Original Article

Updated Long-Term Outcomes and Prognostic Factors for Patients With Unresectable Locally Advanced Pancreatic Cancer Treated With Intraoperative Radiotherapy at the Massachusetts General Hospital, 1978 to 2010

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BACKGROUND: In the current study, the authors evaluated long-term outcomes, intraoperative radiotherapy (IORT)-related toxicity, and prognostic factors for overall survival (OS) among patients with unresectable locally advanced pancreatic cancer (LAPC) who received IORT as part of their treatment at the Massachusetts General Hospital (MGH). **METHODS:** Medical records were reviewed for 194 consecutive patients with unresectable LAPC who were treated with IORT at MGH between 1978 and 2010. OS was calculated using the Kaplan-Meier method. Prognostic factors were evaluated at the univariate level by the log-rank test and at the multivariate level by the Cox proportional hazards model. Rates of disease progression and treatment toxicity were calculated. **RESULTS:** The 1-year, 2-year, and 3-year survival rates were 49%, 16%, and 6%, respectively. Six patients (3%) survived for >5 years. The median OS was 12.0 months. Among 183 patients with known post-IORT disease status, the 2-year local progression-free survival and distant metastasis-free survival rates were 41% and 28%, respectively. On multivariate analysis, an IORT applicator diameter ≤ 8 cm (hazards ratio [HR], 0.51; 95% confidence interval [95% CI], 0.30-0.84 [$P=.009$]), a Charlson age-comorbidity index ≤ 3 (HR, 0.47; 95% CI, 0.31-0.73 [$P=.001$]), and receipt of chemotherapy (HR, 0.46; 95% CI, 0.33-0.66 [$P<.001$]) predicted improved OS. The median OS for patients with all 3 positive prognostic factors was 21.2 months. **CONCLUSIONS:** Well-selected patients with LAPC with small tumors and low Charlson age-comorbidity indices can achieve good long-term survival outcomes with a treatment regimen that incorporates chemotherapy and IORT. ***Cancer* 2013;000:000-000**. © *2013 American Cancer Society.*

KEYWORDS: pancreatic cancer, locally advanced, radiotherapy, chemotherapy, survival.

INTRODUCTION

Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death in the United States, curable only by surgical resection.[1] Approximately 30% of patients present with locally advanced pancreatic cancer (LAPC), defined as nonmetastatic localized cancer that is unresectable due to vascular invasion or occlusion.[2] Although current National Comprehensive Cancer Network guidelines recommend 5-fluorouracil (5-FU)-based or gemcitabine-based chemotherapy as first-line treatment for patients with LAPC, to the best of our knowledge the role of localized radiotherapy remains controversial.[3]

Since 1978, patients with LAPC with good performance status have been considered for consolidative intraoperative radiotherapy (IORT) at the Massachusetts General Hospital (MGH).[4] The goal of IORT is to improve local control by delivering high-dose radiation to the pancreatic bed with the surrounding normal tissue retracted and shielded. In 2005, Willett et al reported that among the first 150 patients with LAPC to receive IORT at MGH as part of their treatment, the 1-year, 2-year, and 3-year overall survival (OS) rates were 54%, 15%, and 7%, respectively. It is worth noting that 5 patients survived past 5 years, and an increased IORT applicator diameter (a tumor diameter surrogate) was found to be predictive of decreased OS.[5]

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The objective of the current study was to update our published experience of long-term outcomes to include 194 consecutive patients with LAPC who received IORT between 1978 and 2010. We also sought prognostic factors to aid in the selection of those patients most likely to achieve long-term survival with IORT.

MATERIALS AND METHODS

Patient Selection

The MGH Institutional Review Board approved the current study. We identified 194 consecutive patients with unresectable, nonmetastatic, histologically confirmed pancreatic adenocarcinoma who received IORT at MGH between August 1978 and April 2010. Patient charts were retrospectively reviewed to collect data regarding baseline demographics, tumor characteristics, pretreatment comorbidities, treatment regimens, disease progression, and IORT-related toxicities. Performance status, serum tumor marker values, and tumor stage were omitted from this analysis due to inconsistent reporting.

Initial Treatment

External-Beam Radiotherapy

The median external-beam radiotherapy (EBRT) dose was 49.6 grays (Gy) (range, 0 Gy-59.4 Gy). A total of 188 patients (97%) received pre-IORT EBRT. Before 1990, 68 of 83 patients (82%) received low-dose pre-IORT EBRT (at a dose of 10 Gy-20 Gy) with additional post-IORT EBRT (with or without concurrent radiosensitizing chemotherapy) to a total EBRT dose of up to 50.4 Gy. Since 1990, the majority of patients have received high-dose pre-IORT EBRT up to 50.4 Gy without post-IORT EBRT.

