

# Phase 2 Multi-institutional Trial Evaluating Gemcitabine and Stereotactic Body Radiotherapy for Patients With Locally Advanced Unresectable Pancreatic Adenocarcinoma

Joseph M. Herman, MD, MSc<sup>1</sup>; Daniel T. Chang, MD<sup>2</sup>; Karyn A. Goodman, MD<sup>3</sup>; Avani S. Dholakia, MD<sup>1</sup>; Siva P. Raman, MD<sup>4</sup>; Amy Hacker-Prietz, PA-C<sup>1</sup>; Christine A. Iacobuzio-Donahue, MD<sup>5</sup>; Mary E. Griffith, RN<sup>1</sup>; Timothy M. Pawlik, MD<sup>6</sup>; Jonathan S. Pai, BA<sup>2</sup>; Eileen O'Reilly, MD<sup>7</sup>; George A. Fisher, MD<sup>8</sup>; Aaron T. Wild, MD<sup>1</sup>; Lauren M. Rosati, BS<sup>1</sup>; Lei Zheng, MD<sup>9</sup>; Christopher L. Wolfgang, MD<sup>6</sup>; Daniel A. Laheru, MD<sup>9</sup>; Laurie A. Columbo, RN<sup>2</sup>; Elizabeth A. Sugar, PhD<sup>10</sup>; and Albert C. Koong, MD, PhD<sup>2</sup>

**BACKGROUND:** This phase 2 multi-institutional study was designed to determine whether gemcitabine (GEM) with fractionated stereotactic body radiotherapy (SBRT) results in acceptable late grade 2 to 4 gastrointestinal toxicity when compared with a prior trial of GEM with single-fraction SBRT in patients with locally advanced pancreatic cancer (LAPC). **METHODS:** A total of 49 patients with LAPC received up to 3 doses of GEM (1000 mg/m<sup>2</sup>) followed by a 1-week break and SBRT (33.0 gray [Gy] in 5 fractions). After SBRT, patients continued to receive GEM until disease progression or toxicity. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events [version 4.0] and the Radiation Therapy Oncology Group radiation morbidity scoring criteria. Patients completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) and pancreatic cancer-specific QLQ-PAN26 module before SBRT and at 4 weeks and 4 months after SBRT. **RESULTS:** The median follow-up was 13.9 months (range, 3.9-45.2 months). The median age of the patients was 67 years and 84% had tumors of the pancreatic head. Rates of acute and late (primary endpoint) grade  $\geq 2$  gastritis, fistula, enteritis, or ulcer toxicities were 2% and 11%, respectively. QLQ-C30 global quality of life scores remained stable from baseline to after SBRT (67 at baseline, median change of 0 at both follow-ups;  $P > .05$  for both). Patients reported a significant improvement in pancreatic pain ( $P = .001$ ) 4 weeks after SBRT on the QLQ-PAN26 questionnaire. The median plasma carbohydrate antigen 19-9 (CA 19-9) level was reduced after SBRT (median time after SBRT, 4.2 weeks; 220 U/mL vs 62 U/mL [ $P < .001$ ]). The median overall survival was 13.9 months (95% confidence interval, 10.2 months-16.7 months). Freedom from local disease progression at 1 year was 78%. Four patients (8%) underwent margin-negative and lymph node-negative surgical resections. **CONCLUSIONS:** Fractionated SBRT with GEM results in minimal acute and late gastrointestinal toxicity. Future studies should incorporate SBRT with more aggressive multiagent chemotherapy. *Cancer* 2015;121:1128-37. © 2014 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of *American Cancer Society*. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

**KEYWORDS:** stereotactic body radiotherapy, pancreatic cancer, chemoradiation, locally advanced, unresectable, positron emission tomography.

## INTRODUCTION

Pancreatic ductal adenocarcinoma remains a devastating malignancy, with a 5-year overall survival (OS) rate of nearly 6%.<sup>1</sup> Approximately 30% of patients who present with locally advanced pancreatic cancer (LAPC) have a median OS of 5 to 15 months.<sup>2,3</sup> Local disease progression is common (approximately 50%) and results in pain and obstructive symptoms.<sup>4,5</sup>

Results of conventional chemoradiation (CRT) in the treatment of patients with LAPC are conflicting. The Gastrointestinal Tumor Study Group 9283<sup>6</sup> and Eastern Cooperative Oncology Group 4201<sup>4</sup> studies reported improved OS with

**Corresponding author:** Joseph M. Herman, MD, MSc, Department of Radiation Oncology and Molecular Radiation Sciences, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, 401 N. Broadway, Weinberg Suite 1440, Baltimore, MD 21231; Fax: (410) 502-1419; jherma15@jhmi.edu

<sup>1</sup>Department of Radiation Oncology & Molecular Radiation Sciences, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland; <sup>2</sup>Department of Radiation Oncology, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California; <sup>3</sup>Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York; <sup>4</sup>Department of Radiology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland; <sup>5</sup>Department of Pathology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland; <sup>6</sup>Department of Surgery, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland; <sup>7</sup>Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, New York; <sup>8</sup>Department of Medical Oncology, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California; <sup>9</sup>Department of Medical Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland; <sup>10</sup>Department of Biostatistics and Epidemiology, Johns Hopkins University School of Medicine, Baltimore, Maryland

Presented at the 48th Annual Meeting of the American Society of Clinical Oncology; June 1-5, 2012; Chicago, IL and the American Society of Radiation Oncology 2013 Annual Meeting; September 22-25, 2013; Atlanta, GA.

**DOI:** 10.1002/cncr.29161, **Received:** August 15, 2014; **Revised:** October 3, 2014; **Accepted:** October 7, 2014, **Published online** December 23, 2014 in Wiley Online Library (wileyonlinelibrary.com)

**TABLE 1.** Treatment Simulation and Planning Prior to Delivery of SBRT

Simulation	Treatment Planning (Dose Constraints)
<ul style="list-style-type: none"> <li>• Thin-slice CT scan</li> <li>• No food 2 h prior</li> <li>• Contrast               <ul style="list-style-type: none"> <li>■ Oral contrast: omnipaque (240 cc)</li> <li>■ Intravenous contrast: omnipaque (100 cc)</li> </ul> </li> <li>• Supine position</li> <li>• Immobilization device</li> <li>• 4D CT               <ul style="list-style-type: none"> <li>■ If &lt;3 mm, free-breathing treatment</li> <li>■ If &gt;3 mm, use ABC, gating, or compression belt</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Proximal* duodenum, stomach, small bowel: 9 cc, &lt;15 Gy; 3 cc, &lt;20 Gy; 1 cc, &lt;33 Gy</li> <li>• Liver: 50%, &lt;12 Gy</li> <li>• Combined kidneys: 75%, &lt;12 Gy</li> <li>• Spinal cord: 1 cc, &gt;8 Gy</li> </ul>

\*Proximal defined as within 1 cm above and below the planning treatment volume.

