Phase II Trial of 5-Fluorouracil, Leucovorin, Interferon-α-2a, and Cisplatin as Neoadjuvant Chemotherapy for Locally Advanced Esophageal Carcinoma

Barbara K. Temeck, M.D.[1]
James E. Liebmann, M.D.[2]
Christopher Theodossiou, M.D.[2]
Seth M. Steinberg, Ph.D.[4]
John A. Cook, Ph.D.[3]
David C. Metz, M.D.[5]
Thomas H. Shawker, M.D.[6]
Carmen J. Allegra, M.D.[7]
Angelo Russo, M.D., Ph.D.[2]
Harvey I. Pass, M.D.[1]

[1] Surgery Branch, National Cancer Institute, Bethesda, Maryland.

[2] Medicine Branch, National Cancer Institute, Bethesda, Maryland.

[3] Radiation Biology Branch, National Cancer Institute, Bethesda, Maryland.

[4] Biostatistics and Data Management Section, National Cancer Institute, Bethesda, Maryland.

[5] National Institutes of Diabetes and Diseases of the Kidney, Bethesda, Maryland.

[6] Department of Radiology, National Institutes of Health, Bethesda, Maryland.

[7] Naval Medical Oncology Branch, National Institutes of Health, Bethesda, Maryland.

Address for reprints: Harvey I. Pass, M.D., National Cancer Institute, National Institutes of Health, Building 10, Rm 2B07, Bethesda MD 20892.

Received November 9, 1995; revision received February 23, 1996; accepted February 23, 1996.

BACKGROUND. Most patients with esophageal carcinoma present with locally advanced disease and a poor prognosis. Surgery or radiation provides palliation for locally advanced esophageal carcinoma. The role of neoadjuvant therapy remains to be defined. We administered neoadjuvant chemotherapy consisting of 5-fluorouracil (5-FU), leucovorin, interferon-α-2a, and ciplastin to 11 patients with locally advanced disease.

METHODS. Eleven patients with squamous cell or adenocarcinoma of the esophagus were treated preoperatively with two to three cycles of combination chemotherapy. Nine patients underwent resection with curative intent.

RESULTS. Six patients received three cycles of chemotherapy, and five received two. Dose reduction was necessary for two patients. One patient achieved a pathologic complete response, histologically confirmed. Of the eleven patients, two did not undergo surgery because of progressive disease during chemotherapy. Seven of the 9 patients relapsed after surgery and 2 have been disease free for 27 months.

CONCLUSIONS. The combination 5-FU, leucovorin, interferon-α-2a, and cisplatin administered in a neoadjuvant setting resulted in a median survival of 11.8 months with a median time to relapse of 7 months. ***Cancer* 1996; 77:2432–9.**
© *American Cancer Society.*

KEYWORDS: neoadjuvant chemotherapy, esophageal carcinoma, interferon.

Approximately 11,000 patients are diagnosed each year in the United States with esophageal carcinoma.[1] Most present with locally advanced disease. These patients are currently treated with either surgical resection or radiation therapy.[2,3] Although both treatments provide effective palliation of symptoms from the primary tumor, survival after either surgery or radiation is short. One-year survival rates of 15 to 20% result from either therapy and the 5-year survival rate is <5%.[2,3] Although most patients who die from esophageal carcinoma will have recurrent local disease, as many as 80% will die with metastases.[4]

The failure of aggressive local therapy of esophageal carcinoma to affect long term patient survival and the high incidence of metastases in this neoplasm have led to interest in chemotherapy as a component of the initial treatment of locally advanced disease. Neoadjuvant therapy prior to local treatment of esophageal carcinoma has been evaluated in several studies.[5–12] In addition to treating metastatic disease, effective neoadjuvant chemotherapy should, ideally, also shrink

© 1996 American Cancer Society

TABLE 1
Patient Characteristics

Patient	Age (yrs)	Location of tumor	Pathology	Cycles of chemotherapy	Disease free survival	Recurrence (mos)
HR	62	lower third	adenocarcinoma	2	N/A	distant
SK	63	lower third	adenocarcinoma	3	N/A	distant
AE	53	lower third	squamous	3	27	N/A
NP	58	middle third	squamous	3	27	N/A
TW	53	lower third	squamous	3	1	distant
AP	28	lower third	adenocarcinoma	3	6	local
HB	67	lower third	adenocarcinoma	3	9	distant
TO	52	lower third	adenocarcinoma	2	8	local
GR	71	lower third	adenocarcinoma	2	10	both
RM	62	lower third	adenocarcinoma	2	4	both
RD	58	lower third	adenocarcinoma	2	2	distant

N/A: not available.

