The Oncologist®

Challenging Cases

The Controversial Role of Chemoradiation for Patients With Locally Advanced Pancreatic Cancer

Presentation of the Case

A 58-year-old woman presents with 2 months of back discomfort. Abdominal computed tomography reveals a 5-cm mass in the body of the pancreas with no obvious metastatic disease. The tumor surrounds the celiac artery, and the superior mesenteric vein is obliterated. Endoscopic ultrasound-guided fine needle aspiration shows adenocarcinoma, positive cytokeratin 7, positive carbohydrate antigen 19–9, and negative cytokeratin 20. She receives 4 months of FOLFIRINOX, with resolution of symptoms and a reduction in the size of the tumor, but the tumor continues to demonstrate superior mesenteric artery encasement and superior mesenteric vein obliteration. Should this patient continue chemotherapy or initiate chemoradiation at this juncture? ***The Oncologist*** 2013;18:981–985

Pro

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Unquestionably, the role of radiation therapy for pancreatic cancer has been one of the most controversial topics in gastrointestinal oncology. At the crux of the debate lies the following question: Is there a role for localized therapy, specifically radiation therapy, in locally advanced pancreatic cancer, given its proclivity for systemic spread? Or is the cat, as they say, already out of the bag? Locally advanced pancreatic cancer is considered to be on a spectrum of metastatic disease, as demonstrated by the myriad of clinical trials that include both metastatic and locally advanced disease.

Among the approximately one-third of pancreatic cancer patients who present with localized yet unresectable disease, the role of radiation therapy has been poorly defined to date. Historically, because of the localized presentation and the lack of effective chemotherapy regimens for patients with locally advanced pancreatic cancer, chemoradiation has been considered a reasonable treatment option. Early promising phase III studies demonstrated an improvement in overall survival (OS) with chemoradiation when compared with best supportive care [1] and chemotherapy alone [2], although this benefit was not uniformly demonstrated [3]. In addition, without a surgical option, chemoradiation offered the potential for significant tumor shrinkage away from key blood vessels, allowing conversion to surgical resectability. Based on this rationale, chemoradiation was long considered a mainstay of therapy for locally advanced pancreatic cancer.

Con

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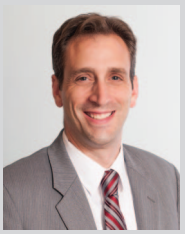

Jason E. Faris

Locally advanced pancreatic cancer, characterized by invasion or significant encasement of critical adjacent arterial and/or venous structures, constitutes one of the most common presentations of the disease, and approximately one-third of patients present with unresectable disease. The survival of patients with locally advanced pancreatic cancer is poor, with survival of a year or less in most series. The ideal treatment paradigm for these patients has been and remains the subject of great debate. Options include chemotherapy alone or chemotherapy and radiation in some combination.

Multiple clinical trials have attempted to clarify the best treatment for these patients. Two randomized studies have evaluated the addition of 5-fluorouracil (5-FU) to radiotherapy versus radiotherapy alone: One demonstrated an overall survival (OS) benefit [1], and the other showed a nonstatistically significant improvement in median OS [2]. A meta-analysis supported the superiority of chemoradiation over radiation alone [3]. Two subsequent randomized studies reached disparate conclusions about the value of chemoradiation followed by maintenance chemotherapy versus chemotherapy alone. A Gastrointestinal Tumors Study Group trial supported a survival benefit with the use of chemoradiation with 5-FU, followed by chemotherapy with streptozocin, mitomycin, and 5-FU [4]. An Eastern Cooperative Oncology Group trial found equivalent survival between chemotherapy versus chemoradiation, both with 5-FU monotherapy [5]. Because both trials were small (both $<$100 patients) and neither

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More recently, with a greater appreciation of the systemic nature of pancreatic cancer, many have argued the lack of benefit from radiation therapy. Because of the outdated imaging modalities, radiation techniques, and chemotherapy regimens used in earlier studies, the Fédération Francophone de Cancérologie Digestive and the Societé Française de Radiothérapie Oncologique sought to evaluate the benefit of induction chemoradiation in the modern treatment era. In this phase III study, patients were randomized to receive gemcitabine alone versus induction chemoradiation followed by maintenance gemcitabine. Radiation was prescribed to a total dose of 60 Gy in 2-Gy fractions and administered with concurrent cisplatin and 5-fluorouracil. Accrual for this study was stopped early after patients randomized to receive chemoradiation were found to have worse median survival. This study, however, has been highly criticized for the nonstandard regimen of concurrent cisplatin as a radiosensitizer and the higher doses of radiation, which likely increased treatment-related toxicity and inability to receive planned gemcitabine maintenance chemotherapy [4]. Nevertheless, this study definitively established the importance of treatment with induction chemotherapy prior to consideration of consolidative chemoradiation. In addition, the radiographic response of the primary tumor to chemoradiation was disappointing and further dampened enthusiasm for induction chemoradiation. Given the dense desmoplastic reaction generated by the primary tumor, significant tumor shrinkage and conversion to surgical resectability with chemoradiation alone are uncommon.

