Evolving Paradigms in the Management of Unresectable Pancreatic Cancer

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A New Direction for Pancreatic Cancer Treatment: FOLFIRINOX in Context

By Hedy Lee Kindler, MD

Overview: Since 1996, the cornerstone of chemotherapy for advanced pancreatic cancer has been gemcitabine, which has a genuine, but modest effect on survival and quality of life. It has been remarkably difficult to improve on these outcomes. Many phase III studies of gemcitabine doublets have been uniformly negative, with the exception of a trial of gemcitabine plus erlotinib, which provided only marginal benefit. In 2010, the FOLFIRINOX regimen (bolus and infusional 5-fluorouracil, irinotecan, and oxaliplatin) emerged as a major treatment advance for patients with metastatic pancreatic cancer. In a trial with 342 patients, FOLFIRINOX yielded a longer median overall survival (11.1 vs. 6.8 months, hazard ratio [HR] 0.57, p < 0.001), a superior progression-free survival (6.4 vs. 3.3 months, HR 0.47, p < 0.001), a higher objective response rate (31.6% vs. 9.4%, p < 0.001), and a significant increase in time until definitive deterioration in quality of life, compared with gemcitabine. FOLFIRINOX is also more cost-effective than gemcitabine. Because of higher rates of grade 3 to 4 neutropenia (46% vs. 21%), febrile neutropenia (5% vs. 1%), and diarrhea (13% vs. 2%) with FOLFIRINOX, vigilant patient selection, education, and monitoring are essential. Retrospective single-institution series confirm the substantial activity of FOLFIRINOX in metastatic, locally advanced, and previously-treated patients; demonstrate its safety in individuals with biliary stents; and elucidate how physicians routinely modify drug doses without clear evidence or guidelines. Ongoing and planned studies will prospectively evaluate FOLFIRINOX in the adjuvant, locally advanced, and borderline resectable settings, will add targeted agents to FOLFIRINOX, and will evaluate how to adjust doses to ameliorate toxicity.

Background

THERE HAS been a long-standing, well-deserved therapeutic nihilism regarding chemotherapy for advanced pancreatic cancer. In countless trials over the past few decades, many drugs and drug combinations have demonstrated minimal to no activity against this devastating disease.

Since 1996, the cornerstone of therapy has been gemcitabine, an agent with a genuine, but modest impact. In the pivotal trial that compared gemcitabine to weekly bolus 5-fluorouracil (5-FU), gemcitabine treatment yielded a response rate of 5% and a median overall survival of 5.7 months.1 Although these results do represent a real advance over 5-FU, gemcitabine is principally given because it provides a clinical benefit, a combination of an improvement of pain and performance status, and a stabilization of weight.

Despite these very modest outcomes, it has been difficult for any agent to displace gemcitabine for advanced pancreatic cancer. Most drugs simply do not work in this disease. Although innumerable phase II trials have reported “promising activity” for various gemcitabine-based cytotoxic and targeted doublets, phase III trials of these combinations have been uniformly disappointing, generally yielding greater toxicity for the multidrug regimen with no improvement in overall survival.3-7

This dismal outlook changed slightly in 2005, when the National Cancer Institute of Canada PA.3 trial demonstrated a small improvement in survival for patients treated with gemcitabine plus erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor.8 Although the results were statistically significant, with a hazard ratio of 0.82, the absolute improvement in median overall survival, 5.91 months with gemcitabine compared with 6.24 months for gemcitabine/erlotinib, was minimal. This combination also came with a substantial economic cost9 and did not improve quality of life. One could easily question whether such an incremental improvement in overall survival was worth the expense and toxicity.10 Over the next 5 years, several more negative phase III trials were reported11-16 and it certainly appeared that any major improvements were a long way off.

It was in this context that the results of the PRODIGE 4/ACCORD 11 trial, presented first at ASCO in 201017 and published in the New England Journal of Medicine in 2011,18 represent a substantial treatment advance for patients with pancreatic cancer. The multidrug combination FOLFIRINOX significantly improved median and progression-free survival, objective response rates, and quality of life, albeit with greater toxicity. Given all of the negative trials that preceded it, these data alone are a major achievement. What is truly unprecedented is the magnitude of the benefit achieved with this regimen.

In this article, we will review the data behind this pivotal study, examine how oncologists are currently using this regimen, and assess the ways that FOLFIRINOX may be incorporated into pancreatic cancer treatment in the future.

Development of the FOLFIRINOX Regimen: Phase I and II Studies

It would seem logical to combine 5-FU, irinotecan, and oxaliplatin: these 3 drugs have activity in several gastrointestinal malignancies, including pancreatic cancer, without many overlapping toxicities. The doses for the FOLFIRINOX regimen were established in a phase I trial of 34 evaluable patients with advanced solid tumors enrolled between 1998 and 2000.19 Although the investigators may have been primarily interested in developing this combination for metastatic colon cancer, they also observed two responses (one complete and one partial) among the six patients with pancreatic cancer enrolled on the study.

These encouraging data prompted the same investigators to evaluate this regimen in a single-arm phase II trial.20 Forty-six chemotherapy-naïve patients with pancreatic cancer with a World Health Organization (WHO) performance status of 0 or 1 enrolled at nine French centers from 2000 to 2002. Most subjects (76%) had metastatic disease, a perfor-
FOLFIRINOX FOR PANCREATIC CANCER

In a pivotal trial in 342 patients with metastatic pancreatic cancer and a good performance status, FOLFIRINOX (oxaliplatin, irinotecan, and 5-fluorouracil) produced a longer median overall survival (11.1 vs. 6.8 months), a superior progression-free survival (6.4 vs. 3.3 months), a higher objective response rate (31.6% vs. 9.4%), and a significant increase in the time until definitive deterioration in quality of life compared with gemcitabine.

FOLFIRINOX is more cost-effective than gemcitabine.

Vigilant patient selection, education, and monitoring are essential with FOLFIRINOX treatment, because of higher rates of grade 3–4 neutropenia, febrile neutropenia, and diarrhea compared with gemcitabine.

Retrospective single-institution series confirm the substantial activity of FOLFIRINOX in metastatic, locally advanced, and previously-treated patients; demonstrate its safety in patients with biliary stents; and elucidate how physicians routinely modify drug doses without clear evidence or guidelines.

Ongoing and planned studies will prospectively evaluate FOLFIRINOX in the adjuvant, locally advanced, and borderline resectable settings, will add targeted agents to FOLFIRINOX, and will evaluate how to adjust doses to ameliorate toxicity.

The PRODIGE 4/ACCORD 11 Study

The impressive activity observed with FOLFIRINOX in the phase I and II trials19,20 prompted the development of a randomized phase II/III study that compared this new regimen with the benchmark therapy, gemcitabine.18 Key eligibility criteria included no prior chemotherapy, an ECOG Performance Status of 0 or 1, age less than 76 years, measurable metastatic disease, and a total bilirubin less than 1.5 times the upper limit of normal.

Patients, stratified by center, performance status (0 vs. 1), and location of the primary tumor (head vs. body/tail) were randomized 1:1 to either FOLFIRINOX (oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 180 mg/m², bolus 5-fluorouracil 400 mg/m² followed by infusional 5-fluorouracil 2,400 mg/m² given over 46 hours, every 14 days) or gemcitabine (1,000 mg/m² over 30 minutes weekly for 7 of 8 weeks, then weekly for 3 of 4 weeks). Each cycle was defined as a 2-week interval for both regimens. Six months of treatment were recommended for responding patients. Filgrastim was not routinely administered for primary prophylaxis, though it was permitted for high-risk patients. Computed tomography (CT) scans were obtained every 2 months. RECIST criteria were employed for response assessment.22 Quality of life was measured by the EORTC QLQ-C30 questionnaires completed every 2 weeks.

Response was the primary efficacy endpoint of the phase II portion of the study, which was planned to proceed to phase III if at least 12 objective responses occurred in the first 40 FOLFIRINOX-treated patients. Overall survival was the primary phase III endpoint. Phase II patients were included in the phase III analysis.

The study was designed to have an 80% power to detect an increase in median overall survival from 7 to 10 months (HR 0.70, α = 0.05). For the final analysis, 360 patients would be required to reach 250 events; an interim analysis was planned after 167 events occurred.23 In September 2009, the Independent Data Management Committee recommended that accrual be stopped early, because a planned interim analysis determined that the primary endpoint was achieved with a p value of less than 0.001.18,23

Between 2005 and 2009, 342 patients enrolled at 48 French centers. Patient characteristics were balanced between the arms for age, sex, performance status, tumor location, biliary stenting, metastatic sites, and baseline Ca 19–9 level, except that a greater percentage of patients on the gemcitabine arm had measurable pulmonary metastases (29% vs. 19%). The median age was 61. Approximately 60% of the subjects in both arms had a PS of 1, and approximately 87% had liver metastases. Only 38% of patients had tumors of the pancreatic head, and only 14% had a biliary stent.

The median number of 2-week treatment cycles was 10 in the FOLFIRINOX and 6 in the gemcitabine arm (p < 0.001). The median relative dose intensity was approximately 80% for each of the component drugs in the FOLFIRINOX regimen and 100% for gemcitabine.

Independent radiologic review confirmed that 15 of the first 44 FOLFIRINOX-treated patients (34%) in the phase II portion of the trial had an objective response, meeting the criteria for the study to proceed to phase III. Patients treated with FOLFIRINOX achieved a much higher objective response rate (31.6%) than those who received single-agent gemcitabine (9.4%).

Median overall survival was significantly longer in the patients treated with FOLFIRINOX (11.1 months vs. 6.8 months, HR = 0.57, 95% CI, 0.45 to 0.73; p < 0.001). Overall survival rates at 6, 12, and 18 months were also superior for FOLFIRINOX-treated patients (76%, 48%, and 19% respectively), compared with 58%, 21%, and 6%, respectively for those who received gemcitabine. Patients on the multidrug regimen also achieved a superior progression-free survival (6.4 months vs. 3.3 months, HR = 0.47; 95% CI, 0.37 to 0.59; p < 0.001). The beneficial effect of FOLFIRINOX was similar in all patient subgroups. These data are summarized in Table 1.
Patients who received FOLFIRINOX experienced significantly higher rates of grade 3 and 4 neutropenia (46% vs. 21%), febrile neutropenia (5% vs. 1%), thrombocytopenia (9% vs. 4%), diarrhea (13% vs. 2%), and sensory neuropathy (9% vs. 0%) than those who received gemcitabine. The presence of a biliary stent did not increase the risk of infection in either arm, and no cholangitis was reported. Filgrastim was given to 43% of FOLFIRINOX-treated patients. Toxicity data are summarized in Table 2.

Significantly more patients on the gemcitabine arm had a definitive decrease in their scores on the Global Health Status and Quality of Life scale compared with those on the FOLFIRINOX arm (66% vs. 31%, HR = 0.47, p < 0.001). A significant increase in the time until definitive deterioration in quality of life was observed in the FOLFIRINOX-treated subjects for all functional and symptom scales.

### FOLFIRINOX Usage in Clinical Practice

Almost immediately after Conroy presented the FOLFIRINOX data at ASCO in 2010, Xcenda, LLC analyzed the prescribing plans of American oncologists using the NMCR Challenging Cases live research vehicle. From July 31 to August 28, 2010, they assessed the prescribing plans of more than 370 U.S. oncologists for first-line therapy of patients with metastatic pancreatic cancer and PS 1 or 2. They observed that the FOLFIRINOX data produced an immediate change in the distribution of planned first-line prescribing. For the PS 1 scenario, FOLFIRINOX had an 18% share; in the previous year, those patients would mostly have received gemcitabine/erlotinib. As expected, plans for FOLFOX were negligible (3%) for PS 2 patients.

In the phase I, II, and III trials described above, FOLFIRINOX was tested in European patients who had predominantly body/tail tumors and a good performance status, which may not be fully representative of other populations of patients with pancreatic cancer. In the absence of data from additional prospective clinical trials, retrospective single-institution series from highly selected academic centers provide some insight into the current state of FOLFIRINOX usage in the United States and elsewhere. These data confirm the considerable activity of this regimen in the metastatic, locally advanced, and previously-treated settings, demonstrate the safety of this combination in patients with indwelling biliary stents, and elucidate how some physicians are routinely modifying drug doses without clear evidence or guidelines.

Between July 2010 and April 2011, investigators at Massachusetts General Hospital treated 29 patients with pancreatic cancer with FOLFIRINOX; 59% had metastatic disease. The median age was 60. Most (62%) were chemotherapy-naive, 17% and 21%, respectively, had received one and two prior regimens. Almost half (48%) had a PS of 1; 55% had head or uncinate tumors, and 28% had biliary stents. A median of eight cycles were delivered. The objective response rate on formal radiologic review was 38%. In chemotherapy-naive patients, the response rate was 56%; stable disease was reported in 39%, for a disease control rate of 94%. In previously-treated patients, the response rate was 9%; the disease control rate was 73%. Response rates were similar in patients with locally advanced and metastatic disease (42% and 35%, respectively). Emergency room visits or hospitalizations were required in 41% of patients, most commonly for neutropenic fever or dehydration (14% each). Seven of the 10 patients who developed grades 3 or 4 neutropenia had not received prophylactic growth factor growth factors from the start of FOLFIRINOX treatment.

Washington University physicians used a registry to document the tolerance and efficacy of FOLFIRINOX. Twenty-nine patients, with a median age of 57, received at least one cycle of FOLFIRINOX. Most (93%) had an ECOG PS of 0 or 1, 38% had pancreatic head tumors, and 24% had biliary stents. The majority (52%) had metastatic disease; the rest were locally advanced. The regimen was empirically modified in the majority of patients because of concern for potential toxicities. The 5-FU bolus was deleted in 48%. Irinotecan was dose-reduced in four patients who had the UGT1A1*28/*28 genotype, and in nine patients who did not. Prophylactic growth factor support was administered to 48% of patients beginning with the first cycle; 10% initiated granulocyte-colony stimulating factor (G-CSF) in subsequent cycles. Grades 3 and 4 neutropenia developed in 14%, but only one patient experienced a neutropenic fever. Fourteen percent of the patients were hospitalized. Of the patients who began treatment on the full-dose regimen, only 25% required any dose adjustment in future cycles, suggesting to these investigators that prophylactic dose adjustments may not have been necessary. On independent review, 26% achieved partial responses and 63% had stable disease. Thus, despite frequent dose reductions, the majority of patients achieved disease control with FOLFIRINOX.

Investigators at Yale University observed that oncologists in community and academic practices were reluctant to use full-dose FOLFIRINOX because of its toxicity profile. To ascertain the potential effect of dose attenuation on toxicity and efficacy, they performed a retrospective review of pa-
tients with pancreatic cancer who were treated with FOLFIRINOX at their institution between June 2010 and June 2011, and compared patient characteristics, toxicities, and response rates with those reported in the pivotal phase III trial.\textsuperscript{18} Thirty-five patients, with a median age of 61, were treated with FOLFIRINOX; 68% had an ECOG PS of 0, 57% had pancreatic head tumors, 46% had locally advanced disease, and only 14% had received prior chemotherapy.

Only 17% of patients received full-dose FOLFIRINOX with the first cycle. Irinotecan was reduced in 93% of patients and omitted in 3%; oxaliplatin was reduced in 34%; bolus 5-FU was reduced in 31% and omitted in 24%; leucovorin was decreased in 37%; and the 5-FU continuous infusion was decreased in 10%. A median of 10 cycles was delivered. The median relative doses of oxaliplatin, irinotecan, bolus 5-FU, and infusional 5-FU were 90%, 68%, 68%, and 100%, respectively (in the phase III trial the median relative doses of oxaliplatin, irinotecan, and 5-FU [bolus and infusion] were 78%, 81%, and 82%, respectively). Yale patients experienced significantly less grade 3/4 fatigue ($p = 0.0089$) and neutropenia ($p < 0.0001$) compared with patients in the phase III trial. Despite routine dose modifications, the response rate, progression-free survival, and overall survival were not significantly different from historic controls. The authors concluded that modest dose attenuations of FOLFIRINOX reduce toxicity but do not appear to compromise its efficacy.

The activity of FOLFIRINOX in previously treated patients has been described in two retrospective series from France.\textsuperscript{28,29} In a retrospective review of 27 patients who received second-line FOLFIRINOX from 2003 to 2009, a median of six cycles were delivered. Grades 3–4 neutropenia developed in 56%, and one patient experienced grade 5 febrile neutropenia; 44% received growth factors as second-line FOLFIRINOX from 2003 to 2009, a systematic review of 27 patients who developed in 56%, and one patient experienced grade 5 febrile neutropenia; 44% received growth factors as second-line prophylaxis. Partial responses were achieved in 19%; 44% had stable disease. The median time to progression was 4.4 months, and median overall survival was 8.5 months.\textsuperscript{29} In a second French series, 13 previously-treated patients, only 69% of whom had a PS of 0 or 1, were treated with FOLFIRINOX, mostly (85%) in the second-line setting. There were no objective responses, but 46% had stable disease. No grade 4 toxicities were reported.\textsuperscript{29}

**FOLFIRINOX Is Cost-effective**

Using a Markov model, Attard and colleagues assessed the cost-effectiveness of FOLFIRINOX compared with gemcitabine in Canadian patients undergoing first-line treatment for metastatic pancreatic cancer.\textsuperscript{31} Since the initial treatment choice affects subsequent therapy, second-line treatment was also included in their analysis.

Their first model, based on the ACCORD 11 trial data, assumed that in one arm patients received first-line FOLFIRINOX and second-line gemcitabine, and in the other arm, they received first-line gemcitabine and second-line platinum-based chemotherapy; in both groups G-CSF usage was allowed.

The second analysis, which mirrored current Ontario treatment patterns, assumed that first-line FOLFIRINOX was followed by second-line gemcitabine in one arm, and first-line gemcitabine was followed by best supportive care in the other arm; no G-CSF was permitted.

In both scenarios, first-line FOLFIRINOX produced more life years and quality-adjusted life years (QALY) than first-line gemcitabine. The costs per QALYs for FOLFIRINOX were about $45,000 to $55,000. Thus, even though the component drugs of the FOLFIRINOX regimen cost more than single-agent gemcitabine, FOLFIRINOX is more cost-effective than gemcitabine. FOLFIRINOX has therefore received a favorable funding recommendation in most Canadian provinces.

**Future Directions with FOLFIRINOX**

Given the impressive activity of FOLFIRINOX in the metastatic setting, plans are underway to prospectively evaluate this regimen in the adjuvant, locally advanced, and borderline resectable settings, studies are ongoing to add targeted agents to FOLFIRINOX, and trials are in development to determine how to adjust doses and ameliorate toxicity.

**PRODIGE 24-ACCORD 24/0610** will be the first trial to evaluate FOLFIRINOX in the adjuvant setting. This study will use a modified regimen, called mFOLFIRINOX, in which the bolus 5-FU has been omitted and all other drug doses remain unchanged. Eligible patients with resected head, body, or tail lesions, PS 0–1, age less than 80 years, total bilirubin less than 1.5 X ULN, and Ca 19–9 less than 180, will be stratified by center, node status, postoperative Ca 19–9 level (90 vs. 91–180), and surgical margin (R0 vs. R1), and randomized to 24 weeks of gemcitabine or mFOLFIRINOX. The primary endpoint will be 3-year disease-free survival. A 30-patient lead-in safety analysis will soon be initiated to ascertain that the rate of grade 3–4 diarrhea is less than 5%. The study requires 490 patients to demonstrate a 10% increase in disease-free survival at 3 years, from 17% to 27%. It will be conducted in France and Canada.

The safety of FOLFIRINOX in borderline resectable patients has been described in a retrospective series.\textsuperscript{30} A021101 is a 50-patient, single-arm, neoadjuvant phase II U.S. Intergroup study of mFOLFIRINOX followed by chemoradiation then surgery and postoperative gemcitabine for patients with borderline resectable pancreatic cancer. This benchmark trial will assess the feasibility of a multi-institutional effort in this patient subgroup and provide a foundation for future trials. The primary endpoint is 1-year overall survival.

FOLFIRINOX may also serve as a platform for the addition of targeted agents, though caution must be used because of the potential for overlapping toxicities. The Cancer and Leukemia Group B (CALGB) will be leading a phase IB/randomized phase II trial of mFOLFIRINOX plus placebo or ganitumumab (a monoclonal antibody to the insulin growth factor 1 receptor), in patients with previously untreated metastatic pancreatic cancer. This will be the first U.S. cooperative group trial to confirm the European experience with FOLFIRINOX.

A phase IB dose-finding study of FOLFIRINOX plus IPI-926, a hedgehog pathway inhibitor, is currently ongoing. Once a phase II dose is determined, this combination will be incorporated in a randomized phase II study in development in CALGB and ECOG, in which patients with locally advanced disease are randomized to FOLFIRINOX plus IPI-926 or placebo, followed by chemoradiation. A phase IB study of FOLFIRINOX plus the hedgehog inhibitor LDE225 is also accruing patients.
The Southwest Oncology Group (SWOG) is in the process of designing a randomized trial that compares FOLFIRINOX with FOLFOX, to determine whether irinotecan is an essential component of the regimen. Another approach is to ascertain which patients would be most likely to develop toxicity from irinotecan and adjust doses accordingly. UGT1A1 is the enzyme responsible for clearing SN-38, the active metabolite of irinotecan; germline polymorphisms in the UGT1A1 gene are known to reduce enzymatic activity.32 Thus, patients treated with FOLFIRINOX who have different UGT1A1 genotypes may tolerate different doses of irinotecan. Using genotype-guided dosing, investigators at the University of Chicago will soon open a phase I study to establish the optimal safe doses of irinotecan in the mFOLFIRINOX regimen for each of three UGT1A1 genotype groups (*1*1, *1*28, and *28*28).

**Conclusion**

After so many negative randomized trials of gemcitabine doublets, the unprecedented outcomes achieved with the FOLFIRINOX regimen clearly represent a major treatment advance for those patients with pancreatic cancer who have a good performance status. No other randomized study has ever achieved a median survival of nearly a year. In no other trial have we even whispered about an 18-month survival in a proportion of patients with metastatic disease. No other phase III study has achieved such a high objective response rate. And despite substantial, though manageable toxicities, FOLFIRINOX also helps patients feel better for longer than if they received gemcitabine, a drug used principally for its effect on symptoms. Remarkably, this new drug combination is even cost-effective.

The investigators in this study are to be commended not only for the decade they spent in developing the highly active FOLFIRINOX regimen. They are also to be applauded for a very well-designed pivotal study, which tested this therapy in a uniform population of patients (all metastatic), who, with their good performance status, were most likely to tolerate the rigors of the multidrug combination and were thus most able to benefit from it.

Unanswered questions remain about the optimal way to dose the component drugs to minimize toxicity while preserving activity. Upcoming studies will address the potential role of this regimen in other disease settings and will use FOLFIRINOX as a platform on which to add new agents.

It has been a long journey, but with the advent of FOLFIRINOX, we are finally beginning to make progress against this dismal disease.

**Author’s Disclosures of Potential Conflicts of Interest**

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A Matter of Timing: Is There a Role for Radiation in Locally Advanced Pancreatic Cancer, and If So, When?