TABLE 2
Greatest Dimensions of Tumor on Computed Tomography[a]

	Prechemo	Post 2 cycles	Post 3 cycles	Best response (%)
HR	11/5.1/56.1	8/4.6/36.8	N/A	34
SK	8/3.8/30.4	8/2.8/22.4	7/2.2	49
AE	8/6.2/49.6	3/4.3/12.9	3/3.2	81
NP	7/4.3/30.1	5/3/15	5/2	67
TW	7/5/35	4/4/16	7/5	54[a]
AP	8/5/40	8/4/32	8/3	40
HB	6/3.5/21	5/2.5/12.5	5/2	52
TO	7/4.8/33.6	6/4.2/25.2	N/A	25
GR	8/4/32	8/4/32	N/A	0
RM	8/4/32	8/3.5/28	N/A	13
RD	7/5.5/38.5	7/5.5/38.5	N/A	0

N/A: not available.
[a] Vertical (cm) and horizontal (cm) and area (calculated as vertical multiplied by horizontal dimension).

the primary tumor and therefore make control by either surgical resection or radiation therapy easier to achieve. Unfortunately, neoadjuvant therapy does not appear to increase resectability and has yet to produce a documented advantage in long term patient survival.

5-fluorouracil (5-FU) is known to have activity against esophageal cancer. A variety of strategies to enhance the cytotoxicity of 5-FU have been tried.[13–19] We thus initiated a neoadjuvant trial based on enhancing the activity of 5-FU. Our results of a chemotherapy combination using 5-FU, leucovorin (LV), interferon-α-2a (INF-a-2a), and cisplatin (CP) are reported here.

MATERIALS AND METHODS

Patients with resectable, histologically proven squamous or adenocarcinoma of the esophagus were eligible for evaluation. Eleven patients were enrolled in the study between 1992 and 1994. Their median age was 57 years (range: 28–71).

In addition to physical examination, staging evaluation prior to chemotherapy involved barium swallow with upper gastrointestinal series, computerized tomographic (CT) scan of the head, chest, abdomen, and pelvis, and bone scan.

In addition to the above tests, all patients underwent upper endoscopy with biopsy before and after chemotherapy. Six patients had endoesophageal ultrasound prior to chemotherapy, five of whom also had endoesophageal ultrasound just prior to resection, i.e., post chemotherapy. Intraluminal obstruction by the tumor prevented ultrasound evaluation in the other five patients. The diagnostic efficacy of endoesopha-

geal ultrasound was evaluated by using an endoscope (Olympus Corp., Melville, New York) which had both 7.5 and 12 megahertz (MHz) transducer heads and side-viewing optics. The rotating transducers provide 360 ° field-of-view perpendicular to the long axis of the scope. Under direct visualization, the endoscope was passed into the stomach. The stomach was filled with deaerated water and the endoscope was directed towards the celiac axis and portal vein. Any adenopathy in this area was noted. Nodes larger than 1 cm in greatest dimension were considered abnormal and, therefore, likely malignant. Tumor was identified as a hypoechoic mass causing thickening of the esophageal wall and disruption of the normal five esophageal wall layers. The endoscope was positioned in the area of maximal thickness of the tumor and its diameter was recorded. Tumor was classified as confined to the esophagus if the outermost area, the muscularis propria, was intact. Tumor was considered extraesophageal if there was disruption of this layer and extension into the periesophageal soft tissue. The lower and upper limits of the tumor were also recorded by moving the endoscope distally and proximally to the junction of the tumor and normal esophagus. Mediastinal nodes were recorded by size and position.

After signing an informed consent, the patients were treated with 5×10^6 U/m^2 INF-α-2a administered subcutaneously (s.c.) on Days 1 to 7, calcium LV 500 mg/m^2 over 30 minutes on Days 2 to 6, 5-FU 370 mg/m^2 administered as a bolus 1 hour after the LV infusion on Days 2 to 6, and CP given over 1 hour on Day 6 at a dose of 40 mg/m^2. In patients who tolerated the regimen without side effects of greater than Grade III severity (National Cancer Institute Common Toxicity Criteria), the CP was escalated to 50 mg/m^2 for the second and third cycle. The cycles were given 21 days apart or when the toxicities were resolved. Three weeks after the completion of the second cycle of chemotherapy all patients were restaged with chest and abdomen CT scans and barium swallow. The decision to administer a third cycle of chemotherapy was based on an assessment of at least a 20% decrease in the maximum horizontal and/or vertical width of the tumor on CT scan. Patients who did not show progressive disease at the completion of chemotherapy underwent surgery.

