Online ISSN: 2682-2628
Print ISSN: 2682-261X

IJCBR

International Journal of Cancer and Biomedical Research

https://jcbr.journals.ekb.eg

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PUBLISHED BY
EACR EGYPTIAN ASSOCIAN FOR CANCER RESEARCH
Since 2014

INTERNATIONAL JOURNAL OF CANCER AND BIOMEDICAL RESEARCH (IJCBR)

RESEARCH ARTICLE

Induction chemotherapy followed by concomitant chemoradiation using intensity modulated radiotherapy technique in locally advanced unresectable pancreatic cancer patients

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ABSTRACT

Background: Induction gemcitabine-based chemotherapy followed by concomitant chemoradiation would increase response rate and resectability in locally advanced unresectable pancreatic cancer. **Patients:** Patients with locally advanced unresectable pancreatic adenocarcinoma**. Methods:** were assigned to receive gemcitabine-based chemotherapy for 2-4 cycles, patients who showed partial response were assigned to receive CCRT with IMRT technique, our primary endpoint was surgical resection, secondary end point was disease progression or unacceptable toxicity. **Results:** After 2-4 cycles of induction chemotherapy. Only 28 patients received the planned protocol of chemoradiation. Nine patients underwent surgical resection. No marginal involvement (R0) was observed in 3 patients. They reached a complete response until the end of the study. Nineteen patients received chemoradiation only. Good partial response was observed in 13 patients, one showed stationary disease. Disease progression occurred in seven patients. Chemotherapy toxicity was mild in all patients. Neutropenia was more with Gemcitabine/oxaloplatin. Thrombocytopenia was more in both gemciatabine monotherapy and gemcitabine/cisplatin arm. Anemia was more common with gemcitabine/cisplatin. Non heametological toxicity included, fatigue, Weight loss, gastrointestinal toxicity, nausea & vomiting. Radiation side effects were mild in all patients and included mild inflammatory skin reaction, delayed gastric emptying, flatulence or diarrhea. Gastrointestinal bleeding was observed in 5 patients. Progression free and overall survival rates were better in patients who received CCRT even who did not proceed for surgery. **Conclusion:** The use of concomitant chemoradiation as part of a neoadjuvant multi-modality treatment is associated with improved outcomes, tumor downstaging, increased rate of R0 resection and better survival.

Keywords: Induction chemotherapy, Concomitant chemoradiation, Locally advanced pancreatic cancer, Intensity modulated radiotherapy

Editor-in-Chief: Prof. M.L. Salem, PhD - Article DOI: 10.21608/JCBR.2023.195990.1293

ARTICLE INFO

Article history
Received: February 24, 2023
Revised: May 06, 2023
Accepted: May 18, 2023

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INTRODUCTION

Pancreatic cancer is the second most common gastrointestinal cancer and the fourth leading cause of cancer-related deaths in men and women of all ages in developed countries, with a 5-year overall survival for all stages combined just about 5% (Jemal et al. 2010). Even with the addition of radiation therapy and chemotherapy in both the adjuvant and neoadjuvant settings, the annual age-adjusted mortality rates from pancreatic cancer have only mildly improved (Gudjonsson 1987; Raimondi et al. 2010).

Several randomized studies have demonstrated that induction chemotherapy can achieve a good clinical response and even survival benefits for patients with locally advanced pancreatic cancer (LAPC), as it helps in accurately selecting patients who may benefit from RT (Torgeson et al. 2017; Huguet et al. 2017; Krishnan et al. 2016). However, most of patients who receive radiation therapy have transient partial responses which make surgical resection more challenging. (Gemenetzis et al. 2019).

Adjuvant concurrent chemoradiation is considered now a standard of care for patients who have undergone surgical resection (Badiyan et al. 2017; Oettle et al. 2013; Uesaka et al. 2016) , but the standard of care for LAPC is still poorly defined.

The role of radiation therapy in LAPC has been intensely debated over the past 30 years (Shinchi et al. 2002; André et al. 2000; Kornek et al. 2001), and despite advances in chemoradiotherapy techniques, patients who present with LAPC have high rates of both distant and local progression with a median survival of 5 to 11 months (Moertel et al. 1981). Induction chemotherapy (ICT) followed by chemoradiotherapy for patients with partial or even stable disease allows for selection of patients with a better prognosis as those patients have a longer time interval to second line therapy and significantly less local tumor progression as demonstrated in the GERCOR LAP07 phase III trial, although overall survival (OS) was not improved in the chemoradiotherapy arm compared to chemotherapy alone (Huguet et al. 2007; Krishnan et al. 2007; Ko et al. 2007).

One of the major challenges of administering radiation therapy to the upper abdomen is the presence of multiple critical structures in the immediate vicinity of the pancreas, including the liver, kidneys, stomach, small bowel, and spinal cord. Since 1990's, radiation treatment equipment and related techniques have been developed dramatically especially intensity modulated radiation therapy (IMRT) that conforms a high dose to the target (tumor) volume while restricting dose to the surrounding sensitive structures (Ben-Josef et al. 2004).

With the aid of these recent advances in both chemotherapeutic regimens and radiation techniques conversion to resectability have been widely studied and become an accepted strategy for responding patients in several randomized trials (Gillen et al. 2010; Satoi et al. 2013).

AIM

Evaluation of the treatment response, toxicity and survival in patients with locally advanced unresectable pancreatic cancer receiving induction chemotherapy followed by concomittant chemoradiation therapy by IMRT technique and whether this protocol can achieve high R0 resection in those patients.

PATIENTS AND METHODS

Patients

This prospective study was carried out at Clinical Oncology Departments Tanta University Hospitals and Gharbia cancer society through the period from March 2018 to December 2020 and included forty patients with locally advanced unresectable pancreatic cancer. The study protocol and sampling were approved by institutional review boards of Faculty of medicine Tanta University with approval code number 32149/02/18.

Inclusion criteria Patients with locally advanced unresectable pancreatic adenocarcinoma, aged ≥ 18 years, ECOG performance status of < 2 with adequate blood picture, liver and renal function tests.

Exclusion criteria Patients with evidence of metastatic pancreatic cancer or who underwent surgical resection. Presence of another primary tumor.

Methods

Careful history taking, clinical examination and laboratory investigations including pretreatment tumor markers: Ca19.9, initial clinical TNM staging according to AJCC eighth edition 2017 by contrast enhanced CT or MRI abdomen and pelvis, CT scan of chest and/or PET CT, bone scan if clinically indicated.

