Adjuvant/Neoadjuvant Chemoradiation for Gastric and Pancreatic Cancer

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By Andrew M. Lowy, MD [2] and Steven D. Leach, MD [3]

Both gastric and pancreatic cancer remain leading causes of cancer death in the United States and worldwide. While surgical resection continues to be required for long-term cure of both these neoplasms, 5-year survival

Introduction

Adenocarcinomas of the stomach and pancreas continue to represent a leading cause of cancer death. In addition to early systemic spread, inadequate local tumor control following surgery contributes to poor patient survival. The addition of chemoradiation either before or after surgery therefore represents a logical strategy to improve outcome in patients with gastric or pancreatic cancer. In this review, we discuss the contribution of chemoradiation to local tumor control for these patients, with an emphasis on novel neoadjuvant approaches.

Gastric Cancer

Carcinoma of the stomach will be diagnosed in an estimated 21,900 patients in the United States in 1999.[1] The signs and symptoms are generally nonspecific, and thus diagnosis is often made at an advanced stage of disease. Cure rates after surgery alone remain uniformly poor unless the disease is confined to the superficial layers of the gastric wall. In Western series, fewer than half of patients present with localized disease; when carcinoma extends beyond the gastric wall, the 5-year survival rate is only 10% to 20%.[2] Even after a potentially curative resection, disease recurs in 70% of patients.

While the high incidence of peritoneal and liver metastases is well recognized, pattern-of-failure studies have repeatedly demonstrated locoregional recurrence to be a frequent site of relapse. In a reoperative series, Gunderson et al identified locoregional recurrence as the only site of failure in 54% of patients and as a component of failure in 88%.[3] Landry et al examined sites of relapse in 130 patients who had undergone gastrectomy with curative intent.[4] Using clinical criteria, they noted locoregional failure as a component of all recurrences in 38% of patients. Local recurrence was the sole site of relapse in 24% of those patients who developed recurrent or progressive disease. Similar figures were reported previously by McNeer et al.[5] in an autopsy series (Table 1).[3-5]

From these collected series, it is evident that locoregional failure is common following apparently curative surgery for gastric cancer and that sites of locoregional failure include both the gastric remnant, the bed of resection, and regional nodal basins. Ongoing prospective randomized trials of D1 vs D2 lymphadenectomy from Britain and the Netherlands have yet to report data on patterns of relapse. However, in the Mayo Clinic series, more radical surgery, such as D2 lymphadenectomy and omentectomy, failed to affect patterns of recurrence or survival. Thus, it is likely that locoregional therapy may be required in addition to surgery to effectively control these tumors.

Studies of Locally Advanced Unresectable Disease

While adding radiation to extirpative surgery has successfully decreased locoregional recurrence when used to treat carcinoma of the esophagus, rectum, and breast, its role in treating gastric adenocarcinoma is not nearly as well defined. Single-institution noncontrolled trials, often comprising heterogeneous patient groups, have generated most of the available data regarding the utility of radiation in treating gastric cancer. Most of the small number of controlled trials that investigated this issue have been flawed by poor randomization schemes or small patient numbers.

Not until the 1960s did investigators first examine the use of radiation to treat gastric cancer.
Takahashi compared patients who received radiation, either alone or after palliative gastrectomy, with historical controls who did not receive radiation.[6] Survival for the irradiated group was 74% at 1 year and averaged 9 to 10 months longer than the control group.

To enhance local disease control and to combat the high incidence of distant metastases in patients with locally advanced gastric cancer, investigators soon sought to combine the use of radiation and chemotherapy. The Mayo Clinic reported a randomized trial of 48 patients with locally advanced "unresectable" disease that compared 35 to 40 Gy external-beam radiation given over 3 to 4 weeks with or without 5-fluorouracil (5-FU) (15 mg/kg bolus, days 1 through 3, week 1).[7] Median survival for the combined-modality arm was 13 months compared with 5 months for the radiation arm (P < .01).

