Chemotherapy and intensity-modulated radiation therapy for locally advanced pancreatic cancer achieves a high rate of R0 resection

Florence Huguet[a,b], **Carla Hajj**[b], **Corrine B. Winston**[c], **Weiji Shi**[d], **Zhigang Zhang**[d], **Abraham J. Wu**[b], **Eileen M. O'Reilly**[e], **Diane L. Reidy**[e], **Peter Allen**[f], and **Karyn A. Goodman**[g]

[a]Department of Radiation Oncology, Tenon Hospital, Hôpitaux Universitaires Est Parisien, University Pierre and Marie Curie Paris VI, Paris

[b]Department of Radiation Oncology at Memorial Sloan-Kettering Cancer Center, New York, NY, USA

[c]Department Radiology at Memorial Sloan-Kettering Cancer Center, New York, NY, USA

[d]Department Biostatistics at Memorial Sloan-Kettering Cancer Center, New York, NY, USA

[e]Department Medical Oncology at Memorial Sloan-Kettering Cancer Center, New York, NY, USA

[f]Department Surgery at Memorial Sloan-Kettering Cancer Center, New York, NY, USA

[g]Department of Radiation Oncology**, University of Colorado School of Medicine, Aurora, CO, USA

Abstract

Background—To assess local control, survival, and conversion to resectability among locally advanced pancreatic cancer (LAPC) patients treated with induction chemotherapy (ICT) followed by chemoradiotherapy treatment using intensity-modulated radiation therapy (IMRT).

Material and Methods—Between 2007 and 2012, 134 LAPC patients were treated with ICT followed by IMRT. After chemoradiotherapy, 40 patients received maintenance chemotherapy.

Results—With a median follow-up of 20 months, median overall survival (OS) was 23 months. One-year and 2-year OS was 85% and 47%, respectively. On multivariate analysis, progression of disease after IMRT was associated with worse overall survival. Cumulative incidence of local failure was 10% at 1 year and 36% at 2 years. Twenty-six patients (19%) underwent resection after chemoradiotherapy including 22 patients (85%) with negative margins. On multivariate analysis, response to IMRT was associated with surgery (p=0.01). Acute grade 3–4 hematologic and non-hematologic toxicity rates were 26% and 4.5%, respectively.

Corresponding author: Florence Huguet, MD, PhD, Department of Radiation Oncology,, Tenon Hospital - Hôpitaux Universitaires Est Parisien, 4, rue de la Chine, 75020 Paris, France, Tel: (33) 156018322; Fax: (33) 156016400, florence.huguet@aphp.fr.

Disclosure statement
The authors declare no conflict of interest.

Conclusion—IMRT is safe in patients with LAPC. Patients with non-progressive LAPC after ICT and who received IMRT had high rates of local control and prolonged survival.

Keywords

intensity-modulated radiation therapy; gemcitabine; locally advanced; pancreatic adenocarcinoma; chemoradiotherapy; FOLFIRINOX

Pancreatic adenocarcinoma is one of the leading causes of cancer-related mortality in the Western world [1]. The role of radiation therapy in locally advanced pancreatic cancer (LAPC) has been intensely debated over the past 30 years. Despite improved systemic agents and advances in chemoradiotherapy, patients who present with LAPC experience high rates of both distant metastatic failure and local progression, with a median survival time ranging from 5 to 11 months [2]. Induction chemotherapy (ICT) followed by chemoradiotherapy for patients without evidence of progressive disease potentially allows for selection of patients with a better prognosis [3–5]. This strategy has been evaluated in the GERCOR LAP07 phase III trial. Although overall survival was not improved in the chemoradiotherapy arm compared to the chemotherapy arm, patients with non-progressive LAPC after 4 months of ICT in the chemoradiotherapy arm had a longer time interval to second line therapy and significantly less local tumor progression [6].

Optimal methods of pancreatic irradiation are not clearly defined [7]. Delivery of adequate radiation dose to the pancreas is limited by the radiosensitivity of adjacent normal organs. It has been suggested that older radiotherapy protocols did not show a clear benefit due to insufficient dose and high toxicity. More conformal radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT) are now commonly employed; however, its use is not well established in pancreatic cancer. IMRT allows dose escalation by reducing the dose received by surrounding organs at risk. A few groups have published retrospective series establishing the feasibility of IMRT in pancreatic cancer [8–19]. Given the controversies regarding the role of radiation therapy in the management of LAPC, the aim of this study was to report the toxicity and outcomes, in particular the conversion to resectability, for patients treated with ICT followed by IMRT.