Since 1988, most patients receiving pre-IORT EBRT have received concurrent radiosensitizing continuous infusion (225 mg/m^2 per 24 hours) or bolus injection (500 mg/m^2 for 3 consecutive days during the first and last weeks of EBRT) chemotherapy with 5-FU. Eleven patients received both continuous infusion 5-FU and weekly doses of 200 mg/m^2 of radiosensitizing gemcitabine on protocol.

Intraoperative Radiotherapy

The IORT technique at MGH has been previously described.[5] A cylindrical metal applicator with a circular (189 patients; 97%) or elliptical cross-section was used to enclose the primary pancreatic tumor, leaving roughly 1 cm on either side of the tumor's longest dimension (median applicator diameter, 7 cm; range, 4 cm-12 cm). After retraction of surrounding organs, a linear accelerator delivered radiation of a given dose (median, 20 Gy; range, 10 Gy-25 Gy) and energy (selected based on tumor depth; median, 15 megaelectron volts [MeV]; range, 6 MeV-29 MeV) to the tumor and regional lymph nodes. Accompanying procedures were often performed before surgical closure: gastrojejunostomy or gastroenterostomy (147 patients; 76%); hepaticojejunostomy (19 patients; 10%); cholecystectomy (38 patients; 20%); and/or choledochojejunostomy, choledochoduodenostomy, or cholecystojejunostomy (28 patients; 14%).

Chemotherapy

Among 166 patients (86%) with documented chemotherapy status (independent of radiosensitizing chemotherapy given concurrently with EBRT), 57 patients (34%) received pre-IORT induction and/or post-IORT maintenance chemotherapy, typically 5-FU and leucovorin (5-FU at a dose of 500 mg/m^2 and leucovorin at a dose of 500 mg/m^2 for 3 of every 4 weeks) or gemcitabine (at a dose of 1000 mg/m^2 for 3 of every 4 weeks). Since 2006, induction gemcitabine chemotherapy followed by chemoradiation and IORT has replaced earlier post-IORT maintenance chemotherapy regimens.

Follow-Up

Patients were seen 6 to 8 weeks after the completion of all radiotherapy and then at 3-month to 6-month intervals. Follow-up included physical examination, serum tumor marker assessment, chest and abdominopelvic computed tomography imaging, and other procedures as indicated. At the occurrence of disease progression, patients received further chemotherapy or best supportive care.

IORT Toxicity

Early radiation-related side effects were graded in accordance with version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events. Late radiation-related side effects were graded in accordance with the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema.

Statistical Analysis

Our primary endpoint was OS. Dates of death from any cause were obtained from medical records and the Social Security Death Index. Secondary endpoints were local progression-free survival, distant metastasis-free survival, and disease-free survival, typically determined by imaging or biopsy. Local disease progression was defined as an increase in the primary tumor size and/or regional lymph nodes. Disease-free survival was defined as survival until

TABLE 1. Patient and Tumor Characteristics (N = 194)

Characteristic	No. of Patients (%)
Age at treatment initiation, y	
Median	63.6
Range	36-80
Sex	
Male	103 (53)
Female	91 (47)
Pretreatment CCI	
0-1	166 (86)
2-3	28 (14)
Pretreatment CACI	
0-3	158 (81)
4-6	36 (19)
Tumor location	
Head	150 (77)
Body and/or tail	44 (23)
Tumor grade	
Well-differentiated	16 (8)
Moderately differentiated	25 (13)
Moderately to poorly or poorly differentiated	58 (30)
Unknown	95 (49)

Abbreviations: CACI, Charlson age-comorbidity index; CCI, Charlson comorbidity index.

TABLE 2. Patient Treatment Profiles (N = 194)

Characteristic	No. of Patients (%)
Pre-IORT EBRT[a]	
EBRT alone	84 (43)
EBRT plus 5-FU	86 (44)
EBRT plus capecitabine	5 (3)
EBRT, 5-FU, and gemcitabine	11 (6)
EBRT plus gemcitabine	1 (0.5)
EBRT plus unknown chemotherapy type	1 (0.5)
None	6 (3)
Post-IORT EBRT[a]	
EBRT alone	14 (7)
EBRT plus 5-FU	68 (35)
None	109 (56)
Unknown status[b]	3 (2)
Total EBRT dose, Gy	
Median	49.6
Range	0-59.4
IORT applicator diameter, cm[c]	
≤ 8	173 (89)
> 8	21 (11)
IORT dose, Gy	
Median	20
Range	10-25
IORT energy, MeV	
Median	15
Range	6-29
Chemotherapy[d]	
5-FU	29 (15)
Gemcitabine	24 (12)
5-FU plus gemcitabine	2 (1)
Other	2 (1)
None	109 (56)
Unknown status[b]	28 (14)

Abbreviations: 5-FU, 5-fluorouracil; EBRT, external-beam radiotherapy; Gy, grays; IORT, intraoperative radiotherapy; MeV, megaelectron volts.
[a] Because some patients received EBRT both before and after IORT, there was some patient overlap between the pre-IORT and post-IORT EBRT categories.
[b] Unknown status was due to incomplete post-IORT follow-up at Massachusetts General Hospital regarding treatment obtained at outside hospitals.
[c] As described in the text, the IORT applicator diameter is an approximate surrogate for (2 cm longer than) tumor diameter.
[d] Nonstandard chemotherapy regimens and palliative chemotherapy received after local progression or distant metastasis were not counted in this table.

local disease progression or distant metastasis occurred. Times were measured relative to treatment initiation dates and censored at dates of last follow-up when applicable.