Abbreviations: 4D, 4-dimensional; ABC, active breathing control; CT, computed tomography; Gy, gray; SBRT, stereotactic body radiotherapy.

CRT. However, the CRT treatment arms were associated with substantial grade 3 to 4 toxicity. In a retrospective review of 2 prospective studies, the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) reported an increase in OS among patients receiving chemotherapy and CRT versus those receiving chemotherapy alone.<sup>7</sup> The Federation Francophone de Cancerologie Digestive and Societe Francaise de Radiotherapie Oncologique study reported inferior OS and worse toxicity with the addition of CRT to chemotherapy.<sup>8</sup> Recently, preliminary results of the phase 3 GERCOR LAP-07 study demonstrated no benefit in OS but improved local control with the addition of CRT.<sup>9</sup>

Stereotactic body radiotherapy (SBRT) involves a short course of radiation ( $\leq 5$  fractions) and has demonstrated high rates of local control in patients with lung cancer and other malignancies.<sup>10</sup> Early phase 1/2 pancreatic ductal adenocarcinoma studies using single-fraction SBRT (25 gray [Gy] in 1 fraction) demonstrated excellent freedom from local disease progression (FFLP) at 1 year (>90%) and minimal acute toxicity in patients with LAPC, but resulted in high rates of late grade 2 to 4 gastrointestinal (GI) toxicity.<sup>11-15</sup>

We conducted a single-arm, phase 2, multi-institutional study to determine whether patients treated with gemcitabine administered with fractionated SBRT (in 5 fractions of 6.6 Gy, to a total 33.0 Gy) would achieve reduced late grade 2 to 4 GI toxicity compared with a historical cohort of patients treated with gemcitabine and a single 25-Gy fraction of SBRT.<sup>13</sup>

## MATERIALS AND METHODS

### **Enrollment and Eligibility**

Patients with histologically confirmed LAPC were treated at Johns Hopkins University, Stanford University, or Memorial Sloan-Kettering Cancer Center after Institutional

Review Board (IRB) approval and in accordance with an assurance filed with and approved by the US Department of Health and Human Services. All patients provided written informed consent (ClinicalTrials.gov identifier NCT01146054). Eligibility criteria included: 1) LAPC classified as per a standardized classification system<sup>16</sup> determined on a thin-cut ( $\leq 3$  mm) 3-dimensional computed tomography (CT) scan with multidisciplinary or tumor board review; 2) a maximum tumor size <7.5 cm; 3) an Eastern Cooperative Oncology Group performance status of 0 to 1; 4) age >18 years; 5) a life expectancy >6 months; and 6) acceptable organ and bone marrow function. Exclusion criteria included: 1) metastatic disease; 2) prior abdominal radiotherapy; 3) other malignancies diagnosed within 5 years; and 4) >3 doses of gemcitabine before SBRT.

### **Treatment Intervention**

Participants received up to 3 weeks of gemcitabine before SBRT was administered. A 1-week break from chemotherapy was required before SBRT delivery. Before simulation, patients had gold fiducials implanted into the pancreatic tumor using endoscopic ultrasound guidance as previously described.<sup>17</sup> During simulation, patients received oral and intravenous contrast and were positioned supine with arms up in an Alpha Cradle (Smithers Medical Products, Inc, North Canton, Ohio) or an equivalent immobilization device. If patients had  $\geq 3$ -mm breathing motion on 4-dimensional CT, motion management techniques were used, including gating, active breathing control (ABC), or abdominal compression based on institutional preference (Table 1). If breathing was <3 mm, patients were treated free breathing (FB) with an internal target volume based on the 0% and 60% phases of the breathing cycle.

Treatment planning was performed using a [18F]fluorodeoxyglucose-positron emission tomography (FDG-

PET) scan when available (48 patients; 98%). The macroscopic (gross) tumor volume (GTV) was defined using diagnostic CT and FDG-PET/CT images. The final planning target volume (PTV) was a 2-mm to 3-mm margin expansion of the GTV (respiratory gating or ABC) or of the internal target volume (FB) unless the margin resulted in expansion into the duodenum or stomach. In these cases, a nonuniform “modified PTV” (mPTV) margin expansion was acceptable, ensuring that the GTV dose constraints were met. Regional (peripancreatic) lymph nodes were included in the PTV if they measured >1.5 cm and dose constraints were met. For SBRT administered at Johns Hopkins Hospital and Memorial Sloan-Kettering Cancer Center, a cone beam CT scan was coregistered (spine) with the FB or ABC simulation scan. To verify tumor positioning before SBRT, patients were then shifted to align with the pancreas fiducial markers for each beam based on fluoroscopy, cone beam CT, or kV images. All patients were treated on linear accelerators. Patients treated at Stanford University received volumetric modulated arc therapy on the TrueBeam system (Varian Medical Systems, Inc, Palo Alto, Calif) using respiratory gating during the expiratory phase.

A total of 33 Gy was given in 5 consecutive fractions (6.6 Gy per fraction) delivered over 1 to 2 weeks. No more than 1 cc of the mPTV received >130% of the prescription dose (49.2 Gy) and >90% of the mPTV received 100% of the prescription dose (33 Gy). If these constraints could not be met, then 100% of the GTV received at least 25 Gy. Patients were excluded from the current study if these constraints were not met. Dose-limiting structures included the proximal duodenum, proximal stomach, liver, kidneys, and spinal cord (Table 1). These dose constraints were based on our prior single-fraction SBRT experience.<sup>18</sup> All plans were centrally reviewed by at least 1 principle investigator from each institution before SBRT delivery.

After SBRT (a 1-week break was recommended), patients continued treatment with gemcitabine until disease progression or toxicity. All patients were prescribed proton pump inhibitors (PPIs) for a minimum of 6 months. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) and the Radiation Therapy Oncology Group radiation morbidity scoring criteria.