Building on the results of the study by the Fédération Francophone de Cancérologie Digestive and the Societé Française de Radiothérapie Oncologique, the Groupe Coopérateur Multidisciplinaire en Oncologie performed a retrospective analysis of prospective phase II/III studies evaluating the potential benefit of consolidative chemoradiation after 3 months of induction chemotherapy. This study highlighted that 30% of patients with locally advanced pancreatic cancer develop metastatic disease within the first 3 months of starting chemotherapy. Arguably, the 30% of patients with occult metastatic disease at presentation would not only fail to realize a benefit from localized radiation therapy but also would be exposed to radiation side effects. This study, however, also suggested that among patients who had controlled disease after 3 months of chemotherapy, patients may experience improved outcomes by switching to consolidative chemoradiation [5]. Consequently, delaying radiation therapy until after induction chemotherapy optimizes systemic disease control, selects for patients with localized disease who respond to chemotherapy, and exposes only patients who may potentially benefit from radiation to radiation-related side effects.

Based on the aforementioned study, the Groupe Coopérateur Multidisciplinaire en Oncologie recently presented final results for LAP 07, a randomized phase III study evaluating the benefit of consolidative chemoradiation after induction chemotherapy. In this study, patients with locally advanced pancreatic cancer were initially randomly assigned to gemcitabine or gemcitabine plus erlotinib. All patients with controlled disease on restaging scans after 4 months of therapy were subsequently assigned randomly to receive either chemoradiation or an additional 2 months of chemotherapy. Of the 442 patients randomly assigned, 269 patients (61%) trial used gemcitabine, the soon-to-be-adopted standard of care for metastatic disease, more recent studies examining the roles of chemotherapy versus chemoradiation have been performed, again with conflicting results.

In the Fédération Francophone de Cancérologie Digestive and Societé Française de Radiothérapie Oncologique trial, gemcitabine alone was superior to chemoradiation with 5-FU and cisplatin followed by gemcitabine (13 months vs. 8.6 months; $p = .03$) [6], whereas the Eastern Cooperative Oncology Group 4201 trial demonstrated improved survival with gemcitabine-based chemoradiation followed by gemcitabine compared with gemcitabine alone (11 months vs. 9.2 months; $p = .044$) [7]. Both trials were characterized by poor accrual and demonstrated higher grade 3–4 [6] or grade 4–5 [7] toxicities in the radiation arms. To summarize these randomized data, obtained from 1981 to 2008, radiation with chemotherapy appears to be superior to radiotherapy alone, and there is no consensus on the superiority of chemotherapy versus chemoradiation, with a potentially important toxicity signal with the use of chemoradiation.

If the story ended with the cited studies, few would favor moving to chemoradiation in our patient's case, at least with regard to OS; however, there is a compelling but hypothetical rationale for induction chemotherapy followed by chemoradiation that was not studied in any of the cited trials. This rationale involves obtaining control of micrometastatic disease with systemic chemotherapy and using subsequent chemoradiation for those demonstrating disease control. The argument posits that a switch to chemoradiation after initial chemotherapy in these patients would permit improved local control, and might do so without mitigating the micrometastatic control achieved by initial chemotherapy. There are promising survival data compared with chemotherapy alone in retrospective series, in which patients completing induction chemotherapy for at least 3 months with no metastases were randomized to chemoradiation or continued chemotherapy. The median survival favored chemoradiation over chemotherapy (15 months vs. 11.7 months) [8]. In another retrospective analysis, patients were treated initially with chemoradiation or chemotherapy followed by chemoradiation. The induction chemotherapy arm demonstrated improved median OS of 11.9 months compared with no induction chemotherapy [9]. This latter study did not include a review of patients who did not receive chemoradiation. Several small phase II trials have demonstrated survival of 9.6–17 months with induction chemotherapy followed by radiation [10].