A Gastrointestinal Tumor Study Group (GITSG) trial examined split-course radiation (50 Gy) given with or without 5-FU (500 mg/m²/day, days 1 through 3, weeks 1 and 6) followed by maintenance 5-FU, methotrexate, and lomustine.[8] The combined-modality arm again had a survival advantage. Four-year survival was 18% compared with 6% for the radiation arm. A second GITSG trial failed to demonstrate a survival advantage for the combined-modality arm.[9] This study has been criticized, however, since 46% of the combined-modality group failed to complete the prescribed course of radiation.

**Adjuvant Radiation Trials**

Most reports of adjuvant radiation as a single modality have used intraoperative radiation alone or in combination with external-beam radiation. Calvo et al used 15 Gy radiation intraoperatively in combination with external-beam radiation 40 to 46 Gy to treat 48 patients postgastrectomy.[10] Most patients had locally advanced disease. The investigators reported an overall survival of 33% at a follow-up of 76 months. Five of 18 patients (28%) had local recurrence.

The Radiation Therapy Oncology Group reported a phase II study of intraoperative radiation (12.5 to 16.5 Gy) plus 45 Gy external-beam radiation postoperatively.[11] Twenty-seven patients received the intraoperative radiation, 23 of whom also received external-beam radiation. Eighty-three percent of patients had serosal involvement, and 70% had lymph node metastases. Actuarial 2-year survival was 47%. Disease recurred locally in 15% of patients.

Three phase III trials using intraoperative radiation and/or external-beam radiation postoperatively have been reported. Abe and Takahashi examined the use of a single intraoperative dose (28 to 35 Gy) after resection and found a survival advantage for patients with disease stages II, III, and IV (gross residual disease without metastases).[12] Unfortunately, patients were randomized without regard to stratification criteria. Results from the other two randomized trials that examined adjuvant radiation alone suggest it may affect local failure rates but does not improve survival.

A three-arm randomized trial from Britain examined gastrectomy alone vs gastrectomy followed by 5-FU, doxorubicin (Adriamycin), and methotrexate vs gastrectomy and postoperative radiation (45 Gy in 25 fractions).[13] This trial failed to reveal a survival benefit for any of the treatment arms. Nonetheless, a decreased rate of local recurrence was noted in the radiation arm.

Small randomized trials from the National Cancer Institute examined the value of external-beam radiation (45 Gy) vs intraoperative radiation plus external-beam radiation (45 Gy) following gastrectomy.[14] No survival advantage was noted for either group, but the group that received radiation intraoperatively had a lower local recurrence rate.

**Adjuvant Chemoradiation for Resectable Disease**

Based on the apparent superiority of 5-FU plus external-beam radiation vs radiation alone in a randomized controlled trial involving patients with unresectable gastric cancer, most investigators have chosen to investigate combined-modality strategies in patients with resectable disease as well. Despite this, much existing data regarding the utility of adjuvant chemoradiation for gastric cancer are derived from single-institution phase II trials (Table 2).[15-18] The Massachusetts General Hospital (Boston, Mass) reported a 4-year survival of 43% among 14 patients treated with resection and adjuvant chemoradiation.[15] All patients had poorly differentiated tumors and 80% had lymph node metastases. Similar results were reported by Gez et al, who treated 25 patients who had locally advanced disease with resection followed by 5-FU-based chemoradiation and maintenance 5-FU.[16] Seven patients had residual disease postresection, and 22 had lymph node metastases. Actuarial median and overall survivals were 33 months and 40%, respectively.