By Theodore S. Hong, MD, Jennifer Y. Wo, MD, and Eunice L. Kwak, MD, PhD

Overview: The role of radiation therapy in the management of locally advanced pancreatic cancer is controversial. Despite its localized presentation, locally advanced pancreatic cancer is characterized by high rates of metastases. Historic data have been mixed, and newer studies have called into question the use of radiation therapy. However, it appears that patients more likely to benefit from chemoradiation can be identified with an induction phase of chemotherapy. Data evaluating this approach suggest that approximately 30% of patients will develop metastatic disease within the first 3 to 4 months of chemotherapy. Patients without progression who receive chemoradiation therapy may experience improved survival. Future directions include the validation of this strategy and the integration of biologic agents.

Pancreatic cancer is the fourth leading cause of cancer deaths in the United States, with 5-year survival rates of less than 5%. Although surgical resection offers the best chance at long-term survival, only 10% to 20% of patients have resectable disease. Nearly half of all patients with pancreatic cancer have clinically evident metastatic disease, and the remaining 40% of patients present with localized but unresectable disease because of vascular involvement, which is considered locally advanced pancreatic cancer (LAPC). However, even patients with apparently localized disease have high rates of occult metastases, with staging laparoscopy studies demonstrating that at least 30% of patients harbor metastatic peritoneal disease that is undetectable by imaging.

With the greater appreciation of the systemic nature of localized pancreatic cancer, there has been a renewed interest in evaluating the optimal timing of radiation therapy, including the early use of systemic chemotherapy both to address metastatic disease and to select patients most likely to benefit from local therapy.

Historic Perspective

Although the trend toward upfront or neoadjuvant chemotherapy has gained traction in recent years, the benefit of chemoradiation therapy has always been controversial. Early randomized trials suggested mixed benefits from chemoradiation. Chemoradiation first came to the forefront of therapy for LAPC based on a randomized trial conducted by the Gastrointestinal Tumor Study Group (GITSG) in 1974. In this study, 228 patients with LAPC were randomly assigned to receive 60 Gy of radiation therapy alone compared with 40 Gy of radiation with concurrent 5-fluorouracil (5-FU) and 60 Gy of radiation with 5-FU. Patients assigned to the two chemoradiation arms also received maintenance 5-FU. Both chemoradiation arms were associated with significantly improved survival compared with the radiation alone arm (p < 0.05 for 40 Gy arm, p = 0.001 for 60 Gy arm). No significant difference was reported between the 60 Gy and 40 Gy chemoradiation arms.

In 1977, the Eastern Cooperative Oncology Group (ECOG) initiated a randomized trial comparing 5-FU alone to chemoradiation therapy. Ninety-one patients with LAPC were randomly assigned to groups receiving either weekly 5-FU alone or 40 Gy of radiation with bolus 5-FU followed by weekly 5-FU. This study showed no difference in survival with or without radiation therapy (median survival [MS] 8.3 months vs. 8.2 months, not significant [NS]). However, this study was criticized because of the poor survival in both groups. Because of these results, GITSG initiated another randomized trial comparing a three-drug regimen of streptozocin, mitomycin C, and 5-FU (SMF) or radiation therapy to 54 Gy with concurrent 5-FU followed by SMF chemotherapy. In this small 43-patient study, the 1-year survival was improved with the inclusion of chemoradiation compared to chemotherapy alone (41% vs. 19%, p < 0.02). Based on this study, chemoradiation therapy was felt to be superior to chemotherapy alone.

Role of Radiation Questioned: the 2000–01 FFCD/SFRO Trial

Because of the limitations of the data defining the role of radiation therapy and the lack of formal evaluation of radiation therapy in the modern treatment era, the Federation Francophone de Cancérologie Digestive (FFCD) and the Societe Francophone de Radiotherapie Oncologique (SFRO) evaluated the role of chemoradiation therapy in patients with LAPC. In this trial, patients were randomly assigned to receive either chemoradiation followed by maintenance gemcitabine or gemcitabine alone until progression. Radiation was delivered to 60 Gy in 2 Gy/fraction with an infusion of 5-FU (300 mg/m2/day) on days 1 to 5 for 6 weeks and cisplatin (20 mg/m2/day) on days 1 to 5 during weeks 1 and 5. This phase III study was designed to demonstrate an improvement from 6 months with gemcitabine alone to 12 months with chemoradiation. However, the study was stopped early because of slow accrual, and a review by an independent data monitoring committee followed. At that time, it was noted that the chemoradiation arm had a shorter overall survival (OS). Survival analysis showed worse median survival with chemoradiation (8.6 months) compared with gemcitabine alone (13.0 months) by intent-to-treat analysis (p = 0.03). Because of concerns of a possibly confusing toxicity, a per-protocol analysis was performed restricting analysis to those who received at least 75% of protocol treatment. By this analysis, patients receiving chemoradiation therapy still experienced a shorter median survival (9.5 months vs. 15.0 months, p = 0.006).

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Although these results suggest that chemoradiation should not be used, the study design limits the ability to interpret the outcome. The choices of chemotherapy agents and radiation dose were nonstandard and may have compromised tolerability in the chemoradiation arm. For instance, although highly emetogenic, cisplatin has not demonstrated significant activity in pancreatic cancer and the dose of radiation used was higher than tested in most clinical trials. Furthermore, this nonstandard regimen was not tested in phase II trials before its use in this randomized trial. The toxicity of this regimen led to fewer than half of the patients receiving 75% of the chemoradiation dose and contributed to the poor tolerance of subsequent maintenance chemotherapy. The median total dose of gemcitabine received by patients in the chemoradiation arm was well below half the total dose received by patients in the chemotherapy-alone group.

Despite the flaws, this trial underscores a key lesson: even when localized in presentation, pancreatic cancer is a largely systemic disease, and it is important for patients to receive chemotherapy early in the treatment course.

Does Anyone Benefit from Radiation Therapy?
The GERCOR Study

In the late 1990s through the early 2000s, the Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) ran a number of phase II and III trials evaluating different chemotherapy regimens. Following the trend of including patients with locally advanced disease in chemotherapy trials but acknowledging the controversial role of radiation therapy, investigators recommended patients for these trials who had no progression after 3 months of receiving chemotherapy and who had ECOG performance status of 2 or better. However, investigators could also continue chemotherapy at their discretion. Radiation therapy was delivered to 45 Gy with a boost to a total dose of 55 Gy with continuous infusion 5-FU. Computed tomography (CT) planning was mandated.

In a retrospective analysis of prospective trials, 167 of the 497 patients enrolled on these trials had locally advanced disease. After 3 months of chemotherapy, 71% of patients with LAPC did not have progressive disease and had performance status scores eligible for chemoradiation. Of the remaining 29% of patients ineligible for chemoradiation, 45 of the 53 patients were ineligible because they had progressive disease. Of the 128 patients eligible for chemoradiation, 72 (56%) patients received chemoradiation and 56 (44%) patients continued receiving chemotherapy alone. Patients in both groups were well matched by chemotherapy regimen, age, performance status, weight loss, and response to chemotherapy. The median progression-free survival (PFS) for the chemoradiation and chemotherapy groups were 10.8 months and 7.4 months, respectively (p = 0.005). The median OS was 15 months for the chemoradiation group and 11.7 months for the chemotherapy group (p = 0.0009).

Because of its retrospective nature, this study was limited by potential patient selection bias; however, the two treatment groups were well balanced for performance status, age, and chemotherapy response. This study suggests that some patients might benefit from chemoradiation therapy. Although previous studies have recognized that some patients have rapidly metastatic disease, this study suggests that an effective strategy to evaluate which patients have aggressive systemic biology is to start with systemic chemotherapy and to move only those patients whose disease does not progress after several months of chemotherapy to receive chemoradiation. This study caused a substantial paradigm shift in the way radiation therapy was timed. Increasingly, institutions would initiate radiation therapy with chemotherapy, primarily to identify patients with rapid, early metastatic progression who would not benefit from aggressive local therapy.

Further Evidence of the Benefit of Radiation Therapy: ECOG 4201

During this period, investigators in the United States were also investigating the role of radiation therapy. Using a gemcitabine platform, ECOG 4201 directly compared gemcitabine alone with gemcitabine-based chemoradiation therapy followed by gemcitabine. The chemotherapy-alone group received one 7-week induction cycle, followed by five additional 4-week cycles (3 weeks on, 1 week off). The chemoradiation arm received 50.4 Gy of radiation as 1.8 Gy/fraction with concurrent gemcitabine (600 mg/m²) weekly during radiation treatment followed by five additional cycles of gemcitabine. The intended study design included 316 patients but was closed after enrolling only 74 patients because of slow accrual.

As expected, the radiation arm had greater toxicity, with 41% of patients experiencing grade 4 toxicity compared to 9% in the chemotherapy-alone arm. Despite this, both arms received a median of three cycles of chemotherapy. Median survival was improved in the radiation arm (11.1 months vs. 9.2 months, p = 0.017). There was no difference in PFS.

This trial was more straightforward than the FFCD trial because it directly compared radiation therapy with gemcitabine to gemcitabine alone. The chemoradiation regimen demonstrated safety in phase I testing, which in contrast to the FFCD trial, is reflected in the fact that both arms received a similar amount of chemotherapy. However, the small number of patients enrolled in this study limited the ability to understand the role of radiation therapy. Additionally, because radiation therapy was used at the beginning of treatment, issues of timing were not addressed. Finally, this small study elicited an OS benefit, despite a lack of difference in PFS. It is unclear why this would be the case, especially in light of the increased toxicity of the radiation arm. However, this study was the first study to demonstrate...
an OS benefit with radiation therapy against a backbone of gemcitabine.

Further Evidence of Delaying Radiation Therapy

Investigators at the University of California, San Francisco (UCSF), seeking to optimize systemic control, performed a phase II study of fixed-dose rate gemcitabine in combination with cisplatin for six cycles, followed by chemoradiation therapy.\(^9\) The gemcitabine was given at 1,000 mg/m\(^2\) infused at 10 mg/m\(^2\)/minute followed by cisplatin (20 mg/m\(^2\)) administered on days 1 and 15 of a 28-day cycle. Patients initiated chemoradiation therapy 2 to 6 weeks after completing six cycles of chemotherapy. Radiation was delivered to a standard 50.4 Gv with continuous infusion 5-FU.

Of the 25 patients enrolled on the study, eight (28%) developed disease progression while receiving chemotherapy between two and 4.5 treatment cycles (median three cycles), consistent with the rate of metastatic progression seen in the GERCOR study. Thirteen patients (56%) proceeded to the chemoradiation phase. The median OS for the entire cohort was 13.5 months, with a median time to progression (TTP) of 10.5 months.

The patterns of treatment failure were informative for the selection that occurs with upfront chemotherapy. Seven of the eight patients who had progressive disease during chemotherapy had metastatic disease. In contrast, six of the 12 patients who received all six cycles of chemotherapy and chemoradiation developed local progression, rather than metastatic progression. This study suggests that delayed radiation therapy enriches the group of patients receiving radiation for those with more localized biology.

Investigators at Massachusetts General Hospital (MGH) also compared upfront chemoradiation therapy with delayed chemoradiation therapy. At MGH, patients with LAPC were historically treated with early chemoradiation therapy. With the publication of the GERCOR study in 2007, a gradual shift to delayed chemoradiation therapy occurred. In a retrospective analysis, investigators compared patients who received chemotherapy before chemoradiation therapy with those who started with chemoradiation therapy to determine the relative outcomes associated with patient selection based on the timing of chemoradiation treatment.\(^10\)

In this study, 70 consecutive patients with unresectable (46 patients) or borderline resectable (24 patients) LAPC were treated with chemoradiation from 2005 to 2009. Patients typically received 50.4 Gv of radiation in 28 fractions (91%) with concurrent 5-FU (84%) or capecitabine (14%). Forty patients received chemoradiation alone, and 30 patients received a median of 4 months of chemotherapy before chemoradiation, typically gemcitabine (93%). All patients without progression after chemotherapy were offered chemoradiation.

Fifty-three percent of the patients in the early chemoradiation group compared with 83% in the delayed chemoradiation group had categorically unresectable tumors at diagnosis. Median OS for the early and delayed chemoradiation groups was 12.4 months and 18.7 months, respectively (\(p = 0.02\)). Median PFS for early compared with delayed chemoradiation was 6.7 months and 11.4 months, respectively (\(p = 0.02\)). On multivariate analysis, administration of chemotherapy before chemoradiation (adjusted hazard ratio [AHR] = 0.49; 95% CI, 0.28 to 0.87; \(p = 0.02\)) and surgical resection (AHR = 0.38; 95% CI, 0.17 to 0.85; \(p = 0.02\)) were associated with increased OS.

These studies are representative of the paradigm shift that has occurred at many institutions over the past 5 years. The use of upfront chemotherapy represents a way to identify patients more likely to benefit from chemoradiation treatment.

A Marker for Different Biologies: DPC4 Status

Although clinical evidence has suggested that upfront chemotherapy could help identify patients more likely to benefit from chemoradiation, a biomarker predictive of clinical course had yet to be identified. To this end, investigators at Johns Hopkins University evaluated 76 patients who had consented to participate in their rapid autopsy program.\(^11\) Patients were grouped according to death with widely metastatic disease or death with locally progressive disease. Grouping was correlated with KRAS and TP53 mutations and DPC4 (which stands for Deleted in Pancreatic Cancer, locus 4) status.

Of the 76 patients, 9 had no metastases at the time of death, 13 had 10 metastases or fewer, 26 had 11 to 99 metastases, and 26 patients had more than 100 metastases. Investigators found a striking correlation between DPC4 status and patterns of treatment failure. Generally, patients with DPC4 loss had widespread disease, whereas patients with intact DPC4 were more likely to have locally destructive disease (\(p = 0.007\)).

This study highlights two major points. First, almost 30% of patients died with either no metastases or fewer than 10 metastases, highlighting that a substantial number of patients succumb to locally destructive disease rather than metastatic disease. Second, intact DPC4 presence as assayed by immunohistochemistry may identify a subgroup of tumors that are destined to be locally destructive as opposed to widely metastatic. Because this finding may have implications for the relative roles of chemotherapy and radiation therapy, the Radiation Therapy Oncology Group (RTOG) has proposed a study in which systemic chemotherapy with a combination of 5-FU, oxaliplatin, irinotecan, and leucovorin (FOLFIRINOX) will be studied in patients with loss of DPC4 and radiation dose escalation will be studied in patients with intact DPC4.

Current Recommendations and Future Directions

The evidence that LAPC represents a heterogeneous group has been mounting. Although the majority of patients will succumb to metastatic disease, there appears to be a group of patients that has more locally destructive disease. Currently, the use of chemotherapy before radiation therapy has the advantages of early treatment of micrometastatic disease and better selection of patients who may benefit from chemoradiation therapy. Efforts are currently ongoing to further clarify the timing of radiation for LAPC. At this writing, the LAP 07 study is evaluating the role of radiation therapy in this very manner (Fig. 1). Led by GERCOR, LAP 07 is evaluating chemoradiation therapy after four cycles of chemotherapy compared with two more cycles of chemotherapy. This trial involving 902 patients will hopefully provide a definitive answer to the role of delayed chemoradiation.

In the future, the use of biomarkers, such as DPC4, may
provide this biologic information at the time of diagnosis. However, the DPC4 assay has not yet been standardized for routine clinical use. The RTOG is currently in the process of validating the feasibility of this assay on fine needle aspiration samples for its proposed trial of patients with LAPC.

Questions remain regarding the optimal duration of therapy. No standard recommendation exists about how much chemotherapy should be given before chemoradiation therapy. As discussed above, the GERCOR study used 3 months. The RTOG plans to use 2 months for the induction phase of chemotherapy. At our institution, we have chosen to use 4 months, in part because adjuvant trials like RTOG 9704 have administered 4 months of chemotherapy when used with 5.5 weeks of chemoradiation therapy. Additionally, because the median TTP on gemcitabine is between 3 and 4 months, 4 months allows adequate time for metastatic biology to declare itself, as demonstrated in the UCSF trial. The use of 2 to 4 months of chemotherapy seems reasonable.

In addition, no consensus has been set on which chemotherapy should be used with standard fractionation radiation therapy. Classically, most studies have used 5-FU, shifting from bolus 5-FU to continuous infusion 5-FU, which follows the trend in rectal cancer. Gemcitabine-based chemoradiation therapy has been studied extensively, including in the randomized ECOG study. For example, RTOG and Alliance cooperative groups are using capecitabine as the standard chemoradiation backbone. Whether a particular platform has substantial advantages over another remains unclear.

There has been increasing interest in the use of stereotactic body radiation therapy (SBRT), where advanced technology delivers high doses of radiation alone to the tumor. In 2004, an initial phase I study out of Stanford University demonstrated the feasibility and safety of SBRT for LAPC. In this study, 15 patients with LAPC and an ECOG performance status of less than 2 were treated with 15 Gy, 20 Gy, or 25 Gy of radiation in a single fraction via CyberKnife®. One of the three patients treated at 15 Gy, two of the four patients treated at 20 Gy, and zero of the six patients treated with 25 Gy had local progression. This phase I study was followed by a phase II study combining conventionally fractionated chemoradiation with a stereotactic radiosurgery (SRS) boost. Sixteen patients were treated with 45 Gy of radiation in 1.8 Gy/fraction to the tumor and regional lymphatics with concurrent 5-FU or capecitabine. Within 1 month of chemoradiation treatment, patients were given an SRS boost of 25 Gy of radiation alone to the tumor using CyberKnife. Sixteen patients were treated. Fifteen of the 16 patients were free from local progression until death. However, TTP (17.5 weeks) and median survival (33 weeks) were modest. In a retrospective study from the Beth Israel Deaconness Medical Center, 47 patients with LAPC were given two cycles of gemcitabine followed by restaging. Patients without metastatic disease were given a third cycle of gemcitabine while undergoing planning. Patients were then treated with 24 Gy to 36 Gy of radiation in three fractions followed by maintenance gemcitabine. Eight patients (17%) developed metastatic disease before undergoing SBRT. Patients undergoing SBRT had a median OS of 20 months.

Efforts are also ongoing to reduce the toxicity of chemoradiation treatment by using advanced radiation technology such as intensity modulated radiation therapy (IMRT). IMRT uses multiple beam angles and a computational process called inverse planning to create irregular dose distributions that can conform to irregular shapes, thereby affording the potential to decrease the toxicity associated with chemoradiation. In a retrospective review from the University of Maryland, 46 patients with pancreatic or ampullary cancers treated with IMRT were evaluated. Investigators noted a grade 3 or 4 nausea and vomiting rate of 0%, compared to the 11% seen with standard CT-based radiation therapy used in RTOG 9704. This study suggests that further improving radiation delivery can positively influence the toxicity profile that was reported in the FFCD and ECOG studies.

Based on the current research, for the treatment of patients with LAPC we recommend 2 to 4 months of chemotherapy followed chemoradiation therapy. Patients typically receive gemcitabine, although select patients are now also receiving FOLFIRINOX. Chemoradiation therapy is delivered with either continuous infusion 5-FU or capecitabine to
a dose of 50.4 Gy to 59.4 Gy of radiation in 1.8 Gy/fraction. Future trials are now focused on the prospective evaluation of biomarkers such as DPC4 and the integration of targeted therapies into this platform.

Authors’ Disclosures of Potential Conflicts of Interest

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REFERENCES

A Myriad of Symptoms: New Approaches to Optimizing Palliative Care of Patients with Advanced Pancreatic Cancer

By Lauren A. Wiebe, MD

Overview: Patients with advanced pancreatic cancer (APC) require early and frequent palliative interventions to achieve optimal quality of life for the duration of illness. Evidence-based supportive treatments exist to maximize quality of life for any patient, whether receiving chemotherapy or not. This article provides a comprehensive review of symptoms with current treatment recommendations and directions for future development. Celiac plexus neurolysis improves pain in the majority of patients with APC and should be moved earlier in the analgesic paradigm. Malignant bowel obstruction can be palliated quickly with optimal management via gastric decompression, octreotide, parenteral opioids, and standing antiemetics. Recommendations are provided for best treatment of malignant gastroparesis, gastric outlet obstruction, and chemotheray-induced nausea and vomiting in this population.

Patients with advanced pancreatic cancer (APC) require early and frequent palliative interventions to achieve optimal quality of life for the duration of illness. Despite recent notable advances in multidisciplinary anti-neoplastic therapy, the majority of patients with APC ultimately die after facing numerous physical and emotional hurdles. As a physician caring for these patients, there are opportunities to relieve suffering from predictable complications of pancreatic cancer. Evidence-based supportive treatments exist to maximize quality of life for any patient, whether receiving chemotherapy or not. This article provides a comprehensive review of symptoms facing patients with APC with current treatment recommendations and directions for future development.

Pain

Pain from cancer in the pancreas is often constant and severe, felt predominantly in the midback and epigastrium. Noxious sensory input from inflamed pancreatic tissue and direct neural invasion is transmitted via the celiac plexus as pain. Opioïds and adjuvant medications remain standard of care for analgesia; however, the titration of opioids can be limited by systemic toxicities and may not adequately address the pain. Successful locoregional intervention minimizes systemic opioid requirements early in the course of the disease.

In the majority of patients, celiac plexus neurolysis (CPN) has been shown to provide effective pain relief simultaneous with reduction in systemic opioids. An injection of either ethanol or phenol destroys afferent nerve fibers and disrupts pain signals for an average of 3 months, though sometimes permanently. CPN can be performed with equivalent efficacy surgically, percutaneously under radiologic guidance, or endoscopically via ultrasound. The most common risks include transient hypotension, constipation, or diarrhea; no serious adverse events were noted in a meta-analysis. More than 80% of patients note significantly improved analgesia after CPN in blinded or sham studies. To evaluate both effect and timing of CPN in pancreatic cancer, Wyse and colleagues performed a double-blind, randomized controlled trial of patients found to have inoperable pancreatic cancer at time of diagnostic endoscopic ultrasound (EUS). The 96 participants were randomized to either CPN or usual medical management at time of EUS diagnosis. Persistently increasing pain scores were noted in the control group during the study; however, patients who underwent neurolysis reported improvements in analgesia both 1 and 3 months later with a statistically significant decrease of 49% in mean pain score.4

The study from Wyse and colleagues adds to the body of evidence supporting early CPN for patients with pancreatic cancer. Optimal timing would be at the moment of diagnosis if patients report abdominal pain attributable to inoperable pancreatic cancer.

Because these investigators took a detailed pain history before diagnostic EUS/endoscopic retrograde cholangiopancreatography (ERCP), patients were able to benefit from CPN with early, lasting pain relief. For patients undergoing surgical exploration, CPN should be considered intraoperatively for early, seamless analgesia once a diagnosis is secured. With recurrent pain, repeat CPN is indicated and effective, particularly if a patient had benefit from prior neurolysis.

Nausea and Vomiting

Nausea or vomiting in a patient with APC can arise from multiple etiologies. With new onset, a patient should be evaluated for potentially reversible causes, some of which are discussed later in this article. While receiving anti-neoplastic therapy, adequate support with antiemetics should be provided per the guidelines of the American Society of Clinical Oncology (ASCO) or the National Cancer Care Network (NCCN), available online. As FOLFIRINOX is

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more commonly given for APC, special attention should be paid to this aspect of patient care.

