A phase II trial of preoperative combined-modality therapy for localized esophageal carcinoma: Initial results

Manjit S. Bains, MD^a
Alexander Stojadinovic, MD^b
Bruce Minsky, MD^d
Valerie Rusch, MD^a
Alan Turnbull, MD^b
Robert Korst, MD^a
Robert Ginsberg, MD^a
David P. Kelsen, MD^c
David H. Ilson, MD, PhD^c

Objective: We sought to evaluate treatment response to a novel combined-modality treatment regimen for localized esophageal carcinoma.

Methods: Localized esophageal carcinoma was confirmed with endoscopic ultrasonography, computed tomography, and positron emission tomography before induction therapy. This therapy consisted of combined cisplatin/paclitaxel (cisplatin, 75 mg/m²; paclitaxel, 175 mg/m²; 2 cycles, 3-hour infusion) for weeks 1 and 4, combined cisplatin (30 mg · m⁻² · wk⁻¹) and paclitaxel (30-80 mg · m⁻² · wk⁻¹, 96-hour infusion) with concurrent radiation (external beam, 1.8 Gy/d; total, 50.4 Gy) for weeks 7 to 12, and esophagectomy for week 16 after restaging confirmed resectability.

Results: Forty-one patients (36 men) with adenocarcinoma (n = 25) or squamous cell carcinoma (n = 16) were enrolled. Thirty-six patients completed treatment, of whom 34 (85%) had locally advanced disease of clinical stage T3-4 N0-1. Symptoms resolved or improved in 35 (92%) of 38 patients after induction chemotherapy. Fourteen (35%) and 10 (24%) patients experienced grade III/IV myelosuppression during induction chemotherapy and chemoradiation, respectively. Two (5%) had grade III and none had grade IV esophagitis during chemoradiation. Only 2 (5%) patients required enteral feeding-tube support during therapy. Of 33 R0 resections, 9 (26%) had complete pathologic disease, and 4 (12%) had microscopic residual disease. Major (eg, anastomotic response, delayed stricture, and respiratory failure) postoperative morbidity occurred in 13 (36%) of 36 patients. Operative mortality was 5.5% (2/36).

Conclusion: This regimen of induction concurrent chemoradiation followed by surgical intervention for esophageal carcinoma produces rapid dysphagia relief with initial chemotherapy, has a high overall response rate, and has acceptable toxicity levels.

From Thoracic^a and Gastric and Mixed Tumor Services,^b Department of Surgery, The Gastrointestinal Oncology Service, the Department of Medicine,^c and the Department of Radiation Oncology,^d Memorial Sloan-Kettering Cancer Center, New York, NY.

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Address for reprints: Manjit S. Bains, MD, Attending Surgeon, Division of Thoracic Surgery, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021 (E-mail: bainism@mskcc.org).

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The incidence of esophageal carcinoma, particularly, adenocarcinoma, is rapidly increasing in the United States. Although early-stage esophageal carcinoma is highly curable, the overall survival of patients with esophageal carcinoma is dismal because most patients present with advanced disease.¹ In the year 2000, 12,300 patients were diagnosed with esophageal cancer, and an estimated 12,100 died of disease.² Single-modality therapy in the form of surgical intervention or radiation therapy for locally advanced cancers has achieved little improvement on the 20% 5-year survival for stage III esophageal carcinoma. The failure of surgical or radiation-based treatment to cure most patients with esophageal cancer is attributable to the high incidence of both extensive locoregional and systemic disease at the time of diagnosis. Such disappointing treatment outcomes have led investigators to examine the role of multimodality therapy.

Prospective trials comparing preoperative or postoperative radiation or chemotherapy alone with surgical intervention alone have found no improvement in survival with either adjuvant treatment modality.³⁻⁵ Randomized clinical trials have shown a survival advantage for concurrent chemoradiation therapy over that of radiation alone for locally advanced esophageal cancer.^{6,7} A prospective randomized controlled trial demonstrated a survival benefit for combined 5-fluorouracil (5-FU)/cisplatin, radiation, and surgical intervention compared with surgical intervention alone for patients with esophageal adenocarcinoma.⁸ The improvement in survival was modest (16 vs 11 months), however, and the toxicity of treatment was significant.

In a multicenter phase II trial of paclitaxel, cisplatin, and 5-FU, we identified significant antitumor activity of the combination of agents in advanced esophageal carcinoma, but the associated toxicity was substantial.⁹ Similar response rates were seen with paclitaxel and cisplatin, with significantly less treatment-related toxicity without the addition of 5-FU. In a second phase II trial, we identified a major treatment response in 38% of patients with locally advanced esophageal cancer treated with preoperative paclitaxel and cisplatin.¹⁰ There were no complete pathologic responses observed. Despite tumor downstaging, the rate of complete resection (62%) after induction chemotherapy was no different than that with surgical intervention alone at our institution.