### **Follow-Up and Endpoints**

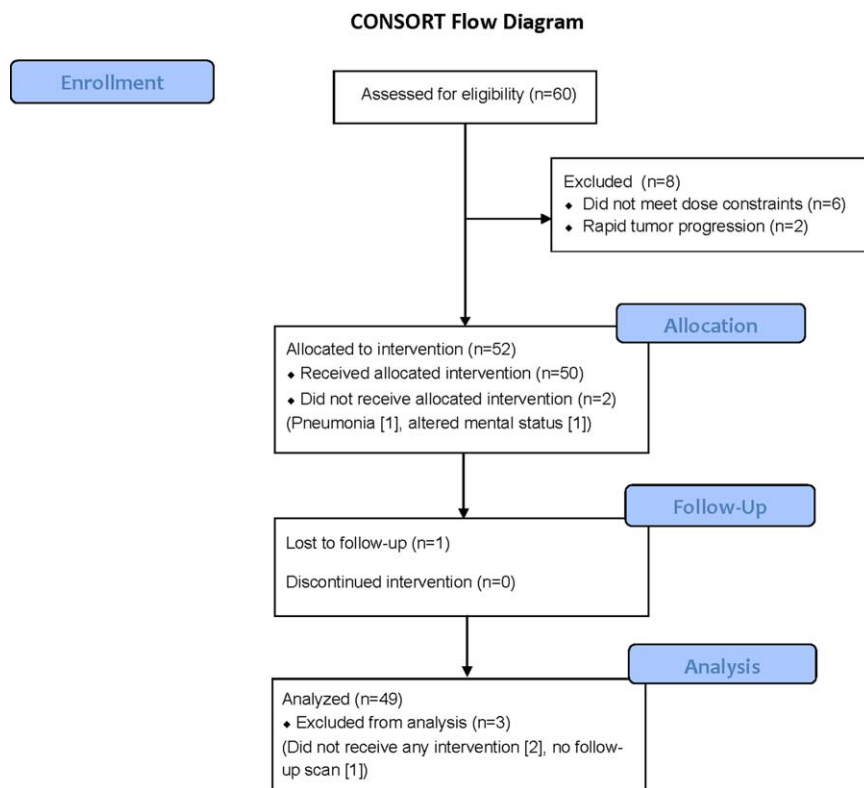
After SBRT, patients underwent routine CT imaging, physical examination, quality of life (QoL) evaluation as assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

(EORTC QLQ-C30; version 3.0)<sup>19</sup> and the pancreatic cancer-specific QLQ-PAN26<sup>20</sup> questionnaire, and laboratory values at 4 to 6 weeks and at 3-month intervals. Follow-up FDG-PET/CT scans were recommended at 2 months to 4 months after SBRT. The primary endpoint was the rate of late (>3 months after SBRT) gastritis, fistula, enteritis, or ulcer of grade  $\geq 2$  and any other late grade 3 to 4 GI toxicity attributable to gemcitabine and SBRT. Planned secondary endpoints included: 1) centralized blinded review of FFLP based on the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines<sup>21</sup>; 2) acute gastritis, fistula, enteritis, or ulcer of grade  $\geq 2$  and any other acute grade 3 to 4 GI toxicity attributable to gemcitabine and SBRT; 3) overall survival (OS); 4) progression-free survival (PFS); 5) usefulness of FDG-PET for estimation of survival outcomes; and 6) QoL.

### **Statistical Analysis**

The primary endpoint of the current study was to determine whether gemcitabine and fractionated SBRT (5.5 Gy in 5 fractions) resulted in a decrease in late grade 2 to 4 GI toxicity (20%) when compared with the rate reported by Schellenberg et al (25 Gy in 1 fraction; 47%).<sup>13</sup> We chose 40% as a comparison to be more conservative. Acute toxicities were defined as those occurring  $\leq 3$  months after SBRT, whereas late toxicities were defined as those occurring >3 months after SBRT. With a 2-sided type I error rate of 2%, 60 patients would provide 91% power to detect a 50% reduction in late grade 2 to 4 GI toxicity rates from those observed for single-fraction (25 Gy in 1 fraction) regimens (from 40% to 20% at 1 year) based on a Simon 2-stage design.<sup>22</sup>

Although not powered to detect a difference in the current study, FFLP at 1 year was a secondary endpoint. FFLP was calculated from the date of diagnosis to the date of local disease progression. We predicted that FFLP would be 80% at 1 year and included stopping rules if FFLP was <70% after the first 20 patients. Individuals who did not develop local disease progression were censored at the date of the last scan. OS was calculated from the date of diagnosis until death and was censored at the date of last follow-up if death was not observed. PFS was calculated from date of diagnosis until disease progression or death, if it occurred within 3 months of the last scan; otherwise, PFS was censored at the date of last scan. Kaplan-Meier techniques were used to estimate the survival functions. Cox proportional hazards modeling assessed whether survival outcomes varied according to risk factors. The FDG-PET threshold of disease avidity



**Figure 1.** Consolidated Standards Of Reporting Trials (CONSORT) flow diagram showing enrollment and outcomes is shown.

was calculated with measurements obtained from a spherical volume-of-interest measuring 3 cm in diameter that was placed within the right lobe of the liver and applied to the following formula:  $Liver_{mean} + (2 * Liver_{sd})$ . Wilcoxon signed rank tests were used to assess the changes in QoL and FDG-PET parameters.

## RESULTS

### **Patient and Treatment Characteristics**

Sixty patients were enrolled from 2010 through 2012, 49 of whom were available for analysis (Fig. 1) (Table 2). At the time of analysis, 8% of patients were alive with a median follow-up from SBRT of 13.9 months (range, 3.9 months-45.2 months). The median age at the time of diagnosis was 67 years. A total of 44 patients (90%) received gemcitabine before SBRT. The median PTV was 71.4 cm<sup>3</sup> (range, 31.9 cm<sup>3</sup>–225.2 cm<sup>3</sup>). The median number of gemcitabine doses after SBRT was 7 (interquartile range, 3 doses-13 doses).