Actuarial OS estimates and 95% pointwise confidence intervals (95% CI) were calculated using the Kaplan-Meier method. Prognostic factors for OS were evaluated at the univariate level by the log-rank test and at the multivariate level by Cox proportional hazards analysis. The pretreatment Charlson comorbidity index (CCI) and Charlson age-comorbidity index (CACI) were calculated from patient age and pretreatment comorbidities, excluding nonmelanoma skin cancers and in situ cervical carcinoma.[6,7] All tests were 2-sided and performed using SAS statistical software (version 9.2; SAS Institute Inc, Cary, NC). A P value $\leq .05$ defined statistical significance.

RESULTS

Patient, Tumor, and Treatment Characteristics

The median age of the patients was 63.6 years (range, 36 years-80 years). 103 patients (53%) were male and 150 patients (77%) had tumors localized to the head of the pancreas (Table 1). Among 99 patients with documented tumor histological grade (51%), 41 (41%) had well-differentiated or moderately differentiated tumors. The pretreatment median CCI and CACI were 0 (range, 0-3) and 2 (range, 0-6), respectively. Table 2 summarizes treatment regimens.

OS and Disease Progression

Over a median follow-up period of 11.6 months (range, 1.0 months-126.4 months), actuarial 1-year, 2-year, and 3-year OS rates were 49% (95% CI, 41%-55%), 16% (95% CI, 11%-21%), and 6% (95% CI, 3%-10%), respectively (Table 3). Six patients lived past 5 years: 4 patients died of their disease at a median of 7.4 years, 1 patient died of other causes, and 1 patient was alive at the time of last follow-up. A total of 187 patients (96%) had died at the time of last follow-up. The median OS was 12.0 months (95% CI, 10.9 months-13.0 months) (Fig. 1).

Among 183 patients (94%) for whom there was available post-IORT disease status follow-up documentation, 130 (71%) had documented disease progression at the time of last follow-up, with 67 patients (37%)

TABLE 3. Overall and Disease-Free Survival Rates

Survival Statistic, (N[a])	1-Year, % (95% CI)	2-Year, % (95% CI)	3-Year, % (95% CI)
Overall survival (N = 194)	49 (41-55)	16 (11-21)	6 (3-10)
Local progression-free survival (N = 183)	61 (52-69)	41 (30-52)	38 (26-50)
Distant metastasis-free survival (N = 183)	49 (40-57)	28 (20-37)	19 (11-29)
Disease-free survival (N = 183)	35 (28-43)	15 (9-22)	10 (5-17)

Abbreviation: 95% CI, 95% confidence interval.
[a] N denotes the sample size of patients with documented statuses for each survival statistic.

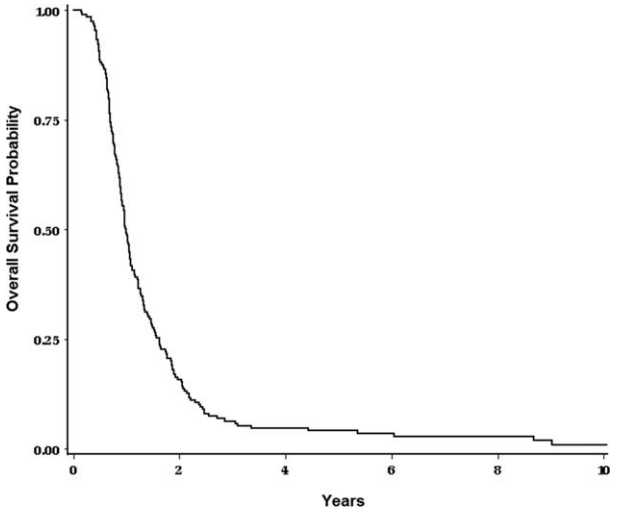

Figure 1. Overall survival is shown among patients with unresectable locally advanced pancreatic cancer who were treated with intraoperative radiotherapy (N = 194).

demonstrating local disease progression and 103 patients (56%) demonstrating distant metastasis. The 2-year local progression-free, distant metastasis-free, and disease-free survival rates were 41% (95% CI, 30%-52%), 28% (95% CI, 20%-37%), and 15% (95% CI, 9%-22%), respectively. Among patients with documented disease progression, the median times to local progression, distant metastasis, and disease progression were 9.0 months (range, 2.8 months-96.2 months), 8.3 months (range, 1.2 months-96.7 months), and 7.9 months (range, 1.2 months-96.2 months), respectively. Among patients with distant metastases, the most common initial sites were the liver (57%), peritoneum (27%), and lung (17%).