A few phase III trials have compared surgery with surgery plus adjuvant chemoradiation (Table 3).[19-21] Unfortunately, each of these studies is fraught with methodologic flaws. The European Organization for Research and Treatment of Cancer performed a trial with four treatment arms: surgery plus postoperative radiation (55.5 Gy), surgery plus radiation with short-term 5-FU (given during days 1 through 4 of radiation only), surgery plus radiation with long-term 5-FU (given every 2
weeks for 18 months or until disease progression), and surgery plus radiation with both short-term and long-term 5-FU.[19] Analysis revealed a survival advantage for the arm incorporating both short-term and long-term 5-FU. Prognostic factors were not properly stratified, however, and correcting for the errors eliminated the statistical significance. Dent et al performed a trial comparing gastrectomy alone with gastrectomy plus 20 Gy external-beam radiation and 5-FU.[20] The study revealed no significant difference between the treatment arms. The study was underpowered, however, enrolling only 66 patients overall. The Mayo Clinic reported a prospective randomized trial comparing gastrectomy alone with gastrectomy and postoperative external-beam radiation (37.5 Gy in 24 fractions) plus 5-FU (15 mg/kg bolus, days 1 through 3).[21] Unfortunately, the study was flawed by a randomization scheme that assigned patients to a treatment arm before their consent was obtained. As a result, 10 patients randomized to chemoradiation ultimately refused the adjuvant therapy. Analyzed by intent-to-treat, the results demonstrated a statistically significant advantage in favor of the adjuvant therapy arm, with a 5-year survival of 23% vs 4% for the patients treated with surgery alone. When the analysis was conducted by actual treatment received, however, the difference between the groups was no longer significant. The authors argued that if patients were compared with regard to poor prognostic factors, the 5-year survival figures favored the combined-modality arm, 20% vs 4%. It is clear that the 10 patients who refused adjuvant therapy had more favorable prognostic factors, including fewer proximal lesions and lower histologic grade. In an attempt to clarify the Mayo Clinic data, Intergroup 0116 has just completed accrual of patients randomized to receive either gastrectomy alone or gastrectomy followed by 5-FU-based chemoradiation. Chemotherapy consists of bolus 5-FU with leucovorin for four courses. External-beam radiation to 45 Gy was initiated concomitantly with the second course of 5-FU. The results of this study await further follow-up.

Rationale for Neoadjuvant Approaches

The use of chemoradiation in the neoadjuvant setting has been widely applied in treating esophageal and rectal cancers. A neoadjuvant strategy has numerous theoretical benefits, including (1) enhanced resectability due to chemoradiation-induced tumor downstaging; (2) avoiding the potential surgery-related delays in adjuvant therapy; (3) assessing both clinical and pathologic responses to treatment since treatment is administered while the disease is measurable; and (4) identifying patients with rapid disease progression during preoperative chemoradiation and thus sparing them a nontherapeutic gastrectomy. Perhaps the most salient argument for preoperative therapy in the treatment of gastric cancer is compliance. Gastric surgery is complex, and many patients have a prolonged recovery, often experiencing significant weight loss and fatigue. Thus, delays in initiating postoperative adjuvant therapy are common. In the British multicenter trial, 24% of patients randomized to adjuvant radiation following gastrectomy failed to begin treatment as planned.[13] Being treated before surgery improves the patient’s ability to tolerate treatment and so enhances compliance. Administering chemoradiation in the neoadjuvant setting may therefore be preferable to assure that all patients receive the prescribed treatment. While no randomized studies of neoadjuvant chemoradiation for gastric cancer have been reported, the addition of multimodality therapy before surgical resection for adenocarcinoma of the esophagus and gastric cardia has been shown to improve survival in one prospective randomized trial.[22] At the University of Texas M. D. Anderson Cancer Center (Houston), a pilot study demonstrated that 5-FU-based neoadjuvant chemoradiation was well tolerated, with 96% of patients receiving all prescribed treatment (Lowy AM, unpublished data, January 1999). Analysis of the gastrectomy specimens revealed significant treatment effect in most patients, and pathologic complete responses occurred. A larger phase II trial seeking to better define the pathologic complete response rate is currently nearing completion.