### **Treatment-Related Toxicity**

Acute and late toxicities attributed to treatment are listed in Table 3. Of the 49 patients, 2% experienced acute enteritis, gastritis, ulcer, or fistula of grade  $\geq 2$ . This patient

developed a duodenal ulcer (grade 4) 43 days after SBRT; however, the patient was not receiving the prescribed PPI. Two patients (4%) had serious adverse events <3 months after SBRT that were considered unlikely to be related to treatment. One patient died of complications associated with dehydration from *Clostridium difficile* infection, and 1 patient died from *Klebsiella pneumoniae* sepsis after perforation of the bile duct during a stent change for cholangitis. All other acute GI toxicities of grade  $\geq 3$  (10%) were attributed to elevated aspartate/alanine aminotransferase.

Late toxicity data was only available for 47 patients because 2 patients died within 3 months of SBRT. The primary endpoint of late enteritis, gastritis, ulcer, or fistula of grade  $\geq 2$  was observed in 5 patients (11%). Three patients (6%) had serious GI toxicities >3 months after SBRT. One patient died of a GI bleed (grade 5) 22.4 months after SBRT. After SBRT, this patient actually experienced a decrease in their pain and carbohydrate antigen 19-9 (CA 19-9) level. However, 6 months after SBRT, a PET/CT scan demonstrated increased FDG uptake consistent with local and systemic disease, including increased tumor invasion into the duodenum. Because of these findings, the patient was removed from the study treatment but follow-up for toxicity and survival was continued.



**TABLE 2.** Patient Demographics and Baseline Disease Characteristics (n = 49)

Characteristic	Value (n=49)
Median age at diagnosis (range), y	67 (35-87)
≤65 (%)	16 (33)
>65 (%)	33 (67)
Sex (%)	
Male	31 (63)
Female	18 (37)
ECOG performance status (%)	
0	21 (43)
1	28 (57)
Location of tumor (%)	
Head	41 (84)
Body/tail	8 (16)
Baseline CA 19-9, U/mL (median) <sup>a</sup>	137 (0-6504)
<90 U/mL (%)	18 (37)
≥90 U/mL (%)	27 (55)
Not available (%)	4 (8)
Pre-SBRT gemcitabine (%)	
No	5 (10)
Yes	44 (90)
Baseline PET avidity (%)	
Not avid	12 (24)
Avid	35 (71)
Not available	2 (4)
Treating institution (%)	
Johns Hopkins	32 (65)
Memorial Sloan-Kettering Cancer Center	3 (6)
Stanford University	14 (29)

Abbreviations: CA 19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group; PET, positron emission tomography; SBRT, stereotactic body radiotherapy.

<sup>a</sup>Values calculated from patients for whom there were available data.

Although local disease progression likely caused the GI bleeding, it is possible it was a late effect of the SBRT. A second patient received SBRT after undergoing a palliative gastrojejunostomy bypass procedure. At the time of surgery, the surgical note commented that the tumor involved the third portion of the duodenum. The patient developed an acute duodenal ulcer 1.5 months after SBRT and a fistula between the tumor and the third portion of the duodenum 4 months after SBRT. The patient subsequently received systemic chemotherapy and was admitted to the hospital 2 days later for neutropenia, anemia, and sepsis. Esophagogastroduodenoscopy at that time showed a duodenal ulcer (grade 3) but no active bleeding. The patient was discharged to hospice care and died 2 weeks later. A third patient was hospitalized secondary to a GI bleed from a migrating stent (grade 3). The stent was changed and the bleeding subsequently resolved.

### Treatment Outcomes and Efficacy

The median OS was 13.9 months (95% confidence interval [95% CI], 10.2 months-16.7 months) (Table 4) (Fig. 2). The 1-year and 2-year OS rates were 59% and 18%,

respectively. The 1-year FFLP rate was 78% (95% CI, 60%-89%), which was approaching the expected rate of 80%. The median PFS was 7.8 months (95% CI, 5.8 months-10.2 months), with 1-year and 2-year PFS rates of 32% and 10%, respectively. Multivariate models indicated that the presence of PET-avid disease at baseline (hazard ratio, 2.87; 95% CI, 1.26-6.50 [ $P = .012$ ]) and a post-SBRT CA 19-9 level >90 U/mL (HR, 2.04; 95% CI, 1.06-3.93 [ $P = .032$ ]) were associated with an increased risk of death. The median plasma CA 19-9 level was reduced after SBRT (median time after SBRT, 4.2 weeks; 220 U/mL vs 62 U/mL [ $P < .001$ ]).

### Treatment Response and Patterns of Failure

Five patients (10%) were deemed to be resectable after multidisciplinary review. One patient refused resection. The four remaining patients (8%) underwent successful margin- and lymph node-negative resections, with 1 patient achieving a pathologic complete response. Of these, one is alive at 14.7 months from diagnosis. The other three patients lived for 13.6, 22.2, and 40.2 months from the date of diagnosis. Forty-six patients were evaluable for tumor progression, 39 (85%) of whom had progressed during follow-up and 7 (15%) who did not. Of the 39 who progressed (defined as progression or death within 3 months of the last scan), 22 patients (56%) first developed disease progression at a distant site, 5 patients (13%) at a local site, 6 patients (15%) experienced synchronous local and distant progression, and 6 patients (15%) died within 3 months of the last scan. The median maximum standardized uptake value on pre-SBRT to post-SBRT FDG-PET scans decreased from 4.75 g/mL to 3.15 g/mL, respectively ( $P = .001$ ).

### Quality of Life

Forty-three patients (88%) had completed the EORTC QLQ-C30 and QLQ-PAN26 QoL forms at baseline and 4 weeks after SBRT. Twenty-two of these patients (51%) completed questionnaires at 4 months. QLQ-C30 global QoL scores remained stable from baseline to after SBRT (67 at baseline, with a median change of 0 at both follow-up times;  $P > .05$  for both). Patients demonstrated a significant improvement in pancreatic pain (25 at baseline, median change of -8 [ $P = .001$ ]) 4 weeks after SBRT using the QLQ-PAN26 assessment.