Predictors of OS

Table 4 summarizes the results of univariate prognostic factor analysis for OS. A CACI ≤ 3 (hazards ratio [HR], 0.60; 95% CI, 0.41-0.88 [$P = .008$]) and receipt of chemotherapy (HR, 0.48; 95% CI, 0.34-0.68 [$P < .001$]) were found to be predictive of improved OS (Fig. 2). An IORT applicator diameter ≤ 8 cm (HR, 0.62; 95% CI, 0.38-1.02 [$P = .057$]) trended toward predicting improved OS (Fig. 2). Although age-unadjusted CCI ≤ 1 also trended toward predicting improved OS (HR, 0.67; 95% CI, 0.45-1.02 [$P = .058$]), only CACI was included in subsequent multivariate analysis. Age, treatment year, presence of diabetes, tumor location, tumor grade, IORT dose, and total IORT plus EBRT dose were not found to be associated with OS.

TABLE 4. Univariate Prognostic Factor Analysis for Overall Survival

Characteristic, (No.[a])	HR (95% CI)	*P*
Age (N = 194)	1.01 (0.99-1.02)	.379
Treatment year (N = 194)	1.00 (0.98-1.02)	.941
CCI ≤ 1 (N = 194)	0.67 (0.45-1.02)	.058
CACI ≤ 3 (N = 194)	0.60 (0.41-0.88)	.008
Diabetes (N = 194)	1.06 (0.73-1.54)	.761
Tumor location (head) (N = 194)	0.98 (0.70-1.39)	.931
Tumor grade (well or moderately differentiated) (N = 99)	0.82 (0.54-1.24)	.344
IORT applicator diameter ≤ 8 cm (N = 194)	0.62 (0.38-1.02)	.057
IORT dose (N = 194)	1.07 (0.99-1.15)	.094
Total IORT plus EBRT dose (N = 194)	1.01 (0.99-1.03)	.285
Chemotherapy (N = 166)	0.48 (0.34-0.68)	$<.001$

Abbreviations: 95% CI, 95% confidence interval; CACI, Charlson age-comorbidity index; CCI, Charlson comorbidity index; EBRT, external-beam radiotherapy; HR, hazards ratio; IORT, intraoperative radiotherapy.
[a] N denotes the sample size of patients with documented statuses for each characteristic.

On multivariate analysis, a CACI ≤ 3 (HR, 0.47; 95% CI, 0.31-0.73 [$P = .001$]), an IORT applicator diameter ≤ 8 cm (HR, 0.51; 95% CI, 0.30-0.84 [$P = .009$]), and receipt of chemotherapy (HR, 0.46; 95% CI, 0.33-0.66 [$P < .001$]) were found to be independently predictive of improved OS (Table 5). Among the 40 patients with all 3 positive prognostic factors (21%), the median OS was 21.2 months (95% CI, 16.1 months-25.7 months), with 1-year, 2-year, and 3-year OS rates of 78% (95% CI, 61%-88%), 43% (95% CI, 27%-57%), and 20% (95% CI, 9%-33%), respectively and a 2-year local progression-free survival rate of 55% (95% CI, 34%-71%).

Subset Analysis of Chemotherapy Recipients

To better reflect current National Comprehensive Cancer Network treatment guidelines for LAPC, we performed subset survival analysis of the 57 patients (29%) in the current study cohort who received pre-IORT induction