Induction chemotherapy

All patients received induction gemcitabine-based chemotherapy for 2 to 4 cycles either [gemcitabine 1000 mg /m2 on day 1 followed by oxaloplatin 100 mg/m^2 on day 2 and (GEMOX)], [gemcitabine 1000mg / m2 on day 1 and day 15, cisplatin 50 mg/m^2 on day 1 and day 15] or Gemcitabine alone 1000 mg/m^2 infusion over 30 minutes given on day 1, 8 and day 15]. Assessment was done 1~3 weeks after completing induction chemotherapy to evaluate response. Patients who showed partial response to chemotherapy entered the concurrent chemoradiation protocol.

Concurrent chemotherapy: single agent gemcitabine (300 mg/m^2) was administrated ionce weekly during IMRT.

Radiotherapy was started 3-4 weeks after the end of induction chemotherapy.

All patients had a contrast-enhanced computed tomography (CT) with a slice thickness of 3 mm in a supine position with the arms raised above the head. Contouring of target volumes and organ at risk was performed according to RTOG guidelines:

The gross target volume (GTV) was defined as gross disease seen on CT scan, fused MRI or PET scan.

The clinical target volume (CTV) encompassed the abdominal regional lymph nodes which included: Peripancreatic, Celiac (CA), superior mesenteric (SMA), Porta hepatis (PV) and Para-aortic lymph nodes.

The planning target volume (**PTV)** included the CTV with a 0.5 cm expansion.

Organs at risk (OAR): It included liver, stomach, spinal cord, small bowel, large bowel, and kidneys. Treatment planning was done on Electa planning system with energy used 6 to 15 MV photons. Dose to PTV nodal was 50.4 G and boost dose to PTV primary was 56 Gy. The IMRT plans were optimized to minimize the volume of PTV receiving <95% of the prescribed dose and the volume receiving >115% of the prescribed dose. Generally, <5% of the target received <95% of the prescribed dose, and <1% of the target received >115% of the dose. Homogeneity index as well as confirmatory index was calculated for every plan. Treatment interruption occurred in 8 patients and the treatment gap was calculated.Patients were subjected to close monitoring and proper medications to overcome any troubles.

Adjuvant chemotherapy: All patients received post treatment chemotherapy to complete 6 cycles. Patients who showed disease progression on gemcitabine-based chemotherapy were shifted to 5FU based regimens to complete 6 cycles. Response was evaluated before surgery according to RECIST criteria version 1.1 (Eisenhauer et al. 2009).

Resection was categorized as: R0 free surgical margin, R1: cancer cells within 1mm from the surgical margin or R2: Macroscopic non-radical surgery

Assessment of toxicity: Toxicity to chemotherapy was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 4.1. Toxicity to radiation therapy was evaluated according to the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC)

Patient follow up: Patients were followed up every 3 months by history, clinical examination, and CA19.9 for 2 years then every 6 months, chest, pelvis and abdominal CT every 6-12 months for 2 years.

End points: Our primary endpoint was surgical resection in patients who became operable after concurrent CRT, secondary end point was disease progression, unacceptable toxicity or facing one or more of the exclusion criteria.

Statistical analysis

The collected data was analyzed using SPSS software statistical computer package version 21. Two tailed P values 0.05 were considered significant. Survival plots were estimated using the Kaplan-Meier method and the Cox proportional hazards model was used for multivariate analysis. Progression free survival (DFS); was calculated from the date of diagnosis to the date of disease recurrence and/or distant metastasis. Overall survival (OS); was calculated from the date of diagnosis to the date of death or last follow up.

RESULTS

Demographic, clinical, radiological and laboratory patients' characteristics are listed in Table 1.

Outcome of induction chemotherapy

All patients received 2-4 cycles of induction chemotherapy thirty patients (75%) showed a good partial response, six patients showed stationary disease and four patient developed disease progression.

Table 1. Demographic Clinical, Radiological and laboratory patients' characteristics

Demographic data	No.	%
Sex (n=40)		
Male	24	60.0
Female	16	40.0
Age (years) (n=40)		
>50	16	40.0
≤50	24	60.0
P.S (n=40)		
0 – 1	29	72.5
2	11	27.5
Smoking (n=40)		
Yes	14	35
No	26	65
Co-morbidities (n=40)	**No.**	**%**
No	16	40.0
Diabetic	12	30.0
HTN	6	15.0
Diabetic &HTN	6	15.0
Obstructive jaundice at present (n=40)	21	52.5
Yes		
No	19	47.5
Stent (n=40)		
Yes	19	47.5
No	21	52.5
Site of tumor (n=40)	**No.**	**%**
Head	23	57.5
Body	8	20.0
Tail	1	2.5
Body & Tail	5	12.5
Head & Body	3	7.5
TNM stage (n=40)	**No.**	**%**
T Stage		
T2	1	2.5
T3	23	57.5
T4	16	40.0
N Stage		
N0	17	42.5
N1	23	57.5
Initial ca19.9 (n=40)		
Elevated	35	87.5
Not	5	12.5

Outcome of chemoradiation

Only 28 patients received the planned protocol of chemoradiation, two patients did not complete the chemoradiation course because of deterioration of general conditions. Overall, nine patients [(9/28), 32.1%] underwent surgical resection. R0 was observed in 3 patients, R1 in 2 patients, R2 in 4 patients. The 3 patients with an R0 resection reached a complete response until the end of the study.

Nineteen patients [(19/28), 67.85] received chemoradiation only. Good partial response was observed in 13 (13/19) patients, one (1/19) patient showed stationary disease. Disease progression occurred in seven (7/19) patients in the form of local recurrence (four patients) and distant liver metastasis in three patients. Correlation between treatment response and different clinic pathological factors are listed in Table 2.

Chemotherapy toxicity was mild in all patients. Interruption of chemotherapy cycles was mainly due to hematological toxicity. Radiation side effects were mild in all patients and included inflammatory skin reaction, delayed gastric emptying, flatulence and diarrhea. Grade 3 diarrhea occurred only in one patient. Melena was observed in 5 patients and revealed spontaneously listed in Table 3.

Survival analysis

Kaplan-Meier curve for overall survival showed that six months and 1-year overall survival rates were better in the chemoradiation arm. The difference was statistically significant (p=0.001) (Figure 1). Patients who did not receive chemoradiation did not reach either the six months or 1-year PFS. Patients who received chemoradiation; the six months and 1-year PFS were 66.2% and 30.9% respectively this difference was statistically significant (p<0.001) (Figure 2). Case presentation for isodose distribution and dose volume histogram using IMRT technique are demonstrated in (Figures 3 and 4).