The operative approach consisted of a laparotomy for mobilization of the stomach and lymph node removal with right thoracotomy for dissection of the esophagus and lymph nodes. The stomach was brought through a substernal tunnel for anastomosis to the cervical esophagus or into the right pleural space for a thoracic anastomosis at the level of the azygous vein.

TABLE 3
Toxicities of Chemotherapy

Grade of Toxicity	1	2	3	4
Hematologic				
WBC	1[a]	7	2	
PMN	1	3	3	3
RBC	2	6		
Platelets	4	4		
GI				
Diarrhea	4	6		1
Stomatitis	4	1		
Nausea	4	7		
Skin				
Rash	3		1	
Alopecia	3			
Neuro				
Motor			1	
Mood	2	1	1	

[a] Number of patients; WBC: white blood cells; PMN: polymorphonuclear cells; RBC: red blood cells; GI: gastrointestinal.

RESULTS

Table 1 describes the 11 patients in the study. Data on the greatest horizontal and vertical dimensions with calculated areas of the tumors on the preoperative CT scans are listed in Table 2. Based on radiologic evaluation, 6 patients received 3 cycles of chemotherapy and 5 received 2. One patient was dilated during the first preoperative evaluation. In the 9 patients who had dysphagia, 2 cycles of chemotherapy resulted in normal swallowing. Partial response was defined as a 50% or greater reduction in the area of the tumor as measured on CT scans. By this criteria, of the 11 patients, 3 (27%) listed as AE, NP, and HB, were partial responders with a 95% confidence interval: 6–61%. In one patient, TW, the tumor grew following the completion of 3 cycles of chemotherapy because the patient delayed consent for surgical resection for 6 weeks.

The toxicities of chemotherapy are tabulated in Table 3. Three patients developed transient Grade III and three patients developed transient Grade IV neutropenia. Thrombocytopenia was mild and no platelet support was required. The gastrointestinal toxicity consisted of diarrhea, nausea, and vomiting in all of the patients, and stomatitis in 5. One patient developed lower abdominal pain after the first cycle which was initially attributed to 5-FU-induced colitis. Subsequently, symptoms recurred after the second cycle and progressed to small bowel obstruction and bloody di-

TABLE 4
Endo-Esophageal Ultrasound and Pathology Findings

	Prechemotherapy endoscopic findings		Postchemotherapy endoscopic findings		Specimen	
Patient	LN	EES	LN	EES	LN	EES
AE	+	+	+	–	–	–
NP	N/A	N/A	–	–	–	–
HB	+	–	–	–	–	–
TO	+	+	–	–	–	–
RD	+	–	–	–	–	–

NA: not available; LN(+): lymph nodes suggestive of tumor; LN(–): lymph nodes normal; EES(+): extraesophageal spread; CCS(–): no extraesophageal spread.