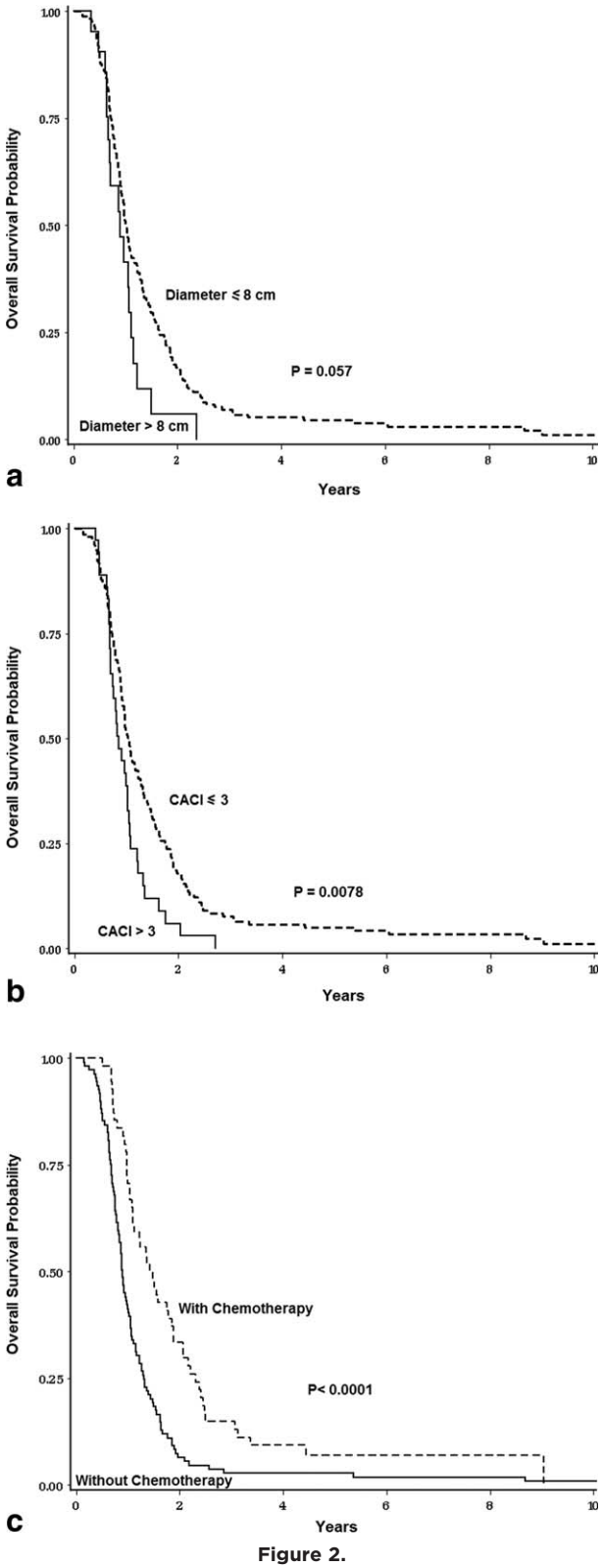

Figure 2.

and/or post-IORT maintenance chemotherapy, independent of radiosensitizing chemotherapy given concurrently with EBRT.[3] The median OS in this smaller cohort was 17.6 months (95% CI, 13.0 months-22.1 months). Actuarial 1-year, 2-year, and 3-year survival rates were 71% (95% CI, 57%-81%), 33% (95% CI, 21%-46%), and 15% (95% CI, 7%-26%), respectively. On univariate analysis, a CACI ≤ 3 (HR, 0.23; 95% CI, 0.10-0.54 [$P = .0002$]) was predictive of improved OS (Fig. 3), whereas an IORT applicator diameter ≤ 8 cm (HR, 0.46; 95% CI, 0.20-1.05 [$P = .058$]) trended toward predicting improved OS. On multivariate analysis, only a CACI ≤ 3 (HR, 0.26; 95% CI, 0.11-0.61 [$P = .002$]) was found to be predictive of improved OS, with a median OS of 20.8 months (95% CI, 16.0 months-24.7 months) noted for patients with a CACI ≤ 3 (Table 6).

IORT Toxicity

Table 7 summarizes IORT-related toxicities. The acute postoperative grade 3 complication rate was 21% (41 patients), with the most frequent complication being delayed gastric emptying (12 patients; 6%). All but 3 of the patients with gastric emptying had undergone a gastrojejunostomy at the time of IORT. The late complication rate was 14% (27 patients), with the most frequent complication being gastrointestinal bleeding (23 patients; 12%). None of the 3 acute or late postoperative radiation-related deaths were reported among patients who were treated within the last decade.

DISCUSSION

In the current study, we updated and expanded our institution's published experience of long-term outcomes among patients with unresectable LAPC who were treated with IORT.[5] To the best of our knowledge, our cohort of 194 patients is the largest to date in the IORT literature for patients with LAPC. Comparable to our institution's previously published values, we reported 1-year, 2-year, 3-year, and 5-year OS rates of 49%, 16%, 6%, and 3%, respectively.[8,9] In addition, we have shown that patients with LAPC who receive chemotherapy, have small tumors, and have low pretreatment CACI scores can

Figure 2. Overall survival of patients is shown stratified by factors found to be significant or of borderline significance on univariate analysis. (*Top*) Overall survival stratified by intraoperative radiotherapy applicator diameter is shown (N = 194). (*Middle*) Overall survival stratified by the Charlson age-comorbidity index (CACI) is shown (N = 194). (*Bottom*) Overall survival stratified by receipt of chemotherapy is shown (N = 166).