### DISCUSSION

SBRT is an attractive option due to its short duration and proven efficacy in other disease sites<sup>10</sup>; however, earlier studies in patients with LAPC reported significant late

**TABLE 3.** Acute and Late GI Toxicities Within 90 Days of SBRT Broken Down by Time Frame, Type, and Severity<sup>a</sup>

Category	Total Grade $\geq 2$ (%)	Total Grade $\geq 3$ (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Acute toxicity (n=49)						
Nonhematologic						
Enteritis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fistula	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastritis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ulcer	1 (2.0)	1 (2.0)	0 (0)	0 (0)	1 (2.0)	0 (0)
Other GI toxicities						
ALT/AST elevation	7 (14.3)	5 (10.2)	2 (4.1)	5 (10.2)	0 (0)	0 (0)
Abdominal pain	12 (24.5)	0 (0)	12 (24.5)	0 (0)	0 (0)	0 (0)
Anorexia	13 (26.5)	0 (0)	13 (26.5)	0 (0)	0 (0)	0 (0)
Constipation	3 (6.1)	0 (0)	3 (6.1)	0 (0)	0 (0)	0 (0)
Dehydration	2 (4.1)	1 (2.0)	1 (2.0)	0 (0)	0 (0)	1 (2.0) <sup>b</sup>
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dyspepsia/heartburn	4 (8.2)	0 (0)	4 (8.2)	0 (0)	0 (0)	0 (0)
Fatigue	13 (26.5)	0 (0)	13 (26.5)	0 (0)	0 (0)	0 (0)
Nausea	6 (12.2)	0 (0)	6 (12.2)	0 (0)	0 (0)	0 (0)
Weight loss	2 (4.1)	0 (0)	2 (4.1)	0 (0)	0 (0)	0 (0)
Other	1 (2.0)	1 (2.0)	0 (0)	0 (0)	0 (0)	1 (2.0) <sup>c</sup>
Hematologic						
Anemia	14 (28.6)	0 (0)	14 (28.6)	0 (0)	0 (0)	0 (0)
Lymphopenia	18 (36.8)	4 (8.2)	14 (28.6)	4 (8.2)	0 (0)	0 (0)
Neutropenia	3 (6.1)	1 (2.0)	2 (4.1)	1 (2.0)	0 (0)	0 (0)
Thrombocytopenia	6 (12.2)	1 (2.0)	5 (10.2)	1 (2.0)	0 (0)	0 (0)
Late toxicity (n=47)						
Enteritis	1 (2.1)	0 (0)	1 (2.1)	0 (0)	0 (0)	0 (0)
Fistula	1 (2.1)	1 (2.1)	0 (0)	0 (0)	1 (2.1)	0 (0)
Gastritis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ulcer	3 (6.4)	3 (6.4)	0 (0)	3 (6.4)	0 (0)	0 (0)
Other						
Pain	1 (2.1)	0 (0)	1 (2.1)	0 (0)	0 (0)	0 (0)
Anorexia	1 (2.1)	0 (0)	1 (2.1)	0 (0)	0 (0)	0 (0)
Other	2 (4.2)	2 (4.2)	0 (0)	1 (2.1) <sup>d</sup>	0 (0)	1 (2.1) <sup>e</sup>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastrointestinal; SBRT, stereotactic body radiotherapy.

<sup>a</sup>Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events [version 4.0] and the Radiation Therapy Oncology Group radiation morbidity scoring criteria.

<sup>b</sup>Death secondary to *Clostridium difficile* dehydration.

<sup>c</sup>Death secondary to sepsis due to perforation during instrumentation.

<sup>d</sup>GI bleed secondary to stent migration.

<sup>e</sup>Death secondary to GI bleed due to direct tumor extension into duodenum.

grade 2 to 4 GI toxicities. To the best of our knowledge, the first report of SBRT in the treatment of patients with LAPC from Stanford University was a phase 1 trial demonstrating excellent FFLP (100%) until death in 6 patients using single-fraction (25 Gy in 1 fraction) SBRT.<sup>11</sup> Three subsequent phase 2 studies proceeded to evaluate the efficacy and safety of this regimen. The first examined a dose of 45 Gy with concurrent 5-fluorouracil followed by a 25-Gy single-fraction SBRT boost to the tumor.<sup>12</sup> This report demonstrated a FFLP rate of >90% until death with a median OS of 7.6 months. Two separate investigations of 25-Gy single-fraction SBRT (1 using CyberKnife [Accuray Inc, Sunnyvale, Calif] and 1 using Trilogy [Varian Medical Systems, Inc, Palo Alto, Calif]) in sequence with gemcitabine demonstrated a high rate of FFLP (>80%) with a median OS of 11.4 months to 11.8 months; however, the rate of duodenal ulcer formation

remained high (15%-47%).<sup>13</sup> In a phase 2 trial of fractionated SBRT (30 Gy in 3 fractions), Hoyer et al reported a poor local control rate of 57% at 6 months with unacceptable toxicity.<sup>23</sup> Approximately 18% of these patients experienced severe GI toxicity, most likely because of larger PTV margins (1 cm) and no motion management. In comparison, the rates of acute and late toxicity in the current study are consistent with other retrospective single-institution reports using fractionated SBRT (Table 5).<sup>11-15,24-29</sup> It is important to note that the primary endpoint of the current study was met: the rate of late enteritis, gastritis, ulcer, or fistula of grade  $\geq 2$  after an SBRT regimen of 33 Gy delivered in 5 fractions was 11%, a >50% decrease from that observed in the single-fraction SBRT regimen (47%).<sup>13</sup>

Although the linear quadratic model for calculating biologically equivalent doses (BED) can be unreliable for

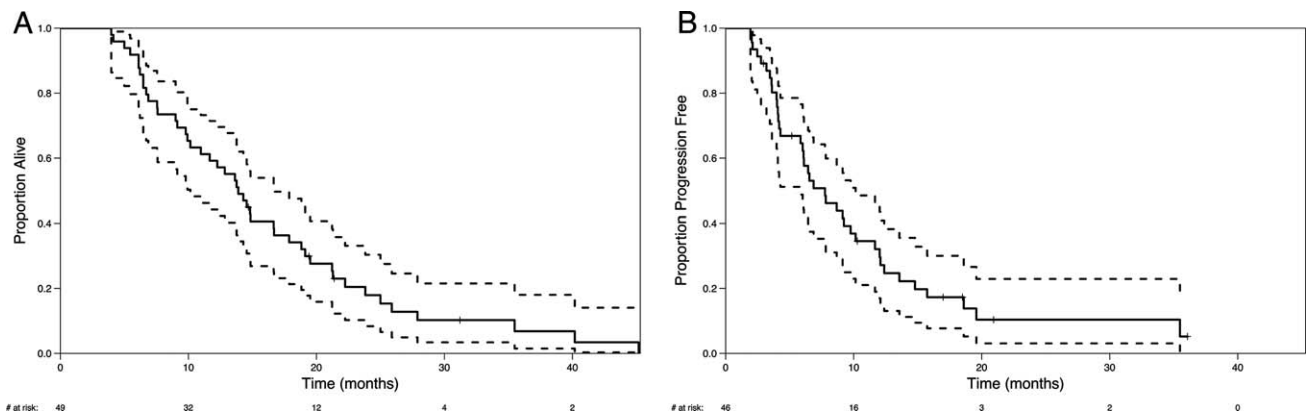
**TABLE 4.** Overall Survival<sup>a</sup>

