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Evaluation of predictive variables in locally advanced pancreatic adenocarcinoma patients receiving definitive chemoradiation

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Abstract

Purpose—To analyze a single-center experience with locally advanced pancreatic cancer (LAPC) patients treated with chemoradiation (CRT) and to evaluate predictive variables of outcome.

Methods and Materials—LAPC patients at our institution between 1997 and 2009 were identified (n = 109). Progression-free survival (PFS) and overall survival (OS) were assessed using Kaplan-Meier analysis. Cox proportional hazard models were used to evaluate predictive factors for survival. Patterns of failure were characterized, and associations between local progression and distant metastasis were explored.

Results—Median OS was 12.1 months (2.5–34.7 months) and median PFS was 6.7 months (1.1–34.7 months). Poor prognostic factors for OS include Karnofsky performance status ≥ 80 ($P = .0062$), treatment interruption ($P = .0474$), and locally progressive disease at time of first post-therapy imaging ($P = .0078$). Karnofsky performance status ≥ 80 ($P = .0128$), pretreatment CA19-9 > 1000 U/mL ($P = .0224$), and treatment interruption ($P = .0009$) were poor prognostic factors for PFS. Both local progression (36%) and distant failure (62%) were common. Local progression was associated with a higher incidence of metastasis ($P < .0001$) and decreased time to metastasis ($P < .0001$).

Conclusions—LAPC patients who suffer local progression following definitive CRT may experience inferior OS and increased risk of metastasis, warranting efforts to improve control of local disease. However, patients with poor pretreatment performance status, elevated CA19-9 levels, and treatment interruptions may experience poor outcomes despite aggressive management with CRT, and may optimally be treated with induction chemotherapy or supportive care. Novel

therapies aimed at controlling both local and systemic progression are needed for patients with LAPC.

Introduction

In 2010, there were an estimated 43,140 cases of pancreatic adenocarcinoma diagnosed in the United States.¹ Although surgery remains the only curative treatment, 10%–20% of patients present with resectable disease, and patients who successfully undergo margin negative resection only achieve 5-year survival rates of 15%–25%.^{2–5} Unfortunately, more than half of all patients with pancreatic cancer have evidence of metastatic spread at initial presentation.^{2–4} The remaining patients present without distant disease but have locally advanced pancreatic cancer (LAPC) preventing surgical resection.³ Typically, patients with locally advanced or metastatic pancreatic cancer are not curable, and a treatment regimen that balances disease control, toxicity, and quality of life is paramount.

In the United States, many institutions have treated LAPC with chemoradiation (CRT) based on 2 reports by the Gastrointestinal Tumor Study Group showing improved survival with 5-fluorouracil (5-FU) based CRT over chemotherapy or radiotherapy alone.^{6,7} However, critics of this approach have cited an Eastern Cooperation Oncology Group (ECOG) trial, which found no difference in survival between 5-FU based CRT and 5-FU alone and a significantly higher rate of toxicity in the CRT arm.¹ More recently, investigators have explored the use of gemcitabine because of its efficacy in the metastatic setting and radiobiological evidence of potent radiosensitization.^{8,9} Nevertheless, studies comparing gemcitabine-based CRT with gemcitabine alone continue to produce mixed outcomes.^{10,11}

Given the variable and often conflicting results in patients with LAPC, the delivery of radiation in this population continues to be controversial. Standard therapy includes a total radiation dose of 50–54 Gy with concurrent chemotherapy, but some radiotherapy regimens can be delivered over shorter intervals.² While different approaches exist for LAPC, a framework for predicting which patients are likely to benefit is lacking because only a few reports have explored prognostic factors in this population.^{1,2,12,13} The purpose of the current study, therefore, is to review a modern large single-center experience with LAPC, identify which prognostic factors influence outcomes, and determine which patients are most likely to benefit from combined modality CRT.

Methods and materials

Study design and participants

After obtaining permission from our institution's Institutional Review Board, the records of all pancreatic cancer patients treated at our institution between 1997 and 2009 were reviewed to identify patients with LAPC treated with radiation. LAPC was defined as primary pancreatic lesions deemed to be unresectable based on preoperative cross-sectional imaging or on findings at the time of surgical exploration. Patients with encasement of the superior mesenteric artery or celiac artery, occlusion of the superior mesenteric vein or portal vein, invasion of the aorta or inferior vena cava, or superior mesenteric vein invasion below the transverse mesocolon were considered unresectable. Patients with metastatic disease, including celiac-para-aortic lymph node involvement, were excluded from this analysis, as were patients who received palliative radiation. The final study population consisted of 109 patients with LAPC.