ASCO provides evidence-based guidelines for medications based on likelihood of emesis by chemotherapy regimen.\(^6\) Published in 2011, the recommended support for highly-emetogenic chemotherapy consists of a three-drug regimen: dexamethasone, a 5HT3 inhibitor, and a neurokinin-1 (NK-1) inhibitor. For moderately-emetogenic chemotherapy, data supports a single dose of palonelastron followed by 3 days of dexamethasone. The guidelines suggest dexamethasone alone as premedication for patients starting a low-emetogenic regimen such as gemcitabine, though the steroid dose may be decreased in APC patients with glucose intolerance or new diabetes.\(^5\)

In the most recent edition, both the NCCN and ASCO guidelines acknowledge the antiemetic effect of olanzapine.\(^5,6\) The authors of ASCO guidelines suggest olanzapine for patients with refractory chemotherapy-induced nausea and vomiting (CINV) that occurs despite appropriate prophylaxis. The NCCN guidelines include olanzapine 2.5–5 mg twice daily for patients with breakthrough CINV.\(^7\) However, subsequent to publication of these guidelines, additional data has emerged showing superior control of delayed nausea with an olanzapine-based regimen over the standard recommendations for patients undergoing highly emetogenic chemotherapy, which included an NK-1 inhibitor.\(^7\)

An atypical antipsychotic, olanzapine blocks several neurotransmitters including serotonin, dopamine, acetylcholine, and histamine. The proposed antiemetic mechanism is thought to be D2 and 5HT3 inhibition, used in an off-label indication for nausea.\(^7,8\) Two recent large randomized studies demonstrate efficacy for patients receiving highly emetogenic chemotherapy. The largest effect of olanzapine appears to be on delayed nausea with complete control as late as day 5 or 7.\(^7,8\) Additional improvements in global functioning, insomnia, appetite, and fatigue have been found to be significant over placebo (p < 0.01).\(^7,8\)

Weight gain and hearty appetite are described side effects of olanzapine.

Olanzapine appears to be well-tolerated in patients undergoing chemotherapy.\(^7,8\) In 123 patients, no grade 3 or 4 toxicity was found by Navari and colleagues, though patients noted fatigue, drowsiness, and dry mouth most often.\(^7\) Prescribers should familiarize themselves with potential toxicities. Prolonged administration, for months to years, increases the risk of diabetes and pancreatitis in the psychiatric population, though this is less concerning with the prognosis of APC. Finally, olanzapine carries a black box warning for increased mortality in elderly patients with dementia-related psychosis.

Malignant Gastroparesis

Gastroparesis associated with pancreatic cancer is a well-described phenomenon. Up to one-half of patients with APC experience slowed gastric emptying with no anatomic obstruction.\(^9\) Cancer in the pancreas alters normal gut motility by direct infiltration of autonomic nerve fibers and by altering neurohormonal pathways within the bowel.\(^9\) Prior abdominal surgery, radiation, or comorbid diabetes also contribute to gastroparesis.\(^9\)

A careful medication review and esophagogastroduodenoscopy may rule out reversible causes of gastroparesis. The gold standard for diagnosis is functional imaging, but APC patients with refractory nausea, vomiting, bloating, and early satiety should be started on prokinetics empirically—either metoclopramide 5–10 mg four times daily or erythromycin.\(^9\) Small high-calorie, low-fiber meals with ample liquids are best. Patients feel better sitting upright postprandially, followed by ambulation. Palliation of severe cases can be achieved with decompressive gastrostomy or Roux-en-Y, although overall prognosis and the presence of ascites should be considered carefully before interventions.\(^9\)

Gastric Outlet Obstruction

Approximately 15% of patients with APC develop gastric outlet obstruction (GOO) during the disease trajectory and present with refractory vomiting.\(^10\) Clinical suspicion can be confirmed with a plain radiograph alone, although patients often undergo ultrasound, CT scan, or endoscopy to confirm the diagnosis. Historically, an open, palliative gastrojejunostomy (GJ) was the definitive treatment for malignant GOO, but surgery can result in substantial morbidity and even mortality.\(^10,11\) More recently, self-expanding metallic stents (SEMS) have become a safer and easier alternative with minimal morbidity and mortality.

In a systematic review of the literature, endoscopic stent placement was feasible in 96% of patients with malignancy-related GOO, only limited by inability to transverse the obstruction or stent deployment failure. After 1 week, 72% of patients who underwent SEMS were eating soft or regular foods compared with 14% of patients post GJ. Mean hospital stay is shorter with stent placement as compared with surgery (7 vs. 13 days). Repeat obstructive symptoms occurred in 18% of patients with a stent compared with 1% of surgical cases, but overall, few complications are seen in patients with SEMS.\(^10\) GJ, particularly laparoscopic, remains a viable palliative option, but only for a select group of healthy patients with a longer prognosis.\(^10,11\)
Malignant Bowel Obstruction

Many patients with APC develop peritoneal implants and carcinomatosis. Unfortunately, this can result in malignant bowel obstruction (MBO) with abdominal distension, profound cramping, and refractory vomiting causing the inability to eat and often death. Palliative surgical or endoscopic interventions can be considered but may be limited by location of disease, multifocal obstruction, presence of ascites, and nutritional status of the patient. Detailed in Figure 1, complex decision making in an urgent setting is difficult, and MBO can quickly change the trajectory of a patient’s life.

A combined approach of gastric decompression with optimal pharmacologic therapy provides relief of suffering as well as reversal of MBO in the majority of cases. Adequate pain control with strong opioids is critical by either intravenous or subcutaneous route; transdermal medications should be reserved for later when a patient has stable opioid requirements. Antisecretory agents are critical to reduce splanchnic blood flow, bowel secretions, fluid loss, and cramping pain. Considered the standard of care in MBO, octreotide has been shown to be effective for palliation in prospective trials. An acceptable total dose of octreotide ranges from 300–1,200 mcg per day given via intravenous or
subcutaneous bolus or infusion. Haloperidol is the gold standard to relieve nausea and vomiting associated with MBO, although a combination of antiemetics may be required. Corticosteroids may help with nausea and bowel edema but are less well studied in this setting.\(^\text{11}\)

The goal for managing MBO is complete relief of vomiting, nausea, and pain. Gastric decompression via nasogastric tube provides immediate symptom relief, but should be temporarily used, on the order of days. With aggressive around-the-clock pharmacologic therapy detailed above, the goal is to eliminate symptoms within 24 hours. Without clear signs of returning bowel function in 2 or 3 days, a venting gastrostomy should be placed early for optimal palliation and return of patient mobility.\(^\text{11}\) Hospice and homecare agencies are familiar with home drainage protocols, which the patient and/or family can learn.

**Malignant Ascites**

Malignant ascites causes discomfort, early satiety, bowel stasis, orthopnea, and diminished mobility. In APC, peritoneal fluid accumulation occurs by several mechanisms, including portal hypertension from intrahepatic metastases, portal vein compression and/or thrombus, peritoneal tumor implants with increased capillary permeability, or direct disruption of lymphatic drainage from the peritoneum.\(^\text{12}\) Treatment goals are to palliate symptoms and preserve normal function as long as possible.

For exudative ascites, dietary sodium restriction and diuretics may provide relief. These patients have a serum-ascites albumin gradient (SAAG) greater than 1.1 and elevated portal pressures from venous occlusion or diffuse hepatic metastases. However, patients with carcinomatosis resulting in transudative ascites and a low SAAG (<1.1) are often primarily refractory to diuretic combinations and should undergo early paracentesis for palliation.\(^\text{12}\) For all patients with malignant ascites, therapeutic paracentesis relieves symptoms 90% of the time with minimal risk of adverse events.\(^\text{12}\)

The majority of patients (88% to 100%) with anticipated survival greater than 2 to 3 months will benefit from placement of an indwelling pigtail or tunneled catheter to control ascites with easy drainage at home or clinic. In a meta-analysis, tunneled catheters have a low risk of infectious complications (2.5%), but no randomized study has been performed. Nontunneled devices have a reported complication rate as high as 30% in some series.\(^\text{12}\) Although an off-label use in the United States, PleurX catheters have been studied in this setting and are commonly used with success for palliation of refractory malignant ascites.\(^\text{12}\)

**Pancreatic Exocrine Insufficiency**

Patients with pancreatic cancer are at high risk for pancreatic exocrine insufficiency (PEI). When rigorously assessed 1 year after partial pancreatectomy, 55% of patients have PEI by diagnostic criteria.\(^\text{13}\) Radiation and surgery may cause ductal fibrosis resulting in poor delivery

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### Table: Management of Symptoms and Complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Management</th>
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<tr>
<td>Pancreatic Pain</td>
<td>Early celiac plexus neurolysis; repeat as needed. Medical management per WHO guidelines. Referral to palliative care if pain needs are complex.</td>
</tr>
<tr>
<td>Malignant Gastroparesis</td>
<td>Metoclopramide 5-10 mg po four times daily. Dietary changes: small, low-fiber meals with liberal liquids. Behavioral changes: sit upright after meals, ambulation.</td>
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<tr>
<td>Gastric Outlet Obstruction</td>
<td>Placement of a SEMS. If SEMS unsuccessful (rare), venting gastrostomy for palliation.</td>
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| Malignant Bowel Obstruction (MBO)| Urgent gastric decompression with NG tube. Aggressive parenteral medical management:  
  - Octreotide 300-1,200 mcg/day divided or continuous dosing  
  - Standing antiemetics: haloperidol or chlorpromazine  
  - Opioids given intravenously or subcutaneously  
  - Consider steroids or intravenous fluids  
  If MBO persists >2-3 days, place venting gastrostomy. |
| Malignant Ascites                | Large-volume paracentesis for comfort. If SAAG ≥ 1.1, patient may benefit from:  
  - Dietary sodium restriction  
  - Diuretics: furosemide and spironolactone  
  If SAAG < 1.1, proceed with paracentesis for palliation. If prognosis >2-3 months, placement of tunneled catheter. |
| Pancreatic Exocrine Insufficiency | Pancreatic enzyme supplementation:  
  - 40,000-50,000 IU of lipase during or after each meal.  
  - 20,000 IU of lipase with each snack.  
  If no clinical benefit with above:  
    - Increase enzymes as tolerated with each meal.  
    - Add H2-blocker or proton-pump inhibitor. |
| Anorexia-Cachexia Syndrome       | Referral to experienced dietician for counseling. Consider megestrol acetate 400-800 mg daily. |
| Depression                       | Early pharmacologic treatment, likely best with SSRI. Supportive counseling with referral to mental health expert. Referral to palliative care for additional support. |
of lipase and trypsin into the gut lumen. In situ pancreatic tumors block secretion of enzymes, leading to failure absorbing fat-soluble vitamins such as A, D, E, and K. Although patients may not manifest clinical steatorrhea until the lipase concentration falls below 10% of normal, symptoms of malabsorption can be debilitating with abdominal cramping, bloating, and urgent stools.\textsuperscript{14} PEI also contributes greatly to the weight loss and malnutrition seen in patients with APC.\textsuperscript{14}

Diagnostic testing can be pursued but is expensive, difficult to perform, and usually unnecessary in this population. Patients with pancreatic cancer and weight loss should be given empiric supplementation with pancreatic enzymes. When taken with each meal or shortly afterward, 40,000–50,000 IU of lipase results in substantial weight gain over placebo in several studies.\textsuperscript{14} If not clinically effective after several weeks, the dose should be increased as tolerated. Because a low gastric pH irreversibly inhibits lipase, enzymes should never be taken on an empty stomach. H2-blockade and proton-pump inhibition both augment the effect of enzyme supplementation; either acid-suppressant can be added for augmented absorption of fat. Low-fat diets have not been shown to improve symptoms, but moderate-fat diets are acceptable paired with enzyme supplements.\textsuperscript{14} Medium-chain fatty acids are absorbed without lipase, so referral to a specialized dietician is helpful for guidance.

Anorexia-Cachexia Syndrome

One of the most striking symptoms observed in patients with pancreatic cancer is the anorexia-cachexia syndrome (ACS). With circulating proinflammatory cytokines, patients demonstrate negative protein-energy balance along with minimal desire to eat, resulting in profound muscle wasting and functional decline. The hallmark of cachexia is that the syndrome is incompletely reversed by appetite stimulants and nutritional intervention.\textsuperscript{15} ACS can be seen in early-stage pancreatic cancer, but occurs in more than one-half of patients with advanced disease leading to poor quality of life and survival.\textsuperscript{15}

The ability to stabilize the weight loss can improve quality of life, but interventions remain limited with no FDA-approved therapy for ACS.\textsuperscript{15} Currently, options include targeted dietary counseling and appetite stimulants, typically with oral progestin.\textsuperscript{16} Berenstein and Ortiz performed a rigorous review of the literature evaluating megestrol acetate compared with placebo in patients with advanced cancer. In total, megestrol was found to have a relative risk of 3.03 (95% CI 1.83 to 5.01) for improved appetite compared with placebo. Most trials utilized a dose between 400 and 800 mg daily. Both physicians and patients should be aware of the prothrombotic tendency of progestins.\textsuperscript{17} No other orexigenics have a documented benefit in ACS, though individual patient response is variable to drugs such as dronabinol.\textsuperscript{16}

Recent research on ACS is promising and may be clinically translatable in the near future. Recent phase II interventions targeted components of the inflammatory pathway such as IL-6, COX-2, TNF-alpha, NF-kappaB, and growth hormone.\textsuperscript{15} A phase II dose-escalation study of thalidomide in 35 patients with cancer-related ACS resulted in significantly improved appetite in 64% of patients after 2 weeks (p < 0.001).\textsuperscript{18} Finally, dietary omega-3 fatty acids suppress inflammatory and angiogenic pathways in pancreatic cancer models, suggesting a potential future role for patients with APC and ACS.\textsuperscript{19}

Depression

Patients with pancreatic cancer have the highest incidence of depression seen in any cancer population.\textsuperscript{20} Studies report rates of depression in APC ranging from 33% to 76% with resultant poor quality of life and difficulty achieving pain control.\textsuperscript{21} Elevated levels of circulating cytokines such as IL-6 and TNF-alpha are thought to alter neurohormonal pathways in the brain causing depressive symptoms even before the diagnosis of cancer is suspected.\textsuperscript{21} In particular, men with pancreatic cancer have a death rate from suicide 11 times that of the general population, reflecting the need for an improved holistic approach to care of these patients.\textsuperscript{2,20,22}

In patients with advanced cancer, it may be difficult to tell clinical depression from normal sadness experienced with a daunting prognosis. Common somatic symptoms of APC such as fatigue, anorexia, and weight loss can overlap with the signs and symptoms of depression.\textsuperscript{21} Simply asking a patient whether he or she has “felt depressed most of the time” is a validated tool with good sensitivity and specificity for depression, even in patients with terminal illness.\textsuperscript{2} Timely treatment of depression is critical in APC, as patients with depression are more likely to endorse a desire for hastened death.\textsuperscript{2}

Antidepressant medications—mainly selective serotonin reuptake inhibitors (SSRIs)—have been shown to be effective in patients with advanced cancer. Selection of SSRIs should be dictated by the side effect profile.\textsuperscript{21} In APC patients suffering marked anorexia, mirtazapine may be an advantageous choice, although not studied for this indication.\textsuperscript{21} Anxiolytics are helpful in patients with underlying anxiety disorders. In clinical practice, lorazepam is used frequently without clear evidence to guide ongoing administration. Patients requiring more than twice daily dosing of a short-acting benzodiazepine could be switched to clonazepam with a longer half-life to avoid rebound anxiety, usually starting at 0.5 mg orally twice daily.

In addition to pharmacologic interventions, patients with APC benefit greatly from supportive counseling to strengthen innate coping strategies and help with anticipatory grief as an integral part of their cancer care.\textsuperscript{2,21} Additional support will be provided by early referral to a palliative care provider. Depression and anxiety often occur because of distress from unaddressed fears of death or the symptoms that may arise in the process of dying.\textsuperscript{2} Early and frequent discussion of symptom concerns and quality of life preserves hope for patients with APC. Active interventions such as Dignity Therapy have shown promise in relief of suffering in patients with limited prognosis.\textsuperscript{2} ASCO recently released a statement of provisional clinical opinion that palliative care leads to better patient and caregiver outcomes.\textsuperscript{23} In the end, patients want to be individuals acknowledged with compassion and healing at this time in their lives.

Conclusion

Patients with advanced pancreatic cancer suffer numerous symptoms throughout the illness. It is critical that these
patients are cared for completely with aggressive palliation of symptoms to maximize their remaining time. Celiac plexus neurolysis improves pain in the majority of APC patients and should be moved earlier in the analgesic paradigm. Antiemetics continue to evolve for maximal prevention of CINV, including olanzapine in recent studies. Nutritional status remains important to patients and families; weight loss related to undiagnosed pancreas exocrine insufficiency improves with aggressive enzyme supplementation. Bowel dysfunction from gastroparesis or malignant obstruction is treatable with palliative interventions. Finally, the existential and psychosocial concerns of patients facing death from pancreatic cancer should be addressed in a holistic manner. Early integration of palliative care will help patients achieve the best quality of life in the face of this unfortunate diagnosis.

Author’s Disclosures of Potential Conflicts of Interest

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*No relevant relationships to disclose.

REFERENCES

GLOBAL PERSPECTIVE OF LOCALLY ADVANCED GASTRIC CANCER: DIFFERENT TREATMENT PARADIGMS AND THEIR RATIONALE

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Varying Lymphadenectomies for Gastric Adenocarcinoma in the East Compared with the West: Effect on Outcomes

By Benjamin Schmidt, MD, and Sam S. Yoon, MD

Overview: There are notable differences in surgical approaches to gastric adenocarcinoma throughout the world, particularly in terms of the extent of lymphadenectomy (LAD). In high-incidence countries such as Japan and South Korea, more extensive (e.g., D2) lymphadenectomies are standard, and these surgeries are generally done by experienced surgeons with low morbidity and mortality. In countries such as the United States, where the incidence of gastric adenocarcinoma is 10-fold lower, the majority of patients are treated at nonreferral centers with less extensive (e.g., D1 or D0) lymphadenectomy. There is little disagreement among gastric cancer (GC) experts that the minimum lymphadenectomy that should be performed for gastric adenocarcinoma should be at least a D1 lymphadenectomy, and many of these experts recommend a D2 lymphadenectomy. More extensive lymphadenectomies provide better staging of patient disease and likely reduce locoregional recurrence rates. Two large, prospective randomized trials performed in the United Kingdom and the Netherlands in the 1990s failed to demonstrate a survival benefit of D2 over D1 lymphadenectomy, but these trials have been criticized for inadequate surgical training and high surgical morbidity and mortality rates (10% to 13%) in the D2 group. More recent studies have demonstrated that Western surgeons can be trained to perform D2 lymphadenectomies on Western patients with low morbidity and mortality. The 15-year follow-up of the Netherlands trial now demonstrates an improved disease-specific survival and locoregional recurrence in the D2 group. Retrospective analyses and one prospective, randomized trial suggest that there may be a survival benefit to more extensive lymphadenectomies when performed safely, but this assertion requires further validation.

It is estimated that there are more than one million cases of GC worldwide per year, making it the fourth most common cancer. Nearly three-quarters of cases occur in developing countries, and nearly half of cases occur in eastern Asia (mainly in China). GC is the second leading worldwide cause of cancer death for both men and women, with a total of more than 700,000 deaths each year. The incidence of gastric adenocarcinoma varies tremendously throughout the world and country by country, with the highest incidence occurring in South Korea at 66.5 to 72.5 per 100,000 males and 19.5 to 30.4 per 100,000 females. The incidence of GC in the United States is only one-tenth that of South Korea. The estimated number of new GC cases in the United States in 2012 was 21,320, and the estimated number of deaths was 10,540.

In addition to the global differences in GC epidemiology, there are also appreciable differences in the surgical treatment of GC, particularly in the extent of LAD. This article will examine the effect of varying LADs in Eastern and Western countries on patient outcomes. Institutional studies from two countries, Japan and South Korea, will be used to represent two high-incidence Eastern countries, and institutional and national database studies from the United States will be used to represent low-volume Western countries.

Definitions

Before discussion of differences in LAD for gastric adenocarcinoma, one should define the terms to be used. The node stations surrounding the stomach were precisely defined by the Japanese Gastric Cancer Association (JGCA), formerly known as the Japanese Research Society for Gastric Cancer, in 1973 (Fig. 1 and Table 1). In its most recent GC treatment guidelines, the JGCA again changed the definitions for D levels of LAD such that they are now defined according to the type of gastrectomy performed rather than the location of the tumor (Table 2). To broadly summarize, a D1 LAD removes the first tier of perigastric nodes and the left gastric artery nodes whereas a D2 LAD removes the second tier of nodes that generally fall along primary and secondary branches of the celiac axis (i.e., splenic artery, common hepatic artery, proper hepatic artery). The JGCA guidelines recommend a D2 LAD for all gastric carcinomas beyond a clinical T1 tumor (e.g., tumor invades lamina propria, muscularis mucosa, or submucosa).

Differences in Surgical Volume and Extent of LAD

Japan and South Korea have two of the highest incidences of gastric adenocarcinoma in the world, but despite the high incidence of gastric adenocarcinoma in these countries, patients are often referred to tertiary centers for treatment. Two-thirds of all GC surgeries in South Korea are performed at 15 high-volume institutions, which perform at least 200 GC surgeries per year. Thus GC surgeons at high-volume institutions in South Korea gain tremendous experience in the surgical management of GC. As noted earlier, the minimum LAD performed by Japanese and Korean surgeons for gastric adenocarcinoma (except for T1 tumors) is a D2 LAD. Despite performing extensive LADs, the morbidity and mortality rates are quite low. For example, Seoul National University Hospital (SNUH), which performs almost 1,000 GC operations per year, recently reported a morbidity rate of 18% and a mortality rate of 0.5%.