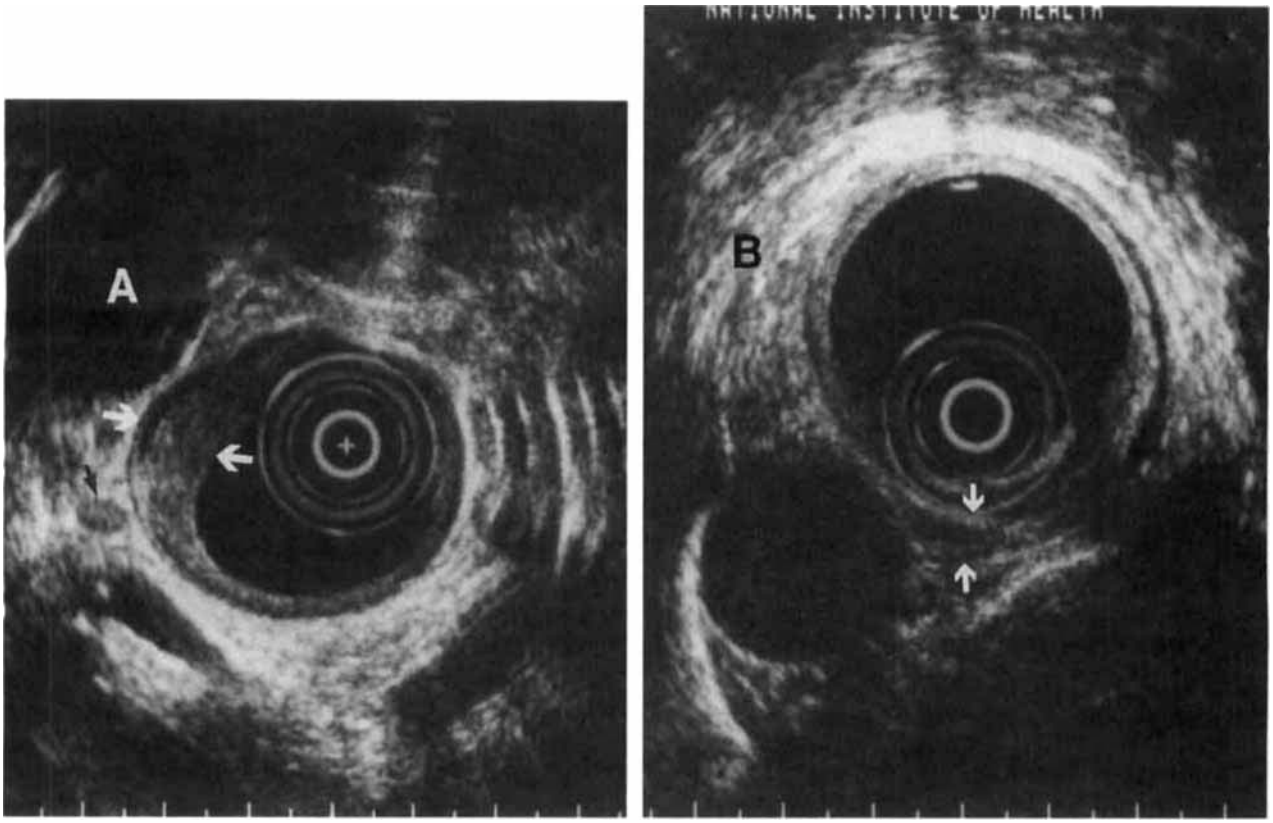

FIGURE 1. (A) Pretreatment scan at the esophageal-gastric junction shows eccentric thickening of the esophageal wall (white arrows) in the direction of the descending aorta (A). Tumor measures 11 mm in greatest dimension. A lymph node of less than 1 cm in greatest dimension is present adjacent to the tumor (black arrow). (B) Posttreatment scan at the same level shows that the greatest dimension of the tumor is now 6 mm (arrows).

arrhea. An exploratory laparotomy was performed and the distal ileum was resected and found to have diffuse cytomegalovirus involvement.[20] He was treated with ganciclovir for 2 weeks, made an uneventful recovery, and subsequently underwent an esophageal resection. One patient developed a skin rash after the first cycle, which reappeared immediately after the first injection of INF-α-2a during the second cycle. The patient did not receive INF during the third cycle and the rash did not recur. One patient had a transient ischemic attack