	N	Median OS (95% CI), Months	1-Year OS	2-Year OS	HR	95% CI	P
All subjects	49	13.9 (10.2-16.7)	59%	18%			
Age ≤65 y	16	18.8 (13.9-21.3)	88%	14%	1	–	.343
Age >65 y	33	11.0 (7.5-14.8)	45%	20%	1.4	0.72- 2.54	
Male	31	14.6 (9.1-18.8)	58%	12%	1	–	.845
Female	18	13.7 (9.0-19.5)	61%	28%	0.94	0.50-1.74	
ECOG PS 0	21	16.7 (13.6-22.2)	81%	28%	1	–	.075
ECOG PS 1	28	9.1 (6.4-14.8)	43%	9%	1.72	0.93-3.15	
Tumor in head	41	14.3 (10.1-19.1)	61%	20%	1	–	.233
Tumor in body/tail	8	10.4 (3.9-16.7)	50%	12%	1.65	0.71-3.77	
Baseline CA 19-9 <90 U/μL	18	16.4 (13.9-19.5)	78%	20%	1	–	.129
Baseline CA 19-9 ≥90 U/μL	27	11.7 (6.4-21.2)	48%	20%	1.66	0.85-3.22	
Post-SBRT CA 19-9 <90 U/μL	26	14.8 (12.2-19.5)	73%	21%	1	–	.071
Post-SBRT CA 19-9 ≥90 U/μL	20	10.2 (6.1-16.7)	45%	12%	1.76	0.94-3.30	
No Pre-SBRT GEM <sup>b</sup>	5	9.0 (4.9-infinity)	40%	20%	1	–	.466
Received Pre-SBRT GEM	44	14.6 (10.1-17.9)	61%	17%	0.70	0.27-1.82	
No surgical resection	45	13.8 (9.8-16.7)	56%	17%	1	–	.182
Surgical resection	4	22.2 (13.6-infinity)	100%	38%	0.45	0.13-1.49	
No baseline PET avidity	12	18.8 (9.0-35.5)	75%	40%	1	–	.028
Baseline PET avidity	35	13.6 (9.8-14.8)	57%	11%	2.35	1.07-5.17	

Abbreviations: 95% CI, 95% confidence interval; CA 19-9, carbohydrate antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group; GEM, gemcitabine; HR, hazards ratio; OS, overall survival; PET, positron emission tomography; SBRT, stereotactic body radiotherapy.

<sup>a</sup>All unadjusted HR and P values were derived from univariate models.

<sup>b</sup>Only Johns Hopkins had patients who received non-gemcitabine treatment.



**Figure 2.** Kaplan-Meier estimates of the survival function for (A) overall survival and (B) progression-free survival are shown. The 95% confidence intervals are included as dotted lines.

large fraction sizes, it can provide an estimate with which to compare different fractionation schedules. Assuming an  $\alpha/\beta$  of 3, the  $BED_3$  delivered to normal tissue in the current study of 6.6 Gy in 5 fractions (105.6 Gy) was lower than the mean  $BED_3$  of 25 Gy in 1 fraction (233.3 Gy). Therefore, we expected a decrease in late toxicities of grade  $\geq 2$  from  $>40\%$  as reported at Stanford University by Schellenberg et al<sup>13</sup> to 20% in the current study. The combined rate of GI and non-GI acute toxicities of grade  $\geq 3$  was 29%, which is less than what is reported with standard CRT.<sup>4</sup> We suspect that a small PTV size, adherence to dose constraints, image guidance, sustained use of PPIs, and motion management collectively contributed to

the favorable toxicity rates noted herein. In addition, the lack of a decline in global QoL and a decrease in pancreatic pain scores among patients are both consistent with retrospective single-institution reports of SBRT using 3 to 5 fractions.<sup>24</sup>

Using this regimen of gemcitabine and fractionated SBRT, we observed a median OS of 13.9 months and a FFLP rate of 78% at 1 year. Although the 1-year FFLP rate noted in the current study (78%) is inferior to the 1-year FFLP rate reported in a previous single-fractionated SBRT trial (100%),<sup>13</sup> our regimen of fractionated SBRT resulted in less toxicity. In addition, the rate of FFLP reported in the current study could be lower than that of

**TABLE 5.** Survival Outcomes in Selected Studies of SBRT in Patients With Locally Advanced Pancreatic Cancer<sup>a</sup>