In contrast, the majority of GC surgeries in the United States are performed at nonreferral centers. A “high volume” institution in the United States has been defined in some studies as centers with as low as 15 to 20 surgeries per year. Birkmeyer and colleagues reviewed a database of Medicare patients and found that hospitals with more than 20 gastrectomies per year had one-third less risk...
of perioperative death (odds ratio 0.55–0.74), yet more than 80% of patients were operated on at centers that performed 20 or fewer gastrectomies per year.7 As most U.S. surgeons see only a few GC patients a year, they likely err on the side of more limited LADs in order to avoid excess morbidity and mortality. In the Intergroup 0116 trial published in 2001, patients were randomly selected after GC surgery to undergo no further therapy or chemoradiation, and more than 50% of operations were less aggressive than a D1 LAD (aka D0 LAD).9 Despite the performance of less extensive LADs in the United States, surgical morbidity and mortality rates for gastric adenocarcinoma are generally much higher in the United States than in South Korea and Japan. An analysis of the Nationwide Inpatient Sample from 1998 to 2003 of more than 50,000 patents with GC found the overall mortality rate following gastric surgery was 6%.10 Single-institution series have reported morbidity rates following gastrectomy of up to 40%.11

Differences in Survival

Gastric adenocarcinoma frequently metastasizes to regional nodes. For T1 lesions invading the submucosa, node involvement is found in approximately 20% of patients.12 For T2 lesions (invading muscularis propria), the node metastasis rate increases to more than 50%. There is some evidence that at least some patients with node metastases beyond the immediate perigastric (D1) nodes and into D2 nodes can be cured with surgical resection alone.13 A sizable minority of GC patients with positive D2 nodes survive for more than 5 years following D2 lymphadenectomy at the Japanese National Cancer Center in Tokyo. Numerous studies have demonstrated decreased overall survival (OS) after potentially curative gastrectomy for gastric adenocarcinoma in the West compared with the East. Table 3 demonstrates 5-year OS results stage-for-stage from four large databases based on the sixth American Joint Committee on Cancer (AJCC) staging system. D2 LADs are generally performed at the National Cancer Center (NCC) in Tokyo, Japan, and at SNUH is South Korea. The median number of examined nodes at both these institutions is greater than 30, and there is a remarkable similarity in the 5-year survival figures from these two institutions. In the U.S. Surveillance Epidemiology and End Results (SEER) database, most patients had either a D0 or D1 LAD, and the median number of examined nodes is 10 to 11.14 For stages I to III, the 5-year survival rate is 14% to 30% lower for SEER database patients.15 Stage for stage, overall survival is worse in the United States than in Japan and South Korea, but much of this difference could be explained by stage migration and clinicopathologic differences between gastric cancers in Eastern versus Western countries.

- More extensive D2 lymphadenectomies are standard in high-incidence Eastern countries such as Japan and South Korea, leading to better staging of disease and likely lower rates of locoregional recurrence.
- In the United States (a low-incidence Western country), the vast majority of gastric resections are performed at low-volume (less than 20 cases per year) centers with generally less extensive lymphadenectomies and higher morbidity and mortality.
- Stage for stage, overall survival is worse in the United States than in Japan and South Korea, but much of this difference could be explained by stage migration and clinicopathologic differences between gastric cancers in Eastern versus Western countries.
- The Dutch and U.K. D1 versus D2 lymphadenectomy randomized trials were flawed, and further prospective randomized trials of lymphadenectomies performed by well-trained Western surgeons on Western patients are needed to determine if there is an overall survival benefit to more extensive lymphadenectomies.
- Strategies to improve the surgical outcomes of patients with gastric cancer in low-incidence Western countries include referral to tertiary centers and improved training of surgeons.

**KEY POINTS**

- More extensive D2 lymphadenectomies are standard in high-incidence Eastern countries such as Japan and South Korea, leading to better staging of disease and likely lower rates of locoregional recurrence.
- In the United States (a low-incidence Western country), the vast majority of gastric resections are performed at low-volume (less than 20 cases per year) centers with generally less extensive lymphadenectomies and higher morbidity and mortality.
- Stage for stage, overall survival is worse in the United States than in Japan and South Korea, but much of this difference could be explained by stage migration and clinicopathologic differences between gastric cancers in Eastern versus Western countries.
- The Dutch and U.K. D1 versus D2 lymphadenectomy randomized trials were flawed, and further prospective randomized trials of lymphadenectomies performed by well-trained Western surgeons on Western patients are needed to determine if there is an overall survival benefit to more extensive lymphadenectomies.
- Strategies to improve the surgical outcomes of patients with gastric cancer in low-incidence Western countries include referral to tertiary centers and improved training of surgeons.

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**Fig 1.** Location of node stations according to the Japanese Gastric Cancer Association.38 (A) Perigastric nodes stations 1 to 7. (B) Second tier node stations 8 to 12 and 14.
ern patients compared to Eastern patients are generally: (1) older, (2) have a higher body mass index, (3) have a lower incidence of H. pylori infection, (4) have more proximal tumors, (5) present with later stage disease, and (6) receive different adjuvant therapies. Many of the factors more common in Western patients are negative prognostic factors for gastric adenocarcinoma. Verdechcia and colleagues compared GC incidence and survival in four regions (Campina, Brazil; Iowa, United States; Varese province, Italy; and Osaka Japan). U.S. patients were older, had more proximal cancers, more commonly presented with metastatic disease, and had worse survival rates than Japanese patients.

One of the best attempts to determine if Eastern patients generally have a better OS than Western patients following more extensive LADs was performed by Strong and colleagues. They analyzed 711 U.S. patients treated at Memorial Sloan-Kettering Cancer Center and 1,646 Korean patients treated at Seoul St. Mary’s Hospital. In this study, the median age of U.S. patients was 10 years older than that of Korean patients (69 vs. 59 years old). Thirty-nine percent of U.S. patients had upper third or gastroesophageal junction tumors compared to only 9.4% of Korean patients, and 59% of U.S. patients had intestinal type tumors compared to 49% of Korean patients. D2 LAD was performed in 84% and 89% of U.S. and Korean patients, respectively, but there were more nodes examined in Korean patients than U.S. patients (97% of Korean patients with ≥ 15 nodes examined compared to 78% of U.S. patients). The T stage, N stage, and overall stage of U.S. patients were significantly more advanced than those of Korean patients (p < 0.0001, p = 0.008, p < 0.0001, respectively). Survival was worse, stage-for-stage, in U.S. patients compared to Korean patients for AJCC stages I to III. Interestingly, the survival of U.S. patients with middle or upper tumors was worse than that of Korean patients, but U.S. and Korean patients had similar OS for distal tumors. After adjusting for clinically important prognostic factors, Korean patients still had a 30% better disease-specific survival rate than U.S. patients. There are some potential confounding variables in this study, including the fact that 316 U.S. patients were excluded because they received neoadjuvant treatment. However, this study does suggest that after controlling for prognostic factors and following relatively uniform D2 LAD, Eastern patients still have a better survival rate compared with Western patients.

### Potential Benefits of More Extensive LADs

LAD for cancer can serve three primary purposes: staging of disease, prevention of locoregional recurrence, and improvement in OS. There is little doubt that more extensive LADs for gastric adenocarcinoma can lead to better staging of disease. The 2010 (seventh edition) AJCC Cancer Staging Manual for gastric adenocarcinoma recommends that at least 16 nodes be examined for correct assessment of the N category. Despite this, our analysis of the SEER database found that only one-third of 18,043 resected GC patients had 16 or more nodes examined. It is difficult to be confident that a GC is truly node-negative when fewer than 10 nodes are examined. and N1 tumors can be upstaged to N2 or even N3 tumors as more nodes are harvested. Furthermore, it is impossible to be categorized as N3b if less than 16 nodes are harvested. Thus many patients are understaged following surgical resection of their GCs because of inadequate node sampling.

In the Unites States, the pathologist is usually the one who finds and examines the dissected nodes. Thus a coordi-

### Table 1. Regional Lymph Nodes of the Stomach

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right paracardial</td>
</tr>
<tr>
<td>2</td>
<td>Left paracardial</td>
</tr>
<tr>
<td>3</td>
<td>Lesser curvature</td>
</tr>
<tr>
<td>a</td>
<td>Along branches of left gastric artery</td>
</tr>
<tr>
<td>b</td>
<td>Along second branch and distal part of right gastric artery</td>
</tr>
<tr>
<td>4</td>
<td>Greater curvature</td>
</tr>
<tr>
<td>a</td>
<td>Along short gastric vessels</td>
</tr>
<tr>
<td>b</td>
<td>Along left gastroepiploic vessels</td>
</tr>
<tr>
<td>d</td>
<td>Along second branch and distal part of right gastroepiploic artery</td>
</tr>
<tr>
<td>5</td>
<td>Suprapyloric along first branch and proximal part of right gastric artery</td>
</tr>
<tr>
<td>6</td>
<td>Infrapyloric along first branch and proximal part of right gastroepiploic artery</td>
</tr>
<tr>
<td>7</td>
<td>Left gastric artery</td>
</tr>
<tr>
<td>8</td>
<td>Common hepatic artery</td>
</tr>
<tr>
<td>a</td>
<td>Anterosuperior group</td>
</tr>
<tr>
<td>p</td>
<td>Posterior group</td>
</tr>
<tr>
<td>9</td>
<td>Celiac artery</td>
</tr>
<tr>
<td>10</td>
<td>Splenic hilum</td>
</tr>
<tr>
<td>11</td>
<td>Alon splenic artery</td>
</tr>
<tr>
<td>p</td>
<td>Along proximal splenic artery</td>
</tr>
<tr>
<td>d</td>
<td>Along distal splenic artery</td>
</tr>
<tr>
<td>12</td>
<td>Hepatoduodenal ligament</td>
</tr>
<tr>
<td>a</td>
<td>Along proper hepatic artery</td>
</tr>
<tr>
<td>b</td>
<td>Along bile duct</td>
</tr>
<tr>
<td>p</td>
<td>Along portal vein</td>
</tr>
<tr>
<td>13</td>
<td>Alon superior mesenteric vessels</td>
</tr>
<tr>
<td>v</td>
<td>Alon superior mesenteric vein</td>
</tr>
<tr>
<td>a</td>
<td>Alon superior mesenteric artery</td>
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*a Adapted from the Japanese Gastric Cancer Association’s 2011 classifications.*

### Table 2. Extent of Lymphadenectomy

<table>
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<tr>
<th>Extent of Gastrectomy</th>
<th>D1 Dissection</th>
<th>D1 + Dissection</th>
<th>D2 Dissection</th>
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<tr>
<td>Total gastrectomy</td>
<td>1–7</td>
<td>D1 + Ba, 9p, 11p</td>
<td>D1 + Ba, 9, 11p</td>
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<tr>
<td>Dist/subtotal gastrectomy</td>
<td>1, 3, 4b, 4d, 5</td>
<td>D1 + Ba, 9</td>
<td>D1 + Ba, 9, 11p</td>
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<tr>
<td>Proximal gastrectomy</td>
<td>1, 2, 3a, 4a, 4b</td>
<td>D1 + Ba, 9, 11p</td>
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<tr>
<td>Gastrectomy</td>
<td>1, 2, 3a, 4a, 4b</td>
<td>D1 + Ba, 9, 11p</td>
<td>N/A</td>
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*a Adapted from the Japanese Gastric Cancer Association’s 2011 classification.*
GASTRIC CANCER LYMPHADENECTOMY AND OUTCOMES

sented effort is required between the surgeon and pathologist if more extensive LADs are to result in improved staging of patients. In Japan and South Korea, following the en bloc dissection of the stomach and nodes, surgeons generally dissect out the individual nodal stations from the surgical specimen, allowing the pathologist to examine and report the number of positive and negative nodes for each nodal station. Thus more extensive LAD must be combined with more rigorous pathologic analysis to optimize the node staging of GC.

There is some evidence that more extensive LADs result in lower rates of locoregional recurrence. Locoregional recurrence after potentially curative surgery for gastric adenocarcinoma can be quite high. In a 1982 series from the University of Minnesota, 107 patients with gastric adenocarcinoma underwent second-look laparotomy, and 80% had recurrence. Of these recurrences, 88% were locoregional, 54% were peritoneal, and 29% were distant. More recently in the U.S. Intergroup 0116 trial, 177 of 275 patients (64%) in the surgery-only group developed recurrent disease. In terms of the site of first relapse, 29% had local recurrence, 72% had regional recurrence, and only 18% had distant recurrence. Rates of locoregional recurrence are generally lower in reports from both Western and Eastern institutions that perform more extensive LADs. In a series of 367 patients with recurrent gastric adenocarcinoma from Memorial Sloan-Kettering Cancer Center over 15 years, 81% of patients had a D2 or greater LAD, and the median number of nodes removed was 22. Of patients in whom disease recurred, locoregional recurrence was the initial and only site of recurrence in 26% of patients and was a component of initial recurrence in 54% of patients. Yoo and colleagues examined 508 patients in whom recurrent disease developed after curative gastrectomy at Yonsei University in South Korea. Nineteen percent of patients had locoregional recurrence only as the first site of recurrence, and 32.5% of patients had locoregional recurrence combined with peritoneal or distant recurrence as the initial site of recurrent disease. In the Japanese prospective randomized trial of adjuvant S-1 chemotherapy, 188 (35.5%) of 530 patients treated with surgery suffered a recurrence. The site of first recurrence in these 188 patients was local in 7.9% and in nodes in 24.5%.

The effect of more extensive LADs on OS for GC is still controversial. Two large, prospective randomized trials in Western countries have failed to identify a survival advantage for D2 over D1 LAD. However, these two trials had fairly high morbidity (43% to 46%) and mortality rates (10% to 13%) for D2 LAD. In these trials, the distal pancreas and spleen were often resected during dissection of station 10 and 11 nodes, which likely increased morbidity. Of note in the Dutch trial, if patients with in-hospital mortality are excluded, patients with N2 disease had a survival advantage when treated with a D2 LAD. Several studies have now demonstrated that D2 LADs can be performed without the need for distal pancreatectomy or splenectomy. Furthermore, a recent randomized trial in Taiwan demonstrated an OS advantage of more extensive LAD over D1 LAD, with the overall 5-year survival rate being 59.5% compared with 53.6%, respectively (p = 0.041). However, the applicability of this trial to Western patients has been called into question. The long-term follow-up of the Dutch trial was recently reported. After a median follow-up of 15 years, D2 LAD was associated with lower locoregional recurrence and gastric cancer–related death rates (37% vs. 48%) than D1 LAD. Degiuli and colleagues in Italy have demonstrated that Western surgeons, following extensive training, can perform D2 LAD on Western patients with low morbidity and almost no mortality, and survival results from a prospective randomized trial of D1 compared with D2 LAD from this group are pending.

Can Western Surgeons Perform More Extensive LADs Safely?

Italian GC Study Group approached the issue of Western surgeons performing more extensive LADs in Western patients in a series of two prospective clinical trials. Following extensive training of 16 surgeons in D2 LAD, a phase II trial of D2 LAD was instituted in which all surgeries were performed by the two attending surgeons. Of the 191 patients enrolled in the study, 106 patients (55%) were ultimately found to be ineligible, usually as a result of more extensive disease. The mean number of nodes removed was 39 (range: 22 to 93). Overall postoperative morbidity and mortality were impressively low at 20.9% and 3.1%, respectively. Subsequent to this study, the surgeons from the five highest-volume centers performed a randomized trial of D1 compared with D2 LAD. Of 267 randomly selected patients, total morbidity and mortality was 12.0% and 3.0%, respectively, in the D1 group and 17.9% and 2.2%, respectively, in the D2 group. Survival results are pending. The experience of the Italian GC Study Group clearly demonstrates that following a period of fairly rigorous training, Western surgeons can perform D2 LADs on Western patients with morbidity and mortality results similar to that of high-volume centers in Korea and Japan.

Several tertiary referral centers in Western countries routinely perform D2 LADs for GC, but as noted earlier, LADs for GC in Western countries are limited and often do not even reach the D1 LAD threshold. There are several reasons why more extensive LADs are not more commonly performed. First and foremost is the lack of a proven benefit in OS of D2 over D1 LAD based on the Dutch and U.K. trials. Unfortunately, many Western surgeons have interpreted the results of these trials to mean any LAD does not improve OS. Certainly some patients with node-positive disease are cured by surgical resection alone, and these patients would undoubtedly not have been cured if diseased nodes were left undissected without additional therapy. Another important obstacle to the performance of more extensive LADs is the relative paucity of gastric adenocarcinomas seen at any given institution. In order for more extensive LADs to benefit GC patients, they must be performed without excess morbidity and mortality, and this can only be achieved with adequate surgical training and adequate case volume. Contributing to the lack of high-volume centers for GC surgery is a potential reluctance of general surgeons to refer GC patients to tertiary referral centers given that gastric surgery has been historically the realm of the general surgeon. Finally, there are geographical and language barriers between different countries that make dissemination of information and techniques on the surgical treatment of GC difficult.
Conclusion

There are clear differences in the extent of LAD performed between Eastern and Western countries. D2 LAD is the standard LAD performed in Japan and South Korea for all resectable tumors except for T1 tumors. Significantly less extensive LADs are generally performed in the United States. How does this difference in extent of LAD affect GC patient outcomes? There is no doubt that less extensive LADs result in understaging of patients. Many U.S. medical oncologists and radiation oncologists already factor this understaging into their medical decision making. For any patient in the SEER database who is stage IB or greater, the 5-year OS rate is 58% or less and adjuvant therapy is likely warranted. However, a patient treated at MSKCC who is stage IB has an 85% 5-year OS and may not warrant adjuvant therapy. Our analysis of the SEER database found wide variations in survival of each AJCC stage based on subgroup analysis, with more than half of patients being misclassified. Thus there are inherent problems with inaccurately staged patients.

Less extensive LADs also likely result in increased locoregional recurrence, making the decisions between adjuvant chemotherapy versus chemoradiation more difficult. GC patients are often limited in the extent of neoadjuvant and adjuvant treatment that can be delivered, and one must often choose between multiagent chemotherapy regimens versus 5-fluorouracil or cap cetabine-based chemoradiation.

In terms of OS, the effects of more extensive LAD are difficult to discern. The Dutch and U.K. trials of D1 compared with D2 LAD demonstrated that when D2 LAD is performed with excess morbidity and mortality, there is no survival benefit compared to D1 LAD. If D2 LAD is performed with low morbidity and mortality, there also may be a benefit in OS, at least in Chinese patients, but this potential benefit needs to be demonstrated by future prospective, randomized trials of Western patients.

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REFERENCES


**Will Disease Heterogeneity Help Define Treatment Paradigms for Gastroesophageal Adenocarcinoma? A Global Perspective**

By Manish A. Shah, MD

**Overview:** Cancers of the upper gastrointestinal (GI) tract form a heterogeneous group of diseases for which treatment paradigms for localized disease continue to emerge. Recently, several phase III studies in esophagus and gastric cancer that have attempted to define new standards of care have been reported. However, controversy still persists and treatment algorithms often depend on individual preference, patient referral patterns, and treatment biases. In the current era of improving quality control and standardization of care, such variations in practice present a substantial challenge for both patients and physicians. In this article, I will highlight differences in disease biology for upper GI diseases, and in particular, gastric cancer.

**DIFFERENT TREATMENT paradigms characterize upper GI malignancies across the globe.** Among the most varied is the approach to patients with locally advanced, but resectable, esophageogastric carcinoma. National Comprehensive Cancer Network (NCCN) guidelines for esophageal carcinoma in patients with localized disease who are medically fit for resection allow for several standard treatment options, including preoperative chemoradiotherapy (CRT), definitive CRT, preoperative chemotherapy (for adenocarcinoma), and resection followed by postoperative CRT. For localized, resectable gastric cancer, acceptable treatment options are nearly equally varied, with the notable exception of definitive CRT. Several important phase III studies were recently reported at the last two annual ASCO meetings. We will attempt to place these studies into context of the current accepted treatment paradigms on the basis of current best evidence.

**Results of Recent Phase III Studies: Gastric Cancer**

The management of localized gastric cancer has become increasingly complicated with emerging data of the survival advantage of systemic chemotherapy alone, as well as the potential benefit of CRT in specific settings. Recently, investigators presented the results of the CLASSIC study, a randomized phase III evaluation of post-operative chemotherapy with capecitabine and oxaliplatin compared with observation in resected gastric cancer. In this study, 1,035 patients with stage II to III gastric cancer who had a D2 (i.e., extended lymphadenectomy) surgical dissection were randomly assigned to receive either observation alone (n = 515) or eight cycles of chemotherapy (n = 520) consisting of oxaliplatin 130 mg/m² plus capecitabine 1,000 mg/m² twice daily for 14 days repeated every 3 weeks. The investigators met their prespecified primary end point of improving 3-year disease-free survival (DFS), demonstrating 74% 3-year DFS versus 60% with observation alone (hazard ratio [HR] = 0.56; Table 1). These data are consistent with the previous adjuvant S1 study reported by Sakuramoto and colleagues and, bolstered by the pooled individual patient-data metaanalysis, further support the use of postoperative chemotherapy alone. The applicability of the recent large phase III studies from Korea and Japan to Western patients remains a question, especially with markedly different epidemiology of increased proximal and GEJ tumors in the West compared with Asia. Even when controlling for the extent of surgical resection, apparent differences in outcomes persist. Furthermore, a recent well-performed, although underpowered, study examined postoperative chemotherapy with cisplatin, epirubicin, fluorouracil (FU), and leucovorin (LV; PELF) in a randomized study and did not show a survival advantage in a European patient population of resected advanced gastric cancer. In this study, 258 patients were randomly assigned to receive four cycles of PELF chemotherapy or observation alone, and with a median follow-up of more than 72 months, no differences in patient outcomes were observed. Specifically, at the end of the study period, 47% of the patients who received chemotherapy were still alive compared with 45.3% of the surgery-alone arm. Thus, despite the recent compelling phase III data, treatment paradigms in the West for locally advanced gastric/gastroesophageal junction (GEJ) adenocarcinoma currently involve either preoperative or perioperative chemotherapy, or postoperative CRT. The role of postoperative chemotherapy in the West remains controversial.

Regarding CRT after curative-intent resection in gastric cancer, the addition of epirubicin and cisplatin importantly did not demonstrate an improvement over standard adjuvant FU/radiotherapy (RT) in the CALGB national phase III study. This was a 546-patient study in which patients were randomly assigned to receive standard postoperative CRT (n = 280) consisting of bolus FU/LV (cycle 1, 3 and 4), along with infusional FU (200 mg/m²/day as an intravenous continuous infusion × 5 weeks, cycle 2) or experimental postoperative CRT (n = 266) consisting of epirubicin, cisplatin, and FU (ECF) chemotherapy (cycle 1, 3 and 4), and the same CRT (infusional FU + RT), to demonstrate an improvement in overall survival of 30% with the addition of ECF. There was no difference in overall survival (HR = 1.03), suggesting that epirubicin and cisplatin do not add significantly to FU adjuvant therapy. Investigators also noted remarkably little improvement in RT planning over the last two large United States–based phase III studies (15% major deviations in the RT plan). In another study (the ARTIST Trial), investigators from Korea investigated...
the role of postoperative RT in a patient population that underwent a standard D2 gastric dissection. In this study, 458 patients were randomly assigned to receive postoperative chemotherapy alone (capecitabine/cisplatin [XP]) or CRT (XP → capecitabine/RT → XP), with the aim to identify a 45% improvement in 3-year DFS. These investigators did observe a modest improvement in the addition of RT, particularly in the large subset of patients who were node positive (3-year DFS, 72% vs. 77%; p = 0.0365; Table 1). These data support the role of adjuvant RT in this disease, as suggested initially by INT-0116, and are currently being prospectively validated in a node-positive resected cohort.