Material and Methods

Patients

Between March 2007 and November 2012, 134 patients with LAPC received ICT followed by chemoradiotherapy using IMRT at our institution.

A waiver of authorization was obtained from the MSKCC Institutional Review Board and data were obtained from a prospectively maintained pancreatic cancer database. All patients had a tissue diagnosis of pancreatic adenocarcinoma.

Locally advanced unresectable disease was defined as superior mesenteric artery or celiac axis encasement greater than 180 degrees, or unreconstructible superior mesenteric vein / portal occlusion, or aortic invasion, according to National Comprehensive Cancer Network Practice Guidelines in Oncology starting in 2007. All patients included in the study had

either 1) an unambiguous clinic note from a hepatobiliary surgeon or the multidisciplinary tumor board stating that the disease was locally advanced or 2) underwent an exploratory laparotomy and were found to have unresectable LAPC. For the patients who were ultimately converted to resectability, the pre-treatment CT scans were re-read at our institution by a radiologist (C.W.) with expertise in abdominal imaging to confirm locally advanced disease prior to chemoradiotherapy.

Treatment Plan

Chemotherapy—All patients received ICT. One hundred patients (75%) received gemcitabine-based chemotherapy and 34 patients (25%) received FOLFIRINOX. The patients received a median duration of 3.2 months of ICT prior to chemoradiation (range, 0.2–15.9).

All patients received chemotherapy concurrently with radiation therapy. Ninety-three patients (69%) received concurrent gemcitabine twice weekly (40 mg/m^2 twice per week), with the 41 others (31%) receiving infusional 5-fluorouracil (200–225 mg/m^2 daily) or oral capecitabine (1600 mg/m^2 divided in twice-daily doses given from Monday to Friday).

Some patients received maintenance chemotherapy after completion of radiation therapy, at the discretion of the medical oncologist.

Radiation therapy—The gross tumor volume (GTV) included gross tumor and enlarged lymph nodes on CT simulation. The clinical target volume (CTV) encompassed the draining lymph node basins including celiac, superior mesenteric and retroperitoneal nodes. A first planning target volume (PTV1) including the GTV and CTV was generated to account for daily setup error. A second PTV (PTV2) included the GTV with a 3 to 5-mm margin. Doses of 50.4 Gy and 56 Gy in 28 daily fractions were prescribed to the PTV1 and PTV2, respectively. Fifty percent of the patients were treated using respiratory gating for motion management [20]. Respiratory gating used a RPM system software (Varian Medical Systems, Palo Alto, CA) that correlates chest wall motion to the respiration phase. Diagnostic quality x-ray images and cone-beam CT were obtained to allow for real-time assessment of tumor positioning before delivery while the patient was on the treatment table.

Toxicity assessment and follow-up

Acute radiation toxicity was evaluated by the clinician during each week of radiation therapy according to the Common Terminology Criteria for Adverse Events version 3.0. Tumor response was assessed by a CT scan in all patients using RECIST 1.0 (Response Evaluation Criteria in Solid Tumors) at three months after the start of induction chemotherapy, at 4–6 weeks after the completion of the chemoradiotherapy, at 3 months after completion of chemoradiotherapy then, at 3-month intervals. Patients were assessed by the surgeons or in our Pancreaticohepatobiliary Multidisciplinary Conference for resectability at each of those post-treatment time points.

Statistical Analysis

The endpoints assessed were overall survival (OS), local failure rate, subsequent surgery rate, and acute toxicity. Kaplan-Meier method was used to estimate the OS, which was calculated from the date of diagnosis till the date of death or last follow-up. The cumulative incidence of local failure was calculated from the date of diagnosis to date of local failure, death without local failure, or last follow-up. Univariate and multivariate analysis of OS were done using respectively a log-rank test and a stepwise Cox proportional hazards model. All factors whose p-values < 0.2 were considered as candidates for the stepwise multivariate logistic regression. Univariate analysis of local failure was done using Gray's competing risks method. Univariate and multivariate analysis of relationship between treatment factors and surgery was done using respectively a Chi-square test and a stepwise logistic regression. In our series, surgery was not a baseline variable; therefore, we did not provide a Kaplan-Meier curve for overall survival for surgical versus non-surgical group to avoid estimation bias. Differences were assumed to be significant when P<0.05.