Pretreatment work-up included a complete history and physical exam, routine laboratory tests including CA19-9 level, review of pathology, and an abdominal pancreas protocol computed tomography (CT) scan with intravenous and oral contrast. Radiation was most

commonly delivered with a 3–5 field conformal technique (70%), although intensity modulated radiation therapy (IMRT) was used in 30% of patients. Median radiation dose was 5040 cGy (range, 1400–5400 cGy) in 180 cGy (range, 180–300 cGy) fractions. Prior to 2006, treatment fields for 5-FU based CRT at our institution typically included the primary tumor and regional lymph nodes. More recently (2006), our target volumes have consisted of the primary tumor with a 2–3 cm margin using IMRT or 3-dimensional conformal radiation based on tumor motion and set up error. Target volumes for gemcitabine-based CRT at our institution have also encompassed gross disease with up to a 3-cm margin. The most commonly used concurrent chemotherapeutic agent was 5-FU (68%) followed by gemcitabine (18%). 5-FU was typically administered as a continuous infusion at 225 mg/m² per day or as a bolus given for 5 consecutive days at both the beginning and end of radiation therapy, while capecitabine was generally prescribed at 800–1000 mg/m² twice per day, Monday through Friday. Of those patients receiving 5-FU based CRT, 7 required a reduction in chemotherapy dose. Alternately, gemcitabine was administered weekly at dose levels between 300 and 600 mg/m² depending on performance status and presence of cytopenia, although 2 patients received gemcitabine at a dose level of 75 mg/m² in combination with paclitaxel. Of those patients treated with gemcitabine-based CRT, 2 required a dose reduction during treatment. Induction chemotherapy was given to 5 patients, of whom 4 received gemcitabine and 1 received 5-FU.

Potential prognostic factors were selected based on previously published reports. In constructing dichotomous variables, thresholds were defined in accordance with the literature.^{1,2,12,13} Patient-specific variables included age and weight loss along with pre-treatment Karnofsky performance status (KPS), hemoglobin level, and CA19-9 level. In those patients for whom KPS was not prospectively recorded, other documented performance status (ECOG) was used to estimate KPS when possible.¹⁴ Tumor-specific variables consisted of size and location of the pancreatic tumor. There was insufficient data on tumor differentiation for formal analysis. Treatment-related factors included administration of induction chemotherapy, type of concurrent chemotherapy, palliative procedure type, radiation dose, and treatment interruption, due to either treatment-related toxicity or planned split-course radiation. Additionally, disease progression was evaluated at each imaging assessment using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1. Progressive disease was subclassified as local progression (LP) or distant metastasis (DM), with LP defined as progressive disease within the primary tumor or regional lymph nodes. Median time to first CT scan after completion of treatment was 30 days (range, 2–110 days). Scans were generally obtained every 3 months thereafter.

The primary endpoints of this study were overall survival (OS) and progression-free survival (PFS). OS and PFS were calculated from date of diagnosis and characterized using Kaplan-Meier techniques. Each potential prognostic factor was examined individually using Cox proportional hazard models. Factors found to be statistically significant were considered in the multivariable analysis along with any other plausible cofactors. Additionally, patterns of failure were tracked, and freedom from local progression (FFLP), time to local progression (TLP), and time to metastasis (TTM) were computed. Both TLP and TTM were calculated from date of diagnosis. In order to capture when treatment was most likely to result in radiographic response, time to local response was calculated from the start date of radiation for patients who experienced either a complete response or partial response (PR). Statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, NC).

Results

Patient and treatment data are summarized in Table 1 and Table 2, respectively. Of the 109 patients, 61 (56%) were male. Median age was 61 years (range, 35–90 years). CRT was

interrupted in 44 patients (40%); of this group, 39 patients (89%) required a break due to treatment-related toxicity while the remaining 5 patients (11%) were on a protocol investigating the use of split-course radiation therapy. The most common treatment-limiting toxicities included emesis-diarrhea (28%), biliary obstruction (15%), sepsis-infection (10%), dehydration (10%), fatigue (8%), hematologic toxicity (8%), and intractable pain (5%). Toxicity grade was available in 85% of cases and included grade 2 (26%), grade 3 (51%), and grade 4 (8%) toxicities. There were no significant differences in toxicity between patients treated with gemcitabine- and 5-FU based CRT ($P = .6302$). Additionally, toxicity was not significantly different between patients who were treated with a conformal (3–5 field) technique and those who received IMRT ($P = .6470$).