Results of Recent Phase III Studies: Esophageal Cancer

In esophageal carcinoma, the CROSS study was presented at the 2011 ASCO Annual Meeting, and examined the effects of preoperative CRT in advanced esophageal cancer. This study found that a combination regimen of CRT before resection is superior to surgery alone. In this multicenter phase III randomized study, 364 patients in the Netherlands with resectable esophageal adenocarcinoma or squamous cell carcinoma (SCC) were randomly assigned to receive combined-modality therapy of CRT followed by surgery or surgery alone. Preoperative CRT consisted of weekly paclitaxel 50 mg/m² and carboplatin dosed at area under the curve (AUC) 2 for 5 weeks with concurrent 41.4 Gy RT administered in 23 fractions. After CRT, patients underwent resection within 6 weeks of completion of preoperative therapy. This study suggests that most patients with T1N1 or T2–3Nx esophageal carcinoma should consider preoperative CRT as a standard care option. The median survival of patients who received CRT and surgery was 49 months, compared with 26 months for those who received surgery alone (HR = 0.67; p = 0.011; Table 1). With a median follow-up of 32 months, 70 patients had died in the CRT group compared with 97 in the surgery-alone group, and 3-year overall survival was also superior in the CRT arm. However, although the majority of patients (74% in both arms) had adenocarcinoma, it appears that the benefit of CRT was primarily derived in patients with esophageal SCC. Patients with esophageal SCC observed an HR of 0.34, representing a dramatic 66% reduction in risk of death with preoperative CRT, whereas in the subset of patients with esophageal adenocarcinoma, the HR for survival in patients receiving CRT was 0.82 (Table 1).

To place these data into context with other randomized studies that predominantly included distal esophageal and GEJ carcinoma as well as a recent updated meta-analysis of if surgery is identified as part of the treatment plan for a patient with localized disease, applying preoperative therapy does confer a survival advantage. In addition, esophageal SCC seems to be more sensitive to CRT. There are data that support either combined preoperative CRT or preoperative chemotherapy alone for esophageal adenocarcinoma, and the data supporting the superiori ty of trimodal therapy (CRT + surgery) over bi modal therapy (chemotherapy + surgery) remains debatable. A recent study by Stahl and colleagues suggested an improved survival with trimodality therapy in adenocarcinoma of the esophagus/GEJ, although the study was closed.

## Key Points

- Significant heterogeneity in treatment paradigms for upper GI malignancies.
- Several recent studies have attempted to redefine the standard of care.
- Global disease heterogeneity make broad applicability somewhat questionable.
- Our challenge is to recognize differences in disease biology to optimize treatment paradigms.
prematurely due to poor accrual. In addition, Mariette and colleagues demonstrated that for early-stage esophageal adenocarcinoma, there appears to be no added benefit of CRT to surgical resection.

**Influence of Disease Heterogeneity on Treatment**

Gastric cancer is a heterogeneous disease and subtypes of gastric cancer exist. More than 95% of all cancers of the stomach are adenocarcinomas. A common distinguishing feature is histopathology, such as the Lauren’s classification, which distinguishes intestinal and diffuse gastric cancer subtypes. The well-differentiated intestinal type tends to expand through the stomach wall, whereas the Lauren’s diffuse-type is more commonly poorly differentiated and spreads as individual discohesive cells in an infiltrative pattern. Diffuse gastric cancer is associated with loss of the cell-surface protein E-cadherin and germ-line mutations in CDH1 are associated with the familial form of diffuse gastric cancer, hereditary diffuse gastric cancer.

Intestinal gastric cancers predominate in high-incidence areas (e.g., China), and this histology is responsible for much of the ethnic variation across the globe.

Gastric cancers may have different outcomes depending on disease subtype. More proximal GEJ and cardia tumors tend to have a worse prognosis compared with distal pyloric, antral, and curvature cancers. Data are also just now emerging on the potential influence of disease subtype on treatment outcome. For example, HER2 amplification and overexpression is far more prevalent in proximal/GEJ adenocarcinoma than in diffuse gastric cancer. In an exploratory analysis, these proximal/GEJ tumors appeared to be less sensitive to bevacizumab therapy than are diffuse and distal nondiffuse gastric cancers.

Thus, disease biology may indeed influence patient outcomes with specific treatments.

**Implications for the Future**

Where do we go from here? Because treatment paradigms are defined on a global basis, it will be important to understand the global heterogeneity of these diseases. The epidemiology, risk factors, and patterns of care for cancers of the upper GI tract are substantially different across the globe. Disease biology in the various regions around the world may also be different, although this needs to be more thoroughly investigated. For example, proximal/GEJ adenocarcinomas seem less frequent in the far East compared with Europe and the Americas. However, it is not clear whether this difference solely contributes to differences in patient outcome between these two regions. Could it be practice patterns (screening and early disease identification), use of second-line therapy, or disease biology? Our challenge is to recognize the influence of disease biology and heterogeneity on treatment paradigms in this disease. If we are able to do so, we will be able to provide better treatment guidelines for specific disease subtypes, and improve patient outcomes in a more directed approach—a laudable goal, indeed!

**Author’s Disclosure of Potential Conflicts of Interest**

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Adjuvant Treatments for Localized Advanced Gastric Cancer: Differences among Geographic Regions

By Yoon-Koo Kang, MD, PhD, and Changhoon Yoo, MD

Overview: After much debate, adjuvant therapy has become the standard of care worldwide for resected localized gastric cancer. However, geographic differences exist in standard adjuvant treatments: postoperative chemoradiation in North America, perioperative chemotherapy in the United Kingdom, and postoperative chemotherapy in East Asia. Now that D2 gastrectomy has been recognized as the optimal surgery for localized gastric cancer in the West as well as in Asia, the standard adjuvant treatments used in the West may need to be reconsidered. One of the most important issues in adjuvant therapy for localized gastric cancer is how to improve the clinical outcomes of current standard treatments. Recent clinical outcomes of current standard treatments. Recent

Although surgery is the only curative treatment option for patients with localized advanced gastric cancer, many patients experience recurrence even after complete resection, leading to poor survival. To improve survival outcomes, many clinical trials have evaluated adjuvant treatments over the decades; however, these studies have produced conflicting results, mainly because of modest sample size and problematic study design. Meta-analyses have consistently described a small but significant survival benefit associated with adjuvant chemotherapy when compared to surgery alone. This finding was recently confirmed by a large patient-level meta-analysis of 17 randomized controlled trials conducted by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group. Since multiple phase III studies with large numbers of patients have demonstrated the survival benefits of adjuvant treatments in localized gastric cancer compared with surgery alone, there is now global agreement that adjuvant therapy improves outcomes in patients with stage II–IV (M0) gastric cancer undergoing curative surgical resection.

Current Standard Adjuvant Treatments

Even though adjuvant treatment in localized advanced gastric cancer has become the standard of care worldwide, no single regimen has been accepted as the global standard. In addition, geographical differences still exist in the treatment of resectable gastric cancer (see Table 1). The Intergroup-0116 study revealed that postoperative chemoradiation consisting of bolus 5-fluorouracil/leucovorin (5-FU/LV) and concurrent radiotherapy significantly prolonged survival compared with surgery alone. Based on the results of this trial, adjuvant chemoradiotherapy has been adopted as the standard adjuvant treatment for curatively resected gastric cancer in North America. Perioperative chemotherapy is currently the standard practice across Europe for patients with resectable gastric cancer. This treatment is based on the results of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial in the United Kingdom. In this study, the perioperative chemotherapy arm consisting of three preoperative and three postoperative cycles of epirubicin, cisplatin, and 5-fluorouracil (ECF) demonstrated longer survival than the surgery alone arm. In Asia, postoperative chemotherapy with fluoropyrimidine-based regimens has been adopted as standard adjuvant therapy, based on the results of the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) and the recent CLASSIC trials conducted in Japan and Korea, respectively. These trials demonstrated improved survival in patients with resected gastric cancer given S-1 for 1 year or the combination of capecitabine and oxaliplatin for 6 months, compared with surgery alone.

Why Do Standard Treatments Differ among Geographic Regions?

Geographic differences in the standard adjuvant therapy for resectable gastric cancer can be explained primarily by differences in the standard surgery. Extended (D2) lymph node dissection is well established as the standard of care in East Asia, whereas Western surgeons have been skeptical of the benefit of D2 resection over D1 surgery because of conflicting results reported by previous randomized trials. However, the 15-year follow-up results of a Dutch D1D2 trial show that D2 surgery is associated with lower rate of disease-related death than D1 surgery in Western patients. This finding suggests that gastric cancer has been surgically undertreated in the West, which may explain why radiation (in North America) and intensive perioperative chemotherapy (in Europe) have improved outcomes in Western countries.

Another potential reason for regional differences is the heterogeneity of study populations in previous clinical trials for gastric cancer. The ACTS-GC and CLASSIC trials, which were conducted in East Asia, included only patients with gastric cancer. However, Western trials, especially in the United Kingdom, developed therapeutic strategies for localized gastric cancer by including considerable numbers of...
patients with adenocarcinoma of the esophagogastric junction or lower esophagus, primarily because of the increasing incidence of these cancers and decreasing incidence of gastric cancer. However, unlike gastric cancer, esophageal cancer tends to easily invade surrounding tissue and regional lymph nodes because of the lack of serosa and abundance of lymphatics in the esophagus. Thus, long-term survival rarely exceeds 20% even after successful resection in advanced disease. For this reason, multimodality therapy including chemotherapy, radiotherapy, and surgery has been widely investigated for treatment of esophageal cancer, and Western trials also used this strategy for treatment of gastric cancer. Given the significant differences between esophageal cancer and gastric cancer in terms of etiology, biology, and clinical characteristics, including patients with adenocarcinoma of the esophagogastric junction or lower esophagus in clinical trials for gastric cancer does not seem appropriate. The standard adjuvant therapies currently used in the West were established before D2 gastrectomy became the standard surgery. Although the superiority of D2 surgery over D0/1 surgery has been consistently demonstrated, it will take considerable time and effort before D2 surgery is widely performed in the West, because of the lack of expertise in this procedure and insufficient number of patients to implement new surgical technique. Nevertheless, we argue that the standard adjuvant treatments used in the West need to be reconsidered, because the D2 gastrectomy has finally become the standard surgery for localized gastric cancer in the West as well as in the East. Adjuvant therapy should be determined according to whether the patient undergoes optimal surgery (D2) or suboptimal surgery (D0/1), not according to where the patient is treated. Despite the success of the Intergroup-0116 trial, the role of radiotherapy was seldom investigated in countries where D2 gastrectomy is the standard of surgery, because many investigators are reluctant to add another local therapy to an “optimal” surgery (extended lymph node dissection). Based on the positive results of a retrospective study, the ARTIST trial, which evaluated adjuvant chemotherapy with or without radiation, was conducted in Korea. In contrast to the Intergroup-0116 study, the control arm in the ARTIST trial underwent chemoradiation rather than observation, and D2 surgery was mandatory. However, this study failed to show that adding radiation to adjuvant chemotherapy improved outcomes for patients who underwent D2 gastrectomy. Although the inclusion of too many patients with early-stage cancer (approximately 60% in stage IB or II) may have limited the power of the study, the negative results in the ARTIST trial suggest that radiation does not improve the efficacy of adjuvant chemotherapy following optimal surgery. The results of the latest trials strongly suggest that all patients with localized gastric cancer should undergo D2 surgery, if technically feasible, and subsequently undergo adjuvant chemotherapy, regardless of ethnicity or geographic location.

**KEY POINTS**

- After much debate over the past decades, adjuvant therapy has become the standard of care worldwide for resected localized gastric cancer.
- However, standard adjuvant treatments vary among geographic regions: postoperative chemoradiation in North America, perioperative chemotherapy in the United Kingdom, and postoperative chemotherapy in East Asia.
- Standard adjuvant treatments in the West may need to be reconsidered as D2 gastrectomy is now the standard surgical treatment for localized gastric cancer in the West, as well as in the East.
- Recent Cancer and Leukemia Group B and AMC studies suggest that simply intensifying chemotherapy by adding more agents or prolonging treatment duration is insufficient. However, new strategies like early initiation of chemotherapy and/or intraperitoneal chemotherapy may further improve the current standard adjuvant therapy.
- The role of targeted agents proven effective in metastatic or recurrent disease should be explored in the adjuvant setting.

### Table 1. Major Pivotal Phase III Trials for Adjuvant Treatments of Gastric Cancer

<table>
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<tr>
<th>Study Name</th>
<th>Treatment Arms</th>
<th>Total Patients</th>
<th>Patients with EGJ or Lower Esophageal Cancer</th>
<th>Patients Who Underwent D2 Surgery</th>
<th>Hazard Ratio for OS (95% CI), p</th>
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<tr>
<td>Intergroup-0116 (United States)</td>
<td>Surgery alone versus postoperative chemoradiation</td>
<td>556</td>
<td>20%</td>
<td>10%</td>
<td>1.35 [1.09–1.66]*</td>
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<tr>
<td>MAGIC (United Kingdom)</td>
<td>Surgery alone versus perioperative chemotherapy</td>
<td>503</td>
<td>26%</td>
<td>38%</td>
<td>0.75 [0.60–0.93] p - .009</td>
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<td>ACTS-GC (Japan)</td>
<td>Surgery alone versus postoperative S-1</td>
<td>1059</td>
<td>0%</td>
<td>100%</td>
<td>0.68 [0.52–0.87] p = .003</td>
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<td>CLASSIC (East Asia)</td>
<td>Surgery alone versus postoperative capecitabine and oxaliplatin</td>
<td>1035</td>
<td>0%</td>
<td>100%</td>
<td>0.72 [0.52–1.00]¶ p = .0493</td>
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Abbreviations: EGJ, esophagogastric junction; OS, overall survival; CI, confidence interval.

* Hazard ratio of surgery only group.
‡ Overall survival data are not yet mature; a primary endpoint of this study was disease-free survival.
Intergroup-0116 trial by adding two more drugs (epirubicin and cisplatin) to the bolus 5-FU/LV before and after 5-FU/radiotherapy for resected gastric or esophagogastric junction adenocarcinoma. The AMC 0201 study\textsuperscript{12} increased the duration of oral fluoropyrimidine treatment (12 months) and added cisplatin to the combination of mitomycin-C and 3 months of oral fluoropyrimidine; the control regimen was based on prolonged survival of patients with resected stage III gastric cancer compared with surgery alone in a Spanish phase III study.\textsuperscript{13} However, both phase III trials failed to show increased survival, suggesting that simply intensifying the adjuvant chemotherapy (with or without radiation) by adding an agent or prolonging treatment duration does not always enhance its efficacy in patients with localized gastric cancer. However, the AMC 0101 study,\textsuperscript{14} a companion trial of AMC 0201, evaluated the efficacy of two more strategies in patients with D2-resected macroscopically serosa-positive gastric cancer than the AMC 0201 with same control arm: intraperoperative intraperitoneal chemotherapy using cisplatin and early initiation (day after surgery) of systemic chemotherapy. In this phase III study, which included 521 patients, these strategies significantly improved recurrence-free survival and overall survival compared with the control regimen (mitomycin-C and 3 months of oral fluoropyrimidine); this finding was verified by follow-up data (median 6.6 years).\textsuperscript{15} In light of the negative results of AMC 0201, improved survival in AMC 0101 is attributable to early initiation of systemic chemotherapy and/or intraperitoneal cisplatin. These two strategies may enhance the efficacy of current standard regimens for gastric cancer such as postoperative chemoradiation and perioperative chemotherapy as well as postoperative chemotherapy. Regarding the potential benefits of early initiation of systemic chemotherapy in localized gastric cancer, neoadjuvant chemotherapy is, in a sense, the earliest possible adjuvant chemotherapy. Despite poor compliance in the postoperative phase of the MAGIC trial, the successful outcome associated with perioperative chemotherapy also suggests the potential benefits of neoadjuvant chemotherapy. However, in the MAGIC trial, perioperative chemotherapy was compared with surgery alone\textsuperscript{6}; therefore, it is not clear whether improved survival was because of perioperative chemotherapy, postoperative chemotherapy, or both. Furthermore, only 40\% of the patients in the MAGIC trial underwent D2 surgery. Therefore, the efficacy of neoadjuvant chemotherapy in countries where D2 surgery and postoperative chemotherapy is the standard of care remains to be determined. The PRODIGY trial (perioperative docetaxel, oxaliplatin, and S-1 followed by postoperative S-1 versus postoperative S-1 for patients with D2 resection; NCT01515748) aims to answer this question.

In the era of targeted therapy in oncology, biologic agents should also be explored in the adjuvant setting. In gastric cancer, especially in metastatic or recurrent disease. If the results are promising, these agents should also be explored in the adjuvant setting. In the future, we should work to improve our understanding of the molecular biology of gastric cancer in order to provide optimized and individualized therapy for patients with localized gastric cancer.

**Conclusion**

After much debate over the past decades, adjuvant therapy has become the standard of care worldwide for resected localized gastric cancer. However, geographic differences exist in standard adjuvant treatments: postoperative chemoradiation in North America, perioperative chemotherapy in the United Kingdom, and postoperative chemotherapy in East Asia. Standard adjuvant treatments in the West may need to be reconsidered as D2 gastrectomy has finally become the standard surgery for localized gastric cancer in the West, as well as in the East. Results of the recent CALGB and AMC studies suggest that simply intensifying chemotherapy by adding more cytotoxic agents or prolonging duration of treatment is insufficient. Instead, new strategies such as early initiation of chemotherapy and/or intraperitoneal chemotherapy may further improve the current standard adjuvant therapy. The role of targeted agents in adjuvant treatment for localized gastric cancer should be investigated in future based on the experiences in recurrent or metastatic disease.

**Authors' Disclosures of Potential Conflicts of Interest**

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LIVER-DIRECTED THERAPEUTIC OPTIONS FOR HEPATOCELLULAR CARCINOMA: PATIENT SELECTION AND CLINICAL OUTCOMES

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Overview: Stereotactic body radiotherapy (SBRT), in which highly conformal potent radiation doses are delivered in fewer fractions than traditional radiation therapy (RT), is an increasingly popular treatment for hepatocellular carcinoma (HCC). The great majority of HCCs smaller than 6 cm and with Child-Pugh A liver function are controlled with SBRT with limited toxicity. Long-term local control is reduced in larger tumors, and toxicity is increased in patients with Child-Pugh B or C liver function. SBRT is an effective treatment for tumor vascular thrombi and can lead to sustained vascular recanalization. The first site of recurrence following SBRT is most often within the liver, away from the high dose volume, providing rationale for combining SBRT with regional or systemic therapies. Randomized trials of SBRT are warranted.

GLOBALLY, HCC IS THE sixth most common cancer and the fourth most common cause of cancer-related death. The overall 5-year survival is poor (approximately 5%), and its incidence is increasing.1 While resection and transplant can cure HCC, only a minority of patients are suitable for surgery because of multifocal or extrahepatic cancer, inadequate liver function, and/or involvement of large vessels. Radiofrequency ablation and percutaneous ethanol injection are associated with excellent local control in small HCCs, but outcomes are reduced in HCCs larger than 4 cm or adjacent to large vessels.

RT is an effective local therapy that has the potential to benefit patients unsuitable for and/or at high risk of complications following standard local-regional therapies. All of the following have facilitated the safe delivery of tumorcidal doses to focal HCCs using conformal RT: advances in imaging, RT planning techniques (to produce three-dimensional conformal RT plans minimizing dose to surrounding tissues), image-guided radiotherapy (IGRT; to localize the tumor at time of treatment), tumor immobilization (to account for breathing-related organ motion), and improved knowledge of what volume of liver is required to be spared from radiation to preserve function. Protons and carbon ions—available at specialized centers—have the ability to spare more liver parenchyma than photons. SBRT—which is shorter radiotherapy schedules (hypofractionation), with higher very conformal doses delivered at each radiation fraction—has more recently been used to treat focal HCC. This has been used when the majority of the liver can be spared from irradiation. Initially stereotactic immobilization body frames were used to aid in patient SBRT positioning, but with recent advancements in IGRT, the requirement for such frames has disappeared, as the liver can be directly visualized before or during RT delivery. SBRT is widely available (unlike protons or carbon ions) and more convenient for patients than conventionally fractionated RT, as it is delivered in far fewer fractions (typically 10 or less) than standard fractionated RT. This article will focus primarily on SBRT for HCC.

Liver Tolerance of RT

Just as a portion of the liver may be resected with surgery or ablated with radiofrequency ablation, portions of the liver can tolerate high doses of radiation, without liver toxicity. With long-term follow-up, atrophy of the irradiated portion of the liver and hypertrophy of the spared portions of the liver are commonly seen. Objective response assessment is challenging within 4 months following RT because of changes in the irradiated liver volume during that time.

The classical described toxicity following RT for liver cancer is a clinical syndrome of anicteric hepatomegaly, ascites, and elevated liver enzymes (particularly serum alkaline phosphatase) occurring within three months after RT, referred to as classic radiation-induced liver disease (RILD).2 For the most part, this toxicity is preventable, as long as a sufficient fraction of liver can be spared from RT. For example, the risk of classic RILD is less than 5% when the mean liver doses are kept less than 14 Gy (in 6 fractions) and 28 Gy (in 1.5 Gy fractions).

Other hepatic toxicities, referred to as “nonclassic RILD” are more challenging to prevent. Such toxicities include reactivation of viral hepatitis, elevation of liver enzymes, and a general decline in liver function. The partial volume tolerance of the liver following RT is less clearly defined for nonclassic RILD, with different dose-volume tolerances and risk factors observed for different types of liver toxicity. In Taiwan, 17 of 89 patients with HCC treated with up to 66 Gy (in 1.8–3 Gy per fraction) developed liver toxicity. The risk was increased in hepatitis B carriers and in Child-Pugh B liver function.3 Treatment of viral hepatitis B is important before initiating RT. Other studies have shown that the risk of toxicity is increased if the spared volume of liver is too small. For example, in a study of 48 patients with HCC treated with three-fraction SBRT (30–39 Gy), 11% of patients had a decline in Child-Pugh class, and this was more likely if less than 800 mL of liver could be spared from 18 Gy or more.4

Outcomes: Non-SBRT RT

The first experience in RT for HCC was with hyper- or conventional fractionation, using conformal RT. The median survival of patients with locally advanced HCC treated with conventional fractionation ranges from 6 to 19 months.5-9 A majority of series demonstrated that patients treated with higher RT doses had better local control and survival than those treated with lower doses.

Protons or carbon ions produced from highly specialized treatment units not widely available have also been used to treat HCC. An advantage of protons is that they are associ-
ated with unique dose distributions that allow rapid falloff in dose and substantial sparing of dose to tissues adjacent to tumors. Proton or carbon RT has the best reported outcomes for treatment of HCC with portal vein or inferior vena cava thrombosis.11

**KEY POINTS**

- Stereotactic body radiation therapy (SBRT)—highly conformal, potent-dose radiation therapy delivered in fewer fractions than usual (usually <10)—is being used more commonly in hepatocellular carcinoma (HCC).
- SBRT is most effective in HCC smaller than 6 cm, with local control rates from 70% to 95% at 2 years.
- SBRT can also lead to sustained control of HCCs larger than 6 cm and the recanalization of vascular tumors from HCC.
- Toxicity risks are increased in patients with Child-Pugh B and C baseline liver function.
- Randomized trials of SBRT for HCC are required.