Results

Patient and Treatment Characteristics

Characteristics of the 134 LAPC patients are reported in Table 1.

All patients first received ICT. Response to chemotherapy was evaluated on CT scan before the start of chemoradiotherapy. Fifty-one patients (38%) had partial response, 63 patients (47%) had stable disease, nine patients (7%) had local progression, and 11 were not assessed.

Response to chemoradiotherapy

The objective tumor response to chemoradiotherapy was assessed on a CT scan one month after the completion of chemoradiotherapy. Three patients (2%) achieved a complete response, 38 patients (28%) a partial response, 74 patients (55%) had stable disease, 13 patients (10%) experienced progressive disease, and six were not assessed.

Forty patients (30%) received maintenance chemotherapy after the completion of radiation therapy. Thirty-two patients (80%) received as maintenance chemotherapy the same regimen as ICT. Median duration of maintenance chemotherapy was 3.8 months (range, 0.5–19.4 months). The reasons for stopping maintenance chemotherapy were mainly surgery, disease progression, and toxicity.

Survival

Median follow-up time was 20 months (range, 12.9–81.8 months). At the time of analysis, 98 deaths occurred. Median OS was 23 months. The 1- and 2-year actuarial OS rates were 86% and 48%, respectively (Figure 1a). On univariate analysis, response to ICT, response to IMRT (Figure 1b), and surgery were significantly associated with a better OS. On multivariate analysis, progression of disease after IMRT (PD vs. CR/PR, HR=4.42; 95%CI=1.96–9.98; p=0.0004) was associated with worse OS, and absence of surgery (HR=1.84; 95%CI=0.99–3.39;p=0.052) was marginally associated with worse OS (Table 2).

At the time of analysis, 93 patients (69%) presented with a relapse: 16 patients (17%) had isolated local relapse, 33 patients (36%) had both local and distant relapse, and 44 patients (47%) had distant metastases without local relapse.

The cumulative incidence of local failure at 1 year and 2 years were 10% (95%CI=5–15%) and 36% (95%CI=27–45%), respectively (Figure 2). None of the factors analyzed was significantly associated with local failure.

The cumulative incidence of distant metastasis at 1 year and 2 years were 30% (95%CI=22–38%) and 64% (95%CI=55–72%), respectively. On univariate analysis, absence of response to IMRT was associated significantly with the development of distant metastases (p=0.03). This was confirmed on multivariate analysis (HR=2.75; 95%CI=1.20–6.34; p=0.02).

Conversion to resectability

Conversion to resectability was achieved in 26 patients (19%) who were initially judged to have unresectable locally advanced disease by imaging and multidisciplinary board assessment (n=21) or prior laparoscopy (n=5). The median time from the end of the chemoradiotherapy to surgery was 3.3 months (range, 1.1–11.6 months). The decision regarding resectability was based on whether there was any improvement in the involvement of the involved vessel(s). While a clear fat-plane was not always achieved prior to surgery, there was generally decreased soft-tissue around the vessel, but there could still be residual stranding that might have been related to fibrosis. Twenty-five patients underwent definitive pancreaticoduodenectomy and one a total pancreatectomy. Twenty-two patients (85%) had negative surgical margins (R0). One patient (4%) had a complete pathologic response (ypT0). The median number of lymph nodes examined was 13 (range, 6–24). Twenty-three patients (88%) had no involved lymph nodes (ypN0). Fifteen of the resected patients (58%) received adjuvant chemotherapy for a median period of 2 months (range, 1.2–3.8 months).

On univariate analysis, response to IMRT was associated with subsequent surgery (p=0.01). This was confirmed on multivariate analysis (HR=3.25; 95%CI=1.31–8.04; p=0.01).