Study	Regimen	Sample Size	1-Year FFLP, %	OS, Months	Acute Toxicity Grade $\geq 3$	Late Toxicity Grade $\geq 2$	Dose Constraints for Organs at Risk
Koong 2004 <sup>11</sup>	25 Gy SBRT, 1 fraction	6	100%	8.0	33%	–	Duodenal wall (50% isodose line)
Hoyer 2005 <sup>23</sup>	15 Gy SBRT, 3 fractions	22	57% (6 mo)	5.4	79%	94%	–
Koong. 2005 <sup>12b</sup>	45 Gy IMRT, 25 fractions plus 5-FU $\rightarrow$ 25 Gy SBRT, 1 fraction	16	94%	8.25	12.5%	–	Liver (70%, <15 Gy), each kidney (70%, <15 Gy), spinal cord (<30 Gy), and bowel (95% <45 Gy)
<b>Schellenberg 2008 (Stanford study)<sup>13</sup></b>	<b>Gemcitabine <math>\rightarrow</math> 25 Gy SBRT, 1 fraction <math>\rightarrow</math> gemcitabine</b>	<b>16</b>	<b>100%</b>	<b>11.4</b>	<b>19%</b>	<b>47%</b>	<b>Stomach, duodenum, bowel, liver, kidney, and spinal cord<sup>h</sup></b>
Chang 2009 <sup>14</sup>	25 Gy SBRT, 1 fraction	77 <sup>c</sup>	95%	11.9	5%	13%	Liver (50%, <5 Gy), kidney (75%, <5 Gy), spinal cord (<5 Gy maximum), stomach (<4%, <22.5 Gy), duodenum (<5%, <22.5 Gy, <50%, <12.5 Gy), and bowel (<21 Gy maximum, <5% <20 Gy)
Mahadevan 2010 <sup>25</sup>	24-36 Gy SBRT, 3 fractions $\rightarrow$ gemcitabine	36	78%	14.3	41%	6%	Liver (<30%, $\geq 21$ Gy; <50%, $\geq 15$ Gy), kidney (<25%, $\geq 12$ Gy), spinal cord (12 Gy maximum), and bowel (<10 Gy/fraction maximum)
Polistina 2010 <sup>24</sup>	Gemcitabine $\rightarrow$ 30 Gy SBRT, 3 fractions	23	50%	10.6	0	0	Mean dose to 50%: duodenum (14.5 Gy), bowel (1.1 Gy), liver (0.7 Gy), left kidney (1.5 Gy), and right kidney (2.0 Gy)
Schellenberg et al <sup>15</sup>	Gemcitabine $\rightarrow$ 25 Gy SBRT, 1 fraction $\rightarrow$ gemcitabine	20	94%	11.8	15%	20%	Liver (50%, <5 Gy), kidney (75%, <5 Gy), spinal cord (<6 Gy maximum), and duodenum (<5%, $\geq 22.5$ Gy, <50%, $\geq 12.5$ Gy)
Lominska 2012 <sup>26b</sup>	50.4 Gy EBRT $\rightarrow$ 20-30 Gy SBRT, 3-5 fractions	28 <sup>d</sup>	86%	5.9	4%	7%	Stomach (10-30 Gy maximum) and small bowel (13-30 Gy maximum)
Tozzi 2013 <sup>27</sup>	Gemcitabine $\rightarrow$ 45 Gy SBRT, 6 fractions	30	86%	11.0	20%	0	Liver (total spread volume > 700 cc), kidney (<35%, 15 Gy), spinal cord (1 cc <18 Gy), duodenum (1 cc <36 Gy), and stomach and small bowels (3 cc <36 Gy)
Gurka 2013 <sup>28</sup>	Gemcitabine $\rightarrow$ 25 Gy SBRT, 5 fractions $\rightarrow$ Gemcitabine	10	40%	12.2	0%	0	Duodenum and bowel (<1 cc 25 Gy)
Chuong 2013 <sup>29</sup>	GTX $\rightarrow$ 25-50 Gy, 5 fractions <sup>e</sup>	16	81% <sup>f</sup>	15.0	0%	5.3%	Liver (10%, 30 Gy), kidney (<10 Gy), spinal cord (20 Gy maximum), and duodenum/small bowel/stomach (35 Gy maximum, 5 cc <30 Gy, 1 cc <35 Gy)
<b>Current study</b>	<b>(Gemcitabine) <math>\rightarrow</math> 33 Gy, 5 fractions <math>\rightarrow</math> gemcitabine</b>	<b>49</b>	<b>78%</b>	<b>13.9</b>	<b>12.2%<sup>g</sup></b>	<b>10.6%</b>	<b>Liver (50% &lt;12 Gy), combined kidneys (75% &lt;12 Gy), spinal cord (1cc &gt;8 Gy), and proximal duodenum and stomach (9 cc &lt;15 Gy; 3cc &lt;20 Gy; 1cc &lt;33 Gy)</b>

Bold type indicates the two studies being compared: historical Stanford single-fraction 25 Gy  $\times$  1 SBRT regimen versus the current study of 6.6 Gy  $\times$  5 SBRT regimen.

Abbreviations: 5-FU, 5-fluorouracil; EBRT, external beam radiotherapy; FFLP, freedom from local disease progression; GTX, gemcitabine, docetaxel, and capecitabine; Gy, gray; IMRT, intensity-modulated radiotherapy; OS, overall survival; SBRT, stereotactic body radiotherapy.

<sup>a</sup>Unless otherwise indicated, event times for median survival were measured from the date of diagnosis.

<sup>b</sup>This study involves a stereotactic radiosurgery boost after delivery of EBRT.

<sup>c</sup>Sample contained all patients with unresectable disease (including locally advanced and metastatic disease).

<sup>d</sup>Sample included patients who received previous chemotherapy (5-FU and/or gemcitabine or other), whereas some received concurrent chemotherapy.

<sup>e</sup>A dose painting technique was employed in which 7 to 10 Gy per fraction was delivered to the region of vessel abutment or encasement whereas 5 to 6 Gy per fraction was delivered to the remainder of the tumor.

<sup>f</sup>FFLP at 1 year of all 73 patients in the study (including those with locally advanced and borderline resectable disease).

<sup>g</sup>One case (2%) of an ulcer and 5 cases of alanine aminotransferase/aspartate aminotransferase elevation (10.2%) were reported.

<sup>h</sup>Specific dose constraints not specified.



other retrospective studies due to strict central review by a single radiologist. It is important to note that the OS rate in the current study was similar to that of most historical reports of LAPC, despite the finding that approximately two-thirds of enrolled patients were aged >65 years. Although all patients were confirmed to have LAPC based on institutional and central review, 4 patients (8%) underwent margin-negative and lymph node-negative surgical resections with 1 pathologic complete response noted. In addition, at the time of last follow-up, 6 patients (approximately 12%) had survived at least 2 years without surgery.

In the current study, patients only received up to 3 doses of gemcitabine before SBRT was administered. Therefore, it is likely that 20% to 40% of these patients had undetected metastatic disease at the time of enrollment. Our current SBRT trial (ClinicalTrials.gov identifier NCT01781728) integrates SBRT only after 2 to 6 months of either gemcitabine alone or combination chemotherapy regimens such as gemcitabine and nab-paclitaxel or 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin. Therefore, SBRT is delivered only to those patients who fail to develop metastatic disease while receiving chemotherapy. Adding SBRT to an aggressive chemotherapy regimen may be better tolerated and result in improved outcomes when compared with standard CRT; however, a randomized study is needed to test this hypothesis. Another consideration is that this regimen (gemcitabine and SBRT) may be a reasonable treatment option for patients with a poor performance status, given its favorable outcome and low toxicity.