TABLE 5. Multivariate Prognostic Factor Analysis for Overall Survival

Characteristic, (No.[a])	Median OS, Months (95% CI)	1-Year, % (95% CI)	2-Year, % (95% CI)	3-Year, % (95% CI)	HR (95% CI)	*P*
CACI (N = 194)						
≤3 (n[b] = 158)	12.5 (11.1-14.0)	51 (43-58)	18 (12-24)	8 (4-13)	0.47 (0.31-0.73)	.001
>3 (n = 36)	10.3 (8.3-12.3)	39 (23-54)	6 (1-17)	0		
IORT applicator diameter, cm (N = 194)						
≤8 (n = 173)	12.0 (11.0-13.2)	49 (42-57)	17 (12-23)	7 (4-11)	0.51 (0.30-0.84)	.009
>8 (n = 21)	10.7 (8.0-13.2)	42 (19-63)	6 (0.4-24)	0		
Chemotherapy (N = 166)						
Yes (n = 57)	17.6 (13.0-22.1)	71 (57-81)	33 (21-46)	15 (7-26)	0.46 (0.33-0.66)	<.001
No (n = 109)	10.7 (9.7-12.0)	40 (31-49)	6 (3-12)	3 (1-7)		

Abbreviations: 95% CI, 95% confidence interval; CACI, Charlson age-comorbidity index; HR, hazards ratio; IORT, intraoperative radiotherapy; OS, overall survival.

[a] N denotes the sample size of patients with documented statuses for each characteristic.

[b] n denotes the number of patients in given category.

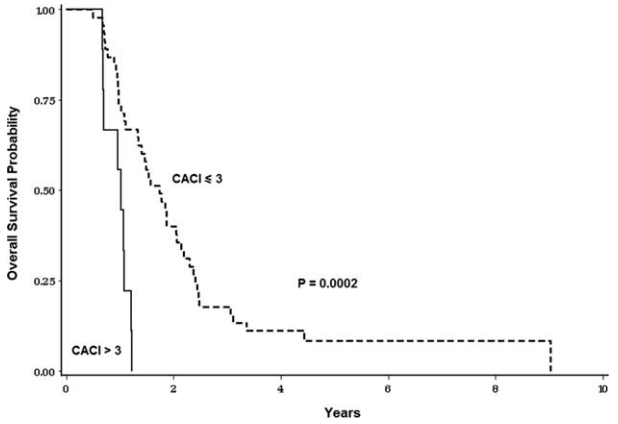

Figure 3. Overall survival of patients treated with chemotherapy is shown stratified by Charlson age-comorbidity index (CACI) (N = 57).

achieve good long-term outcomes, with a median OS of 21.2 months and a 3-year OS rate of 20% reported in the current study cohort.

Our OS and local control rates are comparable to those of 2 other large retrospective studies of patients with LAPC who were treated with IORT. In a 2011 multiinstitution analysis of 144 patients with LAPC treated with IORT with or without EBRT and/or chemotherapy, Ogawa et al reported a median OS of 10.5 months, a 2-year OS rate of 15%, and a 2-year local control rate of 45%.[8] In a 2004 single-institution analysis of patients treated with IORT and EBRT, Okamoto et al reported a median OS of 10.8 months, with 1-year and 3-year OS rates of 57% and 10%, respectively among 65 patients with LAPC.[9]

The strength of chemotherapy as a positive prognostic factor in the current study supports the current emphasis on upfront systemic treatment of patients with pancreatic cancer.[3] Meanwhile, the role of localized radiotherapy has received increasing attention since the results of the 2009 autopsy analysis by Iacobuzio-Donahue et al demonstrated that local tumor progression causes significant morbidity and mortality in patients with unresectable and even frankly metastatic pancreatic cancer.[10] It is interesting to note that the median OS of 17.6 months noted among the patients in the current study who received both IORT and chemotherapy exceeds the 13-month median OS reported by Chauffert et al in their 2008 phase 3 trial demonstrating improved OS among patients with LAPC who are treated with gemcitabine alone versus more aggressive chemoradiation.[11] Since 2006, MGH has increasingly adopted the paradigm of using induction chemotherapy to screen for patients with LAPC who do not immediately develop metastases and thus are more likely to benefit from targeted radiotherapy.[12,13] Therefore, some patients in the current study cohort who received chemotherapy were a favorable subgroup.

It is important to mention the results of the LAP 07 study, which to our knowledge is the largest LAPC randomized trial published to date, and which randomized patients to receive chemoradiation or chemotherapy after 4 months of gemcitabine with or without erlotinib.[14] Results presented at the 2013 annual meeting of the American Society of Clinical Oncology demonstrated no OS benefit with the addition of radiation after induction chemotherapy; however, we await publication of the finalized data regarding secondary endpoints and quality of life. In an era of more effective systemic regimens including FOLFIRINOX (leucovorin calcium [folinic acid] [FOL], 5-FU [F], irinotecan hydrochloride [IRIN], and oxaliplatin [OX]) and gemcitabine/nab-paclitaxel, local control may play an increasingly important role in improving disease outcomes and quality of life.[15,16]

TABLE 6. Subset Multivariate Prognostic Factor Analysis for Overall Survival Among Patients Treated With Chemotherapy (N = 57)