DISCUSSION

Unfortunately, about 30% of patients with pancreatic cancer have locally advanced unresectable disease without evidence of distant metastasis at time of diagnosis. This group of patients has been studied intensively in recent years as conversion to resectability remains the major goal of treatment (Fiore et al. 2017). The prognosis of locally advanced pancreatic cancer had shown a slow improvement in the past few years, mostly because of the progress in chemotherapy combinations and radiotherapy techniques as IMRT.

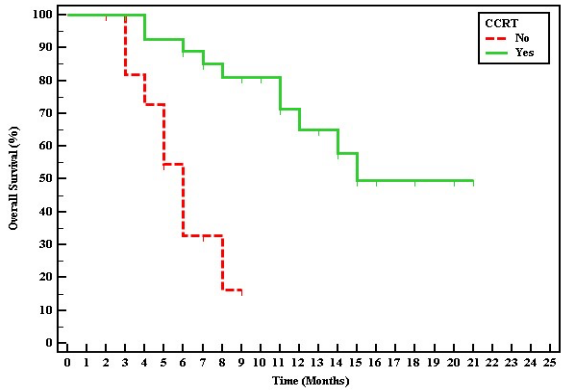

Figure 1. Kaplan-Meier survival curve for overall survival with CCRT (n=40). (p=0.001).

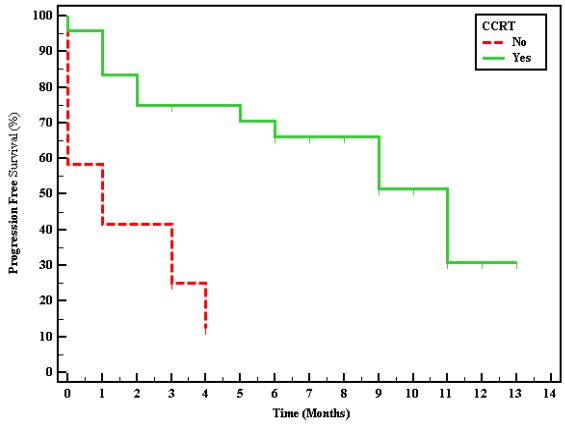

Figure 2. Kaplan-Meier survival curve for progression free survival with CCRT (n=36) Survival analysis**.**

Chemotherapy is still considered the mainstay of the treatment for this category of patients with locally advanced disease. The role of CCRT is still not clear, but consolidative CCRT after induction chemotherapy has been reported and may lead to change patients to resectability (Satoi et al. 2013). Neoadjuvant therapy in locally advanced pancreatic cancer (LAPC) has been an attractive option for patients and physicians due to its benefit in tumor down staging, improved margin-negative resection rates and reducing the number of positive regional lymph nodes; it also allows better patient selection for surgery. On the other hand, concern for tumor progression or functional deterioration during the course of neoadjuvant therapy can lead to the loss of a ‘‘window of opportunity’’ during which the patient may have the chance for tumor resection. In addition, delaying a surgical resection of the tumor may lead to patient anxiety (Chawla et al. 2020).

In this study, 40 patients with locally advanced unresectable pancreatic carcinoma received 2-4 cycles of induction chemotherapy; which facilitated the selection of patients most likely to benefit from local treatment. In addition, induction chemotherapy allowed a patient observation period because restaging patients after completion of induction chemotherapy has helped identify individuals with unfavorable prognosis manifested by disease progression and distant disease. Second, the decrease in the tumor size which has been achieved by induction chemotherapy resulted in a more limited target volume for irradiation, which decreased the radiation toxicity of adjacent organs (ie, gastrointestinal toxicity). These results were supported by Changhoon Yoo et al 2019 who reported less advanced T and N stages, and less frequent lymphovascular and perineural invasion with neoadjuvant chemotherapy compared with upfront surgery, despite having a greater tumor burden at the time of diagnosis (Yoo et al. 2019).

In 2015, Ferrone et al. reported their results of 40 patients with locally advanced unresectable or borderline resectable cancer who underwent resection after using FOLFIRINOX regimen in the neoadjuvant settings and they achieved an high R0 resection rate of 92% (Ferrone et al. 2015). Based on these favorable results, several papers have been published on the effectiveness of neoadjuvant chemotherapy especially FOLFIRINOX regimen including 10 or more cases of conversion surgery for unresectable locally advanced cancer and radiation therapy was also used with FOLFIRINOX in most of the studies (Hosein et al. 2012; Faris et al. 2013; Chapman et al. 2018; Barenboim et al. 2018; Marchegiani et al. 2018). The response rate of FOLFIRINOX treatment was about 20–40%, similar to the ACCORD 11 trial (Conroy et al. 2011). Treatment regimens were well tolerated; grade 1–2 fatigue were the most common non haematological events, the gastrointestinal toxicity included [G1-2 gastritis in 28 patients (70%), G1-2 nausea and vomiting in 19 patients (47.5%) and G1-2 liver toxicity in 11 patients (27.5%)].