Neoadjuvant chemotherapy without radiation is also being investigated ardently in the treatment of gastric cancer. Among patients who respond to chemotherapy, it appears that survival rates are excellent.[23] In the M. D. Anderson experience, the regional nodal basins were a frequent site of disease recurrence following neoadjuvant chemotherapy and subsequent resection. Similar recurrence patterns following neoadjuvant chemotherapy and gastrectomy have been reported by Wilke et al.[24] Thus, it may be beneficial to add chemoradiation to a regimen of systemic therapy to optimize locoregional disease control. In fact, newer studies are evaluating the feasibility and activity of regimens combining neoadjuvant chemotherapy, chemoradiation, and surgery. The combination of 5-FU-based neoadjuvant chemotherapy, chemoradiation, and surgery is being examined in a...
phase II study coordinated by the Radiation Therapy Oncology Group. An institutional phase II trial at
the University of Cincinnati (Cincinnati, Ohio) uses preoperative paclitaxel (Taxol) and gemcitabine
(Gemzar) followed by chemoradiation with 5-FU and cisplatin (Platinol) before surgery in patients
with proximal gastric and esophageal carcinomas. The outcome of such trials will define whether
neoadjuvant chemotherapy alone or in combination with radiation benefits patients with resectable
gastric cancer.

**Pancreatic Cancer**

Pancreatic adenocarcinoma is a common disease that is rarely cured. It represents the tenth most
frequent malignancy and the fifth leading cause of cancer death in the United States.[1] For patients
reported to the National Cancer Data Base, overall 5-year survival is 4%.[25] Several factors contribute to the poor outcome of patients with pancreatic adenocarcinoma. First,
surgical resection remains the only treatment modality with curative potential, and the majority of
patients have unresectable disease at the time of diagnosis. Among 15,210 cases reviewed by the
National Cancer Data Base, only 14.2% underwent surgical resection. Even among patients with
grossly resectable disease, 25% to 60% are left with at least microscopically positive margins of
resection.[26-31] Despite this, the majority of patients undergoing surgical resection do not receive
adjuvant therapy.[25,26,32,33]

Although several recent reports have suggested improved actuarial survival following surgical
resection, the actual survival of patients undergoing surgery alone clearly remains poor. Among 684
patients with pancreatic ductal adenocarcinoma admitted to the Memorial Sloan-Kettering Cancer
Center (New York, NY) between October 1983 and October 1989, 118 (17%) underwent resection with
curative intent.[34] This population demonstrated a preponderance of adenocarcinoma
involving the pancreatic head, with 72% of patients having tumors resected by
pancreaticoduodenectomy, 15% by total pancreatectomy, and 13% by distal pancreatectomy.
Operative mortality was 3.4%. Adjuvant therapy was generally not provided. The median survival for
all patients whose tumors were resected was 14.3 months compared with 4.9 months for patients
who did not undergo resection. Among the 118 patients who underwent resection, only 12 (10.2%)
survived 5 years. Moreover, five of these 12 true 5-year survivors died of recurrent or metastatic
pancreatic cancer at 60, 61, 62, 63, and 64 months. Thus, the true 5-year survival rate following
resection was 10.2%, but the 6-year survival rate was 5.9%. These grim numbers contrast with a
more optimistic previous report from the same institution, in which a 24% actuarial 5-year survival
rate was reported.[32]

**Patterns of Recurrence Following Surgical Resection**

In addition to this overall poor outcome, analysis of patterns of failure from a number of institutions
have documented that local recurrence in the bed of the resected pancreas represents the
predominant mode of failure following surgical therapy (Table 4). Local recurrence occurs in 70% to
80% of patients following pancreaticoduodenectomy.[35-39] In these series, the vast majority of
patients with liver metastases have had uncontrolled local disease. These data demonstrate that
surgery as a single modality is associated not only with poor survival but also with poor rates of local
tumor control. In this setting, adjuvant chemoradiation represents a logical strategy to improve
outcome following pancreaticoduodenectomy.