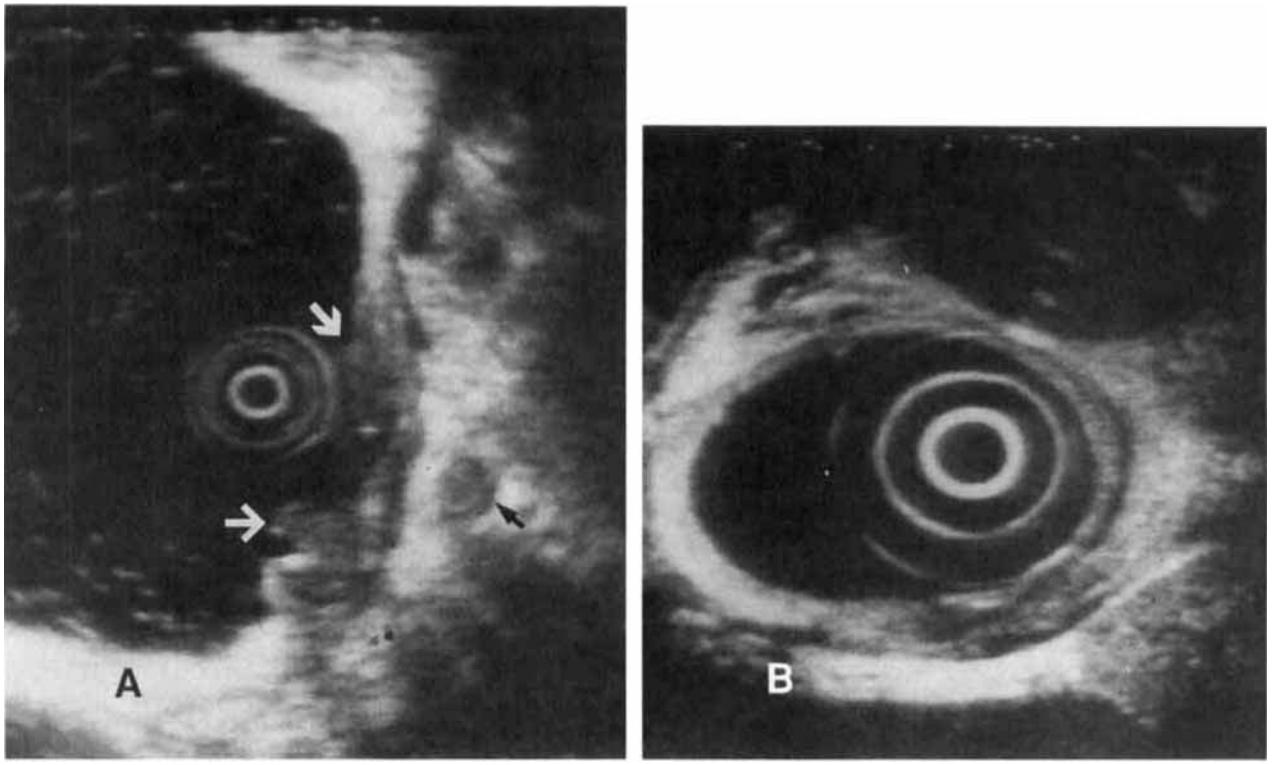

FIGURE 2. (A) Pretreatment scan at the esophageal-gastric junction shows a mass with irregular polypoid extension into the gastric lumen (white arrows). A 1 cm node is seen in the soft tissue adjacent to the mass (black arrow). (B) Posttreatment scan at the same level shows residual tumor but most of the bulky tumor extending into the lumen and the lymph node seen on the pretreatment scan are no longer visible.

during the third cycle of chemotherapy which resolved completely. Mild alopecia was observed in nine patients.

Data from the endoesophageal ultrasound is presented in Table 4. It is correlated with pathologic findings in 4 of 5 patients in terms of measurement of the depth of tumor invasion, and determination of regional lymph node involvement is correlated in 4 of 5 patients. Figures 1 and 2 depict endoesophageal ultrasound findings in two patients prior to and after the completion of chemotherapy. Figure 1 applies to patient RD and Figure 2 to patient AE.

Two patients progressed with metastatic disease while on treatment and were deemed inoperable. Surgery was performed 3 weeks after completion of chemotherapy in 7 patients. Two other patients had surgery delayed for 6 weeks due to colitis and patient cooperation. Nine patients underwent esophagectomy with cervical anastomosis in six and upper thoracic anastomosis in three. Patient AE was found to have a pathologic complete remission (CR) during surgery. There were no deaths in the postoperative 30-day period.

Median potential follow-up for the entire group was 27 months and for the resected patients, 26 months. Seven of the nine resected patients have relapsed. Recurrence in the two nonresected patients was noted at distal sites; whereas, in resected patients, recurrences were distant in two, local in two, and both distant and local in three. Relapses as detected by CT scan at 1 month and then every 3 months postoperatively were observed as early as 1 month and as late as 9 months after surgical resection. The disease free survival after resection is presented in Figure 3A. The median time from esophagectomy to recurrence was 7 months. For the 5 resected patients who died, the median time interval from recurrence to death was 3 months. Overall survival from start of treatment is depicted in Figure 3B, and for resected patients only in Figure 3C. Of the 11 patients, 4 who underwent resection are alive. Two patients with squamous cell carcinomas (including the one who had a pathologic CR) have been disease free for 27 months. The median survival for the entire group is 11.8 months, and for the resected patients, 13.5 months.

DISCUSSION

The prognosis of patients with esophageal carcinoma remains poor. Most patients who undergo surgical re-