Tolerance

One hundred twenty-eight patients (96%) completed the prescribed course of radiation therapy in a median of 38 days. Treatment was discontinued prematurely in six patients (four patients had disease progression while on treatment, one patient had severe treatment-related toxicity, and one patient passed away at an outside hospital due to bleeding from unknown source). Seventeen patients (13%) had an interruption in radiation course due to toxicity (n=16) or social issues (n=1). Acute toxicities are summarized in Table 3. Thirty-five patients (26%) developed grade 3–4 hematological toxicity, primarily thrombocytopenia, and six patients (4.5%) developed grade 3–4 non-hematological toxicity. There was no difference in terms of grade 3–4 toxicity between patients who received concurrent gemcitabine versus fluoropyrimidine (p=0.7).

Discussion

Management of patients with LAPC has been actively debated over the past decade and the optimal therapeutic approach remains unclear [2]. Although distant metastatic disease remains the primary cause of mortality, local progression also poses a significant problem. In a recent autopsy series, the death cause in one-third of patients was locally destructive pancreatic cancer [21]. The strategy combining ICT followed by chemoradiotherapy for LAPC aims to control both local and distant disease [3–5].

The present study is one of the largest to report the results of a strategy of ICT followed by IMRT for LAPC. The regimen was well tolerated with a low rate of grade 3–4 gastrointestinal toxicity (4.5%), indicating that IMRT with an integrated boost to a dose of 56 Gy is safe and feasible when combined with concurrent chemotherapy. Our short-term local control and survival rates are promising and appear better than historical standards. Perhaps the most promising sign of the efficacy of this combined-modality approach is a significant rate (19%) of patients rendered resectable after IMRT and the achievement of margin- and node-negative resections in 85% and 88% of these patients respectively.

Although the recent phase III randomized LAP07 trial did not demonstrate a survival benefit with the use of ICT followed by chemoradiotherapy compared to chemotherapy, there is still evidence that this is a promising therapeutic strategy. Indeed, in the chemoradiotherapy arm, the disease free survival rate was improved with a longer time off therapy prior to initiation of second line therapy [6]. The patterns of failure were also impacted by the use of radiotherapy, with significantly fewer patients developing local progression. Taken together, these results suggest that chemoradiotherapy could confer an advantage for these patients in terms of quality of life.

When compared to patients treated on the LAP07 trial for whom the median OS times ranged from 15 to 16 months, our results appear better, with a median OS of 23 months [6]. Our results compared favorably with those of a recent phase II study including patients with LAPC and borderline resectable pancreatic cancer treated with ICT combining gemcitabine, oxaliplatin and cetuximab, followed by radiation therapy at a dose of 50.4 Gy with concurrent capecitabine and cetuximab [22]. In this phase II trial, none of the patients with LAPC went on to a surgical resection whereas 19% of our patients underwent surgical resection, potentially signifying a benefit of dose escalation to 56 Gy used in our cohort. Interestingly, partial response to IMRT was associated with conversion to resectability, better overall survival, and less distant metastasis on both univariate and multivariate analysis. These observations underscore the therapeutic advantage of combining induction chemotherapy and chemoradiotherapy for LAPC and the role of response to IMRT as a predictive factor of outcome after combined modality treatment.

Several groups have demonstrated the feasibility of IMRT in the treatment of pancreatic tumors (Table 4) [8–19]. Milano et al. reported on 25 patients with pancreatic and bile duct carcinomas, comparing IMRT with three-dimensional conformal radiotherapy plans [11]. The dose received by critical structures such as kidneys, liver, and small bowel was significantly reduced with the use of IMRT plans. Yovino et al. reported on 46 patients with