**Studies Involving Postoperative Adjuvant Chemoradiation**

A randomized trial by the GITSG initially documented the benefits of this approach. In GITSG 9173,
patients undergoing margin-negative pancreaticoduodenectomy were randomized to receive either
surgery alone or surgery plus 5-FU-based adjuvant chemoradiation. Forty-three patients were
accrued over 8 years. Radiation was given in two split doses of 20 Gy separated by a 2-week rest
period. 5-FU was given by rapid infusion at a dose of 500 mg/m²/day on the first 3 days of each
20-Gy treatment course; maintenance 5-FU using a weekly dose of 500 mg/m² was given for 2 years
or until tumor recurrence was documented. In an initial report,[40] median survival for the group
receiving adjuvant chemoradiation was 20 months, compared with 11 months for those patients
undergoing surgical resection without adjuvant therapy (P = .03). Following this randomized trial, an
additional 30 patients were registered by the GITSG and treated with adjuvant chemoradiation;
survival for this group was 18 months, paralleling the experience of the randomized trial.[41]
Two-year survival for patients not receiving adjuvant chemoradiation was 20%, compared with 40%
for patients either randomized or registered to receive radiation plus 5-FU.

Until recently, this trial represented the only randomized data available documenting the benefits of
adjuvant chemoradiation. Within the past year, however, the results of an additional trial conducted
by the European Organization for Research and Treatment of Cancer have been reported.[42] Like the GITSG trial, this study randomized patients with pancreatic (n = 119) and other periampullary malignancies (n = 99) to surgery alone vs surgery plus adjuvant chemoradiation. Radiation was again delivered in split doses, with a median 5-FU total dose of 12,000 mg. Patient outcomes were analyzed according to intent-to-treat, and 22% of patients did not receive intended chemoradiation due to surgical toxicity. Nevertheless, there was a trend toward improved survival associated with chemoradiation in the pancreatic cancer group, with median, 2-year, and 5-year survivals of 17 months, 37%, and 20%, respectively, in the treatment group compared with 13 months, 23%, and 10%, respectively, in the group receiving surgery alone (P = .12). No difference in outcome was observed between the treatment and control groups for the subset of patients with nonpancreatic periampullary malignancy.

In addition to these two randomized trials, several nonrandomized single-institution experiences support the benefit of adjuvant chemoradiation in this disease (Table 5).[27,28,31,40,42,43] Among these, the largest published experience is from the Johns Hopkins University Hospital (Baltimore, Md), providing survival data for 173 patients with resected pancreatic cancer who either did or did not receive subsequent postoperative adjuvant chemoradiation.[31] In this series, 120 patients received adjuvant therapy, with 99 receiving standard 5-FU-based chemoradiation to a total radiation dose of 40 to 45 Gy, followed by 4 months of weekly maintenance 5-FU, and 21 patients receiving a modified intensive chemoradiation regimen, which included prophylactic hepatic irradiation and 4 months of continuous-infusion 5-FU plus leucovorin. Together, the 120 patients receiving adjuvant therapy demonstrated a median survival of 19.5 months compared with 13.5 months in the group receiving surgery alone (P = .003). Of note, the intensive-treatment arm appeared to offer no incremental benefit over standard therapy. Subset analysis demonstrated that virtually every subset of patients examined appeared to benefit from adjuvant therapy; in the case of patients with tumors > 3 cm, negative surgical margins, and positive lymph nodes, these differences proved statistically significant. For patients with positive surgical margins, adding adjuvant chemoradiation improved median survival (18 vs 5 months; P = .06). This contrasts with previous reports suggesting that adjuvant chemoradiation extends survival only in patients who have been able to undergo margin-negative resection.[27,28]

Together, these data provide strong evidence supporting adjuvant therapy after resection of pancreatic adenocarcinoma and establish postoperative 5-FU-based chemoradiation as the current standard of care.