The rationale for induction chemotherapy followed by chemoradiation is compelling, and the data from retrospective analyses and phase II trials are promising; however, until this year, there were no data from randomized phase III studies examining induction chemotherapy followed by chemoradiation versus chemotherapy alone. At the American Society of Clinical Oncology meeting in June 2013, the results of a randomized multicenter trial addressing this issue were presented. In the LAP 07 trial, 442 patients with locally advanced pancreatic cancer and a performance status of 0–2 were randomized to gemcitabine or gemcitabine with erlotinib [11]. Patients with stable disease or better after 4 months ($n = 269$) were then randomized to continued chemotherapy for 2

entered the second randomization. With a median follow-up of 36 months, the study was stopped because of futility. With a median OS of 16.4 months in the chemotherapy alone arm and 15.2 months in the chemoradiation arm, there was no difference in OS [6]. Undoubtedly, the results of LAP 07 have further fueled the debate of the questionable benefit of chemoradiation for locally advanced pancreatic cancer.

Given all of the mounting data for chemotherapy alone, how can one still argue the benefits of chemoradiation?

With emerging appreciation of prognostic and predictive biomarkers, a recent landmark study by Iacobuzio-Donahue et al. identified SMAD4, a tumor suppressor, as a potential predictor of local versus distant progression [7]. In this rapid autopsy series, 16 of 22 patients (73%) who were diagnosed with early resected pancreatic cancer were found to have a component of local persistence or progression at the time of autopsy. Only 4 of 22 patients died of metastatic disease without evidence of local persistence [7]. In addition, all patients diagnosed with locally advanced pancreatic cancer who were treated without surgery were found to have persistent or progressive local disease at autopsy. Of note, 28% of those patients died with only local disease and without evidence of distant spread. When evaluating by SMAD4 status, the investigators found a striking correlation between SMAD4 status and patterns of failure. Patients with intact SMAD4 were significantly more likely to present with locally destructive disease compared with patients with loss of SMAD4 immunostaining. This correlation between SMAD4 and pattern of disease spread has been validated independently at the M.D. Anderson Cancer Center in a phase II study of cetuximab, gemcitabine, and oxaliplatin followed by chemoradiation with cetuximab for locally advanced pancreatic cancer. In this study, of 41 patients with adequate tumor specimens for immunostaining, the dominant pattern of progression determined from clinical and radiographic data was local in 15, distant in 14, and indeterminate in 8. Eleven of 15 patients (73.3%) with intact *SMAD4 (also known as DPC4*) expression had a local dominant pattern of progression, and 10 of 14 patients (71.4%) with *SMAD4* loss had a distant dominant pattern of spread ($p = .016$) [8]. Taken together, these studies suggest that there may be a subgroup of patients with SMAD4-intact disease who may benefit from locally aggressive therapy.

Although an initial report of LAP 07 suggests no survival benefit with chemoradiation [6], final results of the recently published Eastern Cooperative Oncology Group 4201 study reported conflicting results [9]. In this phase III study, 74 patients were randomized to receive gemcitabine alone or gemcitabine-based chemoradiation. Although the study closed early because of slow accrual, chemoradiation was associated with significantly improved median survival from 9.2 months in the chemotherapy alone arm to 11.1 months with chemoradiation ($p = .017$). Final publication of LAP 07 is awaited to further elucidate whether there may be patient subgroups, such as patients with intact SMAD4, that may benefit from chemoradiation with respect to improvement in survival outcomes or even secondary endpoints, such as symptomatic improvement, quality of life, or time off chemotherapy. In addition, extrapolating from the Radiation Therapy Oncology Group 97–04 trial, it will be crucial to perform secondary

months versus capecitabine-based chemoradiation to 54 Gy. The primary endpoint of the trial was OS, and the trial was stopped after a 3-year interim analysis demonstrated futility for superiority of chemoradiation. There was no statistically significant difference between OS or progression-free survival (PFS) for the chemotherapy and chemoradiation arms (OS: 16.4 months vs. 15.2 months, respectively [$p = .83$]; PFS: 11.8 months vs. 12.5 months, respectively [$p = .22$]).

We eagerly await the formal publication of these data, particularly with regard to subgroups of patients that may have benefited from chemoradiation [11]. An important limitation was the choice of chemotherapy used in this trial because neither of the upfront chemotherapy regimens involved the most active regimens used in the metastatic setting: (a) FOLFIRINOX [12] and (b) gemcitabine with nab-paclitaxel [13]. With a more active regimen such as FOLFIRINOX, which has not been studied in a randomized setting for patients with locally advanced pancreatic cancer, a benefit may have been observed with chemoradiation after improved disease control. Moreover, it is possible that patients receiving FOLFIRINOX and subsequent chemoradiation may have had a response significant enough to justify surgical exploration and subsequent resection, a "conversion" scenario, which has been observed in several uncontrolled series [14, 15]; however, the requirement for chemoradiation in the conversion scenario is unproven. For patients who are still unable to undergo resection after completing chemotherapy and subsequent chemoradiation and for those patients who are fortunate enough to undergo resection but who subsequently recur, the use of chemoradiation could make eventual return to systemic chemotherapy more challenging. This concern is substantiated in small studies using chemotherapy after initial chemoradiation [16, 17].