On the basis of the high rate of antitumor activity and improved toxicity profile of induction paclitaxel/cisplatin but because of its failure to improve on curative rates of resection, we added concurrent chemoradiation therapy after induction chemotherapy as part of a combined-modality preoperative treatment approach to localized esophageal cancer. The objectives of this trial were to determine the feasibility of this combined-modality regimen and to assess

the pathologic complete response rate after induction therapy.

Patients and Methods

We conducted a phase I/II study of preoperative combined-modality therapy for localized esophageal carcinoma consisting of paclitaxel/cisplatin followed by radiation therapy concurrent with paclitaxel/cisplatin before esophagectomy. Chemotherapy dose escalation was made on the basis of a tandem nonsurgical phase I trial identifying the tolerable dose of paclitaxel. The primary end point of the phase II study was the feasibility of this combined-modality regimen. Secondary end points included complete pathologic response to preoperative therapy, relief of dysphagia, treatment-related toxicity, and surgical morbidity and mortality.

Eligibility Criteria

Patients were eligible if they were 18 years of age or older and had histologically confirmed, surgically resectable (T2-4 N0-1 M0) adenocarcinoma or squamous cell carcinoma of the middle and distal esophagus. Patients who had T1 tumors were eligible if they had involved regional lymph nodes. The T and N stage were defined by means of endoscopic ultrasonography. Tumors that extended into the proximal stomach had to be located predominantly in the distal esophagus or gastroesophageal junction to be eligible. Additional eligibility criteria included a performance status of 70% or greater (Karnofsky scale) and adequate pulmonary (forced expiratory volume at 1 second >1.2 L) and organ function (absolute granulocytes $\geq 1500/\text{mm}^3$, platelets $\geq 150,000/\text{mm}^3$, serum creatinine ≤ 1.5 mg/dL, serum calcium ≤ 12 mg/dL, and serum bilirubin ≤ 1.5 mg/dL). Patients with prior malignancies were eligible if they were disease free for over 5 years.

Exclusion Criteria

Patients were ineligible if they had another active malignancy, had a cervical esophageal cancer, had Tis or T1 N0 tumors or M1a or M1b disease, or could not tolerate the planned combined-modality treatment medically.

Pretreatment Evaluation

The pretreatment evaluation included history, physical examination, electrocardiography, pulmonary function testing, and laboratory testing. The extent of disease evaluation included chest radiography, esophagogastrroduodenoscopy, barium esophagography, computed tomography of the chest, endoscopic esophageal ultrasonography, and positron emission tomography. Pretreatment bronchoscopy was performed for midesophageal tumors. Laparoscopic staging was performed for patients with distal esophageal or gastroesophageal junction adenocarcinomas at the discretion of the treating surgeon. The clinical TNM status and tumor stage were defined according to the 1997 guidelines of the American Joint Committee on Cancer Staging.¹¹

Dysphagia was assessed according to a 5-tier dysphagia scale, in which a score of 0 corresponded to tolerance of normal diet, a score of 1 corresponded to some solid food, 2 corresponded to semisolid food only, 3 corresponded to liquids only, and 4 corresponded to complete inability to swallow. Quality-of-life assess-

Figure 1. Treatment plan for patients with esophageal carcinoma receiving induction chemotherapy and radiation.

ments were made according to the EORTCCQLQ-C30 and FACT-G (version 2) questionnaire.

Induction Chemotherapy

The treatment plan is shown in Figure 1. It was administered as outpatient therapy starting with paclitaxel/cisplatin once every 3 weeks for 2 cycles (weeks 1 and 4), followed by paclitaxel/cisplatin weekly for 6 weeks with concurrent radiation. Paclitaxel was given by means of 3-hour infusion on day 1 at a dose of 175 mg/m², followed by cisplatin on the same day administered by means of bolus injection at a dose of 75 mg/m² through a central venous catheter. During radiation, cisplatin was given at a fixed dose of 30 mg/m² by means of bolus injection, and paclitaxel was administered at doses of 30 to 80 mg/m² by means of 96-hour infusion once weekly (total of 6 cycles; days 1, 8, 15, 22, and 29). Standard antiemetic therapy was used. The dose escalation of paclitaxel during radiation was based on a nonsurgical phase I trial of paclitaxel, cisplatin, and radiation being conducted in parallel with this preoperative trial. Dose attenuation was made for cisplatin-associated grade III or IV ototoxicity, renal toxicity, and neurotoxicity; mucositis; nausea/vomiting/diarrhea/dehydration (grade III or IV) and fatigue (grade IV only); and paclitaxel-associated hematologic toxicity.