At median follow-up of 11.4 months, 97 patients (88%) had died, 6 patients were alive, and 6 had been lost to follow-up. Deaths were attributed to disease progression, except in 2 patients who died of pneumonia and myocardial infarction, respectively. Among the 6 survivors, median follow-up was 15.9 months (range, 6.7–34.7 months). Median OS for the cohort was 12.1 months (range, 2.5–34.7 months) with 1-year and 2-year OS rates of 47% and 8%, respectively. Median PFS was 6.7 months (range, 1.1–34.7 months) with 1-year and 2-year PFS rates of 25% and 5%, respectively. Following CRT, surgical resection was attempted in 9 patients (8%), of whom 3 successfully underwent a margin negative pancreaticoduodenectomy. None of the patients who became eligible for a pancreaticoduodenectomy after CRT would have been initially considered resectable or borderline resectable based on standard criteria.³ Two of these patients survived for 18.6 months and 28.3 months, while the third is still alive at 20.3 months with no evidence of disease recurrence.

Table 3 summarizes patterns of local and distant failure in this cohort. LP was noted on follow-up imaging in 39 patients (36%). Notably, 20 patients (18%) showed radiographic evidence of LP without DM, of whom 6 patients never developed evidence of DM before the end of follow-up. FFLP at 1 year was 57%. Median TLP was 6.8 months (range, 2.2–30.0 months). There were 15 patients who had a PR with median OS of 13.2 months (range, 6.4–30.3 months). One patient experienced a complete response and survived for 18.8 months. Median time to local response was 6.7 months (range, 1.9–12.2 months). Evidence of DM was found in 68 patients (62%), of whom 35 (32%) showed no radiographic signs of LP before end of follow-up. Median TTM was 6.7 months (range, 1.6–28.0 months).

Univariate analyses

Table 4 summarizes the univariate analysis of potential prognostic factors for OS and PFS. Factors that were significantly associated with inferior OS included age >65 ($P = .0114$), KPS ≤ 80 ($P = .0008$), treatment break ($P = .0006$), or locally progressive disease, either at first post-therapy imaging ($P = .0261$) or at any point during follow-up ($P = .0223$). When local disease status at first post-therapy imaging was stratified by RECIST classification, patients with a PR ($P = .0266$) or stable disease ($P = .0089$) experienced significantly improved OS compared to patients with progressive disease. When patients with a PR were compared to patients with stable disease, there was no difference in OS ($P = .7058$). Additionally, after treatment break was stratified by cause of interruption, toxicity-related breaks ($n = 39$) remained significantly associated with OS ($P = .0021$). Unfavorable prognostic factors for PFS included KPS ≤ 80 ($P = .0056$), pretreatment CA19-9 level >1000 U/mL ($P = .0084$), and treatment break ($P = .0020$). When treatment break was stratified by cause of interruption, toxicity-related breaks remained significant ($P = .0140$).

Multivariable analyses

On multivariable analysis, poor prognostic factors for OS included KPS ≤ 80 (HR, 0.255–0.798, $P = .0062$), treatment break (HR, 1.006–2.795, $P = .0474$), and local progression at first post-therapy imaging ($P = .0290$). Age, pretreatment CA19-9, and palliative procedure type were not significant, including individual comparisons between palliative procedure types. Within local disease status at first post-therapy imaging, PR (HR, 0.159–1.095, $P = .0758$) and stable disease (HR, 0.173–0.766, $P = .0078$) trended toward significance or were significant when compared to progressive disease, but were not significant when compared to each other (HR, 0.566–2.327, $P = .7022$). KPS ≤ 80 (HR, 0.293 – 0.864, $P = .0128$), pretreatment CA19-9 >1000 U/mL (HR, 1.101–3.533, $P = .0224$), and treatment break (HR, 1.452–4.307, $P = .0009$) were all significantly associated with inferior PFS while age and palliative procedure type were not. These results are summarized in Table 5.

Local progression and distant failure

Given that local progression at first post-therapy imaging was a significant prognostic factor for overall survival, we wanted to explore this finding by evaluating whether LP was also a predictor of distant failure. Therefore, we conducted a multivariable analysis of TTM with LP defined as a time-dependent covariate. KPS >80 , pretreatment CA19-9, and treatment break were included as additional covariates in the Cox regression model. As summarized in Table 5, LP was significantly associated with decreased TTM (HR, 5.190–17.764, $P = .0001$). To better characterize the temporal link between LP and DM, we used the period incidence method to analyze the incidence of metastasis based on local disease status.⁴ Specifically, patients' follow-up was divided into 3-month intervals beginning 3 months after the date of diagnosis and excluding those patients who had not begun treatment by the interval start date. Local disease status was determined at the end of each interval, and the denominator was adjusted for censored patients during that period. Patients who were alive, free of metastasis, and with subsequent follow-up were eligible for analysis in the subsequent period. The Cochran-Mantel-Haenszel test was used to assess the overall association of local disease status with incidence of metastasis while the Fisher exact test was used to examine this relationship in individual periods. Despite a small cohort size, patients with LP experienced a significantly higher rate of metastasis (HR, 2.46–5.54, $P < .0001$), as illustrated in Table 6. When the period incidence of metastasis was reanalyzed from the start date of radiation in order to account for inter-patient variation between the date of diagnosis and the beginning of treatment, patients with LP continued to show a significantly higher rate of metastasis ($P < .0001$, complete analysis not shown).