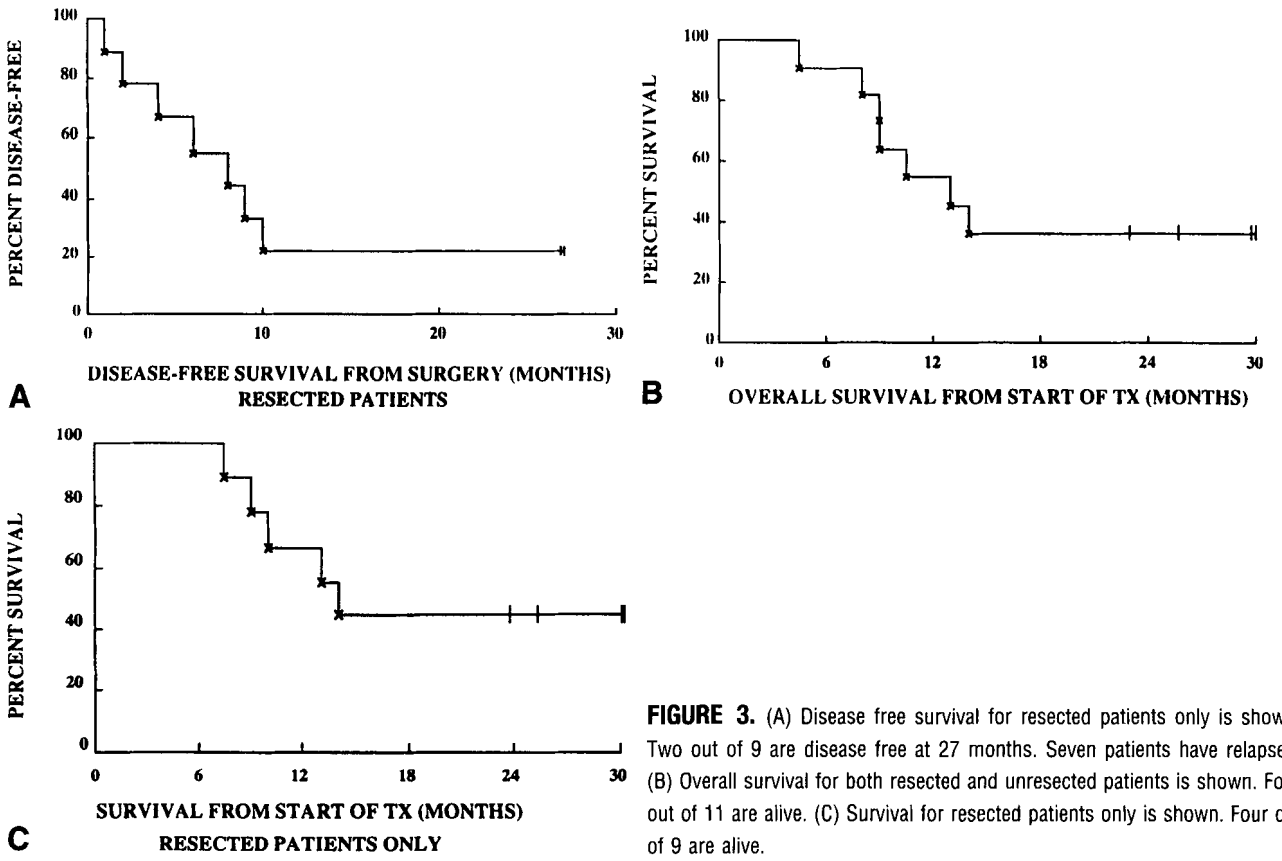

FIGURE 3. (A) Disease free survival for resected patients only is shown. Two out of 9 are disease free at 27 months. Seven patients have relapsed. (B) Overall survival for both resected and unresected patients is shown. Four out of 11 are alive. (C) Survival for resected patients only is shown. Four out of 9 are alive.

section will eventually develop metastatic disease. For this reason neoadjuvant and adjuvant therapy have been explored but have not demonstrated any survival benefit. Neoadjuvant treatment of esophageal carcinoma with 5-FU and CP has been reported in two trials. Hilgenberg et al.[8] treated 35 patients with 2 cycles of continuous infusion 5-FU and CP (100 mg/m^2) every 3 weeks. A response rate of 57% to chemotherapy was observed, with one pathologic CR noted. Kies et al.[21] treated 26 patients with 3 cycles of continuous infusion 5-FU and 100 mg/m^2 CP. Eleven patients responded to chemotherapy, though there were no pathologic CRs documented at surgery. In both studies, mucositis was a major toxicity, observed in 11 patients.

Trials of INF given with either 5-FU alone or 5-FU and LV have been performed.[22–25] INF-α-2a resulted in a dose-dependent decrease in 5-FU clearance. INF modulation of 5-FU and LV has been associated with impressive response rates in patients with gastrointestinal malignancies.[23,24] In the studies by Grem et al.,[23,24] CRs and 21 partial responses occurred in 44 assessable patients (54%). 5×10^6 U/m^2 of INF-α-2a were administered s.c. in combination with 5-FU and LV. However, Wadler et al.[25] found that whereas 5 of 9 patients who received 6 or 9×10^6 U/m^2 of INF-α-2a with 5-FU had a response to therapy, no responses were observed in 9 patients treated at 12, 15, or 18×10^6 U. Based on these data, the dose of INF-α-2a was established at 5×10^6 U/m^2.