Induction Radiation

Multifield, external-beam megavoltage radiation was delivered by using high-energy linear accelerators (>10 MeV). Patients were treated 5 days per week at 1.8 Gy per day administered over a 6-week period (weeks 7-12). Total dose of radiation was 50.4 Gy. All fields were treated each day. Treatment was given with a combination of anterior-posterior, oblique, or lateral fields, such that the dose to the target volume did not differ from the dose specified at isocenter by greater than 10%. The administered dose was prescribed to the isodense line covering the volume at risk.

The superior and inferior borders of the radiation field were 5 cm and the anterior, posterior, and lateral borders were 2 cm beyond the primary tumor, as defined by barium esophagography, computed tomography, or esophageal ultrasonography (whichever was larger). The primary tumor and locoregional lymph nodes were included. If treatment-related toxicity necessitated a delay in treatment exceeding 2 weeks, the patient was removed from the study.

Evaluation During the Study

Patient evaluation during induction chemotherapy and concurrent chemoradiation therapy included interim history and physical examination, performance status and weight measurement, and laboratory testing. After induction chemotherapy was completed, esophagogastroduodenoscopy, barium esophagography, and computed tomography of the chest were performed.

Surgical Resection

Esophageal resection was performed 4 to 8 weeks after completion of induction chemoradiation. Acceptable approaches to resection included the Ivor-Lewis esophagogastrectomy, subtotal thoracic esophagectomy through a left thoracoabdominal approach or complete thoracic esophagectomy through a right thoracotomy, laparotomy, and cervical esophagogastric anastomosis (McKeown approach). Transhiatal esophagectomy with cervical anastomosis was acceptable for tumors at or inferior to the pulmonary vein. Radical en bloc esophagectomy that includes resection of adjacent pericardium, pleura, diaphragm, azygos vein, and thoracic duct and extensive mediastinal, celiac, and retroperitoneal lymphadenectomy were not performed. Frozen sections were obtained to ensure microscopically negative proximal and distal margins.

Mediastinal lymphadenectomy was performed en bloc with resection of the primary tumor when possible. When feasible, lymph node dissection included all lymphatic tissue between the

tracheal bifurcation and the celiac axis, including common hepatic, celiac, and splenic nodal tissue. Bilateral cervical lymphadenectomy (extended lymphadenectomy) was not performed. At a minimum, mediastinal lymph nodes and fat 5 cm proximal and distal to the primary tumor were excised en bloc during esophagectomy. Either the handsewn or stapled anastomotic technique was permissible and was left to the discretion of the operating surgeon.

Criteria for Response and Toxicity

Complete pathologic response was defined as the absence of viable tumor in the resected primary tumor or regional lymph nodes. Progressive disease was evident when an increase in tumor volume exceeded 25% or an unequivocal new lesion or lesions appeared. All toxicities encountered during this study were reported according to the National Cancer Institute Common Toxicity Criteria. Radiation morbidity was scored according to the RTOG Acute Radiation Morbidity Scoring Criteria (0-4).

Surgical complications were identified during treatment but were also scored retrospectively according to a 5-tier surgical morbidity and mortality scale recently developed at Memorial Sloan-Kettering Cancer Center by using predefined criteria for surgical secondary events. Grade I morbidity is that requiring only oral medications for relief of signs or symptoms (eg, oral antimicrobial therapy for wound cellulitis). Grade II morbidity requires intravenous pharmacotherapy or nutrition for significant symptoms (eg, intravenous antiarrhythmic therapy for supraventricular tachycardia). A grade III complication is one that requires endoscopy, interventional radiology, or reoperation (eg, operative drainage of an abscess that follows an anastomotic leak). Grade IV morbidity is one that has attendant chronic disability (eg, postoperative respiratory failure resulting in pulmonary fibrosis and reduction in performance status) or requires major organ resection. The grade V category refers to death associated with the sequelae of the perioperative complication.

Postoperative Follow-up

Patients were evaluated every 3 months for the first 2 years after treatment, every 6 months for the next 3 years, and then annually. Surveillance included interim history and physical examination, performance status and weight measurement, and laboratory testing. Esophagogastroduodenoscopy and computed tomography of the chest and abdomen were performed every 6 months for 2 years and annually thereafter.