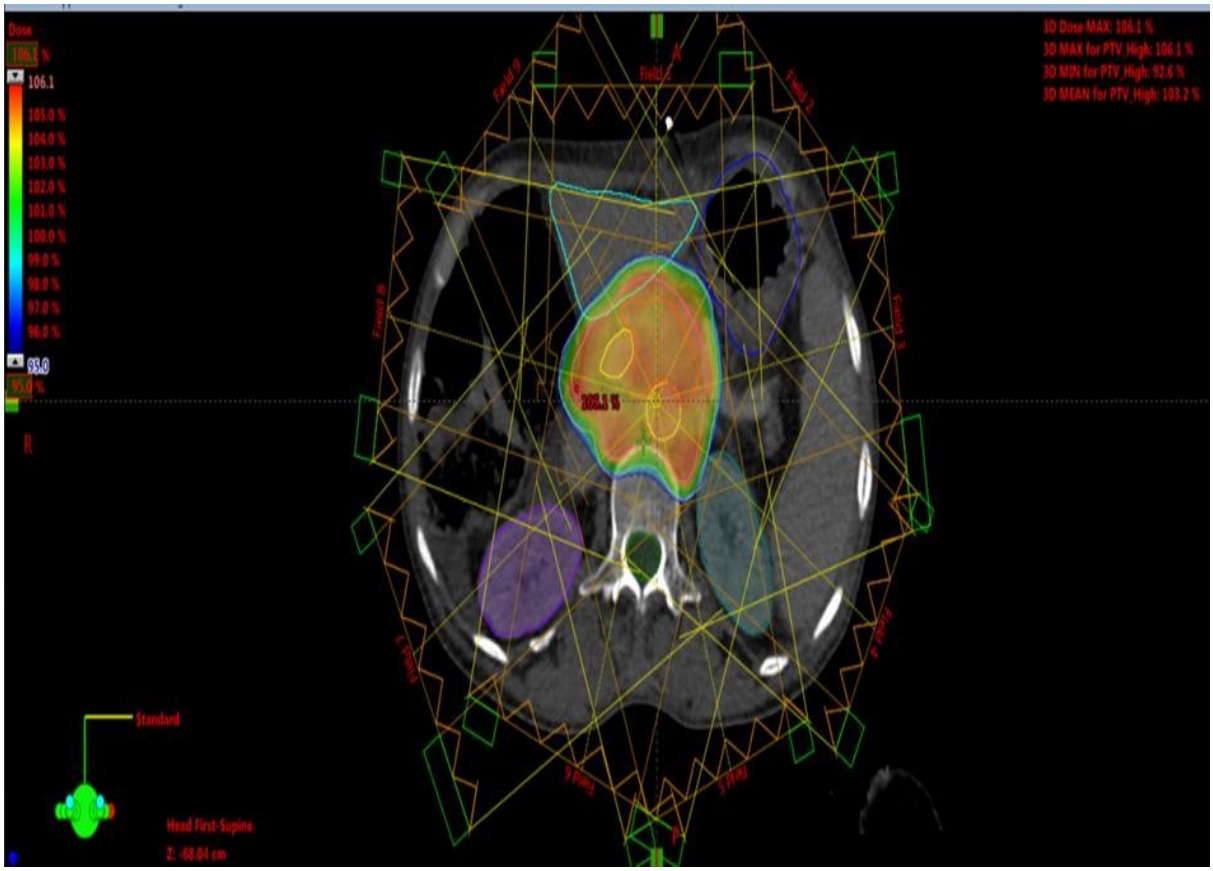

Figure 3. Isodose distribution of 95% of prescribed dose to the planning target volume of the gross tumor and nodal CTV. IMRT technique, nine fields were generated using 6 mv photons

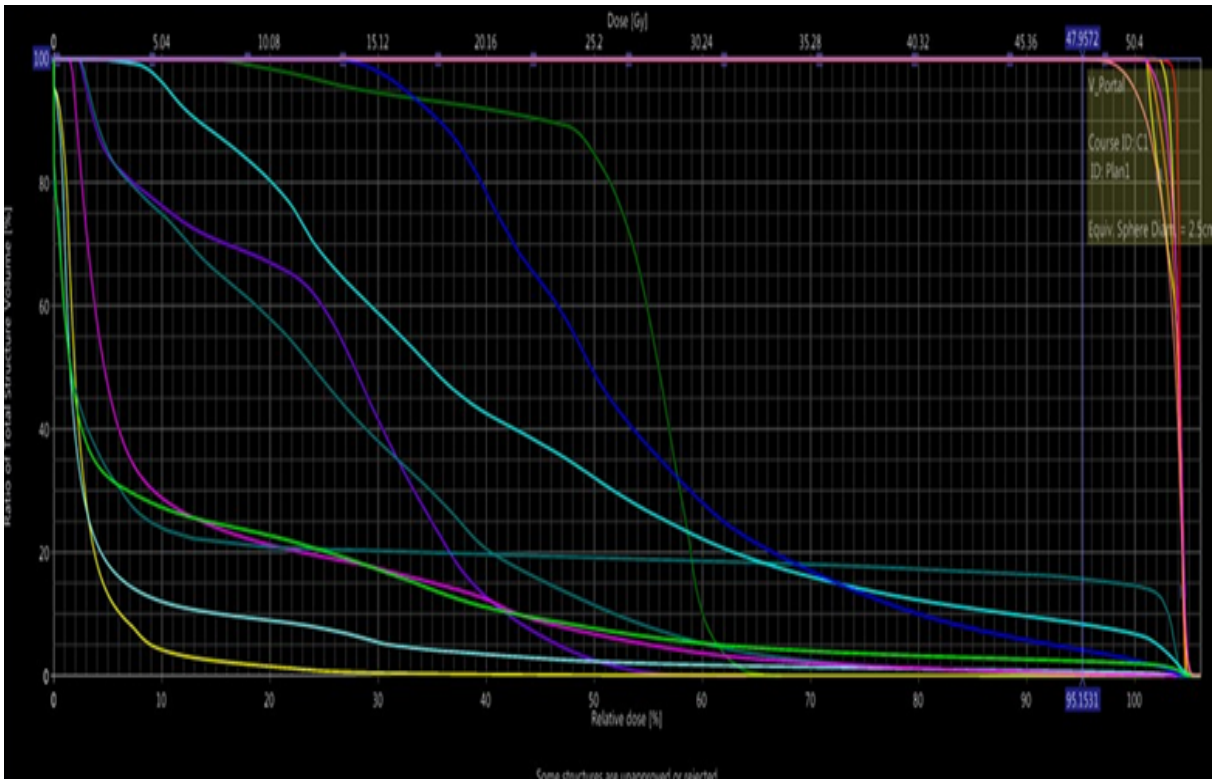

Figure 4. Dose volume Histogram of phase I and II, 50.4Gy in 28 fractions, IMRT technique, showing the minimum, mean ad maximum dose.

Table 2. Relation between response and different parameters (n = 40)

