Ann Surg Oncol
https://doi.org/10.1245/s10434-019-08084-2

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Intraoperative Radiation Therapy (IORT) for Borderline Resectable and Locally Advanced Pancreatic Ductal Adenocarcinoma (BR/LA PDAC) in the Era of Modern Neoadjuvant Treatment: Short-Term and Long-Term Outcomes

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ABSTRACT

Objective. To define short-term and long-term outcomes of IORT for the management of BR/LA PDAC in the era of modern neoadjuvant therapy (NAT).

Background. In the era of neoadjuvant FOLFIRINOX, many patients with borderline resectable/locally advanced (BR/LA) pancreatic ductal adenocarcinoma (PDAC) become candidates for surgical exploration with curative intent. IORT may be used to consolidate treatment for successfully resected patients with close or positive margins or administered in unresectable patients without distant metastases.

Methods. A retrospective review of 158 patients who received IORT in the setting of biopsy-proven BR/LA PDAC following NAT between 2008 and 2017 was performed. The Kaplan–Meier method was used to analyze progression-free survival (PFS) and overall survival (OS) of FOLFIRINOX treated patients.

Results. Most patients (83%) received FOLFIRINOX, and 95% underwent consolidative chemoradiation therapy (50.4–58.8 Gy). Among FOLFIRINOX-treated patients, 86 underwent combined surgical resection with IORT (10 Gy) while 46 received IORT alone (15–20 Gy). The median PFS and OS were 21.5 and 46.7 months for patients who underwent resection with IORT and 14.7 and 23 months in the IORT alone group. Local progression occurred in 12.7% of patients after resection with IORT, and in 15% of patients who received IORT alone. Major complications occurred in 13% of patients following resection, and 5% of patients after IORT alone, including one death.

Conclusion. IORT combined with surgical resection appears to be associated with improved survival and minimal morbidity in patients with positive or close margins. IORT is also associated with improved survival in patients with unresectable, non-metastatic disease.

Although pancreatic cancer accounts for less than 3% of all cancer diagnoses, it is projected to be the 2nd leading cause of cancer-related deaths in the United States by 2030.[1] This discrepancy is due to the tumor's aggressive nature and often late-stage presentation—at the time of diagnosis, 80% of patients are found to have borderline resectable or locally advanced (BR/LA) disease or distant metastases.[2,3]

Within the last 8 years, two combination chemotherapy regimens, FOLFIRINOX and gemcitabine/nab-paclitaxel, have demonstrated a marked survival benefit for patients with metastatic pancreatic cancer.[4,5] Given the success of these therapies in stage IV disease, both therapies are now used as neoadjuvant regimens for patients with BR/LA disease. Consequently, several retrospective and

First Received: 16 August 2019

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Published online: 22 November 2019

prospective series have shown that many formerly unresectable BR/LA tumors can be "down-staged" and become potentially resectable.[6]

Despite these clinical advances, however, challenges remain with fully recognizing the extent of peripancreatic vascular involvement in down-staged disease. Specifically, following completion of neoadjuvant treatment, radiologic evidence of vascular involvement does not reliably correlate with disease extent at time of surgical exploration.[7] A multitude of operative outcomes can therefore occur, including complete resection, resection with positive or close margins, or unresectable (localized) disease without evidence of distant metastases. In the latter two scenarios, intraoperative radiation (IORT) is a potentially valuable adjunct for local disease control, and in some cases, long-term survival.[8–10]

The aim of this study is to review the efficacy and safety of IORT in patients with BR/LA pancreatic cancer following NAT, with focus on FOLFIRINOX-based regimens.