Discussion

This review of our institution's experience with locally advanced pancreatic cancer was conducted to explore factors that affect OS and PFS and to identify which patients are most likely to benefit from CRT. In this cohort of patients, median OS and PFS were 12.1 and 6.7 months, respectively. Among variables that were analyzed as potential pretreatment prognostic factors based on previous experience in the literature, KPS >80 was independently associated with improved OS, while KPS >80 and baseline CA19-9 <1000 U/mL were independently associated with improved PFS. In considering treatment-related variables, treatment interruption was independently associated with inferior OS and PFS. Although the cause of interruptions was twofold, with some patients receiving split-course radiation as part of an institutional protocol, breaks were predominately reflective of treatment-related toxicity. Furthermore, local disease status based on RECIST criteria at first radiographic assessment following completion of therapy was an independent predictor of OS. Specifically, patients who were classified as having had a partial response or stable disease experienced improved OS compared to patients diagnosed with progressive disease.

Interestingly, outcomes were not significantly different between the partial response and stable disease subgroups. When we explored the mechanism of inferior survival in patients with local progression (LP), we determined that LP, defined as a time-dependent covariate, was the most significant predictor of TTM. Additionally, when the incidence of metastasis was analyzed in 3-month intervals and stratified by local disease status, patients without LP after CRT had significantly decreased rates of subsequent metastasis.

The optimal therapeutic regimen for patients with LAPC is a controversial issue. When considering this debate, it is important to recognize that LAPC likely encompasses heterogeneous patient and tumor populations with different responses to various treatment modalities such as CRT. Stratification of LAPC based on prognostic factors can help tailor treatment strategies and clinical trial designs in addition to providing more accurate estimates of prognosis. To date, there have been only 3 retrospective studies and 1 prospective trial that have identified prognostic factors for patients with LAPC treated with CRT, which are outlined in Table 7.^{1,2,12,13} Our study confirms 1 prior LAPC series suggesting the prognostic value of CA19-9, which has also been predictive of outcomes in the resectable and metastatic settings and may reflect overall disease burden or more malignant biology.^{13,15,16} In addition, we corroborate 2 previous reports indicating that KPS <80 is associated with inferior OS and PFS, which is consistent with the association between poor performance status and adverse prognosis across multiple cancers treated with definitive CRT.^{2,13,17,18} Our study also suggests an unfavorable prognosis in patients who require treatment interruption, emphasizing the importance of assessing patients' ability to tolerate CRT before proceeding with therapy. Taken together, these findings may support the use of less locally aggressive alternative strategies, such as chemotherapy alone or induction chemotherapy, in patients with elevated CA19-9 levels or whose poor performance status may limit their ability to complete combined modality therapy. In Europe, LAPC is commonly treated with chemotherapy alone based on the high rate of metastatic disease and the results of 2 ECOG studies which failed to demonstrate a difference in survival between CRT and chemotherapy alone, as well as a French trial suggesting inferior survival in its CRT arm.^{8,11,12} More recently, the use of induction chemotherapy to identify patients with subclinical systemic disease has gained favor.^{19,20}

Certainly, achieving better outcomes in pancreatic cancer will primarily be dependent on controlling the high rate of distant metastasis (DM). In our cohort, for example, the development of DM was far more common than LP, and patients predominately suffered from DM before or concurrently with LP. However, the potential contribution of local failure to distant disease should not be overlooked. In our investigation of this relationship, we found that LP, defined as a time dependent covariate, was the strongest predictor of subsequent metastasis, which our period incidence analysis also supported. The fact that 18% of patients showed evidence of LP without initial DM lends credence to this argument.

The poor prognosis of LP in our cohort highlights the value of pursuing more aggressive local therapies and radiation dose escalation for LAPC. Our findings are consistent with those of Murphy et al.,⁵ who similarly reported a significant association between FFLP and OS in LAPC patients treated with full-dose gemcitabine-based CRT. Moreover, autopsy series have shown that the proportion of patients who succumb to locally advanced disease without evidence of metastasis is significant at roughly 10%-15%.²¹ Unfortunately, with LP rates between 50%-70% in many LAPC trials, conventional radiation has largely been unsuccessful in managing local disease, principally a result of the limited normal tissue tolerance of nearby structures.^{7,22} Our cohort, for instance, experienced a suboptimal 1-year FFLP of 57%.