Results

Clinical and Pathologic Characteristics

Forty-one patients, of which 36 (88%) were men, were entered into the study (Table 1). The median patient age was 59 years (range, 37-77 years). Ninety-three percent (n = 38) of patients had dysphagia as part of the presenting symptomatology. Twelve (29%) patients experienced weight loss exceeding 10% of their premorbid body weight. The median patient performance status was 90% (range, 80%-100%). The majority of cancers involved the distal esophagus (n = 29 [71%]). Over eighty-five percent of patients initially presented with locally advanced transmural disease (T3-4 N0-1, n = 34 [83%]). Twenty-five (61%) tumors were

TABLE 1. Pretreatment patient and tumor characteristics

Characteristic	n	% of total
No. of patients	41	
Male/female	36:5	
Median age, y (range)	59 (35-77)	
Dysphagia	38	93
Weight loss >10% premorbid weight	12	29
Karnofsky performance status		
80%	5	12
≥90%	36	88
Site		
Midesophagus	12	29
Distal esophagus	29	71
Gastroesophageal junction	17	
Histology		
Adenocarcinoma	25	61
Squamous cell carcinoma	16	39
Initial clinical stage		
IIA	9	22
IIB	5	12
III	24	59
IV	1	2
Tx Nx/T3 Nx	2	5

adenocarcinomas, and the remainder were squamous cell cancers.

Dysphagia Relief With Induction Chemotherapy and Chemoradiation

Thirty-eight patients had pretreatment dysphagia. This resolved or improved in 35 (92%), worsened in 1 (3%), and was unchanged in 2 (5%) after induction chemotherapy. Two of the 41 (5%) enrolled study patients had grade III or IV esophagitis during concurrent chemoradiation. Only 2 (5%) patients required enteral feeding-tube support during therapy.

Treatment-related Toxicity and Complications

The median pretreatment and posttreatment performance status was 90% (range, 70%-100%). The lowest median performance status observed during induction therapy was 70% (range, 60%-90%). One patient with a history of peripheral vascular disease had a cerebrovascular accident during treatment that resulted in prolonged treatment delay and removal from the study. One patient died during treatment after a traumatic hip fracture that was complicated by acute respiratory failure. In a third patient brain metastasis was diagnosed by means of brain biopsy after chemoradiation. Two patients were found to have metastatic disease at the time of the operation (pleural and omental metastases) and did not undergo resection. One patient experienced lung metastasis during chemoradiation and underwent palliative esophageal tumor resection.

The most commonly encountered significant treatment-related toxicity was myelosuppression. Toxicity was not

TABLE 2. Results of treatment with combined modality therapy for localized esophageal carcinoma (n = 41)

Characteristic	n	% of total
Completed treatment	36	88
R0 resection	33/36	92
R1 resection	2/36	5
pCR	9/36	22
Microscopic residual disease	4/41	10
pCR adenocarcinoma/squamous cell cancer	4/5	16/31
pCR (paclitaxel 40-80 mg/m ²)	9/25	36
pCR adenocarcinoma/squamous cell cancer (paclitaxel 40-80 mg/m ²)	9/25	36
Downstaged	25/41	60
No change	8/41	20
Stage increased	6/41	15

Four patients had disease progression during induction therapy, and 2 went off study because of treatment delays unrelated to toxicity.

pCR, Complete pathologic response.

dose related. Fourteen (35%) patients experienced grade III or IV neutropenia during induction chemotherapy. Ten (24%) patients had grade III or IV neutropenia, and 13 had grade III anemia during chemoradiation. Six (15%) patients had treatment delays, and 10 (24%) patients were hospitalized for treatment-related toxicity.

Significant nonhematologic toxicity was infrequent and limited to nausea and vomiting of grade III or IV in 3 (14%) patients. Two patients had grade III and none had grade IV esophagitis during chemoradiation. Four patients required endoscopic esophageal dilatation during preoperative treatment for tumor-related stricture. One patient was dilated on 2 separate occasions, each complicated by esophageal perforation that was successfully managed with nonoperative therapy. Seven (17%) other patients required intravenous fluids, and 5 of these experienced treatment delays. Diarrhea and constipation were all grades I or II in severity. No patient experienced grade III or IV stomatitis, and only 2 (5%) had grade III neurotoxicity. No patient had grade III or IV nephrotoxicity.

Clinical Response to Induction Therapy

Response to therapy is outlined in Table 2. Thirty-six (87.8%) of 41 patients completed the preoperative treatment regimen. Four (10%) patients had disease progression, and 2 (5%) did not complete treatment because one died after a hip fracture and one had a stroke during neoadjuvant therapy.

Surgical Intervention and Operative Morbidity and Mortality

Thirty-six patients have completed the entire treatment protocol and are evaluable for response. The operative mortality rate was 5.5% (2/36). The majority of patients (78% [28/36]) underwent an Ivor Lewis esophagogastrrectomy.