	Response								χ^2	MCp
	CR (n = 4)		PR (n = 18)		SD (n = 5)		PD (n = 13)			
	No.	%	No.	%	No.	%	No.	%		
Sex										
Male	2	50.0	12	66.7	4	80.0	6	46.2	2.378	0.546
Female	2	50.0	6	33.3	1	20.0	7	53.8		
Age (years)										
>50	2	50.0	8	44.4	2	40.0	4	30.8	1.028	0.863
<50	2	50.0	10	55.6	3	60.0	9	69.2		
P.S										
0 – 1	4	100.0	15	83.3	5	100.0	5	38.5	9.956*	0.010*
2	0	0.0	3	16.7	0	0.0	8	61.5		
Smoking										
Yes	1	25.0	9	50.0	2	40.0	2	15.4	4.227	0.225
No	3	75.0	9	50.0	3	60.0	11	84.6		
Co-morbidities										
No	2	50.0	8	44.4	2	40.0	4	30.8		
Diabetic	1	25.0	3	16.7	2	40.0	6	46.2	11.304	0.171
HTN	1	25.0	1	5.6	1	20.0	3	23.1		
Diabetic & HTN	0	0.0	6	33.3	0	0.0	0	0.0		
T Stage										
T2	1	25.0	0	0.0	0	0.0	0	0.0		
T3	3	75.0	10	55.6	3	60.0	7	53.8	7.362	0.288
T4	0	0.0	8	44.4	2	40.0	6	46.2		
N Stage										
N0	2	50.0	8	44.4	2	40.0	5	38.5	0.487	1.000
N1	2	50.0	10	55.6	3	60.0	8	61.5		
Site of tumor										
Head	2	50.0	10	55.6	3	60.0	8	61.5		
Body	1	25.0	4	22.2	0	0.0	3	23.1	12.379	0.336
Tail	1	25.0	0	0.0	0	0.0	0	0.0		
Body & Tail	0	0.0	3	16.7	2	40.0	0	0.0		
Head & Body	0	0.0	1	5.6	0	0.0	2	15.4		
Jaundice at present										
Yes	2	50.0	7	38.9	2	40.0	10	76.9	4.855	0.192
No	2	50.0	11	61.1	3	60.0	3	23.1		
Stent										
Yes	2	50.0	8	44.4	2	40.0	7	53.8	0.635	0.963
No	2	50.0	10	55.6	3	60.0	6	46.2		
Initial ca19.9										
Elevated	4	100.0	16	88.9	4	80.0	11	84.6	1.164	0.899
Not	0	0.0	2	11.1	1	20.0	2	15.4		
CCRT										
No	0	0.0	3	16.7	2	40.0	7	53.8	6.384	0.072
Yes	4	100.0	15	83.3	3	60.0	6	46.2		
Surgery										
Yes	4	100.0	5	27.8	0	0.0	0	0.0	15.705*	0.001*
No	0	0.0	13	72.2	5	100.0	13	100.0		
Resection margin	**(n = 4)**		**(n = 5)**		**(n = 0)**		**(n = 0)**			
R0	3 75.0		0.0		–		–		6.427*	0.025*
R1	1 25.0		20.0		–		–			
R2	0.0		4 80.0		–		–			

	Induction CTH (n=40)						X2	MCp
	Gemcitabine only (n = 11)		Gemcitabine /oxaloplatin (n = 16)		Gemcitabine /cisplati (n = 13)			
	No.	%	No.	%	No.	%		
Response PR	6	54.5	14	87.5	10	76.9		
SD	3	27.2	1	6.25	2	15.38	3.994	0.400
PD	2	18.1	1	6.25	1	7.69		

Chi square test, MC: Monte Carlo, *: Statistically significant at $p \leq 0.05$

Table 3. Chemotherapy and radiotherapy related toxicity.

Toxicity	CTH (n=40)						X2	MCp
	Gem only (n = 14)		Gem/oxalo (n =15)		Gem/cis (n = 11)			
	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4		
Non hematological								
Fatigue	5	0	10	2	8	2	0.916	0.821
Weight loss	5	3	6	1	4	1	1.169	0.810
gastritis	12	0	10	1	4	2	3.968	0.093
Nausea & vomiting	7	0	8	1	4	4	5.307*	0.043*
Liver toxicity	2	0	5	0	4	0	1.981	0.440
Hematological								
Neutropenia	3	0	5	3	6	1	1.711	0.453
Thrombocytopenia	6	3	4	1	8	1	1.371	0.804
Anemia	7	2	7	1	6	4	1.714	0.553

Radiation Toxicity	No.	%	Grade 1-2		Grade 3-4	
			No.	%	No.	%
Skin	12	42.8	12	42.8	0	0.0
GIT toxicity	20	71.4	19	67.8	1	3.6
GIT bleeding	5	17.9	4	14.3	1	3.6
Weight loss	7	25	7	25	0	0.0
Liver injury	3	10.7	3	10.7	0	0

The most common G1-2 Hematological toxicity included neutropenia in 14 patients (35%), thrombocytopenia in 18 patients (45%) and anemia in 20 patients (50%). Grade 3 neutropenia, thrombocytopenia and anemia occurred in 4, 5 and 7 respectively. Hidenori Takahashi et al 2013 reported higher rates of G1-2 gastrointestinal toxicity which occurred in 97% of their patients and thrombocytopenia was the most common hematological toxicity reported in 94.8% of patients (Takahashi et al. 2013). The data reported by Goto et al 2018 demonstrated higher rates of grade 3 hematological toxicities which were able to be well managed (Goto et al. 2018).

The most frequent toxicities during CCRT were grade 1-2 gastrointestinal toxicity and weight loss, only 1 patient developed grade 3 vomiting and diarrhea, one patient developed d grade 3 gastrointestinal bleeding. Most toxicity was controlled with appropriate medical therapy and nutritional support. These toxicity profiles were nearly similar to Michele Fiore et al 2017 who reported minimal gastrointestinal toxicity during concurrent radiation despite the relatively high irradiation dose (50.4 Gy) (Fiore et al. 2017). A systematic review conducted by Bittner et al 2015 showed the superiority of IMRT technique in the treatment of pancreatic cancer with reduction in acute and late toxicities including; nausea, vomiting, diarrhea and gastrointestinal bleeding/duodenal ulcer but with no significant changes in progression-free survival or overall survival (Bittner, Grosu, and Brunner 2015).

Table 4. Univariate and multivariate COX regression analysis for the parameters affecting progression free survival (n = 40)

		Univariate	#Multivariate	
	p	HR (95%C.I)	p	HR (95% C.I)
Male	0.798	0.892 (0.371 – 2.144)		
<50 years	0.242	1.742 (0.687 – 4.413)		
P.S	0.056	2.432 (0.976 – 6.058)		
Smoking	0.689	0.838 (0.352 – 1.992)		
Co-morbidities				
No		1.000		
Diabetic	0.067	2.675 (0.935 – 7.659)		
HTN	0.119	2.842 (0.764 – 10.569)		
Diabetic & HTN	0.830	0.858 (0.212 – 3.469)		
T Stage	0.618	0.801 (0.336 – 1.913)		
N Stage	0.862	0.928 (0.400 – 2.154)		
Jaundice at present	0.155	1.888 (0.787 – 4.529)		
Stent	0.796	1.117 (0.483 – 2.585)		
Initial ca19.9	0.744	0.815 (0.238 – 2.788)		
CCRT	0.002*	0.197 (0.070 – 0.552)		
No Surgery	0.128	3.148 (.719 – 13.790)		

HR: Hazard ratio, C.I: Confidence interval, #: All variables with p<0.05 was included in the multivariate,
*: Statistically significant at p ≤ 0.05

In our study 32 %, (9/28) of patients become resectable after receiving neoadjuvant CCRT and three patients have achieved a pathological complete response with R0 resection which was confirmed pathologically and radiologically. These patients also maintained their marvelous response till the end of the study. Also, overall survival and PFS rates were significantly better even patients with R1 and R2 resection and the one year overall survival was about 89% compared with 34.5% in patients who did not undergo surgical resection.