pancreatic/ampullary cancer treated with concurrent 5-fluorouracil based chemoradiotherapy using IMRT [13]. When compared to patients who had three-dimensional treatment planning in the RTOG 97–04 trial, IMRT significantly reduced the incidence of grade 3–4 nausea and vomiting (0% vs. 11%, p=0.024) and diarrhea (3% vs. 18%, p=0.017). One limitation of these studies is that they included both post-operative and LAPC patients even though the treatment intent, prognosis, and potential toxicities are different in these two settings. Ben-Josef et al. published the results of a phase I/II trial of IMRT dose escalation with concurrent fixed-dose gemcitabine in 50 patients with LAPC [14]. The recommended dose was 55 Gy. The median and 2-year OS were 14.8 months and 30%, respectively. Similar to our cohort, 12 (24%) patients underwent resection (10 R0, 2 R1). In another recent phase II trial, patients were treated with ICT followed by chemoradiotherapy with IMRT at a dose of 54 Gy and concurrent capecitabine [18]. This regimen was well tolerated with 9.5% of grade 3–4 gastrointestinal toxicity. Among the 24 LAPC included in this trial, the median OS was 9.3 months and the resection rate 8%. Interestingly, Krishnan et al. have shown in a retrospective study of MDACC cohort that patients who received focal dose escalation with IMRT had an improved OS and locoregional relapse free survival without additional toxicity [23]. This has to be confirmed prospectively.

Although all patients in our study were treated with the same therapeutic strategy, our study is retrospective and thus hypothesis-generating. While the IMRT was homogeneously administered, the chemotherapy approach was more heterogeneous. Patients were treated with different induction chemotherapeutic regimens, concurrent chemotherapy was either gemcitabine or 5-FU based, and only one third of patients received maintenance chemotherapy. The efficacy of maintenance chemotherapy needs to be prospectively evaluated.

Advances in both systemic and local therapies may be contributing to incremental improvement in outcome for patients with LAPC. Intensified chemotherapy regimen such as FOLFIRINOX allows a higher rate of resection when followed by chemoradiotherapy, ranging from 23% to 41% [17, 24–27]. However, in our study, the number of patients treated with FOLFIRINOX was insufficient to assess its impact on outcome compared to gemcitabine-based chemotherapy. In a recent publication evaluating LAPC patients who received FOLFIRINOX with or without chemoradiation, the median OS was 25 months [27]. In view of the good tolerance of IMRT, the next step is to assess the influence of dose escalation on conversion to resectability and survival. Two ongoing randomized phase II trials are investigating this approach, SCALOP2 (NCT02024009) and RTOG 1201 (NCT01921751).

Finally, identifying both clinical and genomic predictors of response to chemoradiotherapy may help in selecting a subgroup of patients with LAPC who could benefit from chemoradiotherapy with the goal of allowing for surgical resection and improving survival.