TABLE 3. Operative complications (n = 36)

Grade	n	% of total
I	2	5
II	13	36
III	10	28
IV	3	8
V	2	5

Grade I, Supportive or bedside care, oral antibiotics, etc; Grade II, intravenous fluids or medications, parenteral or enteral nutrition, etc; Grade III, interventional radiology, endoscopy, or operative intervention required; Grade IV, chronic disability, major organ resection or intensive medical therapy; Grade V, death associated with sequelae of the event.

Five (14%) and 3 (8%) patients underwent a McKeown approach and a transhiatal esophagectomy, respectively. Thirty-three (92%) of 36 patients had R0 resections. Two (5%) patients had palliative esophagectomy. The median number of lymph nodes resected en bloc with the tumor-containing esophagus for transhiatal esophagectomy, McKeown approach, and Ivor Lewis esophagectomy was 16 (range, 14-23), 13 (range, 11-32), and 17 (range, 4-40), respectively.

Two (5.5%) patients had grade I and 13 (36.1%) had grade II complications (Table 3). Over half of the grade II morbidity represented postoperative, hemodynamically stable supraventricular tachycardia that rapidly resolved in all cases with intravenous antiarrhythmic therapy. There were 5 anastomotic leaks that were managed without reoperation.

Seven (19%) patients had anastomotic leaks (2 handsewn and 5 stapled anastomoses). Two patients required reoperation for anastomotic dehiscence, and the remaining leaks were managed nonsurgically. There were no instances of recurrent laryngeal nerve injury or chylothorax.

Three (8.3%) patients had grade IV morbidity characterized by chronic disability or organ dysfunction after sepsis (ie, acute renal and respiratory failure during a prolonged intensive care unit course in all 3 patients, one of whom later died). In 2 of these patients, the sepsis was precipitated by anastomotic leak and in one patient by nosocomial pneumonia. One patient required reoperation after the anastomotic disruption, and another required tracheostomy for chronic ventilator dependence. The other death or grade V complication occurred in a patient who experienced massive intrathoracic hemorrhage of unknown cause 1 week after resection that could not be controlled at reoperation.

Pathologic Findings After Clinical Staging

Nine (22% of all resections and 26% of R0 resections) patients had no evidence of carcinoma in the resected specimen, and 4 had microscopic residual disease. Five (31%) of 16 patients with squamous cell carcinoma and 4 (22%) of 25 patients with adenocarcinoma had complete pathologic response to treatment. All complete pathologic responses

were observed in patients receiving 40 to 80 mg/m² paclitaxel (n = 25). Thus 36% (9/25) of patients receiving 40 to 80 mg/m² had a complete pathologic response. Twenty-five (60%) patients responded to preoperative treatments and were downstaged. Eight (20%) failed to respond to treatment, and the tumor stage increased in 6 (15%) during treatment.

Discussion

In an effort to identify novel combined-modality treatment regimens that are both potentially more effective and less toxic than cisplatin/5-FU, we conducted a phase II trial of a novel induction chemoradiation regimen for localized esophageal carcinoma. The treatment regimen consisted of preoperative combined paclitaxel/cisplatin induction chemotherapy, followed by radiation with concurrent paclitaxel/cisplatin. There are 3 notable findings in this study. First, dysphagia resolved or improved rapidly in the majority of patients (92%), with induction chemotherapy obviating the need for nutritional support. Second, the gastrointestinal toxicity was markedly less than that reported previously with 5-FU-based regimens because only 2 (4.9%) patients in this trial required enteral feeding tubes during chemoradiation therapy. Myelosuppression was the most common significant treatment-related toxicity. Finally, response rates with the present multimodality regimen are at least comparable with those reported for cisplatin/5-FU-based therapies. Complete (R0) resection was possible in 33 (92%) of 36 patients who underwent surgical intervention. Postoperative morbidity and mortality was similar or even lower than what has been reported in previous combined modality studies. The complete pathologic response rate of 22% also compares favorably with those of other previously reported studies.

Because of poor survival with surgical intervention alone for locally advanced esophageal cancer, induction chemotherapy was introduced to increase the likelihood of eradicating locoregional and distant micrometastatic disease and downstaging the primary tumor. These studies have failed to show an overall survival benefit with preoperative chemotherapy versus that with surgical intervention alone.^{5,12} Resectability rates were significantly higher with induction therapy (67% vs 35%), yet complete response rates were only 7%.¹¹ More than half of the patients did not benefit from chemotherapy before the operation but were exposed to treatment-related toxicity.

Low complete response rates to preoperative chemotherapy alone prompted investigators to evaluate neoadjuvant chemoradiation. Of 5 randomized trials that have compared induction chemoradiation therapy with surgical intervention alone, only one has demonstrated a significant survival advantage for multimodality treatment.^{8,13-16} These trials used preoperative platinum-based regimens with 5-FU or bleomycin, and radiation doses ranged from 20 to 50 Gy.