This percentage of conversion surgery was quietly similar to data reported by KENTA SUI et al 2017 in which about 38% of cases were reclassified as resectable after CCRT treatment (Sui et al. 2017). This percentage is much lower than the percentage reported in the results of a phase II study conducted by Michele Fiore et al 2017[24] . Another results published by Lili Wu et al 2020 found that only 4 (6.2%) patients underwent radical pancreatectomy (Wu et al. 2020). Gillen et al. reported a systematic review and meta-analysis of neoadjuvant therapy analyzing 111 studies including 4394 patients. They reported that surgical resection following neoadjuvant therapy was performed in 33.2% of patients with non-resectable pancreatic cancer and the median survival of these patients was 20.5 months, which was better than that of patients who did not undergo resection. Surprisingly, this survival time was within the range of patients who were treated with primary resection and adjuvant therapy for resectable cancer (20.1–23.6 months) (Gillen et al. 2010).

Survival rates were also better for patients who received chemoradiation. These results were in agreement with Leone et al. 2013 (Leone et al. 2013) and Passardi et al. 2019 who reported similar results of their study (Passardi et al. 2019). However, these results were not in agreement with Hammel et al.2016 who have reported their results of the LAP07 study which showed no overall survival benefit between the two arms, but an increase in progression-free survival (Hammel et al. 2016).

In our study patients with pathological complete response (pCR) or R0 had better PFS and overall survival rates as compared with those with residual disease (R2). Therefore, pCR can be considered an independent prognostic factor for improved OS and DFS which can support the

use of neoadjuvant chemoradiation treatment in patients with locally advanced disease and the use of pCR as an endpoint for future studies. These findings were in agreement with He, Jin et al 2018 which found that pCR was associated with better survival (He et al. 2018). In a cohort described by Chatterjee et al 2012 showed that the pathologic was an independent prognostic factor for OS but not DFS (Chatterjee et al. 2012). Another results published by Truty et al 2021 support the impact of pCR on survival (Truty et al. 2021) , Also from MD Anderson Lee et al 2016 reported that pCR was an independent factor of improved DFS, but not OS (Lee et al. 2016). Conversely the recent ALLIANCE A021501 study published by Katz et al 2021 found that neoadjuvant radiotherapy improved rates of R0 resection, but there was a significant reduction in survival compared to those receiving only neoadjuvant FOLFIRINOX (Katz et al. 2021).

CONCLUSION

The current results indicate that induction chemotherapy in patients with locally advanced disease is a useful screening method for selecting patients with less-aggressive biological behavior who will not early metastasize and hence can offer more aggressive protocols to achieve complete cure also the incorporating of radiotherapy as part of a neoadjuvant multi-modality treatment regimen is associated with improved outcomes, such as tumor downstaging, increased rate of R0 resection, which is associated with better survival.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

FUNDING

No fund was received for this work.

REFERENCES

André, Thierry, Jacques Balosso, Christophe Louvet, Laurent Hannoun, Sidney Houry, Michel Huguier, Marc Colonna, Jean Pierre Lotz, Aimery De Gramont, and Annie Bellaïche. (2000). Combined radiotherapy and chemotherapy (cisplatin and 5-fluorouracil) as palliative treatment for localized unresectable or adjuvant treatment for resected pancreatic adenocarcinoma: results of a feasibility study, International Journal of Radiation Oncology Biology Physics, 46: 903-11.

Badiyan, Shahed N, Jason K Molitoris, Michael D Chuong, William F Regine, and Adeel Kaiser. (2017). The role of radiation therapy for pancreatic cancer in the adjuvant and neoadjuvant settings, Surgical Oncology Clinics, 26: 431-53.

Barenboim, Alex, Guy Lahat, Ravit Geva, Ido Nachmany, Richard Nakache, Yaacov Goykhman, Eli Brazowski, Galia Rosen, Ofer Isakov, and Ido Wolf (2018). 'Neoadjuvant FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer: an intention to treat analysis, European Journal of Surgical Oncology, 44: 1619-23.

Ben-Josef, Edgar, Anthony F. Shields, Ulka Vaishampayan, Vainutis Vaitkevicius, Basil F. El-Rayes, Patrick McDermott, Jay Burmeister, Todd Bossenberger, and Philip A. Philip (2004). 'Intensity-modulated radiotherapy (IMRT) and concurrent capecitabine for pancreatic cancer, International Journal of Radiation Oncology Biology Physics, 59: 454-59.

Bittner, Martin-Immanuel, Anca-Ligia Grosu, and Thomas B Brunner (2015). Comparison of toxicity after IMRT and 3D-conformal radiotherapy for patients with pancreatic cancer–a systematic review, Radiotherapy and Oncology, 114: 117-21.

Chapman, Brandon C, Ana Gleisner, Devin Rigg, Wells Messersmith, Alessandro Paniccia, Cheryl Meguid, Csaba Gajdos, Martin D McCarter, Richard D Schulick, and Barish H Edil (2018). Perioperative and survival outcomes following neoadjuvant FOLFIRINOX versus gemcitabine abraxane in patients with pancreatic adenocarcinoma, JOP: Journal of the pancreas, 19: 75.

Chatterjee, Deyali, Matthew H Katz, Asif Rashid, Gauri R Varadhachary, Robert A Wolff, Hua Wang, Jeffrey E Lee, Peter WT Pisters, Jean-Nicolas Vauthey, and Christopher Crane (2012). Histologic grading of the extent of residual carcinoma following neoadjuvant chemoradiation in pancreatic ductal adenocarcinoma: a predictor for patient outcome, Cancer, 118: 3182-90.

Chawla, Akhil, George Molina, Linda M Pak, Michael Rosenthal, Joseph D Mancias, Thomas E Clancy, Brian M Wolpin, and Jiping Wang. (2020). Neoadjuvant therapy is associated with improved survival in borderline-resectable pancreatic cancer, Annals of surgical oncology, 27: 1191-200.

Conroy, Thierry, Françoise Desseigne, Marc Ychou, Olivier Bouché, Rosine Guimbaud, Yves

Bécouarn, Antoine Adenis, Jean-Luc Raoul, Sophie Gourgou-Bourgade, and Christelle de la Fouchardière (2011). FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer, New England Journal of Medicine, 364: 1817-25.