Limitations of Traditional Postoperative Adjuvant Chemoradiation

Despite these benefits, traditional adjuvant chemoradiation has significant limitations in this disease. First, a sizable fraction of patients are unable to receive postoperative adjuvant therapy in a timely manner. Multiple protocol-based experiences now document that 22% to 30% of patients who would potentially benefit from adjuvant therapy are unable to receive it due to postoperative complications and excessive toxicity associated with pancreaticoduodenectomy.[31,42,44] For patients treated outside of high-volume specialty centers, the fraction of patients unable to receive adjuvant therapy may be considerably higher. Examination of treatment patterns by the American College of Surgeons Commission on Cancer suggests that nationally only 33% of patients with resectable pancreatic cancer receive adjuvant chemoradiation.[33]

In addition to limitations regarding a patient’s ability to tolerate adjuvant treatment, traditional postoperative chemoradiation does not exploit preoperative tumor downsizing to minimize the risk of margin-positive resection. The 25% to 60% rate of positive margins reported for patients undergoing pancreaticoduodenectomy in major referral centers documents the need to evaluate strategies designed to decrease this risk.[26-31] Median survival for patients undergoing margin-positive resection is typically less than 1 year (Table 6) and is no different from that reported for patients with locally advanced disease who are treated with nonoperative palliative chemoradiation.

Neoadjuvant Chemoradiation

Several centers have investigated the potential benefit of neoadjuvant chemoradiation delivered before surgery in patients with resectable pancreatic cancer. This neoadjuvant strategy provides several theoretical advantages.[46,47] First, radiation may be most effective when delivered to well-oxygenated tissues not devascularized by surgery. Second, chemoradiation delivered before surgery may prevent dissemination and implantation of tumor cells at laparotomy. Third, downsizing tumors with preoperative chemoradiation may increase the likelihood of margin-negative resection. Fourth, patients whose previously occult metastatic disease progresses during preoperative
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chemoradiation will be spared a nontherapeutic laparotomy. Finally, reserving surgery as the final component of multimodality therapy allows the most toxic constituent of the multimodality regimen to be delivered last, thereby maximizing the likelihood that all patients will receive the fullest treatment in a timely manner.

One of the initial hopes regarding neoadjuvant chemoradiation in pancreatic cancer was that chemoradiation-induced tumor downsizing might render unresectable disease resectable. Several reports have evaluated this issue in patients with initially unresectable pancreatic cancer. Pilepich and Miller provided one of the earliest reports.[48] In this series, 17 patients with adenocarcinoma of the pancreas underwent an initial laparotomy and were deemed to have localized tumors that were either unresectable or of borderline resectability. These patients were subsequently treated with external-beam radiation alone to a total dose of 40 to 50 Gy. Eleven patients continued to show no evidence of metastatic disease at restaging and were re-explored; six of the 11 patients underwent pancreaticoduodenectomy, and two of the six remained disease-free 5 years following surgery.