Complete pathologic response rates were less than 27%. Operative mortality rates were significantly higher with combined-modality therapy (8.5%-24% vs 3.6%-13%). The trial reported by Walsh and colleagues⁸ demonstrated a significant survival advantage for multimodality therapy (32% vs 6%, 3-year survival). It is unclear whether patients in the 2 treatment arms were identically staged; short follow-up, selection bias, high operative mortality, and an unusually poor survival in the surgical intervention-only control arm confound the findings of this trial. Although the results of nonrandomized and randomized trials of combined-modality therapy are conflicting and not fully comparable because of differences in eligibility criteria and treatment regimens, no sustained benefit has been shown for combined-modality therapy, making it imperative to develop novel treatment regimens.

Cisplatin/5-FU-based multimodality regimens are also associated with significant gastrointestinal toxicity. Forastiere and associates¹⁷ reported severe esophagitis in 86% of patients treated with concurrent cisplatin, 5-FU, vinblastine, and radiotherapy before esophagectomy; 79% of these patients required nutritional support. On the basis of these data, recent trials of cisplatin/5-FU-containing multimodality regimens have required placement of feeding enterostomies in all participating patients before treatment.¹⁸ The lack of clear efficacy of cisplatin/5-FU regimens and their associated toxicity have led many investigators to look for alternatives to 5-FU-based chemotherapy as an induction therapy agent.¹⁹⁻²²

Antitumor synergy and nonoverlapping toxicity make combined paclitaxel/cisplatin an attractive alternative to traditional cisplatin/5-FU therapy. Our results demonstrate that initial therapy with paclitaxel and cisplatin is very effective in providing relief of dysphagia, thereby facilitating rapid resumption of oral intake. The incidence of grade III or IV esophagitis during chemoradiation is low (5%), and only 5% of our patients required enteral nutritional support through a feeding tube. No patient required other invasive palliative measures (eg, stents or laser ablation).

Major operative morbidity and mortality rates with this multimodality regimen for esophageal cancer are similar to those reported in other trials of trimodality therapy.^{8,13-16} The toxicity profile of this preoperative induction cisplatin and paclitaxel chemotherapy followed by concurrent chemoradiation is more favorable than that of cisplatin/5-FU and suggests that omitting 5-FU ameliorates toxicity without compromising treatment response. The rate of complete pathologic response with the multimodality treatment used in this study is similar to that seen in other trials and leaves room for improvement. Therefore we continue to test other novel induction therapy regimens, including the addition of targeted therapies to standard chemotherapy, to determine

whether we can increase the complete pathologic response rate further.