Eisenhauer, Elizabeth A, Patrick Therasse, Jan Bogaerts, Lawrence H Schwartz, D Sargent, Robert Ford, Janet Dancey, S Arbuck, Steve Gwyther, and Margaret Mooney (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), European journal of cancer, 45: 228-47.

Faris, Jason E, Lawrence S Blaszkowsky, Shaunagh McDermott, Alexander R Guimaraes, Jackie Szymonifka, Mai Anh Huynh, Cristina R Ferrone, Jennifer A Wargo, Jill N Allen, and Lauren E Dias (2013). 'FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience, The oncologist, 18: 543-48.

Ferrone, Cristina R, Giovanni Marchegiani, Theodore S Hong, David P Ryan, Vikram Deshpande, Erin I McDonnell, Francesco Sabbatino, Daniela Dias Santos, Jill N Allen, and Lawrence S Blaszkowsky (2015). Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer, Annals of surgery, 261: 12.

Fiore, Michele, Sara Ramella, Sergio Valeri, Damiano Caputo, Barnaba Floreno, Pasquale Trecca, Luca Eolo Trodella, Lucio Trodella, Rolando Maria D'Angelillo, and Roberto Coppola (2017). Phase II study of induction chemotherapy followed by chemoradiotherapy in patients with borderline resectable and unresectable locally advanced pancreatic cancer, Scientific reports, 7: 1-8.

Gemenetzis, G., V. P. Groot, A. B. Blair, D. A. Laheru, L. Zheng, A. K. Narang, E. K. Fishman, R. H. Hruban, J. Yu, R. A. Burkhart, J. L. Cameron, M. J. Weiss, C. L. Wolfgang, and J. He (2019). Survival in Locally Advanced Pancreatic Cancer After Neoadjuvant Therapy and Surgical Resection, Ann Surg, 270: 340-47.

Gillen, Sonja, Tibor Schuster, Christian Meyer zum Büschenfelde, Helmut Friess, and Jörg Kleeff (2010). Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages, PLoS medicine, 7: e1000267.

Goto, Yoko, Akira Nakamura, Ryo Ashida, Katsuyuki Sakanaka, Satoshi Itasaka, Keiko Shibuya, Shigemi Matsumoto, Masashi Kanai, Hiroyoshi Isoda, and Toshihiko Masui (2018). Clinical evaluation of intensity-modulated radiotherapy for locally advanced pancreatic cancer, Radiation oncology, 13: 1-9.

Gudjonsson, Birgir (1987). Cancer of the pancreas: 50 years of surgery, Cancer, 60: 2284-303.

Hammel, Pascal, Florence Huguet, Jean-Luc van Laethem, David Goldstein, Bengt Glimelius, Pascal Artru, Ivan Borbath, Olivier Bouché, Jenny Shannon, and Thierry André (2016). Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial, Jama, 315: 1844-53.

He, Jin, Alex B Blair, Vincent P Groot, Ammar A Javed, Richard A Burkhart, Georgios Gemenetzis, Ralph H Hruban, Kevin M Waters, Justin Poling, and Lei Zheng (2018). Is a pathological complete response following neoadjuvant chemoradiation associated with prolonged survival in patients with pancreatic cancer?, Annals of surgery, 268: 1.

Hosein, Peter J, Jessica Macintyre, Carolina Kawamura, Jennifer Cudris Maldonado, Vinicius Ernani, Arturo Loaiza-Bonilla, Govindarajan Narayanan, Afonso Ribeiro, Lorraine Portelance, and Jaime R Merchan (2012). A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma, BMC cancer, 12: 1-7.

Huguet, F., T. André, P. Hammel, P. Artru, J. Balosso, F. Selle, E. Deniaud-Alexandre, P. Ruszniewski, E. Touboul, R. Labianca, A. de Gramont, and C. Louvet (2007). Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies, J Clin Oncol, 25: 326-31.

Huguet, F., C. Hajj, C. B. Winston, W. Shi, Z. Zhang, A. J. Wu, E. M. O'Reilly, D. L. Reidy, P. Allen, and K. A. Goodman (2017). Chemotherapy and intensity-modulated radiation therapy for locally advanced pancreatic cancer achieves a high rate of R0 resection, Acta Oncol, 56: 384-90.

Jemal, Ahmedin, Rebecca Siegel, Jiaquan Xu, and Elizabeth Ward (2010). Cancer statistics, 2010, CA: a cancer journal for clinicians, 60: 277-300.

Katz, Matthew HG, Qian Shi, Jeffrey P Meyers, Joseph M Herman, Michael Choung, Brian M Wolpin, Syed Ahmad, Robert de Wilton Marsh, Lawrence Howard Schwartz, and Spencer Behr (2021). Alliance A021501: preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of

the pancreas. In.: American Society of Clinical Oncology.

Ko, Andrew H., Jeanne M. Quivey, Alan P. Venook, Emily K. Bergsland, Elizabeth Dito, Brian Schillinger, and Margaret A. Tempero (2007). A Phase II Study of Fixed-Dose Rate Gemcitabine Plus Low-Dose Cisplatin Followed by Consolidative Chemoradiation for Locally Advanced Pancreatic Cancer, International Journal of Radiation Oncology Biology Physics, 68: 809-16.

Kornek, Gabriela V, Richard Pötter, Edgar Selzer, Annemarie Schratter, Herbert Ulrich-Pur, Michael Rogy, Gwendolyn Kraus, and Werner Scheithauer (2001). Combined radiochemotherapy of locally advanced unresectable pancreatic adenocarcinoma with mitomycin C plus 24-hour continuous infusional gemcitabine, International Journal of Radiation Oncology Biology Physics, 49: 665-71.

Krishnan, S., A. S. Chadha, Y. Suh, H. C. Chen, A. Rao, P. Das, B. D. Minsky, U. Mahmood, M. E. Delclos, G. O. Sawakuchi, S. Beddar, M. H. Katz, J. B. Fleming, M. M. Javle, G. R. Varadhachary, R. A. Wolff, and C. H. Crane (2016). Focal Radiation Therapy Dose Escalation Improves Overall Survival in Locally Advanced Pancreatic Cancer Patients Receiving Induction Chemotherapy and Consolidative Chemoradiation, Int J Radiat Oncol Biol Phys, 94: 755-65.