CP is an active agent in esophageal carcinoma.[26] It appears to be a crucial component of chemotherapy regimens for squamous cell carcinoma of the aerodigestive tract. In head and neck cancer, Vokes et al.[27] reported on a regimen of a 100 mg/m^2 dose of CP followed by a 5-day continuous infusion of 5-FU. INF-α-2a was given prior to CP and for 5 subsequent days. Surgery was performed and, postoperatively, 5-FU, hydroxyurea, and concurrent radiation were administered. Fifty-one percent of patients had a CR with preoperative chemotherapy, 54% had severe or life-threatening mucositis, and 60% myelosuppression. Five patients died of toxicity. In a trial at NCI of infusional continuous CP given with 5-FU and LV and INF-α-2a for gastric cancer, CP was dropped from the regimen because of excessive toxicity in 3 of 4 patients even at a total CP dose of 33.5 mg/m^2/cycle. This may have been the result of the infusion and schedule of

CP or possibly an effect of INF-α-2a on CP clearance.[28] In an effort to minimize toxicity, the starting dose of CP was 40 mg/m^2/cycle, and was escalated to 50 mg/m^2 in the 5 patients in whom toxicities remained acceptable. Although the majority of our patients reported significant improvement of their dysphagia, the toxicities of the regimen were such that escalation of CP greater than 50 mg/m^2 could not be achieved. Chemotherapy proved more effective in squamous cell carcinoma which was the histology in the two surgically resected patients who have remained free of disease. This excellent response in two of the three patients with squamous cell carcinoma is in keeping with the established sensitivity of squamous cell cancer to CP, 5-FU, and LV chemotherapy regimen and suggests that a future study should focus on using these agents in a selected group of patients with squamous cell cancer of the esophagus. The present study was closed for lack of further patient accrual.

The esophageal ultrasound was performed to assess its role in the preoperative staging of esophageal cancer. The depth of tumor invasion was correctly estimated in 80% of patients with a false negative rate of 20%. For regional lymph node status there was an 80% accuracy rate and 20% false positive rate. These results correlate with previously reported data[29] and support the consideration of the procedure in the preoperative staging of esophageal carcinoma.

The long term, disease free survival was 18% and the median time to recurrence after surgery was only 7 months. Due to the small number of patients, no comment can be made on the response to the regimen based on the histology of the tumor. Additional studies are needed to determine the role and type of neoadjuvant agents in the treatment of esophageal carcinoma.