New technologies that may increase the precision of radiation treatments and thereby permit dose escalation have garnered considerable enthusiasm for improving local control. These include alternate methods for delivering radiation such as intensity modulated and stereotactic body radiation therapy,^{23–28} the combination of radiation with more aggressive chemotherapies and targeted agents,^{29,30} and the use of functional imaging, image guidance, and airway breathing control.^{31–33} In addition, identifying genetic subtypes of pancreatic cancer with locally aggressive, non-metastatic phenotypes may lead to a more tailored approach in applying local therapies.²³ Interestingly, a systemic regimen combining gemcitabine, docetaxel, and capecitabine has shown significant local activity, achieving a partial response in 6 out of 14 LAPC patients when used as induction therapy prior to gemcitabine-based CRT.³⁴ Given its apparent effect on the primary tumor, it may be beneficial to include combination chemotherapy either before or after CRT in an effort to improve both local and systemic control.

Proper interpretation of our results requires an appreciation of the study's limitations. Given its retrospective nature, the study is subject to potential selection biases and can only be considered exploratory in nature. The limitations of CT for determining treatment response should also be acknowledged. Although the role of functional imaging in pancreatic cancer is undefined, investigations of positron emission tomography (PET) imaging for monitoring tumor response to CRT have highlighted the complexity of distinguishing residual tumor from radiation changes using CT.³⁵ In our own cohort, 1 patient whose tumor was resected following CRT received PET imaging as part of the preoperative evaluation. While CT suggested residual encasement of the superior mesenteric artery after neoadjuvant therapy, a PET scan showed no abnormal uptake in the region, which was confirmed during surgery. Indeed, the difficulty of capturing treatment response on CT may explain why we found no difference in survival between those patients who had a partial response and those patients who appeared to have stable disease. Additionally, our cohort contains heterogeneity in the type of treatment fields that were used due to evolving practice patterns at our institution over time, and the number of patients in our study precluded meaningful analysis with respect to the significance of this variable. Furthermore, our findings should not be applied to borderline resectable disease, as these patients were not part of our study population and growing evidence suggests that aggressive neoadjuvant therapy may be particularly beneficial in this population.^{4,36}

Two statistical considerations should also be highlighted. First, while the strong association between LP and both TTM and incidence of metastasis supports a link between local and distant failure, it does not prove a causative relationship, and potential confounding factors must be acknowledged. Certainly, disease that is radio-resistant and has an increased tendency for metastatic spread could partially explain our results. Perhaps a more plausible explanation is that select pancreatic tumors may be resistant to both chemotherapy and radiation. Second, time intervals in our study were predominantly calculated from date of diagnosis as opposed to first day of treatment. We felt that date of diagnosis was more appropriate because response was predominately determined by radiographic comparison with baseline imaging, which was generally closer to the date of diagnosis than treatment start date. In recognizing these limitations, it is also important to appreciate that this study serves as one of the larger single-institution reviews of LAPC. These patients were treated in the modern era, and the majority received what is still thought to represent the standard treatment for locally advanced pancreatic cancer in 5-FU or gemcitabine-based conformal CRT.

Conclusions

In summary, pretreatment performance status and CA19-9 levels may serve as important prognostic factors for patients with LAPC treated with definitive CRT. In addition, patients who require treatment interruption due to toxicity may experience worse outcomes, emphasizing the importance of assessing the likelihood of treatment completion before initiating CRT. These patients may benefit from alternative approaches such as induction chemotherapy, chemotherapy alone, or supportive care. Furthermore, radiographic evidence of LP may predict distant failure, potentially providing a rationale for pursuing novel strategies to prevent local progression. Combination of radiation with more aggressive chemotherapeutic regimens (concurrently or sequentially) and novel targeted agents may also improve both local and distant progression.

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References

1. Klaassen DJ, MacIntyre JM, Catton GE, et al. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil—an Eastern Cooperative Oncology Group study. *J Clin Oncol.* 1985; 3:373–378.
2. Crane CH, Janjan NA, Evans DB, et al. Toxicity and efficacy of concurrent gemcitabine and radiotherapy for locally advanced pancreatic cancer. *Int J Pancreatol.* 2001; 29:9–18. [PubMed: 11560155]
3. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol.* 2009; 16:1727–1733.
4. Leibel SA, Scott CB, Mohiuddin M, et al. The effect of local-regional control on distant metastatic dissemination in carcinoma of the head and neck: results of the analysis from the RTOG head and neck database. *Int J Radiat Oncol Biol Phys.* 1991; 21:549–556.
5. Murphy JD, Adusumilli S, Griffith KA, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2007; 68:801–808. [PubMed: 17379445]
6. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: the Gastrointestinal Tumor Study Group. *Cancer.* 1981; 48:1705–1710. [PubMed: 7284971]
7. The Gastrointestinal Tumor Study Group. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. *J Natl Cancer Inst.* 1988; 80:751–755. [PubMed: 2898536]
8. Burris HA III, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol.* 1997; 15:2403–2413. [PubMed: 9196156]
9. Lawrence TS, Eisbruch A, Shewach DS. Gemcitabine-mediated radiosensitization. *Semin Oncol.* 1997; 24(S7):24–28.
10. Loehrer PJ, Powell ME, Cardenes HR, et al. A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer: E4201. [Abstract]. *J Clin Oncol.* 2008; 26(suppl):4506.
11. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000–01 FFCD/SFRO study. *Ann Oncol.* 2008; 19:1592–1599.