References

- Kelsen D. Preoperative chemoradiotherapy for esophageal cancer [editorial]. *J Clin Oncol*. 2001;19:283-5.
- Greenlee RT, Murray T, Bolden S, et al. Cancer statistics 2000. *CA Cancer J Clin*. 2000;50:7-33.
- Zieren HU, Muller JM, Jacobi CA, et al. Adjuvant postoperative radiation therapy after curative resection of squamous cell carcinoma of the thoracic esophagus: a prospective randomized trial. *World J Surg*. 1995;19:444-9.
- Ando N, Iizuka T, Kakegawa T, et al. A randomized trial of surgery with and without chemotherapy for localized squamous carcinoma of the thoracic esophagus: the Japan Clinical Oncology Group study. *J Thorac Cardiovasc Surg*. 1997;114:205-9.
- Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med*. 1998;339:1979-84.
- Herskovic A, Martz K, Al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med*. 1992;326:1593-8.
- Al-Sarraf M, Martz K, Herskovic A, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an Intergroup study. *J Clin Oncol*. 1997;15:277-84.
- Walsh, TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med*. 1996;335:462-7.
- Ilson DH, Forastiere A, Arquette M, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. *Cancer J Sci Am*. 2000;6:316-23.
- Ilson D, Arquette M, Costa F, et al. Preoperative paclitaxel and cisplatin in esophageal cancer: a phase II multicenter trial [abstract]. *Proc Am Soc Clin Oncol*. 1997;16:A926.
- Fleming ID, Cooper JS, Henson DE, et al, editors. Digestive system: esophagus. In: *AJCC Cancer Staging Manual*. 5th ed. Philadelphia: Lippincott-Raven; 1997. p. 65-9.
- Law S, Fok M, Chow S, et al. Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial. *J Thorac Cardiovasc Surg*. 1997;114:210-7.
- Nygaard K, Hagen S, Hansen HS, et al. Preoperative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized multicenter study of preoperative radiotherapy and chemotherapy: the Scandinavian trial in esophageal cancer. *World J Surg*. 1992;16:1104-10.
- LePrise E, Etienne PL, Meunier B, et al. A randomized study of chemotherapy, radiation therapy and surgery versus surgery for localized squamous cell carcinoma of the esophagus. *Cancer*. 1994;73:1779-84.
- Bosset JF, Giguoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous cell cancer of the esophagus. *N Engl J Med*. 1997;337:161-7.
- Urba S, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol*. 2001;19:305-13.
- Forastiere AA, Orringer MB, Perez-Tamayo C, et al. Concurrent chemotherapy and radiation therapy followed by transhiatal esophagectomy for local-regional cancer of the esophagus. *J Clin Oncol*. 1990;8:119-27.
- Heath EI, Burtness BA, Heitmiller RF, et al. Phase II evaluation of preoperative chemoradiation and postoperative adjuvant chemotherapy for squamous cell and adenocarcinoma of the esophagus. *J Clin Oncol*. 2000;18:868-76.
- Wright CD, Wain JC, Lynch TJ, et al. Induction therapy for esophageal cancer with paclitaxel and hyperfractionated radiotherapy: a phase I and II study. *J Thorac Cardiovasc Surg*. 1997;114:811-6.
- Adelstein DJ, Rice TW, Rybicki LA, et al. Does paclitaxel improve the chemoradiotherapy of locoregionally advanced esophageal cancer? A nonrandomized comparison with fluorouracil-based therapy. *J Clin Oncol*. 2000;18:2032-9.
- Meluch AA, Hainsworth JD, Gray JR, et al. Preoperative combined modality therapy with paclitaxel, carboplatin, prolonged infusion 5-fluorouracil, and radiation therapy in localized esophageal cancer: preliminary results of a Minnie Pearl Cancer Research Network phase II trial. *Cancer J Sci Am*. 1999;5:84-91.
- Blanke CD, Choy H, Teng M, et al. Concurrent paclitaxel and thoracic irradiation for locally advanced esophageal cancer. *Semin Radiat Oncol*. 1999;9:43-52.

Discussion

Dr Richard F. Heitmiller (Reisterstown, Md). I appreciate the opportunity to review and discuss this article by Dr Stojadinovic and colleagues from the Memorial Sloan-Kettering Hospital in New York, who have long been leaders in the treatment of patients with esophageal cancer.

In this study Dr Stojadinovic and colleagues describe a phase II trial that uses induction chemotherapy before concurrent chemoradiation therapy, followed by surgical intervention. In our experience at Johns Hopkins, trials with chemoradiation therapy followed by surgical intervention have demonstrated excellent local control of tumor. In other words, the pattern of treatment failure is predominantly systemically with distant metastatic disease. Attempts to increase the systemic component of therapy before or after surgical intervention have been limited by toxicity, poor compliance, and lack of measurable benefit. The treatment protocol used by Dr Stojadinovic and colleagues is a very intriguing way to increase the total chemotherapy dosage, thereby intensifying the systemic component of therapy in a neoadjuvant manner, which appears to improve patient tolerance and toxicity. Furthermore, the authors select cisplatin/paclitaxel instead of cisplatin/5-FU to minimize the risk of gastrointestinal toxicity.

The authors are to be congratulated on their efforts using this very aggressive therapy. However, I am sure that even they are disappointed by the lack of improvement in complete response rates and survival compared with that seen in other neoadjuvant series in which induction chemotherapy was not used.

For comparison, I cite the results from our most recent published series, which appeared in the *Journal of Clinical Oncology* (*J Clin Oncol*. 2000;18:868-76). In this trial cisplatin/5-FU and radiation followed by surgical intervention were administered in 42 patients with esophageal cancer compared with the 41 patients from this particular series. The 2 series are roughly concurrent. Outcome results are presented for this study followed by our results, respectively, for each of the following parameters: grade 3/4 myelosuppression, 59% and 52%; grade 3/4 esophagitis, 19% and 14%; enteral tube feeding, 4.9% and 21%; successful completion of therapy, 88% and 93%; R0 resection, 94% and 83%; surgical complications, 36% and 37%; and anastomotic leak, 19% and 2.4%. The complete response rate is approximately the same, 22% and 26%, and 2-year survival is 62% in both series, although their reported survival is disease specific and ours is overall.

The authors conclude that induction chemotherapy improves the symptom of dysphagia in 92% of patients, which obviates the need for enteral feeding supplementation. Clearly their enteral feeding rate is lower than ours. The authors seem to believe that enteral feeding is a liability. We do not. It is our belief that strictly maintaining nutritional status during therapy is essential to a successful treatment outcome. Therefore, our policy has been to

place jejunostomy tubes at the time of pretreatment laparoscopic staging and to use these liberally during therapy.