Krishnan, Sunil, Vishal Rana, Nora A Janjan, Gauri R Varadhachary, James L Abbruzzese, Prajnan Das, Marc E Delclos, Morris S Gould, Douglas B Evans, and Robert A Wolff (2007). Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy, Cancer, 110: 47-55.

Lee, Sun Mi, Matthew H Katz, Li Liu, Manonmani Sundar, Hua Wang, Gauri R Varadhachary, Robert A Wolff, Jeffrey E Lee, Anirban Maitra, and Jason B Fleming (2016). Validation of a proposed tumor regression grading scheme for pancreatic ductal adenocarcinoma after neoadjuvant therapy as a prognostic indicator for survival, The American journal of surgical pathology, 40: 1653.

Leone, Francesco, Marco Gatti, Paolo Massucco, Federica Colombi, Elisa Sperti, Delia Campanella, Daniele Regge, Pietro Gabriele, Lorenzo Capussotti, and Massimo Aglietta (2013). Induction gemcitabine and oxaliplatin therapy followed by a twice-weekly infusion of gemcitabine and concurrent external-beam radiation for neoadjuvant treatment of locally advanced pancreatic cancer: A single institutional experience, Cancer, 119: 277-84.

Marchegiani, Giovanni, Valentina Todaro, Enrico Boninsegna, Riccardo Negrelli, Binit Sureka, Debora Bonamini, Roberto Salvia, Riccardo Manfredi, Roberto Pozzi Mucelli, and Claudio Bassi (2018). Surgery after FOLFIRINOX treatment for locally advanced and borderline resectable pancreatic cancer: increase in tumour attenuation on CT correlates with R0 resection, European Radiology, 28: 4265-73.

Moertel, CG, S Frytak, RG Hahn, MJ O'Connell, RJ Reitemeier, J Rubin, AJ Schutt, LH Weiland, DS Childs, and MA Holbrook (1981). Therapy of locally unresectable pancreatic carcinoma: A randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads+ 5-fluorouracil), and high dose radiation+ 5-fluorouracil. The gastrointestinal tumor study group, Cancer, 48: 1705-10.

Oettle, Helmut, Peter Neuhaus, Andreas Hochhaus, Jörg Thomas Hartmann, Klaus Gellert, Karsten Ridwelski, Marco Niedergethmann, Carl Zülke, Jörg Fahlke, and Michael B Arning (2013). Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial, Jama, 310: 1473-81.

Passardi, Alessandro, Emanuela Scarpi, Elisa Neri, Elisabetta Parisi, Giulia Ghigi, Giorgio Ercolani, Andrea Gardini, Giuliano La Barba, Flavia Pagan, and Andrea Casadei-Gardini (2019). Chemoradiotherapy (Gemox Plus Helical Tomotherapy) for unresectable locally advanced pancreatic cancer: a phase II study, Cancers, 11: 663.

Raimondi, Sara, Albert B Lowenfels, Antonio M Morselli-Labate, Patrick Maisonneuve, and Raffaele Pezzilli (2010). Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection, Best practice & research Clinical gastroenterology, 24: 349-58.

Satoi, Sohei, Hiroki Yamaue, Kentaro Kato, Shinichiro Takahashi, Seiko Hirono, Shin Takeda, Hidetoshi Eguchi, Masayuki Sho, Keita Wada, and Hiroyuki Shinchi (2013). Role of adjuvant surgery for patients with initially unresectable pancreatic cancer with a long-term favorable response to non-surgical anti-cancer treatments: results of a project study for pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery, Journal of Hepato-Biliary-Pancreatic Sciences, 20: 590-600.

Shinchi, Hiroyuki, Sonshin Takao, Hidetoshi Noma, Yoichiro Matsuo, Yuko Mataki, Shinichiro Mori, and Takashi Aikou (2002). Length and quality of

survival after external-beam radiotherapy with concurrent continuous 5-fluorouracil infusion for locally unresectable pancreatic cancer, International Journal of Radiation Oncology Biology Physics, 53: 146-50.

Sui, Kenta, Takehiro Okabayashi, Yasuo Shima, Sojiro Morita, Jun Iwata, Tatsuaki Sumiyoshi, Yuichi Saisaka, Yasuhiro Hata, Yoshihiro Noda, and Manabu Matsumoto (2017). Clinical effects of chemoradiotherapy in pursuit of optimal treatment of locally advanced unresectable pancreatic cancer, The British journal of radiology, 90: 20170165.

Takahashi, Hidenori, Hiroaki Ohigashi, Kunihito Gotoh, Shigeru Marubashi, Terumasa Yamada, Masayuki Murata, Tatsuya Ioka, Hiroyuki Uehara, Masahiko Yano, and Osamu Ishikawa (2013). Preoperative gemcitabine-based chemoradiation therapy for resectable and borderline resectable pancreatic cancer, Annals of surgery, 258: 1040-50.

Torgeson, A., S. Lloyd, D. Boothe, R. Tao, J. Whisenant, I. Garrido-Laguna, and G. M. Cannon (2017). Multiagent induction chemotherapy followed by chemoradiation is associated with improved survival in locally advanced pancreatic cancer, Cancer, 123: 3816-24.

Truty, Mark J, Michael L Kendrick, David M Nagorney, Rory L Smoot, Sean P Cleary, Rondell P Graham, Ajit H Goenka, Christopher L Hallemeier, Michel G Haddock, and William S Harmsen (2021). Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer, Annals of surgery, 273: 341-49.

Uesaka, Katsuhiko, Narikazu Boku, Akira Fukutomi, Yukiyasu Okamura, Masaru Konishi, Ippei Matsumoto, Yuji Kaneoka, Yasuhiro Shimizu, Shoji Nakamori, and Hirohiko Sakamoto (2016). Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01), The Lancet, 388: 248-57.

Wu, Lili, Yuhong Zhou, Yue Fan, Shengxiang Rao, Yuan Ji, Jing Sun, Tingting Li, Shisuo Du, Xi Guo, and Zhaochong Zeng (2020). Consolidative chemoradiotherapy after induced chemotherapy is an optimal regimen for locally advanced pancreatic cancer, Frontiers in oncology, 9: 1543.

Yoo, Changhoon, Sang Hyun Shin, Kyu-pyo Kim, Jae Ho Jeong, Heung-Moon Chang, Jun Ho Kang, Sang Soo Lee, Do Hyun Park, Tae Jun Song, and Dong Wan Seo (2019). Clinical outcomes of conversion surgery after neoadjuvant chemotherapy in patients with borderline resectable and locally advanced unresectable pancreatic cancer: A single-center, retrospective analysis, Cancers, 11: 278.