12. Ikeda M, Okada S, Tokuyue K, et al. Prognostic factors in patients with locally advanced pancreatic carcinoma receiving chemoradiotherapy. *Cancer*. 2001; 91:490–495. [PubMed: 11169931]
13. Huang PI, Chao Y, Li CP, et al. Efficacy and factors affecting outcome of gemcitabine concurrent chemoradiotherapy in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2009; 73:159–165. [PubMed: 18508203]
14. Clement M, Bandukwala S, Burman D, et al. Interconversion of three measures of performance status: an empirical analysis. *Eur J Cancer*. 2010; 46:3175–3183. [PubMed: 20674334]
15. Ishii H, Okada S, Nose H, et al. Prognostic factor in patients with advanced pancreatic cancer treated with systemic chemotherapy. *Pancreas*. 1996; 12:267–271. [PubMed: 8830333]
16. Lundin J, Roberts PJ, Kuusela P, et al. The prognostic value of preoperative serum levels of CA 19-9 and CEA in patients with pancreatic cancer. *Br J Cancer*. 1994; 69:515–519. [PubMed: 7510116]
17. Laws ER, Parney IF, Huang W, et al. Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. *J Neurosurg*. 2003; 99:467–473. [PubMed: 12959431]
18. Jeremic B, Milicic B, Dagovic A, et al. Pretreatment clinical prognostic factors in patients with stage IV non-small cell lung cancer (NSCLC) treated with chemotherapy. *J Cancer Res Clin Oncol*. 2003; 129:114–122. [PubMed: 12669236]
19. Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer*. 2007; 110:47–55.
20. Huguet F, Andre T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol*. 2007; 25:326–331. [PubMed: 17235048]
21. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol*. 2009; 27:1806–1813. [PubMed: 19273710]
22. Whittington R, Solin L, Mohiuddin M, et al. Multimodality therapy of unresectable pancreatic adenocarcinoma. *Cancer*. 1984; 54:1991–1998. [PubMed: 6478433]
23. Ben-Josef E, Shields AF, Vaishampayan U, et al. Intensity modulated radiation therapy (IMRT) and concurrent capecitabine for pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2004; 59:454–459. [PubMed: 15145162]
24. Yovino S, Poppe M, Jabbour S, et al. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. *Int J Radiat Oncol Biol Phys*. 2011; 79:158–162. [PubMed: 20399035]
25. Willett C, DelCastillo F, Goldberg S, et al. Long-term results of intraoperative electron beam radiation therapy for unresectable pancreatic cancer. *Ann Surg*. 2005; 241:295–299. [PubMed: 15650640]
26. Koong AC, Christofferson E, Le QT, et al. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2005; 63:320–323. [PubMed: 16168826]
27. Schellenberg D, Goodman KA, Lee F, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2008; 72:678–686. [PubMed: 18395362]
28. Stanford University. clinicaltrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Phase II multi-institutional study to evaluate the efficacy of gemcitabine and fractionated stereotactic radiotherapy for unresectable pancreatic adenocarcinoma. [cited 2011 Jan 18]. Available at <http://clinicaltrials.gov/ct2/show/NCT01146054>. [NLM identifier: NCT01146054]
29. Munter M, Timke C, Abdollahi A, et al. Final results of phase II trial [PARC-Study ISRCTN56652283] for patients with primary inoperable locally advanced pancreatic cancer