METHODS

Following institutional review board approval, a retrospective review was performed of pancreatic cancer patients who had received neoadjuvant therapy and IORT for borderline resectable or locally advanced disease at the Massachusetts General Hospital between 2008 and 2017. A total of 341 patients had received neoadjuvant treatment (NAT), and of these, 158 received both NAT and IORT. As noted, all patients had biopsy-proven BR/LA pancreatic adenocarcinoma (PDAC), which had been reviewed by a multidisciplinary tumor board at the time of diagnosis and prior to completing a course of NAT. At the surgeon's discretion, these patients were explored in a custom OR suite with IORT capability, and for a higher likelihood of residual microscopic disease or for an aborted resection, IORT was administered. Prior to 2015, this was with a Siemen's ME electron-only device; however, since 2015, an IntraOp Mobetron electron-beam linear accelerator has been used. The IORT dosage was determined in accordance with a standardized protocol developed by the Radiation Oncology group at our institution.[11]

A review of this cohort's demographic information, oncologic treatment data, and operative details, such as type of operation, length of case, estimated blood loss, intraoperative radiation dose, and pathology findings was then completed. Additionally, outcomes following intervention including 30-day readmission, complications by Clavien-Dindo classification including delayed gastric emptying (DGE) were assessed. For FOLFIRINOX-treated patients only, progression and survival data were analyzed. Progression-free survival (PFS) was defined as time to any recurrence (local or distant) or death from time of surgery, and overall survival (OS) as time to death from time of diagnosis; event times were censored at date of last follow-up. PFS and OS were estimated using the Kaplan–Meier method and compared between subgroups via the log-rank test. Statistical analyses were conducted using SAS 9.4 with a two-sided significance level of 0.05.

RESULTS

One hundred fifty-eight NAT-treated patients with BR/LA PDAC were surgically explored and received IORT. Eighty-nine patients (56%) were males, and the average age was 63.8 years (range 35–91 years). All patients were treated with neoadjuvant chemotherapy prior to surgery, and 83% (132) received a FOLFIRINOX-based regimen (8 cycles over 4 months). The remaining patients were treated with either gemcitabine or capecitabine-based therapies (Fig. 1). Following chemotherapy, 95% of patients had received a consolidative form of radiation (50.4–58.8 Gy over 6 weeks) with photons. The remaining 5% received either stereotactic body radiation (SBR) or proton therapy.

Operative Details

Of all 158 patients that received NAT, 94 patients (60%) underwent pancreatic resection in addition to IORT (Table 1). In 60 patients (38%), a pancreatoduodenectomy (Whipple procedure) or total pancreatectomy was performed, with an average length of case of 453 min (± 102 min) and estimated blood loss of 840 cc (± 546 cc). The remaining 34 patients (22%) underwent distal pancreatectomy or an Appleby procedure with an

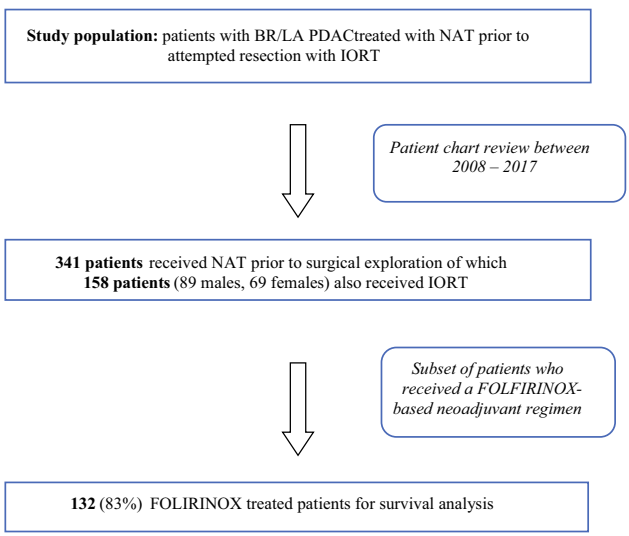

FIG. 1 Description of study methods and demographic data

TABLE 1 Operative details by treatment method for *all* NAT BR/LA PDAC patients (N = 158)

Procedure	Number of patients	Case length (min.)	Estimated blood loss (cc)	Average radiation administered (Gy)	Median IORT cone size (cm)	Median tumor size (cm)	R0 resections
Whipple or total pancreatectomy with IORT	60	453 (± 102)	840 (± 546)	10.2 (± 1.0)	4	2 (± 1.8)	81.7%
Distal pancreatectomy or Appleby with IORT	34	329 (± 99)	612 (± 348)	10.3 (± 1.9)	4.5	2.35 (± 1.5)	85.3%
IORT alone	64	175 (± 178)	173 (± 80)	15 (± 1.6)	5	N/A	N/A

average case length of 329 min (± 99 min) and mean estimated blood loss 612 cc (± 348 cc).