In the absence of reliable clinicopathologic criteria with which to select patients with LAPC who may benefit from radiotherapy, the identification of clinically relevant biomarkers is necessary. Protein-based biomarkers associated with tumor biology hold promise as diagnostic markers of disease states and differential outcomes in clinical cancer management, which could allow for the stratification of patients with respect to systemic versus locoregional disease progression. For example, *SMAD4* encodes a protein, Smad4, which functions as a central mediator of the transforming growth factor- $\beta$  signaling pathway.<sup>30</sup> The significance of *SMAD4* in patients with pancreatic cancer, and hence transforming growth factor- $\beta$  signaling, is exemplified by its inactivation in approximately 55% of pancreatic tumors.<sup>31</sup> We previously reported that intact Smad4 correlates with local disease progression whereas the loss of DPC4 expression more commonly correlates with distant disease progression.<sup>32</sup> In an attempt to personalize the future treatment of patients with LAPC, we are currently evaluating the serum and cell blocks (fine-needle aspiration

specimens) of patients included in the current study to identify potential biomarkers.

To the best of our knowledge, the current study is the first prospective, multi-institutional, phase 2 trial to demonstrate low toxicity in concordance with favorable FFLP with the delivery of gemcitabine and fractionated SBRT among patients with LAPC. Findings of favorable OS and disease stabilization are consistent with those of other retrospective reports (Table 5),<sup>11-15,24-29</sup> and suggest that this regimen is a reasonable option in patients with LAPC. SBRT in combination with more aggressive chemotherapy in patients with good performance status may improve survival outcomes further and requires additional investigation.

## FUNDING SUPPORT

Supported by the Claudio X. Gonzalez Family Foundation, the Flannery Family Foundation, the Alexander Family Foundation, the Keeling Family Foundation, the DeSanti Family Foundation, the McKnight Family, and the My Blue Dots Foundation.

## CONFLICT OF INTEREST DISCLOSURES

Dr. Sugar was supported by a grant from the Viragh Family Foundation Inc for work performed as part of the current study and by a grant from the National Cancer Institute for work performed outside of the current study.

## REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62:10-29.
2. Tempero MA, Arnoletti JP, Behrman SW, et al; National Comprehensive Cancer Networks. Pancreatic Adenocarcinoma, version 2.2012: featured updates to the NCCN guidelines. *J Natl Compr Canc Netw*. 2012;10:703-713.
3. Herman JM, Wild AT, Wang H, et al. Randomized phase III multi-institutional study of TNFerade biologic with fluorouracil and radiotherapy for locally advanced pancreatic cancer: final results. *J Clin Oncol*. 2013;31:886-894.
4. Loehrer PJ Sr, Feng Y, Cardenas H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol*. 2011;29:4105-4112.
5. Ben-Josef E, Schipper M, Francis IR, et al. A phase I/II trial of intensity modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2012;84:1166-1171.
6. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. *J Natl Cancer Inst*. 1988;80:751-755.
7. 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.
8. 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.

9. Huguet F, Hammel P, Vernerey D, et al. Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study [abstract]. *J Clin Oncol*. 2014;32(suppl 5):Page. Abstract 4001.
10. Timmerman RD, Kavanagh BD, Cho LC, Papiez L, Xing L. Stereotactic body radiation therapy in multiple organ sites. *J Clin Oncol*. 2007;25:947-952.
11. Koong AC, Le QT, Ho A, et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2004;58:1017-1021.
12. 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.
13. 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.
14. Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer*. 2009;115:665-672.
15. 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.
16. Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol*. 2009;16:1727-1733.
17. Khashab MA, Kim KJ, Tryggstad EJ, et al. Comparative analysis of traditional and coiled fiducials implanted during EUS for pancreatic cancer patients receiving stereotactic body radiation therapy. *Gastrointest Endosc*. 2012;76:962-971.
18. Murphy JD, Christman-Skieller C, Kim J, Dieterich S, Chang DT, Koong AC. A dosimetric model of duodenal toxicity after stereotactic body radiotherapy for pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2010;78:1420-1426.
19. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365-376.
20. Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. *EORTC Study Group on Quality of Life. Eur J Cancer*. 1999;35:939-941.
21. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.
22. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*. 1989;10:1-10.
23. Hoyer M, Roed H, Sengelov L, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. *Radiother Oncol*. 2005;76:48-53.
24. Polistina F, Costantin G, Casamassima F, et al. Unresectable locally advanced pancreatic cancer: a multimodal treatment using neoadjuvant chemoradiotherapy (gemcitabine plus stereotactic radiosurgery) and subsequent surgical exploration. *Ann Surg Oncol*. 2010;17:2092-2101.
25. Mahadevan A, Jain S, Goldstein M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2010;78:735-742.
26. Lominska CE, Unger K, Nasr NM, Haddad N, Gagnon G. Stereotactic body radiation therapy for irradiation of localized adenocarcinoma of the pancreas. *Radiat Oncol*. 2012;7:74.
27. Tozzi A, Comito T, Alongi F, et al. SBRT in unresectable advanced pancreatic cancer: preliminary results of a mono-institutional experience. *Radiat Oncol*. 2013;8:148.
28. Gurka MK, Collins SP, Slack R, et al. Stereotactic body radiation therapy with concurrent full-dose gemcitabine for locally advanced pancreatic cancer: a pilot trial demonstrating safety. *Radiat Oncol*. 2013;8:44.
29. Chuong MD, Springett GM, Freilich JM, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. *Int J Radiat Oncol Biol Phys*. 2013;86:516-522.
30. Shin SH, Kim SC, Hong SM, et al. Genetic alterations of K-ras, p53, c-erbB-2, and DPC4 in pancreatic ductal adenocarcinoma and their correlation with patient survival. *Pancreas*. 2013;42:216-222.
31. McCarthy DM, Brat DJ, Wilentz RE, et al. Pancreatic intraepithelial neoplasia and infiltrating adenocarcinoma: analysis of progression and recurrence by DPC4 immunohistochemical labeling. *Hum Pathol*. 2001;32:638-642.
32. 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.