A similar small series of patients treated with neoadjuvant chemoradiation in the setting of initially unresectable disease was reported from the New England Deaconess Hospital (Boston, Mass).[49] External-beam radiation (45 Gy) was delivered in conjunction with continuous infusion of 5-FU at a dose of 225 mg/m²/day. In this series, neoadjuvant therapy was well tolerated but not associated with a significant rate of tumor downsizing (assessed by the tumor diameter as measured by computed tomography). Ten patients completed neoadjuvant therapy without evidence of tumor progression and underwent laparotomy. Two who were found to have resectable disease amendable to pancreaticoduodenectomy remained disease-free at 20 and 22.5 months postresection. While these small series involving patients with initially unresectable disease provide evidence that pancreatic resection is safe after neoadjuvant chemoradiation, it is clear that 5-FU–based neoadjuvant chemoradiation rarely converts an unresectable to a resectable tumor. Even in the face of significant tumor cell kill, the tumor may remain unresectable. For example, desmoplastic infiltration of the superior mesenteric vessels is likely to persist even in the face of a tumoricidal response to treatment. In a recent update of a pilot program initiated at Brown University (Providence, RI),[50] 14 patients with locally advanced, initially unresectable adenocarcinoma were treated with an aggressive regimen of neoadjuvant chemoradiation involving 45 Gy with continuous infusion of cisplatin (25 mg/m²/day ×3 days) and bolus 5-FU (400 mg/m²/day × 3 days) on the first and fourth weeks. Nine patients eventually underwent surgical exploration following chemoradiation, and the tumors of eight patients were resected. Three of the eight resected specimens demonstrated a complete pathologic response to neoadjuvant therapy with no tumor in the resected specimen. However, five patients required en-bloc resection of the portal vein because of perceived tumor infiltration. These results underscore the fact that apparent conversion from [unresectable] to [resectable] disease is often a function of the experience and aggressiveness of the operating surgeon, and that dramatic cellular responses to therapy may not correlate with a reduction in the required extent of resection.

The Fox Chase Cancer Center (Philadelphia, Pa) has reported substantial experience using a neoadjuvant chemoradiation protocol involving 50.4 Gy radiation in conjunction with two cycles of chemotherapy.[51-54] In this program, chemotherapy consisted of continuous-infusion 5-FU (1000 mg/m²/day on days 2 through 5 and 28 through 32) and bolus mitomycin C (Mutamycin) (10 mg/m² on day 2). Over a 6-year period, 34 patients with localized pancreatic cancer were treated using this regimen. Of note, locally advanced lesions that would have been considered unresectable in many centers predominated in this cohort; only 13% of patients had evidence of an uninvolved superior mesenteric vein as assessed by venous angiography. Thirteen patients had undergone previous laparotomy, where their disease had been classified as unresectable. Following chemoradiation, radiographic determination of tumor volume suggested a single partial response and three minor responses. At restaging, 21 patients were eventually confirmed to have metastatic or unresectable disease, while 11 patients underwent a potentially curative resection. Margin-negative tumor excision was accomplished in 10 of these 11 patients (91%). Among the small number of patients whose disease was resected with curative intent, actuarial 5-year survival was 40%, and local tumor recurrence was documented in only one of 11 patients.

In contrast to these series involving primarily patients with locally advanced disease, two centers have evaluated the utility of chemoradiation delivered before surgery to patients whose tumors are judged to be resectable at the initial evaluation. The largest such series has been reported from the M. D. Anderson Cancer Center.[46,47,55] In this series, careful attention was paid to preoperative patient selection using contrast-enhanced, thin-section computed tomography and staging laparoscopy to limit accrual to patients with localized adenocarcinoma of the pancreatic head with or
without involvement of the superior mesenteric vein (American Joint Committee on Cancer stage I, II, or III disease; T1-3, N0-1, M0). Patients were treated with neoadjuvant chemoradiation delivered to a total dose of 50.4 Gy, with concurrent continuous-infusion 5-FU at a dose of 300 mg/m²/day, 5 days/week. The outcome of 39 patients who underwent pancreaticoduodenectomy following this protocol has recently been reported.[55] Intraoperative radiation to a dose of 10 Gy was used in 33 of these 39 patients, and 13 required segmental resection of the superior mesenteric-portal vein confluence. Margin-negative resection was accomplished in 32 of 39 patients (82%). At a median follow-up of 19 months (range, 4 to 56), median survival was 19 months, and actuarial 4-year survival was 19%. This regimen appeared to significantly improve local tumor control and alter the pattern of disease recurrence; local or peritoneal recurrence was reported in only four patients (10%). The liver became the most frequent site of failure, with 53% of patients eventually developing liver metastases. A separate pilot protocol investigated the ability of additional low-dose (23.4 Gy) hepatic irradiation to further reduce the incidence of hepatic recurrence;[56] this protocol was terminated prematurely due to excessive liver-specific toxicity.