- combining intensity modulated radiotherapy (IMRT) with cetuximab and gemcitabine. *J Clin Oncol.* 2008; 26:S4613.
30. Ma WW, Herman JM, Jimeno A, et al. A tolerability and pharmaco-kinetic study of adjuvant erlotinib and capecitabine with concurrent radiation in resected pancreatic cancer. *Transl Oncol.* 2010; 3:373–379. [PubMed: 21151476]
31. Goldstein SD, Ford EC, Duhon M, et al. Use of respiratory-correlated four dimensional computed tomography to determine acceptable treatment margins for locally advanced pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys.* 2010; 76:597–602. [PubMed: 19836156]
32. Parg WG, Yan BM, Schellenberg D, et al. EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer: 50 successful cases with fluoroscopy. *Gastrointest Endosc.* 2010; 71:513–518. [PubMed: 20189509]
33. Ford EC, Herman J, Yorke E, et al. 18F-FDG PET/CT for image-guided and intensity-modulated radiotherapy. *J Nucl Med.* 2009; 50:1655–1665. [PubMed: 19759099]
34. Fogelman DR, Schreiber S, Sherman W, et al. Neoadjuvant GTX and radiation for unresectable pancreatic cancer: A prospective phase II Trial. *Proc GI Am Soc Clin Oncol.* 2007 (Abstract 143).
35. Rose DM, Delbeke D, Beauchamp RD, et al. 18-Fluorodeoxyglucose positron emission tomography (18-FDG PET) in the management of patients with pancreatic cancer. *Ann Surg.* 1998; 229:1784–1792.
36. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol.* 2008; 26:3496–3502. [PubMed: 18640930]

Table 1

Patient characteristics

Characteristic	No. (%)
Age	
Median	61 y
Range	35–90 y
Gender	
Male	61 (56)
Female	48 (44)
Race	
Caucasian	81 (74)
African-American	22 (20)
Other	6 (6)
Karnofsky performance status	
80	23 (21)
>80	75 (69)
Indeterminate	11 (10)
Presenting symptoms	
Abdominal pain	88 (81)
Weight loss	81 (74)
Jaundice	56 (51)
Nausea/vomiting	32 (29)
Pruritis	16 (15)
Fevers/chills	6 (6)
GI bleed	4 (4)
Weight loss	
30 lbs	29 (27)
>30 lbs	69 (63)
Missing	11 (10)
Pretreatment CA19-9 (U/mL)	
1000	75 (69)
>1000	16 (15)
Missing	18 (17)
Hemoglobin (g/dL)	
12	53 (49)
>12	55 (50)
Missing	1 (1)
Albumin (g/dL)	
4	57 (52)
>4	50 (46)
Missing	2 (2)

Table 2**Tumor and treatment characteristics**

Characteristic	No. (%)
Tumor size (maximum diameter on CT)	
Median	3.8 cm
Range	1.3–8.0 cm
Tumor location	
Head	63 (58)
Other (body/tail)	46 (42)
Grade	
Poorly differentiated	23 (21)
Moderately differentiated	12 (11)
Well differentiated	5 (5)
Missing	69 (63)
Radiation dose	
5040 cGy	29 (27)
>5040 cGy	78 (72)
Missing	2 (2)
Beam arrangement	
3-field	18 (17)
4-field	43 (39)
5-field	3 (3)
IMRT	28 (26)
Missing	17 (16)
Induction chemotherapy	
Yes	5 (5)
Gemcitabine	4 (4)
5-FU	1 (1)
No	104 (95)
Concurrent chemotherapy	
5-FU based	73 (67)
Gemcitabine based	20 (18)
Paclitaxel	7 (7)
No chemo	7 (7)
Missing	2 (2)
Treatment break	
No break	65 (60)
Break	44 (40)
Toxicity break	39 (36)
Planned break	5 (4)
Palliative procedure	
Bypass	28 (26)

Characteristic	No. (%)
Stent	46 (42)
None	35 (32)

IMRT, intensity modulated radiation therapy.

Table 3

Patterns of failure

Site of progression	No. (%)
Any progression	74 (68)
Any local progression	39 (36)
Local w/ no distant	6 (6)
Local before distant	14 (13)
Local and distant concurrent	14 (13)
Local after distant	5 (5)
Any distant progression	68 (62)
Distant w/ no local	35 (32)
Distant before local	5 (5)
Distant and local concurrent	14 (13)
Distant after local	14 (13)