For all resected patients included for analysis, IORT was administered to the resection bed. In patients who underwent pancreatoduodenectomy or total pancreatectomy an average radiation dose of 10.2 Gy (± 1 Gy) was administered through a median cone size of 4 cm (range 3.5–8 cm) (Table 1). On pathologic examination, the average tumor size was 2.0 cm (± 1.8 cm), and the R0 resection rate was 81.7%. In the distal pancreatectomy or Appleby cohort, the average dose of IORT given was 10.3 Gy (± 1.9 Gy) through a median cone size of 4.5 cm (range 4–6 cm) (Table 1). The average tumor size on pathologic evaluation was 2.4 cm (± 1.5 cm), and the R0 rate was 85.3% (Fig. 2).

In 57 of the 64 unresectable patients, a surgical bypass was performed after IORT was administered to the tumor.

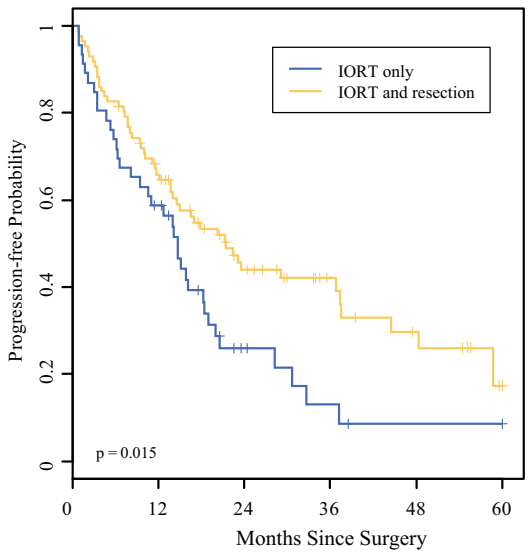

FIG. 2 Progression-free survival in resected patients treated with IORT versus those treated with IORT alone after FOLFIRINOX-based neoadjuvant chemoradiation therapy (N = 132)

The most common bypass was a gastrojejunostomy (81%) followed by gastrojejunostomy with hepaticojejunostomy (19%). In this cohort, the average radiation dose was 15 Gy (± 1.6 Gy) through a median cone size of 5 cm (range 2–8 cm) (Table 1). The average length of the operation was 175 min (± 178 min) with an estimated blood loss of 170 cc (± 80 cc).

Survival Outcomes

Of the 132 patients who received FOLFIRINOX-based NAT, the median PFS and OS for those after a Whipple procedure or total pancreatectomy with IORT was 23.5 months and 42.7 months, respectively (Table 2), and following distal pancreatectomy or Appleby procedure with IORT, 15.1 and 53 months (Table 2). Combining all resection patients with IORT, the PFS was 21.5 months and OS was 46.7 months (Table 2; Fig. 3). In the 46 patients who received IORT alone after FOLFIRINOX-based NAT, the progression-free survival was 14.7 months and the overall survival was 23 months (Table 2; Fig. 3).

After FOLFIRINOX-based NAT, the survival rates at 12, 24, 48, and 60 months were 98%, 79%, 43%, and 32% for Whipple and total pancreatectomy with IORT and 100%, 79%, 55% and 21% for distal pancreatectomy and Appleby procedure with IORT (Table 3). For all forms of resection with IORT, the survival rates at 12, 24, 48, and 60 months were 99%, 79%, 47%, and 28%. For patients who only received IORT, the 12-, 24-, 48-, and 60-month survival rates were 98%, 49%, 13%, and 9% (Table 3). The longest OS in the resection with IORT cohort was 64 and 96 months. In the IORT only cohort, 2 patients had OS of 72 and 93 months, respectively.