Acknowledgments

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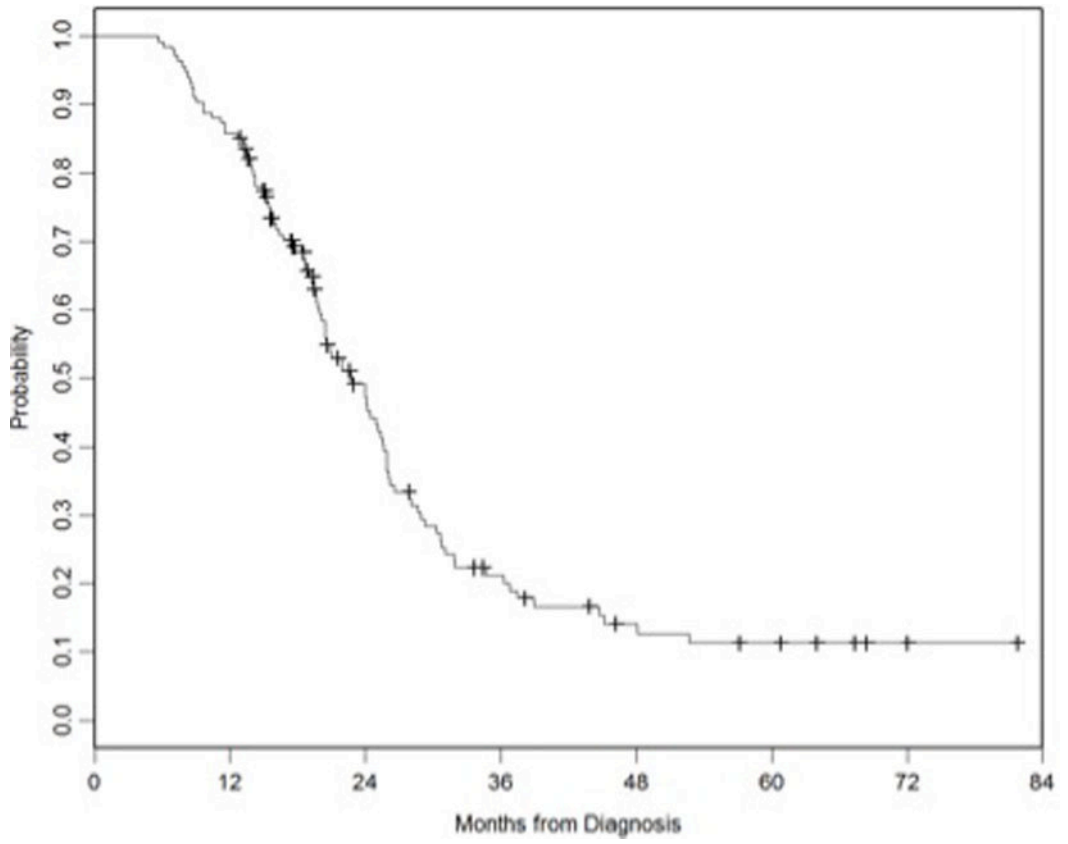
Figure 1a.
Kaplan Meier overall survival curve for all patients.
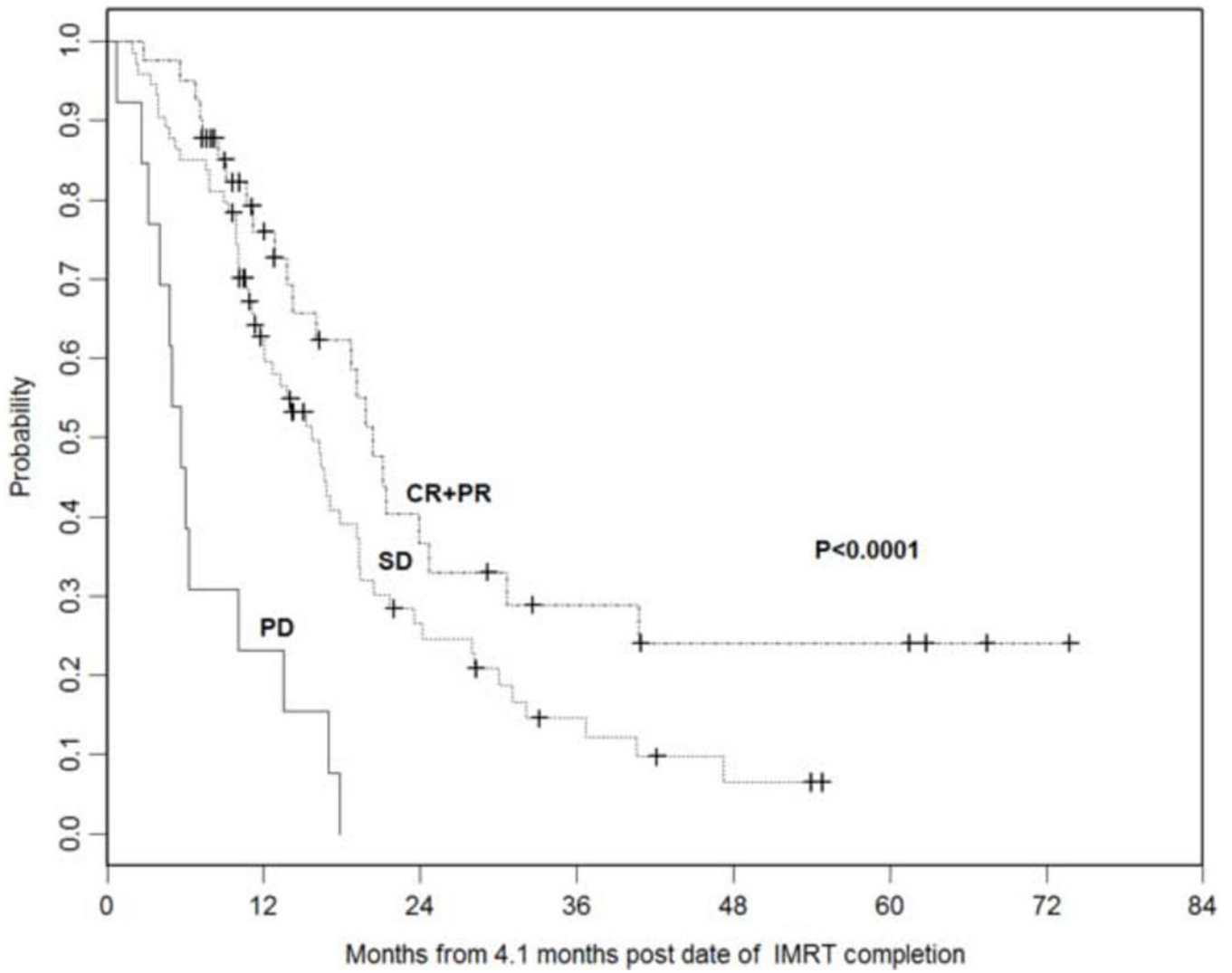
Figure 1b.