**Outcomes: SBRT**

More recently, SBRT has been used to treat patients with HCC, with a summary of outcomes shown in Table 1. Blomgren et al first reported on the use of SBRT on extracranial sites in 1995 and 1998.13,14 In one prospective study, patients with Child-Pugh A liver disease and potentially resectable single HCCs, had a 5-year survival of 56% following proton therapy.10 In another series, in six patients with HCC who went on to have liver transplantation 6 to 18 months after proton therapy (63 Gy equivalent in 15 fractions), two complete pathologic responses were observed, demonstrating proof that high-dose RT may ablate HCC.12 Proton and photon therapy have been used to successfully treat HCC with portal vein or inferior vena cava thrombosis.11

**Table 1. Selected Outcomes from HCC SBRT Series**

<table>
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<tr>
<th>Number of Patients</th>
<th>Dose/Fraction</th>
<th>Median Follow-up (Months)</th>
<th>Tumor Size</th>
<th>Overall Response Rate</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blomgren, 199814</td>
<td>9 pts HCC, 1 pt IHC</td>
<td>5-15 Gy/1–3 #</td>
<td>NR</td>
<td>50%</td>
<td>NR</td>
</tr>
<tr>
<td>Choi, 200623</td>
<td>20 pts HCC</td>
<td>50 Gy/5–10 #</td>
<td>23</td>
<td>3.8 cm (2–6.5 cm)</td>
<td>80% overall</td>
</tr>
<tr>
<td>Mendez Romero, 200617</td>
<td>11 pts HCC</td>
<td>25 Gy/5 #</td>
<td>NR</td>
<td>&lt; 7 cm</td>
<td>1-yr LC: 82%</td>
</tr>
<tr>
<td>Tse, 200818</td>
<td>31 pts HCC</td>
<td>36 Gy (median)/6 #</td>
<td>18</td>
<td>Median: 173 cm³</td>
<td>1-yr infeld LC: 65%</td>
</tr>
<tr>
<td>Louis, 201026</td>
<td>25 pts HCC</td>
<td>45 Gy/3 #</td>
<td>13</td>
<td>Median: 150 cm³</td>
<td>86% overall</td>
</tr>
<tr>
<td>Kwon, 201024</td>
<td>42 pts HCC</td>
<td>30–39 Gy/3#</td>
<td>29</td>
<td>15.4 cm³ (3–82 cm³)</td>
<td>Overall: 86%</td>
</tr>
<tr>
<td>Facciuto, 201122</td>
<td>27 pts HCC</td>
<td>24–36/2–4 #</td>
<td>22</td>
<td>2.0 cm ± 0.8 cm</td>
<td>Overall: 37%</td>
</tr>
<tr>
<td>Andolina, 201120</td>
<td>60 pts HCC</td>
<td>44 Gy (median)/3 # CP A</td>
<td>27</td>
<td>Median: 3 cm</td>
<td>Overall: 90%</td>
</tr>
</tbody>
</table>

**Abbreviations:** HCC, hepatocellular carcinoma; SBRT, stereotactic body radiotherapy; Pts, patients; IHC, immunohistochemical; #, fractions; NR, not reported; OS, overall survival; CR, complete response; PR, partial response; LC, local control; CP, Child-Pugh.
disease included hepatitis B, 39%; hepatitis C, 40%; and alcohol, 25%. Prior therapies were delivered in 50% of patients. Baseline Barcelona Clinic Liver Cancer stage was class C in 66%. Multiple lesions were present in 59% of patients, and the median sum of liver lesion diameters was 10 cm (1.8–43 cm). Tumor vascular thrombosis was present in 55% and extrahepatic disease in 14%. At one year, the local control of irradiated HCC was 79% (CI 95%, 66–87%). Median overall survival was 17.0 months (CI 95%, 10.6–21.8 months).

The Indiana University School of Medicine has also conducted prospective studies of HCC SBRT. In a phase I study by Cardenes et al, in 17 patients with HCC with 25 lesions (median diameter 3.2 cm), dose was escalated in patients with Child-Pugh A from 36 Gy in three fractions to 48 Gy in three fractions, without dose-limiting toxicity. In patients with Child-Pugh B, two developed grade 3 hepatic toxicity at 42 Gy in three fractions. Subsequently, five patients with Child-Pugh B were treated with 40 Gy in five fractions, and one patient developed liver failure. Overall, 20% of patients experienced an increase in Child-Pugh class: seven of 36 patients with Child-Pugh A experienced progression to Child-Pugh B, and five of 24 patients with Child-Pugh B progressed to Child-Pugh C, demonstrating an increased risk of any toxicity in patients with worse Child-Pugh class at baseline. After a median follow-up of 27 months, 2-year local control was 90%, progression-free survival was 48%, and overall survival was 67%.

Retrospective series of SBRT have also been published. Kwon et al treated 42 patients with HCC with 30 to 39 Gy in three fractions. With a median follow-up of 29 months, the response rate was 86% (60% complete response and 26% partial response). Seo et al treated 38 patients with HCC with 33 to 57 Gy in three to four fractions, with a 61% 2-year survival and 79% local control rate. Doses of more than 42 Gy in three fractions were associated with improved local control. Twenty-five European patients with HCC have also been treated with SBRT (45 Gy in 3 fractions), with a 1-year local control rate of 95.

SBRT has been used to effectively treat HCC tumor thrombi and has been used as a bridge to liver transplant. In most series, following SBRT, the first site of recurrence is in the liver outside the irradiated volume, providing rationale for studies combining regional or systemic therapies with SBRT.

Toxicity: SBRT

In addition to the potential for liver toxicity (including classic and nonclassic RILD), as previously described, SBRT is associated with the possibility for other late toxicity. Gastric, duodenum, and small and large bowel late toxicity (e.g., ulcer, fistula, bleed) are more likely to occur following SBRT potent doses than conventional radiation fractionations. Therefore, HCC tumors best suited for SBRT are located at least 1 cm away from luminal gastrointestinal structures. Proton pump inhibitors may reduce the risk of luminal gastrointestinal toxicity, and strategies to move gastrointestinal structures away from the tumor itself may be beneficial to patients.

A potential toxicity that is unique to SBRT is chest pain and rib fracture. This has not commonly been reported but is a possible late sequelae from therapy for peripherally located HCCs. The risk of toxicities can be reduced by ensuring that radiation “hot spots” are within the target volume and not near adjacent critical normal tissues.

Another potential toxicity is biliary. For caudate lesions and HCC invading the biliary track, edema may occur following SBRT, so care is required to stent the patient before therapy and/or to premedicate patients with steroids to reduce this risk. In the long term, there is a risk of late biliary stenosis, which has been rarely reported following proton therapy and not yet reported following SBRT. Nonetheless, being cautious to reduce the dose per fraction and/or overall maximal dose is reasonable for caudate lesions to reduce the risk of this potential late toxicity.

Conclusion

Technical advances in radiation oncology have made it possible for SBRT to be used safely for the treatment of...
HCC, with encouraging outcomes in early and locally advanced HCC. The risk of liver toxicity is increased in patients with Child-Pugh B or C cirrhosis, hepatitis B carrier status, and large tumor size relative to the liver. Improved tumor control and survival are seen in patients who can be treated with higher doses. Randomized trials are required to better understand the benefits and toxicities of SBRT. An international phase III study (RTOG 1112, in development) of sorafenib versus SBRT followed by sorafenib in locally advanced HCC should provide some insight into the benefits of SBRT in this setting.

Authors’ Disclosures of Potential Conflicts of Interest

<table>
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<td>Alexis Bujold*</td>
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*No relevant relationships to disclose.

REFERENCES

Patient Selection, Resection, and Outcomes for Hepatocellular Carcinoma

Overview: Hepatocellular carcinoma (HCC) is an aggressive malignancy of the liver that most often arises in patients with cirrhosis and other chronic liver diseases. Worldwide, it is the sixth most common cancer and the third most common cause of cancer-related death. Median survival is poor, ranging from 6 to 20 months. Definitive treatment options for HCC are surgical resection, ablation, or transplantation. The selection of patients for surgical resection is based on clinical findings, laboratory data, and imaging. Although a number of staging systems exist, all have their limitations. A multidisciplinary approach to patient selection for surgery that includes the input of an experienced liver surgeon assures optimal outcomes. Sound understanding of liver segmentation, modern surgical techniques, and the use of intraoperative ultrasound have led to a reported perioperative mortality rate below 3%, blood transfusion requirements of less than 10%, and 5-year survival rates of at least 50%. Advances in laparoscopic technique and technology have expanded the indications for a safe and oncologically appropriate minimally invasive resection. Deciding which treatment option to employ depends on tumor resectability and the degree of underlying liver disease, which is present in 80% to 85% of patients with HCC; however, despite these surgical advances, a high recurrence rate of 70% in patients with cirrhosis and a survival rate of 65% to 80% in well-selected transplant patients are expected. This article will focus on the evaluation and selection of patients for surgical intervention, considerations in selecting the appropriate type of resection, and expected outcomes following liver resection.

The incidence of HCC is rising. HCC represents the fastest growing cause of cancer-related death in men in the United States, with reported overall survival rates of 20% to 60% for resected patients. In contrast to other malignancies, the resectability of this tumor is not only affected by its anatomic location, the extent of disease, and the overall medical condition of the patient but also by the degree of underlying chronic cirrhosis of the liver that is present in more than 80% of patients. The etiology of the liver cirrhosis is chronic hepatitis B and C in the majority of cases, although alcoholic liver disease; cryptogenic cirrhosis; and, increasingly, nonalcoholic steatohepatitis secondary to the increasing incidence of obesity are clinically relevant as well. The increased incidence of HCC in the United States has been primarily attributed to the concomitant increase in hepatitis C infection. However, one must keep in mind that 15% to 20% of patients with HCC in the United States develop HCC without any known risk factors. HCC is now identified earlier with screening of high-risk patients. For patients with cirrhosis, portal hypertension, and tumors confined to the liver, orthotopic liver transplantation has been considered the most effective treatment. However, there are no prospective randomized controlled trials that directly compare liver transplantation with liver resection for HCC. Most studies compare either transplantation or resection with historical controls and do not analyze according to “intent to treat,” and a significant selection bias of these studies cannot be excluded. Transplantation for HCC is limited by the donor organ shortage, which results in disease progression and death among patients with HCC awaiting a donor liver. In addition to the limitations of liver transplantation, surgical resection for HCC has its challenges as well. Only 20% to 30% of all patients with HCC in the United States will be candidates for either resection or even locoregional therapies, including radiofrequency and cryoablation or transcatheter chemoembolization. This article will focus on patient selection for surgical resection, which is mainly determined by extent of disease and liver function, advances in operative technique, and prognostic factors that determine outcome.

Patient Selection and Assessment of Hepatic Reserve

The existence of a multitude of scoring and staging systems (e.g., Okuda, Cancer of the Liver Italian Program, and American Joint Committee on Cancer) suggests that the ideal one has yet to be identified. Thorough clinical, laboratory, and imaging assessment and careful preoperative patient selection by experienced liver surgeons are necessary for optimal surgical outcomes. Assessment of HCC resectability and extent of resection requires evaluation of patient functional status and comorbidities, tumor location, and underlying liver function. Routine grayscale ultrasound has value for screening patients with cirrhosis but rarely has value in surgical planning. Multidetector computed tomography (CT) with three-dimensional reconstruction and magnetic resonance imaging (MRI) are superior for surgical planning, and they provide information on the morphologic characteristics of the tumor, presence of intrahepatic metastasis and secondary lesions, extent of chronic liver disease, and vascular involvement. Special focus should be given to the number and location of suspicious lesions and any suspicious regional nodes, as well as any signs of advanced liver disease (ascites, nodular hepatic contour, enlarged caudate lobe, splenomegaly, gastrospenic and umbilical venous collateral vessels, and fatty hepatic infiltration). In addition, the anatomic relationship of the tumor to important vascular structures as well as the presence of a portal or hepatic vein thrombus are important findings on CT and MRI. A vascular thrombus that is bulging in appearance and enhances with contrast is suspicious for tumor thrombus, whereas nonenhancing thrombus may represent venous clot rather than tumor. Macrovascular involvement portends a poor prognosis, unlikely to be improved with surgical resection, and represents a contraindication to liver transplanta-
tion. Advanced computer-based image reconstruction provides a virtual three-dimensional model for accurate quantitative assessment of areas at risk for devascularization or venous congestion, thus influencing the extent of resection or need for vascular reconstruction. Liver volumetry using axial images from two-dimensional CT scans is used to build a virtual model of the liver to measure the future liver remnant (FLR) as a predictor of postoperative hepatic dysfunction. The following formula for the estimation of the total liver volume (TLV) in adults was found to be the most precise:

\[
\text{TLV (cm}^3\) = -794.41 + 1267.28 \times \text{body-surface area (m}^2)\]

Preoperative portal vein embolization of the branches supplying the portion of the liver to be resected may be used to induce hypertrophy to increase the FLR and reduce the risk of morbidity and mortality. This is particularly helpful if the future remnant volume is below 40% in a noncirrhotic liver or below 60% in a cirrhotic liver. This technique allows liver regeneration (and therefore an increase in FLR) to take place before definitive major liver resection. Failure of the liver to undergo hypertrophy and regenerative hyperplasia in response to portal vein embolization should be a warning sign of a decreased ability of the liver to regenerate and an increased risk of liver failure after resection. Portal vein ligation (rather than percutaneous embolization) can also be performed laparoscopically in a safe manner and may be particularly useful in patients undergoing staging laparoscopy to rule out disseminated disease. Before any regional therapy including resection or transplantation, chest imaging should be performed to rule out distant metastases.

In addition to imaging and clinical evaluation, laboratory studies (total bilirubin, albumin, International normalized ratio) provide information required to determine Child-Pugh classification. Patients with class A cirrhosis may be good surgical candidates, whereas almost no patients with class B cirrhosis are appropriate for resection. Thrombocytopenia, especially when combined with splenomegaly, is generally a sign of portal hypertension and excludes a patient from consideration of resection (though liver transplantation remains a potential option). Preoperative percutaneous biopsy to confirm a diagnosis of HCC is not typically required for lesions that meet radiographic criteria for HCC in the setting of underlying liver disease.

Advances in Operative Techniques

It is well-accepted that HCC resection should be performed with at least 1-cm margins and sound oncologic principles (avoidance of tumor spillage). Controversy exists as to whether there is a survival benefit of anatomic resections according to the Couinaud classification of liver segmentation over nonanatomic resection. A series from an Asian center demonstrated significantly improved survival of the group that underwent resection according to Couinaud classification over nonanatomic resection: 66% compared with 35%, \(p = 0.01\) for 5-year survival, and 34% compared with 16%, \(p = 0.006\) for disease-free survival. A comparison of the outcome with anatomic and nonanatomic resection for HCC, using a nationwide Japanese database of 72,744 patients, demonstrated an improved disease-free survival rate with anatomic resection but no difference in the overall survival rate. When survival was stratified by tumor size, the disease-free survival rate was significantly improved with an anatomic resection for HCC with a diameter of 2 to 5 cm (\(p < 0.0005\)). This finding was not confirmed by Western studies, where only tumor size and presence of vascular invasion affected survival.

Full liver mobilization and ultrasound examination allow full ultrasonic inspection of the liver and delineation of the intrahepatic anatomy and may spare the patient from undergoing a potentially noncurative operation or one in which a tumor is unknowingly left behind. Depending on the

### Table 1. Overall and Disease-Free Survival Rates after Resection According to Prognostic Factors

<table>
<thead>
<tr>
<th>Prognosticator</th>
<th>Factor</th>
<th>5-yr OS (%)</th>
<th>5-yr DFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>HCC and cirrhosis</td>
<td>23–48</td>
<td>22–36</td>
</tr>
<tr>
<td></td>
<td>HCC, no cirrhosis</td>
<td>44–58</td>
<td>24–45</td>
</tr>
<tr>
<td>Tumor Size</td>
<td>HCC ≤ 3 cm</td>
<td>55–78</td>
<td>30–51</td>
</tr>
<tr>
<td></td>
<td>HCC ≤ 5 cm</td>
<td>41–67</td>
<td>21–44</td>
</tr>
<tr>
<td></td>
<td>HCC &gt; 5 cm</td>
<td>29–56</td>
<td>22–23</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>Single</td>
<td>35–68</td>
<td>19–46</td>
</tr>
<tr>
<td></td>
<td>Multiple</td>
<td>21–58</td>
<td>6–25</td>
</tr>
</tbody>
</table>

Abbreviations: DFS, disease-free survival; HCC, hepatocellular carcinoma; OS, overall survival.

* Adapted from Rahbari and colleagues. The three most important prognosticators for long-term survival after liver resection for HCC are the absence or degree of liver cirrhosis; size of the lesion below 3 cm, below 5 cm, or above 5 cm; and the presence of single or multiple lesions.

---

**KEY POINTS**

- A multidisciplinary approach to patient selection for surgery that includes the input of an experienced liver surgeon is necessary for optimal surgical outcomes, which are a perioperative mortality rate below 3%, blood transfusion requirements in less than 10% of cases, and 5-year survival rates of 50%.
- Underlying liver disease is present in more than 80% of patients with hepatocellular carcinoma. Thorough preoperative clinical, laboratory, and imaging assessment is necessary to optimize patient selection and avoid small-for-size future liver remnant leading to liver failure.
- Intraoperative ultrasound with full liver mobilization is an essential component of every liver cancer operation. Anterior approach, hanging maneuver, and diverse parenchymal transaction devices have improved surgical outcome.
- Laparoscopic resection is a viable alternative to open resection with an improved perioperative period and similar oncologic outcomes. A laparoscopic approach may decrease morbidity of salvage liver transplantation.
- Risk factors associated with early recurrence are tumor size, microvascular invasion, satellite nodules, alpha-fetoprotein levels, and nonanatomical resection. Risk factors associated with late recurrence include presence of cirrhosis, active hepatitis, vascular invasion, moderate or poor differentiation, and multinodularity.
quality of preoperative imaging, new lesions are detected in up to 30% of cases by intraoperative ultrasound, of which one-third will turn out to be malignant, underscoring the importance of this diagnostic tool. Historically, resection of the right liver has involved mobilization of the right liver with extreme left displacement to expose the retrohepatic inferior vena cava followed by extrahepatic control of the right hepatic vein. Potential deleterious consequences of this approach are iatrogenic rupture of the tumor and hemodynamic compromise of the left lobe. The so-called anterior approach entails initial vascular inflow control and parenchymal transection before mobilization of the right liver. This technique minimizes manipulation of the tumor-bearing liver and spillage of tumor cells. Results from a prospective randomized controlled study of anterior compared with a conventional approach for patients with HCC measuring 5 cm or more demonstrated significantly less major operative blood loss of 2 L or more (28.3% vs. 8.3%, p = 0.005) and superior overall survival (median 68.1 months vs. 22.6 months, p = 0.006) with the anterior approach.

The liver-hanging maneuver originally described by Belli and colleagues consists of passing a tape in the avascular retroprehepatic, prevascular space to suspend the liver during parenchymal transaction. Elevation of the tape compresses the liver and reduces bleeding of the deeper parenchymal plane while simultaneously guiding the plane of the parenchymal transection. The hanging maneuver approach, which greatly facilitates the anterior approach described above, has been modified based on the three Glisson’s pedicles and hepatic veins facilitating right and left anatomic liver resections.

The best technique of parenchymal transection remains a matter of debate. A Cochrane Collaborative meta-analysis of seven trials evaluated 556 randomly selected patients who had undergone liver resection using the most common liver parenchymal transection devices available today. The comparisons include cavitron ultrasound surgical aspirator (CUSA) compared with the clamp-crush technique (two trials); radiofrequency dissecting sealer (RFDS) compared with the clamp-crush technique (two trials); sharp dissection compared with the clamp-crush technique (one trial); and hydrojet compared with CUSA (one trial). The clamp-crush technique is a liver parenchymal transection technique that involves crushing the liver parenchyma with a clamp, which leaves blood vessels and bile ducts behind. Those structures can subsequently be ligated or clipped. One trial compared CUSA, RFDS, hydrojet, and the clamp-crush technique. The report found that the clamp-crush technique was 2 to 6 times less expensive than the other methods depending on the number of surgeries performed each year and therefore was favored by the authors. An additional technique that is now commonly used for parenchymal liver transection is stapling with a vascular stapler. Currently, there is an open prospective trial comparing the clamp-crush technique to vascular stapler hepatectomy for parenchymal transection in elective hepatic resection (CRUNSH, NCT01049607). Weber and colleagues reported on liver tumor resections using radiofrequency energy in 15 patients between January 2000 and June 2001. The device creates zones of necrosis that are subsequently transected with a scalpel, thereby rendering this approach suitable for laparoscopic liver resections.

A growing body of literature has confirmed the safety and good long-term outcome of laparoscopic liver resection. The largest series of laparoscopic liver resection for HCC was a recent multicenter European trial in which 163 laparoscopic liver resections were performed in a population of 74% cirrhotics. Inclusion criteria were predefined and included patients with compensated cirrhosis, esophageal varices of grade 1 or less, a platelet count of at least 80,000/mm³, tumors less than 10 cm in size, an absence of major vascular invasion, and an American Society of Anesthesiologists (ASA) score of 3 or less, as well as those without evidence of cirrhosis. Median follow-up was 30.4 months after resection with 1- and 3-year overall survival rates of 93% and 69%, respectively. Since this series was reported, operative time, blood loss, number of transfused packed red blood cells, and open conversion rates have continued to decline, suggesting a learning curve of this relatively novel technique. A small study has suggested patients who had previously undergone laparoscopic resection compared with those who had undergone open surgery for HCC had decreased morbidity following salvage liver transplantation. In this study, 24 total patients underwent salvage liver transplant after either prior laparoscopic (12 patients) or open resection (12 patients). The laparoscopy group demonstrated shorter resection and total operative time, less blood loss, and reduced need for blood transfusions. However, the most important question in comparing open resection with laparoscopic resection is whether oncologic outcomes are the same. A recent meta-analysis evaluated 10 nonrandomized controlled studies with 494 subjects, of whom 213 underwent laparoscopic and 281 underwent open resection for HCC. In addition to the improved morbidity among patients undergoing laparoscopic compared with open resection, there was no difference between the groups with respect to surgical margins, overall survival rates, and disease-free survival rates. These findings were similar to those observed in a recent meta-analysis of 10 studies looking at 627 patients from China. Despite the absence of higher-level evidence, laparoscopic liver resection for HCC is rapidly becoming preferable to open resection in well-selected patients.

Outcomes and Prognostic Factors

Hepatic resection for HCC has become a safer operation, with a reported in-hospital mortality rate of around 2% and a 90-day mortality rate of 5%, largely due to advances in surgical technique and improved patient selection, as demonstrated in a recent series of 129 patients with HCC from Toronto. These marked improvements in outcomes can, in part, be attributed to increased utilization of segmental and parenchymal-sparing resections and decreased intraoperative blood loss. Nevertheless, morbidity for liver resections remains high at 20% to 50% and include complications such as pleural effusion (9%), perihepatic abscesses (6%), ileus (6%), sterile perihepatic fluid collections (5%), wound infection (5%), urinary tract infection (4%), bile leak/biloma (3%), pneumonia (3%), and deep venous thrombosis (2%), as reported in a series of 1,803 patients consisting of 21% patients with HCC. Expected 1-, 3-, 5-, and 10-year survival rates following HCC resection are 85%, 64%, 45%, and 21%, respectively, as reported by the Liver Cancer Study Group in Japan. These data are derived from the largest report to date, which includes 6,785 patients with cirrhosis operated on between 1988 and 1999. Patients without significant portal hypertension and normal bilirubin achieve
a 5-year survival rate of 70% following liver resection for HCC. In those with portal hypertension, however, the rate of 5-year survival is 50% and even lower in the setting of an abnormal bilirubin. Similar results have been reported from Western and other Asian centers. Survival rates as high as 60% at 5 years may be achieved in Child class A patients with well-encapsulated tumors of 2 cm in diameter, which are equivalent to results following liver transplantation. Unfortunately, few patients (<10%) meet these selection criteria. Furthermore, recurrence after resection is common, occurring in up to 80% of the patients at 5 years. Approximately two-thirds of recurrences occur within 2 years after treatment; these are considered early recurrence by convention.