Table 4

Univariate analysis for overall survival and progression-free survival

Outcomes	P value	Hazard ratio
Overall survival		
Age >65 y	.0114	1.729
KPS >80	.0008	0.425
Weight loss >30 lbs	.4496	0.832
Hgb >12 g/dL	.5618	0.887
CA19-9 >1000 U/mL	.2552	1.378
Tumor size >3 cm	.8786	1.040
Pancreatic head involvement	.6266	1.107
Induction chemotherapy	.3439	0.573
5-FU vs gemcitabine (concurrent chemotherapy)	.1904	0.705
Treatment break	.0006	2.073
Toxicity break vs no break	.0021	1.955
Planned break vs no break	.2848	1.654
Palliative procedure	.1275	
Bypass vs none	.1481	0.667
Stent vs none	.6371	1.121
Stent vs bypass	.0400	1.680
Local disease status at 1st post-therapy imaging	.0261	
Partial response vs progressive disease	.0266	0.364
Stable disease vs progressive disease	.0089	0.415
Partial response vs stable disease	.7058	0.877
Best local response	.0223	
Partial response vs progressive disease	.0099	0.346
Stable disease vs progressive disease	.0115	0.425
Partial response vs stable disease	.4803	0.814
Progression-free survival		
Age >65 y	.0662	1.474
KPS >80	.0056	0.507
Weight loss >30 lbs	.6661	1.107
Hgb >12 g/dL	.7331	2.115
CA19-9 >1000 U/mL	.0084	2.115
Tumor size >3 cm	.3655	1.251
Pancreatic head involvement	.8779	1.031
Induction chemotherapy	.2107	0.527
5-FU vs gemcitabine (concurrent chemotherapy)	.6406	0.887
Treatment break	.0020	1.910
Toxicity break vs no break	.0140	1.680
Planned break vs no break	.0908	2.245
Palliative procedure	.3397	

Outcomes	<i>P</i> value	Hazard ratio
Bypass vs nothing	.1463	0.683
Stent vs nothing	.5790	0.878
Bypass vs stent	.3080	0.778

KPS, Karnofsky performance status; Hgb, hemoglobin.

Table 5

Multivariate analysis for overall survival, progression-free survival, and time to metastasis

Outcomes	P value	Hazard ratio (95% CI)
Overall survival		
KPS >80	.0062	0.451 (0.255–0.798)
Treatment break	.0474	1.677 (1.006–2.795)
Local disease status at first post-therapy imaging	.0290	
Partial response vs progressive disease	.0758	0.417 (0.159–1.095)
Stable disease vs progressive disease	.0078	0.364 (0.173–0.766)
Partial response vs stable disease	.7022	1.148 (0.566–2.327)
Progression-free survival		
KPS >80	.0128	0.503 (0.293–0.864)
CA 19-9 >1000 U/mL	.0224	1.972 (1.101–3.533)
Treatment break	.0009	2.501 (1.452–4.307)
Time to metastasis		
Local progression (time-dependent covariate)	<.0001	9.602 (5.190–17.764)
KPS >80	.0013	0.327 (0.165–0.646)
CA19-9 >1000 U/mL	.0382	2.050 (1.040–4.041)
Treatment break	.4418	1.293 (0.672–2.486)

CI, confidence interval; KPS, Karnofsky performance status.

Table 6

Period incidence analysis

Interval (mo)	Free of local progression	Local progression	P value
3–6	12/64 (18.8%)	8/14 (57.1%)	.0058
6–9	11/50 (22.0%)	9/12 (75.0%)	.0010
9–12	3/30 (10.0%)	3/6 (50.0%)	.0451
12–15	3/19 (15.8%)	4/7 (57.1%)	.0572
15–18	1/12 (8.3%)	1/4 (25.0%)	.4500
18–21	0/7 (0%)	2/2 (100.0%)	.0278
21–24	1/7 (14.3%)	0/0 (N/A)	N/A

N/A, not applicable.

Table 7

Prior studies identifying prognostic factors for locally advanced pancreatic cancer

Authors	Group / Institution	No. of Patients	Range of treatment dates	Treatment	Poor prognostic factors for OS	Poor prognostic factors for PFS
Klaassen et al ¹ (1985)	ECOG	91	1974–1984	5FU-based CRT, maintenance 5FU chemo	ECOG <2, Broder's grade <3, reduced appetite	Not performed
Ikeda et al ¹² (2001)	NCCH	55	1993–1998	5FU or cisplatin-based CRT	ECOG <2, CA19-9 >1000, regional node swelling	Not performed
Krishnan et al ¹⁹ (2007)	MDACC	247	1993–2005	5FU capecitabine, or gemcitabine-based CRT	KPS 80, Hgb <12	KPS 80
Huang et al ¹³ (2009)	NYMUSM	55	2002–2005	Gemcitabine-based CRT	KPS 80, CA19-9 >1000	KPS 80, CA19-9 >1000
Current study	JHU	109	1997–2009	5FU or gemcitabine-based CRT	KPS 80, treatment break, local disease status	KPS 80, CA19-9 >1000, treatment break

CRT, chemoradiation; ECOG, Eastern Cooperative Oncology Group; JHU, Johns Hopkins University; KPS, Karnofsky performance status; NCCHT, National Cancer Center Hospital of Tokyo; MDACC, M.D. Anderson Cancer Center; NYMUSM, National Yang-Ming University School of Medicine; PFS, progression-free survival; OS, overall survival.