Kaplan Meier overall survival curves stratified by response to IMRT. (PD, progressive disease; SD, stable disease; CR+PR, complete response + partial response)
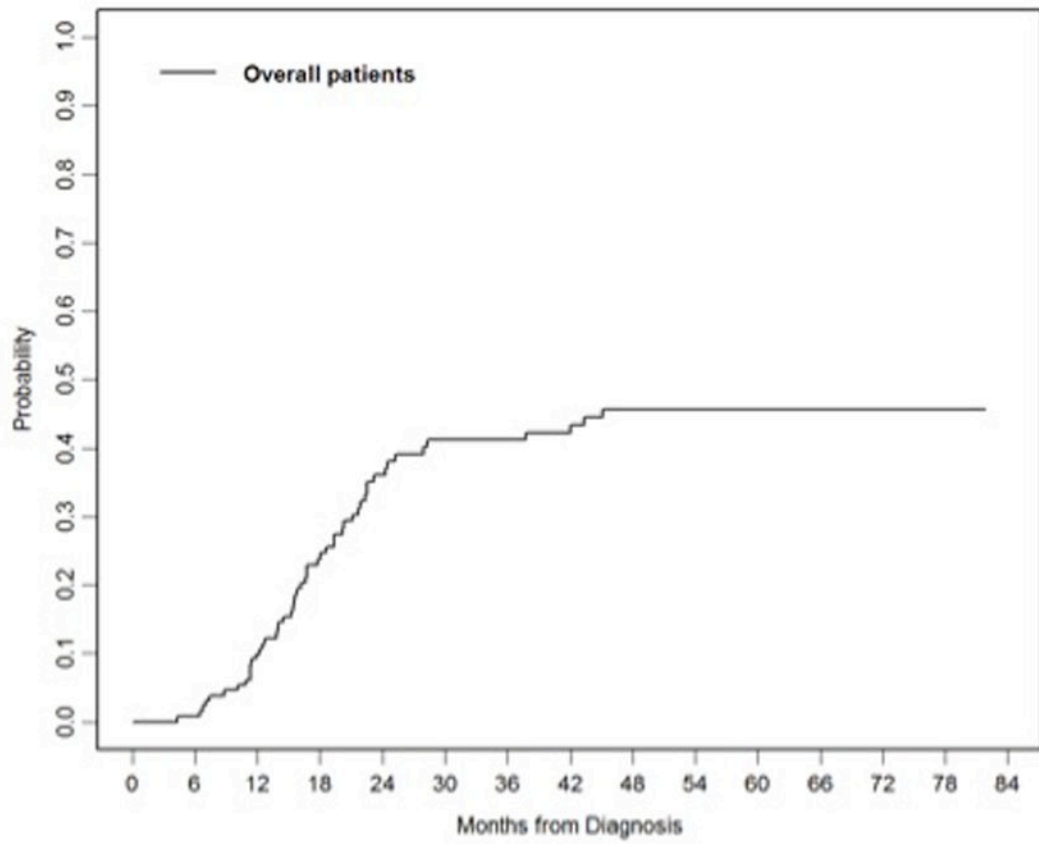
Figure 2.
Cumulative incidence of local failure for all patients.