Characteristic	Median OS, Months (95% CI)	1-Year, % (95% CI)	2-Year, % (95% CI)	3-Year, % (95% CI)	HR (95% CI)	*P*
CACI						
≤3 (n[a] = 46)	20.8 (16.0-24.7)	73 (58-84)	40 (26-54)	18 (8-30)	0.26 (0.11-0.61)	.002
>3 (n = 11)	12.3 (8.0-14.5)	56 (20-80)	0	0		
IORT applicator diameter, cm						
≤8 (n = 47)	18.4 (13.0-22.4)	75 (59-85)	36 (23-50)	17 (8-29)	0.58 (0.25-1.36)	.211
>8 (n = 10)	11.5 (8.0-17.9)	45 (11-75)	15 (1-48)	0		

Abbreviations: 95% CI, 95% confidence interval; CACI, Charlson age-comorbidity index; HR, hazards ratio; IORT, intraoperative radiotherapy; OS, overall survival.
[a] n denotes the number of patients in given category.

TABLE 7. IORT Toxicity (N = 194)

Characteristic	No. of Patients (%)
Acute complications (grade ≥3)	41 (21)
Postoperative death	1 (0.5)
Wound infection	7 (4)
Abdominal abscess or fistula	6 (3)
Delayed gastric emptying	12 (6)
Other	18 (9)
Late complications	27 (14)
GI bleeding	23 (12)
Death from GI bleeding	2 (1)
Duodenal obstruction	1 (0.5)
Other	3 (2)

Abbreviations: GI, gastrointestinal; IORT, intraoperative radiotherapy.

IORT given at the study institution offers the opportunity for local dose intensification. Several small single-institution studies have reported encouraging local control and OS results for patients with LAPC who are treated with stereotactic body radiotherapy, a noninvasive, high-dose, targeted radiation modality.[17,18] Irreversible electroporation is a minimally invasive tumor ablation technique that may also improve outcomes in patients with pancreatic cancer.[19] Larger studies evaluating these newer targeted local modalities will help to elucidate further the role of high-dose local therapy in patients with LAPC.

To our knowledge, we are the first to highlight a prognostic role for the CACI in patients with LAPC. Although the prognostic value of the age-unadjusted CCI has been previously demonstrated in patients with head and neck, breast, prostate, lung, and colorectal cancers and the age-adjusted CACI has been reported as a prognostic factor in patients with colorectal and bladder cancer, to the best of our knowledge the implications of pretreatment comorbidity in patients with pancreatic cancer have not been sufficiently studied.[20-25] In 2011, Nakai et al found CCI and performance status, but not age, to be prognostic factors among 237 patients treated with gemcitabine-based chemotherapy for unresectable (including metastatic) pancreatic cancer.[26] Similar to theirs, in the current study age was not itself found to be a prognostic factor for OS, but embedding age within the CACI yielded stronger prognostic value than the CCI alone.

Given that the patients in the current study cohort were preselected to have generally good performance statuses, and given that most patients with pancreatic cancer die of cancer rather than other causes, the question of how CACI comorbidities (dominated in our patient cohort by diabetes, peptic ulcer disease, chronic pulmonary disease, and a history of myocardial infarction) may modulate outcomes in patients with LAPC merits further investigation. Nakai et al have suggested that improved comorbidity may correlate with a higher likelihood of receiving chemotherapy.[26] Physiologically, given the potential for using systemic inflammation indices such as the Glasgow Prognostic Score to predict OS in patients with pancreatic cancer, it is also possible that a lower baseline CACI correlates with lower levels of cancer-promoting systemic inflammation and/or better treatment tolerance.[27] It is interesting to note that despite growing interest in the specific comorbidity of diabetes as a potential negative prognostic factor in patients with pancreatic cancer, diabetes status was not found to be associated with OS in the current study cohort.[28]

Finally, in comparison with our institution's previously published experience, although an IORT applicator diameter ≤ 8 cm predicted improved OS in our overall multivariate model, our subset analysis of patients treated with chemotherapy, which was most reflective of current practice patterns, suggested that appropriately timed chemotherapy coupled with favorable CACI can yield good survival outcomes even in patients with larger primary tumors.

Overall, the patient cohort in the current study confirms that there is significant variability in outcomes among patients with LAPC, even when they are preselected to have good performance statuses. Greater than one-half of the patients in this cohort did not survive to 1 year, but a significant percentage survived to 3 years, and the longest-surviving patient lived over 10 years. In an era of targeted chemotherapy, genetic profiling is an increasingly sought-after technique for selecting those patients most likely to respond to particular treatment regimens. The genetic determinants of heterogeneity in the natural course of pancreatic cancer have thus far remained elusive, but the results of the current study suggest that clinical determinants may still be of some value.