The M. D. Anderson Cancer Center data suggest that 5-FU-based neoadjuvant chemoradiation offers a long-term survival benefit equivalent to that offered by postoperative radiation as documented by the GITSG.[44] In addition, the low rate of local recurrence documented following neoadjuvant chemoradiation in patients with resectable disease compares favorably with the 43% rate of local recurrence reported following postoperative chemoradiation.[40] To date, no randomized trial has documented these apparent benefits of neoadjuvant chemoradiation. However, a retrospective analysis of patients with resectable pancreatic cancer treated with neoadjuvant chemoradiation vs traditional postoperative chemoradiation has recently been reported.[55] This report reviewed the outcome of 60 patients undergoing 5-FU-based chemoradiation and resection: 41 patients received preoperative chemoradiation followed by pancreaticoduodenectomy, while 19 patients received surgery first followed by traditional postoperative chemoradiation. The median tumor diameter was larger in the preoperative chemoradiation group, reflecting the need for successful preoperative tissue diagnosis by computed tomography-guided percutaneous needle biopsy. Trends toward a higher rate of margin-negative resection (88% vs 74%) and a lower rate of locoregional tumor recurrence (10% vs 21%) were observed in the preoperative group.

A retrospective comparison of patients treated by neoadjuvant radiation followed by surgery vs surgery alone has been reported by Ishikawa and colleagues from Osaka, Japan.[57] In this series, 54 consecutive patients with apparently resectable cancer of the pancreatic head were selected to receive neoadjuvant radiation (n = 23) vs immediate surgery (n = 31) based on patient preference. These two groups were similar in terms of tumor size, extent, histologic differentiation, and incidence of nodal metastasis. The group receiving neoadjuvant therapy was treated to a dose of 50 Gy targeted to the pancreatic head as well as surrounding nodal and retroperitoneal tissues. No radiation-sensitizing chemotherapy was employed. At the time of surgical exploration, seven patients who had received neoadjuvant therapy and 19 who had not were found to have disease amenable to surgical resection. Data regarding the status of the surgical margins in each group were not provided. Among the patients who underwent surgery, the group treated with neoadjuvant radiation demonstrated a reduced incidence of death with regional recurrence (12% vs 35%; P < .05), improved median survival (15 vs 11 months; P = NS), and improved 1-year survival (75% vs 43%; P < .05). However, the 3-year and 5-year survival rates were not different between the two groups, indicating an identical rate of hepatic metastases.

**Future Directions**

**Gastric Cancer**

For patients with unresectable gastric cancer, limited but nonetheless convincing data demonstrate that 5-FU-based chemoradiation, when given at sufficient doses, can provide effective palliation. The indications for such treatment are limited, however, as most patients have coexistent distant disease that is more effectively treated with systemic chemotherapy. Currently, the use of chemoradiation in treating resectable gastric cancer remains investigational. When available, the results of the Intergroup 0016 trial will provide additional information about the utility of a 5-FU-based regimen in the adjuvant setting. Future studies will no doubt include the use of other radiation sensitizers like paclitaxel and gemcitabine, alone or in combination with 5-FU. Further neoadjuvant trials are necessary to assess whether the theoretical benefits of this approach are realized.

**Pancreatic Cancer**
For surgeons, the primary goal in managing patients with resectable pancreatic cancer should be to perform a margin-negative pancreaticoduodenectomy safely. Together with careful preoperative staging[58] and the selective application of extended resection techniques,[59,60] the use of neoadjuvant chemoradiation may increase the likelihood of achieving this goal. Future studies will continue to provide important data regarding optimal neoadjuvant treatment regimens and will determine which subgroups of patients are most likely to benefit from this approach.

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