Table 1

Patient characteristics.

Characteristic	Whole population (n, %) n=134
Age (years)	
Mean ± SD	64.1 ± 9.9
Median	64.5
Range	36.7 – 84.1
Gender	
Male	71 (53)
Female	63 (47)
Karnofsky performance status	
100–90%	52 (39)
80–70%	79 (59)
<70%	3 (2)
Location	
Head	83 (62)
Body or tail	51 (38)
Tumor size (cm)	
Mean ± SD	3.8 ± 1.4
Median	3.5
Range	1.2 – 8.9
Exploratory laparotomy	
no	101 (75)
yes	33 (25)
Level of CA19-9 at diagnosis	
Mean ± SD	564 ± 1066.5
Median	185
Range	0 – 6806
Not evaluated	25

Table 2

Univariate and multivariate analysis of overall survival.

Factor	Univariate analysis		Multivariate analysis	
	Number of death / censored, n	P-value[1]		P-value[1]
Radiographic arterial involvement		0.30		
No	36 / 6			
Yes	62 / 30			
Response to ICT		0.0009		
PR	33 / 18			
SD	47 / 16			
PD	8 / 1			
Response to IMRT[1]		<0.0001		
CR + PR	23 / 18		1.00	
SD	57 / 17		1.37 (0.82 – 2.28)	0.23
PD	13 / 0		4.42 (1.96 – 9.98)	0.0004
Maintenance chemotherapy		0.58		
No	29 / 21			
Yes	66 / 15			
Duration of induction chemotherapy		0.47		
< 3.2 months	46 / 19			
3.2 months	51 / 17			
Surgery[1]		0.004[1]		
Yes	13 / 13		1.00	
No	69 / 23		1.84 (0.99 – 3.39)	0.052

[1] Time to overall survival (OS) was calculated from 4.1 months post RT end date for response to IMRT and surgery on univariate analysis (UVA), and for stepwise multivariate analysis; Time to OS was calculated from RT end date for other factors on UVA.

Table 3

Acute Treatment-Related Toxicity According to NCI CTCAE Version 3.0.

Toxicity (CTCAE)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematologic toxicity			
Anemia	47 (35)	12 (9)	0
Neutropenia	13 (10)	4 (3)	1 (1)
Thrombocytopenia	20 (15)	22 (16)	4 (3)
Non hematologic toxicity			
Fatigue	55 (41)	3 (2)	0
Nausea	18 (13)	1 (1)	0
Vomiting	3 (2)	0	1 (1)
Diarrhea	8 (6)	3 (2)	0
Rash	1 (1)	0	0
Mucositis	2 (1)	0	0

Table 4

Summary of IMRT Studies in Locally Advanced Pancreatic Adenocarcinoma.

Author	Year	N	Treatment	Grade 3–4 GI Acute Toxicity (%)	Median OS (months)	1-year OS (%)	Rate of resection (%)
Current study	2016	134	56 Gy 5-FU or Gem	4.5	23	85	19
Krishnan	2016	200	50–67.5 Gy Capecitabine or 5-FU or Gem	2	15.3	60	–
Ke	2014	32	54 Gy S-1	25	15.2	75	–
Esnaola	2014	37 (24 LA)	54 Gy Capecitabine	9.5	9.3	50	8
Badiyan	2013	32 (25 LA)	55 Gy Gem	22	23.1	–	24
Abelson	2012	47 (18 LA)	50.4–54 Gy 5-FU or capecitabine	9	7.7	24	–
Tunceroglu	2012	20	50.4–54 Gy 5-FU or Gem	20	11.6	55	–
Ben-Josef	2012	50	50–60 Gy Gem	24	14.8	73	24
Yovino	2010	46 (15 LA)	50.4–59.4 Gy 5-FU or capecitabine	4	9.7	–	–
Fuss	2007	41 (24 LA)	54 Gy Concurrent CT	7	10	33	–
Ben-Josef	2004	15 (8 LA)	45–55 Gy Capecitabine or Gem	7	–	69	25
Milano	2004	20 (14 LA)	50.4–59.4 Gy 5-FU	20	9.3	–	32
Bai	2003	16	30 Gy then 21–30 Gy 5-FU or Gem	–	–	35	–
Crane	2001	5	33 Gy Gem	50	–	–	20

Abbreviations: GI, gastrointestinal; OS, overall survival; LA, locally advanced; 5-FU, 5-fluorouracil; Gem, gemcitabine.