The authors conclude that their protocol has less gastrointestinal toxicity than those such as ours using cisplatin/5-FU. This was true in our initial experience, but now our incidence of gastrointestinal toxicity is the same as they report.

Finally, the authors conclude that complete response rates and survivals are comparable with those of series using cisplatin and 5-FU. This is certainly true, although their treatment requires more time and is associated with greater anastomotic complications.

I have the following questions. What are the real or theoretical disadvantages of supplemental enteral feedings? Again, I think we have a difference in our position on that. Why was there such a high incidence of major complications and anastomotic dehiscences in particular? The third question, which I think you have answered, is, "What is the pattern of tumor recurrence?" Finally, how will these results influence the treatment plans at Memorial Sloan-Kettering in the future?

Dr Jack A. Roth (*Houston, Tex*). The authors are to be congratulated for the presentation of this novel strategy for treating locally advanced esophageal cancer. We have treated approximately 100 patients at the M.D. Anderson Cancer Center using this strategy, and credit for its development should go to Dr Jaffer Ajani, a medical oncologist at M.D. Anderson, who proposed this strategy 6 years ago. The results of the first 38 patients treated at our institution will be presented at the Western Thoracic meeting by Dr Stephen Swisher.

One of the differences between your series and ours is the percentage of patients free of cancer, which, if calculated on the basis of intention to treat, in your series is 15 of 42 patients, or 36%. This contrasts with the 26 of 38 patients, or 68%, free of cancer with a median length of follow-up of 40 months in the M.D. Anderson series, which is twice the length of follow-up in your report. Why do these results differ?

5-FU used with cisplatin and taxol in the induction phase and with cisplatin in the concurrent chemoradiation phase in the M.D. Anderson Cancer Center series is not included in your regimen. 5-FU might be a critical drug in the chemotherapy regimen, as suggested by its important role in the adjuvant chemotherapy gastric cancer studies. Also, taxol was used during radiation in your study, and this has been reported to increase toxicity but not efficacy.

In our study severe neutropenia occurred in 25% of patients compared with grade 3 and 4 toxicities of over 45% in your series. I wonder if you could comment on dose reductions in chemotherapy that might have been detrimental to efficacy.

This strategy appears to improve outcome in patients with cancer of the esophagus without undue toxicity, and I think it

merits phase III intergroup trials, which are now under discussion. Your study represents an important contribution in this area.

Dr Bains. I thank you for your comments and questions.

The first question posed by Dr Heitmiller regards our estimation of enteral feedings in terms of whether it is a disadvantage or a liability as stated. The purpose for emphasizing this point was not to say that it is not important to nutritionally support the patient but rather to say that we have tried to achieve an induction regimen that lowers the rate of esophagitis and the need for enteral feeding-tube placement to support nutrition because the patients cannot sustain it on their own.

The second question relates to the high incidence of anastomotic problems. We tried to be very critical and forthcoming in terms of defining the major operative morbidity in terms of anastomotic complications. Clearly there was a majority of patients with distal esophageal tumors, and those are the ones that experienced the anastomotic leaks, 7 in total of the 36 that underwent resection. This has caused us to critically review our radiation fields and to determine what the exposure of the greater curvature of the stomach was in induction therapy. We have reviewed and cannot show at this point the literature that addresses this question in specific and find that the morbidity and mortality rates of this particular regimen are coincident with those reported over the last 17 years using trimodality therapy.

The other question was how does this influence our future treatment. What we have done is we have omitted the induction taxol and cisplatin and rely on concurrent cisplatin/taxol and radiation as induction therapy and used the first 2 doses selectively in the face of dysphagia. We have chosen the 3-hour infusion in this study to try to limit the need for granulocyte colony stimulating factor support and myelosuppression and have selected as part of concurrent chemoradiation the 96-hour infusion in an attempt to optimize radiosensitivity and yet limit peak drug doses and attendant toxicity. Other phase I trials that we are launching include novel approaches that involve paclitaxel/cisplatin and CPT-11, tyrosine kinase inhibitors, and antiangiogenesis agents. We are formulating a trial now that will directly compare 96-hour infusion of paclitaxel/cisplatin and radiation with induction 5-FU/paclitaxel/cisplatin and 5-FU/cisplatin and radiotherapy.

The last question refers to why our results differ with regard to 5-FU. I think that the complete response rates, although clearly suboptimal to what we would hope for, are no different; the toxicity, we would say, is less than that with regard to the gastrointestinal toxicity, and the myelosuppressive effects have been comparable. Have we considered a dose reduction with paclitaxel? Yes, and that has been part of our planning for subsequent trials.