Certainly one provisional conclusion we can draw from the LAP 07 study is that the upper range of "better" outcomes for patients with locally advanced pancreatic cancer detailed in prior nonrandomized studies with chemoradiation appear to be attainable without the use of chemoradiation [11]. Caution is warranted in the absence of randomized data demonstrating an OS or PFS benefit for chemoradiation and, now, in the presence of yet-to-be-published randomized data indicating a lack of benefit with chemoradiation in patients with controlled disease after initial chemotherapy. This caution is particularly warranted for a therapy that may compromise the ability to deliver continued control of distant metastatic disease. Continuation of chemotherapy in an initially chemoresponsive patient is the standard treatment option and could conceivably result in prolonged stable disease or even conversions to surgical resectability in subsets of patients.

The ideal method to resolve the controversy regarding the use of chemoradiation would be to perform a trial similar to LAP 07 with patients with good performance status treated with FOLFIRINOX. Those patients with stable disease or better after an initial period of induction chemotherapy would be randomized to chemoradiation or continued chemotherapy with FOLFIRINOX. In the meantime, the decision to use chemoradiation in a patient with locally advanced disease who has demonstrated disease control on upfront chemotherapy should proceed on an ad hoc basis. For those patients who have disease control and active tumor reduction on initial chemotherapy, it would be reasonable to continue chemo-

analysis based on quality assurance of radiation treatment fields [10].

In the last 3 years, great strides have been made in finding new, effective, multidrug combinations. The ACCORD/PRODIGE study established FOLFIRINOX as the most effective regimen in pancreatic cancer to date, with an improvement in median OS from 6.8 months with gemcitabine alone to 11.1 months among patients with metastatic disease [11]. With reported objective response rates in the metastatic setting of 31.6%, this aggressive and effective regimen has been moved increasingly to the locally advanced setting in an attempt to maximize conversion to surgical resectability. Our recent series of neoadjuvant FOLFIRINOX at Massachusetts General Hospital demonstrated an overall response rate of 27.3%, with 5 of 22 patients (22%) achieving R0 resection following neoadjuvant FOLFIRINOX and chemoradiation [12]. In the era of FOLFIRINOX and now gemcitabine plus abraxane, with improved systemic therapy, the importance of local therapy has the potential to be realized.

Along these lines, the Radiation Therapy Oncology Group has launched RTOG 1201, a randomized phase II trial evaluating the benefit of both intensified chemoradiation and intensified chemotherapy in patients with locally advanced, unresectable pancreatic cancer. Patients will be stratified by carbohydrate antigen 19–9 level and SMAD4 status and then randomized to (a) arm 1, with gemcitabine for 12 weeks followed by intensity-modulated radiation therapy to 63 Gy, given with concurrent capecitabine; (b) Arm 2, with gemcitabine for 12 weeks followed by three-dimensional conformal radiation therapy to 50.4 Gy with concurrent capecitabine; or (c) Arm 3, with FOLFIRINOX for 12 weeks followed by three-dimensional conformal radiation therapy to 50.4 Gy with concurrent capecitabine. Similarly, the proposed ALLIANCE/Eastern Cooperative Oncology Group phase II study proposes eight cycles of FOLFIRINOX, followed by randomization to receive either an additional four cycles of FOLFIRINOX or chemoradiation with concurrent capecitabine. These two studies will hopefully further elucidate the role of chemoradiation with high-dose radiation and intensified systemic therapy. For now, based on the LAP 07 data, I agree with Dr. Faris that for patients responding to chemotherapy, continuation of chemotherapy is a reasonable option. For patients with localized disease who have difficulty tolerating chemotherapy, patients experiencing symptoms from their primary tumor, or patients who may be considered for surgical exploration, I would recommend consolidative chemoradiation to optimize local tumor control and surgical resectability.

Disclosures

The author indicated no financial relationships.

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therapy if side effects are not limiting. In those experiencing significant side effects from the chemotherapy but still without metastatic disease or in those patients with complications from local tumor (e.g., abdominal pain or biliary/duodenal obstruction), a change to chemoradiation in the hope of achieving further stable disease may be warranted.

Although I do refer many patients with locally advanced pancreatic cancer for chemoradiation after stability or improvement on scans following initial chemotherapy, at this juncture, I do not regard chemoradiation to be the standard of care after initial chemotherapy. We must obtain data from an optimally designed, randomized phase III trial before using an across-the-board approach with potential toxicities and implications for systemic therapy in our treatment of patients with locally advanced pancreatic cancer.

Disclosures

Jason Faris: N-of-One (C/A); Exelixis, Novartis, Genentech, Millenium (RF).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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