REFERENCES

1. American Cancer Society. Cancer facts and figures. *Cancer* 1990;40:18.
2. Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of esophageal carcinoma. *Br J Surg* 1990;77:845–57.
3. Petrovich Z, Langholz B, Formenti S, Luxton G, Astrahan M. Management of carcinoma of the esophagus: the role of radiotherapy. *Am J Clin Oncol* 1991;14:80–6.
4. Anderson LL, Lad TE. Autopsy findings in squamous cell carcinoma of the esophagus. *Cancer* 1982;50:1587–90.
5. Bains M, Kelsen D, Beattie D, Martini N. Treatment of esophageal carcinoma by combined preoperative chemotherapy. *Ann Thorac Surg* 1982;34:521–8.
6. Kelsen D, Bains M, Burt M. Neoadjuvant chemotherapy and surgery of cancer of the esophagus. *Semin Surg Oncol* 1990;6:268–73.
7. Kelsen D, Minsky B, Smith M, Beitler J, Niedzwiecki D, Chapman D, et al. Preoperative therapy for esophageal cancer: a randomized comparison of chemotherapy versus radiation therapy. *J Clin Oncol* 1990;8:1352–61.
8. Hilgenberg A, Carey RW, Wilkins EW Jr, Choi NC, Mathisen DJ, Grillo HC. Preoperative chemotherapy, surgical resection, and selective postoperative therapy for squamous cell cancer of the esophagus. *Ann Thorac Surg* 1988;45:357–63.
9. Steiger Z, Franklin R, Wilson RF, Leichman L, Seydel H, Loh SSK, et al. Eradication and palliation of squamous cell carcinoma of the esophagus with chemotherapy, radiotherapy, and surgical therapy. *J Thorac Cardiovasc Surg* 1981;82:713–9.
10. Roth JA, Pass HI, Flanagan MM, Graber GM, Rosenberg JC, Steinberg SM. Randomized clinical trial of preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin for carcinoma of the esophagus. *J Thorac Cardiovasc Surg* 1988;96:242–8.
11. Carey RW, Hildenberg AD, Wilkins EW, Choi NC, Methesen DJ, Grillo H. Preoperative chemotherapy followed by surgery with possible postoperative radiotherapy in squamous cell carcinoma of the esophagus: evaluation of the chemotherapy component. *J Clin Oncol* 1986;4:697–701.
12. Poplin E, Fleming T, Leichman L, Seydel HG, Steiger Z, Taylor S. Combined therapies for squamous cell carcinoma of the esophagus: A Southwest Oncology Group Study (SWOG-8037). *J Clin Oncol* 1987;5:622–8.
13. Houghton JA, Torrance PM, Radparvar S. Binding of 5-fluorodeoxyuridylate to thymidylate synthase in human colon adenocarcinoma xenografts. *Eur J Cancer Clin Oncol* 1986;22:505–10.
14. Grem JL, Hoth DF, Hamilton SM, King SA, Leyland-Jones B. An overview of the current status and future directions of clinical trials of 5-fluorouracil and folinic acid. *Cancer Treat Rep* 71987;1:1249–64.
15. Miyoshi T, Ogawa S, Kanamori T, Nobuhara M, Namba M. Interferon potentiates cytotoxic effects of 5-fluorouracil on cell proliferation of established human cell lines originating from neoplastic tissues. *Cancer Lett* 1983;17:239–47.
16. Stolfi RL, Martin DS. Modulation of chemotherapeutic drug activity with polyribonucleotides or with interferon. *J Biol Response Modif* 1985;4:634–9.
17. Kelsen D, Bains M, Hilaris B, Martini M. Combined modality therapy of esophageal cancer. *Semin Oncol* 1984;11:169–77.
18. Pratesi G, Gianni L, Manzotti C, Zunino F. Sequence dependance of the anti-tumor and toxic effects of 5-fluorouracil and cis-diaminodichloroplatinum combination on primary colon tumors in mice. *Cancer Chemother Pharmacol* 1988;21:237–40.
19. Scanlon KS, Newman EM, Lu Y, Priest DG. Biochemical basis for cisplatin and 5-fluorouracil synergism in a human ovarian cancer line. *Proc Natl Acad Sci* 1986;83:8923–5.
20. Theodossiou C, Temeck B, Vargas H, Yang J, Vargas M, Hahn S, et al. Cytomegalovirus Enteritis after Treatment with 5-Fluorouracil, Leukovorin, Cisplatin and Interferon Alpha. *Am J Gastroenterol* 1995;90:1174–6.
21. Kies MS, Rosen ST, Tsang TK, Shetty R, Schneider PA, Wallemark CB, et al. Cisplatin and 5-fluorouracil in the primary management of squamous esophageal carcinoma. *Cancer* 1987;60:2156–60.
22. Palmeri S, Russo A, Gebbia V, Borsellino N, Gebbia N, Rustum Y, et al. A phase I-II study on the toxicity and therapeutic efficacy of 5-fluorouracil in combination with leucovorin and cisplatin in patients with advanced colorectal carcinoma. *J Chemother* 1990;2 (Suppl 1):28–32.

23. Grem JL, Allegra CJ, McAtee N, Balis FM, Santor O, Goldstein LJ, et al. Phase I study of interferon-α-2a, 5-fluorouracil and high-dose leucovorin in metastatic gastrointestinal cancer. *Proc Am Soc Clin Oncol* 1990;9:70.
24. Grem JL, Jordan E, Robson ME, Binder RA, Hamilton JM, Steinberg SM, et al. Phase II study of 5-Fluorouracil, Leucovorin and Interferon-α-2a in metastatic colorectal carcinoma. *J Clin Oncol* 1993;11:1737–45.
25. Wadler S, Goldman M, Lyver A, Wiernik PH. Phase I trial of 5-fluorouracil and recombinant α_{2a}-Interferon in patients with advanced colorectal carcinoma. *Cancer Res* 1990; 50:2056–9.
26. Ferguson MK, Reeder LB, Hoffman PC, Haraf DJ, Drinkard LC, Vokes EE. Intensive multimodality therapy for carcinoma of the esophagus and gastroesophageal junction. *Ann Surg Oncol* 1995;2:101–6.
27. Vokes EE, Kies M, Haraf DJ, Mick R, Moran WJ, Kozloff M, et al. Induction chemotherapy followed by concomitant chemoradiotherapy for advanced head and neck cancer: impact on the natural history of the disease. *J Clin Oncol* 1995;13:876–83.
28. Alexander HR, Grem JL, Hamilton JM, Pass HI, Hong M, Fraker DL, et al. Thymidylate synthase protein expression. Association with response to neoadjuvant chemotherapy and resection for locally advanced gastric and gastroesophageal adenocarcinoma. *Cancer J Sci Amer* 1995;1:49–54.
29. Rice TW, Boyce GA, Sivak MV. Esophageal ultrasound and the preoperative staging of carcinoma of the esophagus. *J Thorac Cardiovasc Surg* 1991;101:536–44.