the esophagus, GE junction, and stomach.

GC has been shown to express varying amounts of epidermal growth factor receptors (EGFR), with high levels of EGFR associated with a shorter overall survival.85 A recent phase 2 trial conducted by the Southwest Oncology Group (SWOG 0127 trial) studied erlotinib, an oral EGFR inhibitor, as a possible treatment for GE junction and distal gastric AC in patients who had no prior chemotherapy.86 There was an overall response probability rate of 9%, all occurring in the subgroup with GE junction tumors; no responses were observed in group with distal GC. The median survival was 6.7 months in patients who had GE junction tumors and 3.5 months in the distal GC. Investigators concluded that erlotinib was active in patients who had GE AC, but inactive in GC. Another phase 2 trial evaluated gefitinib, another EGFR tyrosine kinase inhibitor, as adjuvant treatment for advanced, inoperable EC.87 The primary endpoint was tumor response, with the effect of EGFR inhibition evaluated by gene expression analysis of tumor biopsies taken before gefitinib treatment and 28 days after. Out of 27 patients, three had a partial response, and seven had stable disease, giving a disease control rate of 37%. Microarray experiments on tumor biopsies showed that gefitinib also down-regulated oncogenes associated with tumor progression.

The use of bevacizumab, an angiogenesis inhibitor that targets and inhibits vascular endothelial growth factor (VEGF), has shown benefit in patients who have advanced colorectal,88,89 lung,90,91 and ovarian92 cancers. Shah and colleagues93 investigated its addition to irinotecan and cisplatin in patients who had metastatic or unresectable
AC of the GE junction and stomach. The primary endpoint was to demonstrate a 50% improvement in time to progression over historical values. With a median follow-up of 12.2 months, median time to progression was 8.3 months. In patients who had measurable disease, the overall response rate was 65%. Median survival was 12.3 months. The response rate and overall survival rates were encouraging, with time to progression improved over historical controls by 75%.

SUMMARY

Although surgery still plays a central role in the treatment paradigm for esophageal and gastric cancers, chemotherapy and radiation therapy have had increasingly important roles for treating these malignancies, such that their inclusion in treatment schema is now considered standard. Their use as pre- or peri-operative treatments in particular has been supported by several recent trials. As new drugs and biologic therapies are developed, and as the ability to assess tumor response to induction therapy continues to improve, strategies for managing these malignancies will continue to evolve.

REFERENCES