The current analysis has several limitations: it is a single-institutional retrospective study with significant treatment heterogeneity; we were unable to assess several potentially valuable prognostic factors such as performance status; and our patient cohort was fairly homogeneous, with a relatively small number of patients in the patient groups with poor prognostic factors.[25,26] Nevertheless, as what to our knowledge is the largest study in the literature to date to examine patients with LAPC who are treated with IORT, the current study offers new insight into some simple clinical guidelines that may help to identify those patients with LAPC who are most likely to achieve long-term survival after a multimodality treatment regimen.

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REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin.* 2012;62:10-29.
2. Huguet F, Goodman KA, Azria D, Racadot S, Abrams RA. Radiotherapy technical considerations in the management of locally advanced pancreatic cancer: American-French consensus recommendations. *Int J Radiat Oncol Biol Phys.* 2012;83:1355-1364.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed November 21, 2012.
4. Wood WC, Shipley WU, Gunderson LL, Cohen AM, Nardi GL. Intraoperative irradiation for unresectable pancreatic carcinoma. *Cancer.* 1982;49:1272-1275.
5. Willett CG, Del Castillo CF, Shih HA, et al. Long-term results of intraoperative electron beam irradiation (IOERT) for patients with unresectable pancreatic cancer. *Ann Surg.* 2005;241:295-299.
6. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol.* 1994;47:1245-1251.
7. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40:373-383.
8. Ogawa K, Karasawa K, Ito Y, et al. Intraoperative radiotherapy for unresectable pancreatic cancer: a multi-institutional retrospective analysis of 144 patients. *Int J Radiat Oncol Biol Phys.* 2011;80:111-118.
9. Okamoto A, Matsumoto G, Tsuruta K, et al. Intraoperative radiation therapy for pancreatic adenocarcinoma: the Komagome hospital experience. *Pancreas.* 2004;28:296-300.
10. 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.
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. Arvold ND, Ryan DP, Niemierko A, et al. Long-term outcomes of neoadjuvant chemotherapy before chemoradiation for locally advanced pancreatic cancer. *Cancer.* 2012;118:3026-3035.
13. 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.
14. Hammel P, Huguet F, Van Laethem JL, et al. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: final results of the international phase III LAP 07 study. Paper presented at: ASCO Annual Meeting; May 31-June 4, 2013; Chicago, IL.
15. Conroy T, Desseigne F, Ychou M, et al; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011;364:1817-1825.
16. Von Hoff DD, Ervin TJ, Arena FP, et al. Randomized phase III study of weekly *nab*-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT). Paper presented at: 2013 Gastrointestinal Cancers Symposium; January 24-26, 2013; San Francisco, CA.
17. Mahadevan A, Miksad R, Goldstein M, et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. *Int J Radiat Oncol Biol Phys.* 2011;81:e615-e622.
18. Schellenberg D, Kim J, Christman-Skieller C, et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2011;81:181-188.
19. Martin RC 2nd, McFarland K, Ellis S, Velanovich V. Irreversible electroporation in locally advanced pancreatic cancer: potential improved overall survival [published online ahead of print November 6, 2012]. *Ann Surg Oncol.*
20. Iversen LH, Norgaard M, Jacobsen J, Laurberg S, Sorensen HT. The impact of comorbidity on survival of Danish colorectal cancer patients from 1995 to 2006-a population-based cohort study. *Dis Colon Rectum.* 2009;52:71-78.
21. Koppie TM, Serio AM, Vickers AJ, et al. Age-adjusted Charlson comorbidity score is associated with treatment decisions and clinical outcomes for patients undergoing radical cystectomy for bladder cancer. *Cancer.* 2008;112:2384-2392.
22. Ouellette JR, Small DG, Termuhlen PM. Evaluation of Charlson-Age Comorbidity Index as predictor of morbidity and mortality in patients with colorectal carcinoma. *J Gastrointest Surg.* 2004;8:1061-1067.
23. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA.* 2004;291:2441-2447.
24. Reid BC, Alberg AJ, Klassen AC, et al. Comorbidity and survival of elderly head and neck carcinoma patients. *Cancer.* 2001;92:2109-2116.

25. Vickers MM, Powell ED, Asmis TR, et al. Comorbidity, age and overall survival in patients with advanced pancreatic cancer- results from NCIC CTG PA.3: a phase III trial of gemcitabine plus erlotinib or placebo. *Eur J Cancer.* 2012;48:1434-1442.
26. Nakai Y, Isayama H, Sasaki T, et al. Comorbidity, not age, is prognostic in patients with advanced pancreatic cancer receiving gemcitabine-based chemotherapy. *Crit Rev Oncol Hematol.* 2011;78:252-259.
27. Shimoda M, Katoh M, Kita J, Sawada T, Kubota K. The Glasgow Prognostic Score is a good predictor of treatment outcome in patients with unresectable pancreatic cancer. *Chemotherapy.* 2010;56: 501-506.
28. Chu CK, Mazo AE, Goodman M, et al. Preoperative diabetes mellitus and long-term survival after resection of pancreatic adenocarcinoma. *Ann Surg Oncol.* 2010;17:502-513.