The factors associated with early recurrence are vascular invasion, tumor size (only 25% of patients with HCC of less than 2 cm have vascular invasion), satellite nodules, alpha-fetoprotein levels, nonanatomic resection, and extent of underlying disease. There has been some debate as to whether tumor recurrence 2 or more years following resection represents a true recurrence of the initial lesion or a de novo HCC in the oncogenic cirrhotic liver. Risk factors associated with late recurrence include presence of cirrhosis, active hepatitis, vascular invasion, moderate or poorly differentiated HCC, and multinodularity. Genomic analyses to better define recurrence risk based on primary tumor characteristics and molecular evaluation of the cirrhotic liver may be valuable for prognostication in the future, and future research will show whether neoadjuvant therapy with radiation, retinoids, chemoembolization, interferon, or sorafenib (an inhibitor of several tyrosine protein kinases [VEGFR, PDGFR, Raf]) leads to delayed recurrence. Despite the fact that recurrence following resection of HCC is a poor prognosticator, there is evidence that some patients will benefit from aggressive surgical approaches if recurrence occurs. It is our practice to offer patients regional therapy—occasionally including resection—for recurrent HCC when the recurrence is limited to the liver. If recurrence occurs, it has been reported that multimodality therapy including transarterial chemoembolization, percutaneous ablutions, and surgery results in an overall 5-year survival rate of 20%.

Conclusion

Surgical resection, ablation, and liver transplantation offer the highest likelihood of long-term survival or cure in carefully selected patients. A multidisciplinary approach by a team consisting of surgical oncologists, transplant surgeons, medical oncologists, interventional radiologists, radiation oncologists, social workers, and other ancillary staff provides best outcomes. Advances in surgical techniques, technology, and understanding of liver anatomy allow experienced liver surgeons to perform resections that are safer than before, and resections are available to more patients than before. Whereas neoadjuvant therapy has not been shown to convert unresectable tumors to resectable ones, preoperative portal vein embolization can increase the FLR and convert patients from unresectable to resectable. Ablative techniques can be valuable adjuncts in the surgical therapy of patients with HCC. And in some instances ablation can be the sole local treatment modality during an open or laparoscopic operation, recognizing that ablation is similarly effective as resection for early HCC. Improvements in surgical techniques have contributed to decreased perioperative morbidity and mortality. Important prognostic factors associated with survival after resection include vascular invasion, satellite nodules, and extent of underlying liver disease. Further improvements in survival after hepatectomy for HCC will depend on strategies for early detection as well as effective neoadjuvant or adjuvant therapies.

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*No relevant relationships to disclose.

### REFERENCES


THE MANAGEMENT OF LESS COMMON BUT COMPLEX UPPER GASTROINTESTINAL MALIGNANCIES: HEPATOCELLULAR CARCINOMA, Pancreatic Neuroendocrine Tumors, and Biliary Tract Tumors

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A Renaissance in Therapeutic Options for Pancreatic Neuroendocrine Tumors

By Pamela L. Kunz, MD

Overview: The field of pancreatic neuroendocrine tumors (NETs) has seen a remarkable renaissance in recent years with exponential increases in published research, clinical trials, and U.S. Food and Drug Administration (FDA)-approved treatments. Surgical resection remains the foundation for management of locoregional disease. However, for patients with advanced disease, novel therapeutic options have emerged.

NETs arise from neuroendocrine cells throughout the body, most commonly in the lungs, gastrointestinal tract, and pancreas. The field of pancreatic NETs has seen a remarkable renaissance in recent years, with exponential increases in published research, clinical trials, and FDA-approved treatments (Fig. 1). Pancreatic NETs have an estimated incidence of 0.32 cases/100,000 people1 and account for 1% of all pancreatic cancers by incidence and 10% of pancreatic cancers by prevalence.2 The median age at diagnosis is age 60, with a white male predominance. The majority of NETs are functionally inactive but some produce hormones that lead to the clinical syndromes associated with hormone excess. Though most pancreatic NETs are indolent, the spectrum of clinical behavior is quite variable and sometimes difficult to predict. The nomenclature, classification, and grading systems for NETs have historically been inconsistent. Through critical evaluations of these systems, common principles have emerged.3,4 NETs are generally divided into two main categories: well-differentiated (low and intermediate grade) and poorly differentiated (high grade). The proliferative rate (mitotic index and Ki67) is considered a critical component of pathologic evaluation. Well-differentiated tumors usually have less than 20 mitoses/high powered field (hpf) and a Ki67 index of less than 20%, and poorly differentiated tumors more than 20 mitoses/hpf and a Ki67 more than 20%. This discussion will focus on the management of well-differentiated pancreatic NETs.

Approach to Treatment

Locoregional Disease

At the time of diagnosis, approximately 40% of patients with pancreatic NETs have locoregional disease.2 Surgical resection remains the mainstay of treatment for these patients. There is currently no role for adjuvant treatment following resection of a primary pancreatic NET, as little is known about patient and tumor characteristics that predict for recurrence.

Unresectable and Metastatic Disease

Nonsurgical therapies play a role in the setting of unresectable and metastatic disease, which account for approximately 50% of newly diagnosed patients.2 Patient selection is a critical first step in the treatment algorithm. For patients with functional tumors, somatostatin analogs should be considered to alleviate symptoms of peptide release. For patients with nonfunctional tumors, systemic treatments are generally indicated for patients with progressive, bulky, or symptomatic disease. Otherwise, patients with low-volume, stable, and asymptomatic disease may be monitored closely without treatment.

Mediating Symptoms of Hormone Excess

An estimated 40% to 53% of pancreatic NETs are functional.5,6 Functional tumors are defined as having inappropriate elevation of serum hormone markers combined with clinical evidence of hormone oversecretion, including insulinomas, gastrinomas, VIPomas, glucagonomas, and somatostatinomas. Somatostatin analogs are the foundation of symptom management for patients with functional pancreatic NETs and can both decrease the secretion of such hormones and inhibit their end-organ effects. Somatostatin analogs are naturally occurring polypeptide produced by paracrine cells that are scattered throughout the gastrointestinal tract and inhibits gastrointestinal endocrine and exocrine function. Its effects are mediated through G-coupled protein somatostatin receptors (SSTR1–5). Short- and long-acting octreotide (with high affinity for SSTR2) is available in the United States. Lanreotide, available in Europe, is a long-acting analog with similar binding affinity to octreotide. Pasireotide, a novel somatostatin analog with a different binding affinity profile compared to octreotide or lanreotide, is currently in development. Note that somatostatin analogs should be used with caution for patients with insulinomas, as it may precipitate or worsen hypoglycemia.

Oncologic Control

Biologic Agents

Recent studies with inhibitors of signaling pathways that target vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR) have demonstrated considerable activity in pancreatic NETs. RADIANT-3 was a randomized phase III study that evaluated the efficacy of everolimus, an mTOR inhibitor, in advanced pancreatic NETs.7 In this international, multisite study, 410 patients with low- or intermediate-grade progressive advanced pancreatic NETs were randomly selected to show prolonged progression-free survival (PFS) with everolimus or sunitinib. Future studies are designed to answer questions about the role of somatostatin analogs as antiproliferative agents, combinations of biologic therapies, and new cytotoxic chemotherapy backbones.
receive everolimus 10 mg orally daily or placebo. The primary endpoint was PFS; secondary endpoints were overall survival (OS), response rate (RR), and safety. The median PFS was 11.0 months with everolimus as compared to 4.6 months with placebo (hazard ratio [HR] 0.35; 95% CI 0.27 to 0.45; p < 0.001). The RR was 5% in the everolimus arm compared to 2% in the placebo arm. Updated OS showed no difference between arms; however, patients in the placebo arm crossed over to treatment at progression, likely reducing the chance of observing a survival difference (Table 1).

Another randomized study evaluated the efficacy of sunitinib, an inhibitor of the VEGF pathway, in advanced pancreatic NETs. One hundred seventy-one patients with advanced, well-differentiated, progressive pancreatic NETs were randomly selected to receive sunitinib 37.5 mg orally daily or placebo.\(^8\) Primary endpoints were PFS; secondary endpoints were RR, OS, and safety. The study was discontinued before the preplanned interim efficacy analysis, after an independent data and safety monitoring committee observed more serious adverse events and deaths in the placebo arm and a difference in PFS that favored the sunitinib arm. At the time of study closure, median PFS was 11.4 months in the sunitinib arm compared with 5.5 months in the placebo arm (HR 0.42; 95% CI 0.26 to 0.66; p < 0.001).

### Table 1. Studies Leading to FDA Approval of Agents in Advanced Pancreatic NETs

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of Patients</th>
<th>RR (%)</th>
<th>TTP or PFS (mo)</th>
<th>OS (mo)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strep/dox vs.</td>
<td>36</td>
<td>69</td>
<td>20</td>
<td>26.4</td>
<td>Moertel et al.(^9)</td>
</tr>
<tr>
<td>Strep/5FU vs.</td>
<td>33</td>
<td>45</td>
<td>6.9</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>Chlorozocin</td>
<td>33</td>
<td>30</td>
<td>6.9</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>Everolimus vs.</td>
<td>207</td>
<td>5</td>
<td>11.0</td>
<td>NR</td>
<td>Yao et al.(^7)</td>
</tr>
<tr>
<td>Placebo</td>
<td>203</td>
<td>2</td>
<td>4.6</td>
<td>36.6</td>
<td></td>
</tr>
<tr>
<td>Sunitinib vs.</td>
<td>86</td>
<td>9</td>
<td>11.4</td>
<td>30.5</td>
<td>Raymond et al.(^8)</td>
</tr>
<tr>
<td>Placebo</td>
<td>85</td>
<td>0</td>
<td>5.5</td>
<td>24.4</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: mo, months; NET, pancreatic neuroendocrine tumor; NR, not reached; OS, overall survival; PFS, progression-free survival; RR, response rate; TTP, time to progression.

**Abbreviations:** mo, months; NET, pancreatic neuroendocrine tumor; NR, not reached; OS, overall survival; PFS, progression-free survival; RR, response rate; TTP, time to progression.

### Cytotoxic Chemotherapy

Patients with advanced pancreatic NETs currently have few treatment options that yield objective radiographic tumor regression. Recent studies evaluating everolimus\(^7\) and sunitinib\(^8\) in this patient population have demonstrated prolongation of PFS compared to placebo, but overall tumor RRs (by RECIST) with these agents are less than 10%.

Historical studies reporting the highest RRs include regimens with cytotoxic chemotherapy. In an initial randomized study of 106 patients, Moertel and colleagues reported activity associated with the combination of streptozocin and doxorubicin in patients with advanced islet-cell tumors (Table 1).\(^9\) The RR associated with this regimen was reported to be 69%; however, because of the use of nonstandard response criteria, the true objective radiologic RR was likely much lower. Retrospective series have reported overall RRs of 6% to 39% associated with streptozocin-based regimens in pancreatic NETs.\(^10,11\) Although clearly associated with activity, the combination of streptozocin and doxorubicin is also associated with considerable toxicity, including myelosuppression, asthenia, and renal insufficiency, precluding its routine use in this disease. Additionally, recent issues with drug availability have made routine use difficult.

Recent retrospective series and small, prospective phase II studies suggest that temozolomide is similarly active but less toxic than streptozocin-based therapy when treating patients with pancreatic NETs. In a retrospective series of 36 patients treated with temozolomide monotherapy, tumor regression was observed in 31% of bronchial carcinoid tumors and 8% of pancreatic NETs.\(^12\) In a series of 97 patients, 18 of 53 patients with pancreatic NETs (34%) achieved a partial or complete response to temozolomide-based therapies.\(^13\) A third retrospective series of 21 patients treated with temozolomide monotherapy demonstrated responses in 25% of pancreatic NETs.\(^14\)

Temozolomide has also been investigated prospectively in phase II studies of patients with NETs, though usually in combination with other agents. In an initial study, 29 patients with metastatic NETs were treated with a combination of temozolomide, administered at a dose of 150 mg/m\(^2\).

### Key Points

- Surgical resection continues to be the mainstay of treatment for patients with locoregional disease.
- Somatostatin analogs are indicated for patients experiencing symptoms of hormone excess; there are currently no prospective data to support the use of somatostatin analogs as antitumor agents for pancreatic neuroendocrine tumors.
- For patients with advanced disease, single-agent everolimus and sunitinib have recently been shown to improve progression-free survival.
- Temozolomide-based chemotherapy regimens are emerging as an acceptable alternative to streptozocin; prospective randomized studies are in development.
for 7 days, every other week, and thalidomide at doses of 50 to 400 mg daily; this combination was associated with objective tumor responses in 5 of 11 patients (45%). A subsequent phase II study evaluated the combination of temozolomide and bevacizumab in the treatment of 34 patients with NETs (15 pancreatic, 19 carcinoid). Patients received 150 mg/m²/day of temozolomide orally for 7 days, every other week, and 5 mg/kg of bevacizumab intravenously every other week. Because of anticipated lymphopenia, patients also received prophylaxis with trimethoprim/ sulfamethoxazole (1 double strength tablet every Monday, Wednesday, Friday). Objective tumor responses were observed in 33% of patients with pancreatic NETs, but not in patients with carcinoid tumors. In a third, prospective study, a regimen of everolimus and temozolomide was associated with an overall tumor RR of 35% for patients with advanced pancreatic NETs. Taken together, these prospective and retrospective studies suggest that temozolomide-based therapy is comparable to streptozocin-based regimens and might reasonably be associated with an overall tumor RR of 30% to 40% for patients with advanced pancreatic NETs.

Interestingly, preclinical and early clinical evidence suggests that capecitabine may be synergistic with temozolomide. In a series of 17 patients with pancreatic NETs, combination therapy with temozolomide and capecitabine was associated with a tumor RR of 59%. A recent single-institution retrospective study by Strosberg and colleagues reported RRs of 70% and median PFS of 18 months for 30 patients with advanced pancreatic NETs. In this study, temozolomide was administered at a dose of 200 mg/m² on days 10 to 14, and capecitabine was administered at a dose of 750 mg/m² twice daily on days 1 to 14. The combination and specific dosing schedules were well-tolerated, with only four patients experiencing grade 3 or 4 adverse events (anemia, thrombocytopenia, elevated aspartate aminotransferase, and elevated alanine aminotransferase). The most common grade 1 and 2 adverse events were fatigue, nausea, myelosuppression, and hand-foot syndrome. Based on this study, the combination of temozolomide and capecitabine has become popular and commonly used in patients with advanced pancreatic NETs.

Other Therapies for Advanced Disease

Hepatic metastases commonly occur in patients with pancreatic NETs and adversely affect overall prognosis and quality of life. Therapies directed at locoregional control of hepatic disease may be necessary to decrease symptoms associated with hormone excess. Surgery for hepatic metastases should be considered whenever the metastases are considered resectable and when there is no evidence of extrahepatic disease. Thermal ablation or cryoablation may be considered as an adjunct to surgery or in settings where extrahepatic disease or comorbidities might favor a less aggressive intervention. Selective catheterization of the hepatic artery and embolization of vessels perfusing the tumors can result in clinically significant responses. Embolization options include bland embolization, chemoembolization, and radioembolization. Retrospective studies report benefit, though no prospective studies have been conducted.

Radiolabeled somatostatin analogs with therapeutic doses of the radioactive isotope can also provide disease control in patients with advanced disease and are used routinely in Europe. The most commonly used radionuclides are indium (¹¹¹In), yttrium (⁹⁰Y), and lutetium (¹⁷⁷Lu) and are only available in Europe. The largest retrospective study of patients with gastroenteropancreatic NETs demonstrated clinical responses in 46% of patients at 3 months (complete 2%, partial 28%, and minor 16%) and stable disease in 36%; the minority had progressive disease (20%). Median time to progression (TTP) was 40 months; median OS was 128 months. The bone marrow and kidneys are the most important dose-limiting organs in peptide receptor radionuclide therapy. Prospective randomized studies are needed to confirm these observed benefits.

Ongoing and Future Directions

The renaissance of clinical research in the field of NETs has only just begun. Ongoing and proposed studies are poised to answer important questions.

First, do somatostatin analogs have antitumor activity in pancreatic NETs? Though many physicians extrapolate the findings from the PROMID study, there is currently no prospective data to support the use of somatostatin analogs as antitumor agents for pancreatic NETs. An ongoing international study was designed to answer this question by randomly selecting patients with advanced nonfunctioning pancreatic NETs to receive lanreotide autoceil versus placebo (CLARINET, NCT00353496). Primary endpoints are TTP and death. The study opened in June 2006, and accrual is ongoing.

Second, does the combination of two biologic agents improve efficacy outcomes in pancreatic NETs? A CALGB study (80701, NCT01229943) addresses this question and randomly selects patients with advanced pancreatic NETs to receive everolimus and octreotide long-acting release (LAR) versus everolimus, bevacizumab, and octreotide LAR. The primary endpoint is PFS. The study opened in October 2010, and accrual is ongoing.

The development of thoughtful future studies is critical in moving the field forward. In fact, a National Cancer Institute Neuroendocrine Tumor Clinical Trials Planning Meeting held in 2009 identified key unmet needs, recommended appropriate study endpoints and inclusion criteria, and formulated priorities for future NET studies. The prospective evaluation of single-agent temozolomide and a comparison to temozolomide-based combinations for pancreatic NETs was a key recommendation of this meeting. ECOG 2211 is a proposed study in which patients with advanced pancreatic NETs will be randomly selected to receive temozolomide versus temozolomide and capecitabine. The principal objective of the study will be to assess whether the addition of capecitabine to temozolomide improves RRs when compared to temozolomide alone. It is anticipated that the superior arm will serve as a building block in future studies.

Conclusion

The recent advances in the field of pancreatic NETs are truly exciting. We now have additional agents in our arsenal of therapeutic options for patients with this disease, including everolimus and sunitinib, both of which have been shown to prolong PFS. Given the increasing number
of therapeutic options, patient selection and treatment sequence can be complicated. A number of tools are available for the treating physician, including the National Comprehensive Cancer Network Neuroendocrine Tumor Guidelines and guidelines from the North American Neuroendocrine Tumor Society. Additionally, a multidisciplinary approach can be helpful as modalities from medical oncology, interventional radiology, and surgery need to be weighed. Future studies are aimed at answering questions about the utility of somatostatin analogs for tumor control, use of combined biologics, and temozolomide-based chemotherapy regimens.

Author’s Disclosure of Potential Conflicts of Interest

<table>
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<tr>
<th>Author</th>
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<th>Consultant or Advisory Role</th>
<th>Stock Ownership</th>
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<th>Research Funding</th>
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REFERENCES


A Review of the Management of Hepatocellular Carcinoma: Standard Therapy and a Look to New Targets

By Andrew X. Zhu, MD, PhD

Overview: Management of hepatocellular carcinoma (HCC) continues to be challenging, but new treatment options are evolving. A multidisciplinary evaluation will help make the best treatment decisions for each patient. Although we continue to improve the outcomes of curative treatment with resection, liver transplant, and radiofrequency ablation (RFA), many new liver-directed regional therapies including drug-eluting beads, radioembolization, and radiation are emerging. Sorafenib remains the only approved agent for advanced HCC, and its role in the adjuvant setting following resection or RFA, with transarterial chemoembolization, or in combination with other targeted agents or chemotherapy in the advanced stage is under investigation. Many molecularly targeted agents with novel mechanisms of action are under active development.

HCC is a malignancy of global importance: it is the sixth most common cancer and the third most common cause of cancer-related mortality worldwide. In the United States, the incidence of HCC has tripled, and the 5-year survival rate has remained below 12% during the past two decades. HCC is the most common primary liver cancer, accounting for 90% of all liver malignancies and has become the fastest-rising cause of cancer-related death in the United States. Management of HCC continues to present with many challenges. First, despite the well-recognized risk factors, including hepatitis B infection (HBV), hepatitis C infection (HCV), alcoholic liver disease, and nonalcoholic fatty liver disease, as well as the increased use of surveillance programs, most patients still present with unresectable or advanced-stage disease. Unfortunately, these patients do not benefit from curative treatment options including surgical resection or liver transplantation. Second, despite the availability of many local-regional therapies, including radiofrequency ablation (RFA) and transarterial chemoembolization (TACE), there is a paucity of data from definitive phase III studies. It is often confusing to the community oncologist how to select the most appropriate treatment for HCC patients, underscoring the importance of multidisciplinary evaluation. Third, most patients with HCC have underlying cirrhosis, which adversely affects the overall survival (OS) of these patients and greatly limits the treatment options. Fourth, despite the approval of sorafenib based on phase III trials demonstrating OS benefits and its extensive application in clinical practice during the past few years, it is increasingly clear that the benefits of sorafenib remain modest. More importantly, the mechanisms of sorafenib’s efficacy, toxicity, and resistance remain elusive. On the other hand, we have witnessed an unparalleled time period of active drug development in HCC. Many molecularly targeted agents that inhibit different pathways of hepatocarcinogenesis are under various phases of clinical development. This review will attempt to summarize briefly the current status of management of HCC with a focus on the advanced stage of disease and potential new targeted agents under investigation in HCC.

Staging and General Principles for the Management of HCC

Once HCC is diagnosed, clinicians would aim to assess the extent of disease, the presence and severity of underlying cirrhosis, the performance status, and the access to institutional or local-regional expertise in formulating a treatment decision. Every effort should be made to ensure a careful evaluation of whether the patient is a candidate for surgical resection or liver transplant. A referral to a tertiary medical center is often helpful to render a definitive decision. A multidisciplinary team evaluation is critical to assess the pros and cons of each treatment option for individual patients, particularly in the setting of assessing local-regional therapy. The clinicians should be familiar with the indications of sorafenib and how to manage the sorafenib-related side effects. It is important to be aware of the ongoing clinical trials available for HCC and to support the enrollment of HCC-specific clinical trials. When the patients have advanced HCC with poor performance status or worsening cirrhosis, symptomatic management and preserving the quality of life of these patients should be the primary considerations.

Numerous staging systems for HCC have been developed. These systems are useful for stratification of patients based on their prognosis, allocating specific treatment based on the stage, and allowing comparison of clinical outcomes from different clinical studies. Many different staging systems have been developed—Barcelona Clinic Liver Cancer (BCLC), Cancer of the Liver Italian Program (CLIP), tumor–node–metastasis (tumor, node, metastasis staging system), Groupe d’Etude et de Traitement du Carcinome Hépatocellulaire (GRETCH), Chinese University Prognostic Index (CUP), and Japanese Integrated Staging (JIS)—and there is currently no universally accepted staging system. The BCLC staging classification is increasingly used in western regions, and it tries to capture the tumor features, severity of cirrhosis, performance status, and a recommended treatment algorithm for each stage. However, because of the geographic variation of different risk factors, one staging system may perform better than others in certain regions. In addition, depending on the stage of the disease, certain staging system may be more prognostic, as suggested by one report comparing the various staging systems for patients with advanced disease. In this study, the BCLC system was found to be...
less informative than the GRETCH and CLIP classifications. Clinicians should become familiar with some of these staging systems, their limitations, and controversies in the assessment of HCC. Although genomic analysis and molecular markers have been used to identify possible sub-classification of HCC, these findings would require additional validation and have not been incorporated in clinical staging.

Management of Early-Stage HCC

Despite some variation of practice patterns worldwide, it is clear that early-stage HCC can be cured by several treatment options including surgical resection, liver transplantation, and ablative therapies (Table 1).

The aim of surgical resection is to remove the entire portal territory of the neoplastic segment(s) with a clear margin, while preserving maximum liver parenchyma to avoid hepatic failure. Because of the presence of extrahepatic disease, severe underlying cirrhosis, anatomic location of tumor, and vascular invasion, less than 20% of patients with HCC are suitable for surgical resection. Resection and transplantation achieve the best outcomes in well-selected candidates (5-year survival of 60% to 80%) and compete as the first option in patients with early tumors on an intention-to-treat perspective. Hepatic resection is the treatment of choice for HCC in noncirrhotic patients, where major resections can be performed with low rates of life-threatening complications and acceptable outcome (5-year survival: 30% to 50%).

Orthotopic liver transplantation is considered to be the first-line treatment option for patients with single tumors less than 5 cm or 3 nodules or less with each measuring 3 cm or less (Milan criteria) and advanced liver dysfunction not suitable for resection. In a landmark study by Mazzaferro and colleagues, patients with HCC who meet the Milan criteria have an expected 4-year overall survival rate of 85% and a recurrence-free survival rate of 92%. Therefore, Milan criteria have been adopted by the United Network for Organ Sharing (UNOS) and widely around the world. Efforts have been made to expand the transplant criteria, for example, the University of San Francisco criteria (solitary HCC measuring up to 6.5 cm in diameter or up to three lesions, each measuring no more than 4.5 cm in diameter, with a total combined measurement of less than 8 cm) has been proposed and used in select centers.

For patients with small HCCs who are poor surgical candidates because of impaired liver function or serious comorbid medical conditions, local ablative therapy represents another attractive treatment option. RFA has become the most commonly used local ablation therapy, as recent randomized trials have shown RFA to be more effective than percutaneous ethanol injection (PEI) in treating patients with small HCC (2–3 cm in diameter), with lower rates of local recurrence and higher rates of overall and disease-free survival. In addition, a randomized controlled trial has compared RFA with surgical resection and shown no significant differences in overall or recurrence-free survival, with lower rates of complications and hospitalization associated with RFA.

An ongoing study is assessing the benefits of sorafenib in the adjuvant setting following surgical resection and RFA. Various bridging therapies including RFA and TACE are continuing to be used while patients are waiting for transplant, although the definitive benefits remain to be defined (p < 0.05).

Management of Intermediate-Stage HCC

For patients with intermediate-stage disease with multifocal lesions and without vascular invasion, TACE has been the default treatment option (Table 1). TACE takes advantage of the fact that HCCs derive their blood supply almost entirely from the hepatic artery. The experience with TACE has been mixed, leaving many unanswered questions and controversies. Although several studies have shown negative survival benefits, two studies have demonstrated improved OS compared with best supportive care (BSC) alone in highly selective patient populations. In a randomized controlled trial, Llovet and colleagues demonstrated that patients (more than 80% with underlying HCV-related cirrhosis) who received doxorubicin-based

**KEY POINTS**

- Management of hepatocellular carcinoma (HCC) requires a multidisciplinary approach with careful evaluation of the extent of the tumor, the presence and severity of underlying cirrhosis, and performance status before a treatment decision can be made.
- Surgical resection, liver transplantation, and radiofrequency represent curative treatment options for HCC. There is no established role of adjuvant therapy.
- Transarterial chemoembolization and other local-regional therapies including drug-eluting beads, radioembolization, and radiation are evolving treatment options for unresectable HCC. The role of sorafenib, when given in combination with these treatments, is under investigation.
- Sorafenib remains the only agent approved for advanced HCC. Careful selection of patients and timely management of side effects are important to optimize the efficacy of sorafenib.
- Molecularly targeted agents are under active development and hold promise to improve the outcomes in patients with HCC.

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**Table 1. Management of Hepatocellular Carcinoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early stage</td>
<td>Surgical resection, Transplantation, RFA, PEI</td>
</tr>
<tr>
<td>Intermediate</td>
<td>TACE, drug-eluting beads, radioembolization, radiation</td>
</tr>
<tr>
<td>Advanced</td>
<td>Sorafenib, Clinical trials, Best supportive care</td>
</tr>
</tbody>
</table>

**Abbreviations:** RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization.

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TACE had improved OS compared with those who received BSC (p = 0.009).\textsuperscript{17} Survival probabilities at 1 year and 2 years were 82% and 63% for chemoembolization and 63% and 27% for control. In another single-center study conducted in Hong Kong where the majority of patients had underlying HBV infection, Lo and colleagues showed that patients with unresectable HCC who received cisplatin-based TACE had improved survival (1 year, 57%; 2 years, 31%; 3 years, 26%) compared with those who received only symptomatic control (1 year, 32%; 2 years, 11%; 3 years, 3%; p = 0.002).\textsuperscript{18} A meta-analysis of randomized, controlled trials assessing the use of arterial embolization, chemoembolization, or both as primary palliative treatment for HCC showed that these procedures were associated with an improved 2-year survival rate as compared with conservative treatment.\textsuperscript{19}

In addition to conventional TACE, several novel regional therapies, including drug-eluting beads TACE, radioembolization, and external beam radiation, are under active investigation in HCC. Whether certain techniques will perform better than others and how to incorporate regional therapy for patients with portal vein invasion requires additional studies. Current clinical studies are also assessing the role of sorafenib given concurrently or following TACE or other regional treatment modalities. Despite the early studies demonstrating the tolerability of combining sorafenib with TACE,\textsuperscript{20,21} this approach has not definitively shown clinical benefits of sorafenib either following TACE or concurrently with TACE.\textsuperscript{22,23}

### Management of Advanced-Stage HCC

Following the initial experience in a phase II study,\textsuperscript{24} two randomized phase III trials definitively demonstrated the improved OS benefit of sorafenib in advanced HCC (Table 2). The approval and wide application of sorafenib has changed the treatment paradigm for HCC. However, as sorafenib is gaining more clinical experience, several important findings and related questions have emerged. First, the clinical benefits are modest and only seen in certain patients. This highlights the importance of understanding the mechanism of action of sorafenib and identifying potential predictive markers. Second, as sorafenib-related toxicities, including hand and foot skin reaction, diarrhea, and fatigue can be challenging to manage and affect the quality of life of patients, many clinicians and investigators have asked the relevant question: what is the optimal dose of sorafenib? Although the targeted dose of sorafenib should be 400 mg twice daily based on phase III data, many clinicians have adopted a dose titration step-up approach, starting at 400 mg daily and increasing the dosage by 200 mg every 1–2 weeks to the targeted 800 mg daily as tolerated. Experience form the observational GIDEON study showed that 34% of patients in the United States started sorafenib at 400 mg daily. Third, because the agent was tested only in patients with underlying Child A cirrhosis in the phase III trials, the benefits of sorafenib in patients with worsening hepatic function remains uncertain. Several institutional-based retrospective studies have examined the use of sorafenib in patients with Child B cirrhosis. Although these studies have their inherent limitation, these findings suggest that sorafenib can be safely given to most patients with underlying Child B cirrhosis. However, increased hyperbilirubinemia and other side effects can be encountered at higher frequency. The pharmacokinetic (PK) parameters are similar or modestly different in patients with Child B in comparison with those with Child A. The treatment duration and OS are generally shorter in Child B than those with underlying Child A cirrhosis. Based on the available data, the starting dose for patients with good performance status and compensated hepatic function should be 800 mg daily. However, in patients with borderline performance status and compromised hepatic function, a reduced dose of sorafenib at 200–400 mg can be started with the goal of escalating to full dosage if tolerated. The PK study of sorafenib in patients with hepatic and renal dysfunction also provides some guideline for dosing for these patients.

### New Targets and Regimens under Development for Advanced HCC

The approval of sorafenib has greatly stimulated research in drug development in HCC. Many molecularly targeted agents that inhibit different pathways of hepatocarcinogenesis are under various phases of clinical development, and novel targets are being assessed in HCC. There are three main strategies in this area: (1) identifying and testing targeted agents with novel mechanisms of action; (2) combining various targeted agents that blocks specific targets in different or same pathways; (3) combining targeted agents with chemotherapy. Despite the excitement for these extensive efforts in the past few years, we have observed a few worrisome trends. First, all ongoing phase III studies with targeted agents are conducted in unselected populations. Second, most agents that are in phase III testing are not based on robust data from randomized phase II studies. Third, there is a high rate of failure of phase III trials in HCC. Table 3 lists some of the key studies in various phases of clinical development.

#### Antiangiogenic Agents

HCCs are vascular tumors, and increased levels of vascular endothelial growth factor (VEGF) and microvessel density (MVD) have been observed.\textsuperscript{25} VEGF is one of the main inducers of liver tumor angiogenesis. High VEGF expression has been associated with lower survival. Inhibition of angiogenesis represents a potential therapeutic strategy and has been extensively tested in HCC.

Several VEGF-R inhibitors have moved to phase III development based on the initial phase II data.\textsuperscript{25} Sunitinib is an oral multikinase inhibitor that targets receptor tyrosine

### Table 2. Phase III Studies of Sorafenib in Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
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<tbody>
<tr>
<td>OS</td>
<td>10.7 vs. 7.9 mo</td>
<td>&lt;0.001</td>
<td>6.5 vs. 4.2 mo</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>0.69 (0.55–0.87)</td>
<td></td>
<td>0.68 (0.50–0.93)</td>
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<tr>
<td>TTSP</td>
<td>1.08 (0.88–1.31)</td>
<td>0.768</td>
<td>0.90 (0.67–1.22)</td>
<td>0.50</td>
</tr>
<tr>
<td>TTP</td>
<td>5.5 vs. 2.8 mo</td>
<td>&lt;0.001</td>
<td>2.8 vs. 1.4 mo</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RR</td>
<td>0.58 (0.45–0.74)</td>
<td>0.57</td>
<td>0.42 (0.79)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2% vs. 1%</td>
<td>3.3%</td>
<td>3.3% vs. 1.3%</td>
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</tr>
</tbody>
</table>

Abbreviations: OS, overall survival; TTSP, time to symptomatic progression; TTP, time to tumor progression; RR, response rate.
kinases (RTKs) including VEGFR-1, VEGFR-2, PDGFR-alpha/beta, c-KIT, FLT3, and RET kinases. Following the initial experience of sunitinib from several single-arm phase II studies that used three different dose schedules, a randomized phase III study comparing sunitinib at 37.5 mg continuous daily dosing with sorafenib at 400 mg twice daily in advanced HCC was conducted. Unfortunately, in this large study of 1,073 patients, sunitinib failed to demonstrate either superiority or noninferiority in OS when compared with sorafenib.26 Toxicities including thrombocytopenia and neutropenia were seen with sunitinib leading to discontinuation. Brivanib alaninate is a dual inhibitor of VEGFR and fibroblast growth factor receptor (FGFR) signaling pathways that can induce tumor growth inhibition in mouse HCC xenograft models. A phase II study was conducted to assess the efficacy and safety of brivanib in patients with unresectable, locally advanced, or metastatic HCC who had received either no prior systemic therapy (Cohort A, 55 patients) or one prior regimen of angiogenesis inhibitor (Cohort B, 46 patients). Treatment schedule consisted of continuous daily dosing of brivanib at 800 mg. Both schedules reported preliminary evidence of antitumor activity. Median OS and time to progression (TTP) as assessed by study investigators following second-line treatment with brivanib were 9.79 and 2.7 months, respectively.28 Despite the ambitious phase III development program with brivanib in HCC, a recent press release reported that brivanib failed to demonstrate improved OS when compared with placebo in patients with advanced HCC who failed sorafenib. Linifanib (ABT-869) is a potent and selective inhibitor of VEGFR and PDGFR. Preliminary results from an open label, multicenter phase II study of linifanib in advanced HCC were reported. Linifanib was given at 0.25 mg/kg daily in Child-Pugh A. For all 34 patients, median TTP was 112 days and median OS was 295 days (95% CI, 182–333). A phase III study comparing linifanib with sorafenib should complete in the near future. Ramucirumab (IMC-1121B), a recombinant human monoclonal antibody against VEGFR-2, has been examined in a phase II study. This demonstrated a response rate (RR) of 10%, PFS of 4.0 months, and OS of 12.0 months in patients who have not received prior systemic therapy. Ramucirumab is undergoing phase III development in the second-line setting against placebo in patients where sorafenib failed.

Several other antiangiogenic agents are at early stages of clinical development in HCC. These include bevacizumab,29 cediranib, pazopanib, lenvatinib, and axitinib. The abundance of VEGF inhibitors that entered HCC clinical trials and the failure of sunitinib and brivanib in phase III trials have prompted us to reconsider the relevance of targeting VEGF receptors in HCC. The challenge of developing additional antiangiogenic agents in HCC is to understand the mechanisms of action and develop potential surrogate and predictive markers to identify patients likely to benefit from treatment. Although we aim to select the most potent inhibitors, the safety profiles of these agents including bleeding, thromboembolic events, skin rashes, and hypertension should be carefully evaluated.

### Epidermal Growth Factor Receptor (EGFR) Inhibitors

Increasing evidence has highlighted the importance of EGFR/HER1 and its ligands EGF and transforming growth factor-alpha (TGF-alpha) in hepatocarcinogenesis. The expression of several EGFR family members, specifically EGF, TGF-alpha, and heparin-binding–epidermal growth factor, as well as EGFR, has been described in several HCC cell lines and tissues. Multiple strategies to target EGFR signaling pathways have been developed, and two classes of anti-EGFR agents are tested in HCC: monoclonal antibodies that competitively inhibit extracellular endogenous ligand binding and small molecules that inhibit the intracellular tyrosine kinase (TK) domain. With the exception of erlotinib showing modest activity in single-arm studies, the other EGFR inhibitors (gefitinib, lapatinib, and cetuximab) have not demonstrated convincing antitumor activity as single agents. Only erlotinib is being examined in an ongoing phase III study in combination with sorafenib.

#### mTOR Inhibitors

Mammalian target of rapamycin (mTOR) functions to regulate protein translation, angiogenesis, and cell cycle progression in many cancers including HCC. Preclinical data have demonstrated that mTOR inhibitors were effective in inhibiting cell growth and tumor vascularity in HCC cell lines and HCC tumor models. Aberrant mTOR signaling was present in half of the HCC cases and correlated with HCC recurrence following resection.

A number of mTOR inhibitors (sirolimus, temsirolimus, and everolimus) are under clinical development in HCC. Early evidence of tolerability and efficacy has emerged from phase I and II studies with everolimus, which has led to the ongoing randomized phase III study comparing everolimus

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**Table 3. New Agents/Regimens under Development in Advanced Hepatocellular Carcinoma**

<table>
<thead>
<tr>
<th>Agents/Regimen</th>
<th>Phase III, first-line</th>
<th>Phase III, second-line</th>
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<tbody>
<tr>
<td><strong>Single-agent study:</strong></td>
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<tr>
<td>Antiangiogenic agents</td>
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<tr>
<td>Sunitinib, brivanib, bevacizumab, ramucirumab, TSU-68, linifanib, cediranib, pazopanib, lenvatinib, lenalidomide, and axitinib</td>
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<tr>
<td>Epidermal growth factor receptor inhibitors</td>
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<tr>
<td>Erlotinib, gefitinib, lapatinib, cetuximab</td>
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<td>MEK inhibitors</td>
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<tr>
<td>Selumetinib (AZD6244)</td>
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<tr>
<td>Histone deacetylase inhibitor</td>
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<td>Belinostat</td>
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<td>HSP-90 inhibitor</td>
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<tr>
<td>STA-9090</td>
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<tr>
<td>Combined targeted agents</td>
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<tr>
<td>Bevacizumab + erlotinib, sorafenib + everolimus, sorafenib + AZD6244, sorafenib + bevacizumab, sorafenib + temsirolimus, sorafenib and vorinostat, sorafenib + GC33, sorafenib + OSI-906</td>
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against placebo for patients who failed or could not tolerate sorafenib.

Hepatocyte Growth Factor (HGF)/c-Met Inhibitors

Dysregulation of c-Met is seen in HCC, and silencing the expression of c-Met inhibits HCC growth in HCC cell lines and tumor models. Tivantinib (ARQ197), a selective, non-ATP-competitive inhibitor targeting MET tyrosine kinase, is under early clinical evaluation. In a press release, tivantinib reportedly met the primary endpoint of improving TTP in a randomized phase II study comparing tivantinib with placebo in previously treated patients. Cabozantinib (XL184), a dual c-Met/VEGFR-2 inhibitor, also demonstrated early evidence of antitumor activity in a randomized discontinuation phase II study with a median PFS of 4.2 months.

MEK Inhibitors

HCC is characterized by frequent MEK/ERK activation in the absence of RAS or RAF mutation. A multicenter, single-arm study with a two-stage design was conducted using selumetinib (AZD6244), a specific inhibitor of MEK, in advanced HCC. The primary endpoint was RR. No radiographic responses were seen and TTP was only 8 weeks suggesting minimal single-agent activity despite evidence of inhibition of ERK phosphorylation.

Author’s Disclosures of Potential Conflicts of Interest

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Overview: Single-agent management of metastatic biliary tract cancers with 5-fluorouracil (5-FU) or gemcitabine has shown limited efficacy, although 5-FU has been shown to be more effective than best supportive care alone. An analysis of phase II trials has suggested that platinums enhanced the efficacy of single-agent fluoropyrimidines. In a phase III randomized trial comparing single-agent gemcitabine with gemcitabine plus cisplatin, the gemcitabine/cisplatin combination significantly improved median overall survival (OS) and progression-free survival (PFS), which established a new option for standard of care. However, the future of cancer medicine lies in newer, targeted agents. In the management of biliary tract cancers, preliminary evidence with epidermal growth factor receptor inhibitors has already demonstrated activity. This article reviews systemic therapies for metastatic biliary tract cancers as they relate to current and emerging standards of care.

Biliary Tract cancers consist of a somewhat heterogeneous group of tumors that include gallbladder cancer, extrahepatic biliary tract cancer, and intrahepatic cholangiocarcinoma. The exact incidence of each of these cancers is difficult to discern from annual cancer statistics because, for example, intrahepatic cholangiocarcinoma is still combined with hepatocellular carcinoma despite the fact that these are biologically distinct entities. In 2011, 9,250 new cases and 3,300 deaths from biliary tract cancers and gallbladder cancer (excluding intrahepatic cholangiocarcinoma) were anticipated. Cancers of the biliary tract are often found at late stages when resection is not feasible and treatment options are limited. Overall, 5-year survival rates are estimated to be approximately 15%.

Cytotoxic Chemotherapy

The systemic treatment of biliary tract cancers has largely been based on cytotoxic chemotherapy. Data comparing 5-FU–based chemotherapy with best supportive care demonstrated that median survival times are significantly prolonged (6.0 months vs. 2.5 months) with treatment. In addition, the time before declines in quality of life was prolonged with 5-FU–based chemotherapy. Rates of response to either single-agent 5-FU or 5-FU with leucovorin range up to approximately 20% with survival times up to 8 months. Similarly, single-agent gemcitabine has been explored as an alternative treatment option for biliary tract cancers. Response rates for single-agent gemcitabine have ranged from 16% to 36% and survival times from 6 months to 16 months. Phase II study of combinations of gemcitabine with either 5-FU or its oral prodrug, capecitabine, has not clearly improved on the results of single-agent phase II data. The most promising results came from the combination of gemcitabine and capecitabine with a response rate of 31% in 45 patients and an OS of 14 months.

However, studies combining 5-FU or gemcitabine with platinums have yielded very promising response rates. Therefore, a study was undertaken to evaluate the effects of gemcitabine plus cisplatin compared to gemcitabine alone. This study had an initial randomized phase II portion (ABC-01) and, when its endpoints were met, the trial proceeded to phase III (ABC-02). The ABC-02 trial demonstrated a significant benefit in both response rate and PFS favoring the gemcitabine/cisplatin arm. Most importantly, OS increased from 8.1 months for those treated with single-agent gemcitabine to 11.7 months for those treated with gemcitabine/cisplatin. These results have established the standard of care for biliary tract cancers at the current time.

KEY POINTS

- Single-agent management of advanced biliary cancers with 5-fluorouracil or gemcitabine yields short survival times.
- Adding cisplatin to gemcitabine significantly improves progression-free survival and overall survival for patients with biliary tract cancers.
- Targeted therapies are being evaluated in patients with biliary tract cancers, showing some preliminary evidence of activity for epidermal growth factor receptor inhibition.

Targeted Agents

Because of the limited likelihood that cytotoxic therapy will substantially change the natural history of biliary tract cancers, investigation is now focusing on the use of targeted agents. One of the first agents studied in biliary tract cancers was erlotinib, an oral tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR). EGFR is overexpressed in most biliary tract cancers. In a single-agent, multi-institutional study, erlotinib produced rare responses (8%) in 42 patients. Although the median time to tumor progression was only 2.6 months, 17% of patients were progression-free at 6 months and OS was 7.5 months. Because adding EGFR inhibition to chemotherapy has worked in other diseases such as colorectal cancer, investigators have added cetuximab to gemcitabine and oxaliplatin in a phase II study. A small randomized trial comparing the combination of gemcitabine plus oxaliplatin with gemcitabine/oxaliplatin plus erlotinib has been reported. In the 133 randomly assigned patients, there was a trend toward a PFS benefit from adding erlotinib, but OS was identical for both arms at 9.5 months. However, the EGFR pathway is actually a complex network and has interactions with several other pathways. Others have tried...
to optimize the use of erlotinib by adding other targeted agents. One phase II study of combined EGFR and vascular endothelial growth factor inhibition with erlotinib and bevacizumab showed promising results. In 53 patients, six (12%) patients had confirmed partial responses. Median time to progression was 4.4 months and OS was 9.9 months. Other investigators have evaluated targeting different proteins downstream of EGFR for better results. Some evidence of activity has been seen with MEK inhibition and biliary tract cancers. However, better understanding of these pathways in biliary tract cancer will help us to better use the new, targeted therapies for patients with biliary tract cancers.

**Conclusion**

Management of biliary tract cancers has previously been limited to fluoropyrimidines; however, over the last several years, new two-drug combinations have been developed with evidence of better activity than single-agent regimens. Although gemcitabine/cisplatin have been established as a standard option for these cancers, other two-drug regimens appear to have similar results. Now that the era of targeted agents for biliary tract cancers is starting, it is important that we improve our understanding of the biology of the disease and how best to use these new classes of agents to improve the outcomes for patients with these deadly diseases.

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