Progression Data

At the time of study follow-up, disease progression had occurred in 44 of 86 FOLFIRINOX treated patients (51%) following resection and IORT, and the liver was the most common site of metastases (19.7%) followed by lung

TABLE 2 Median progression-free and overall survival times after *FOLFIRNOX-based* treatment ($N = 132$)

	Median PFS (months) (95% CI)	P value[1]	Median OS (months) 95% CI	P value[1]
All resections with IORT ($N = 86$)	21.5 (14.0, 37.4)	0.015	46.7 (32.8, 58.7)	< 0.0001
Whipple or total pancreatectomy and IORT ($N = 55$)	23.5 (13.8, 44.6)		42.7 (30.0, NR[2])	
Distal pancreatectomy or Appleby and IORT ($N = 31$)	15.1 (8.0, 36.7)		53.0 (26.4, NR[2])	
IORT alone ($N = 46$)	14.7 (8.2, 18.4)		23.0 (18.9, 29.4)	

[1]P value from log-rank test comparing distribution of PFS/OS in patients treated with resection and IORT versus those treated with IORT alone
[2]Upper 95% confidence limit not reached (NR)

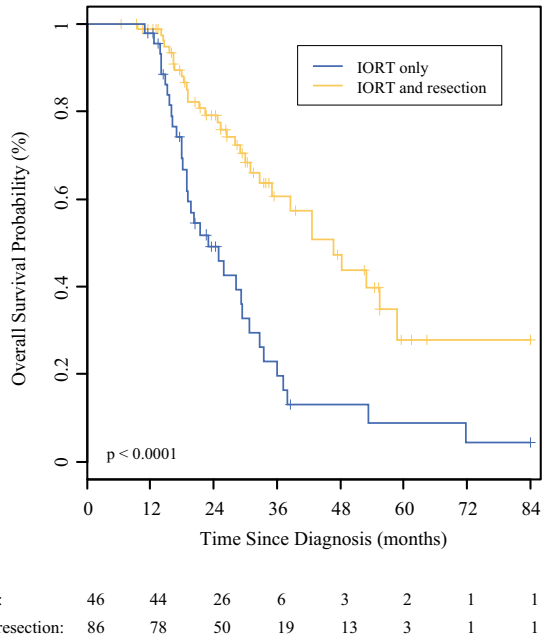

FIG. 3 Overall survival in resected patients treated with IORT versus those treated with IORT alone after FOLFIRNOX-based neoadjuvant chemoradiation therapy ($N = 132$)

with a R1 resection ($N = 14$), 1 patient had no disease progression, and 3 had a local recurrence (Table 4). For patients who received only IORT after FOLFIRINOX-based NAT, 15 (33%) had no evidence of disease progression. As in the resection with IORT cohort, patients with progression most commonly developed liver metastases (30%). Local progression was seen in only 15% of patients (Table 4).

Safety of IORT

Postoperatively the average length of stay was 7.6 days (± 3.9 days) with a 30-day readmission rate of 10% for the 60 patients following Whipple or total pancreatectomy with IORT after NAT (Table 5). The overall complication rate was 26.7%. The rate of major Clavien-Dindo III/IV complications was 12%, and there were no perioperative or postoperative mortalities. Notably, the rate of DGE was 5%. For the 34 distal pancreatectomy or Appleby patients and IORT after NAT, the average length of stay was 5.8 days (± 2.5 days) with a 30-day readmission rate of 5.9% (Table 5). The overall complication rate was 23.5%,

TABLE 3 Overall 12, 24, 48 and 60-month survival by treatment method after *FOLFIRINOX-based* treatment ($N = 132$)

Months	Whipple/total pancreatectomy with IORT ($N = 55$) (%)	Distal pancreatectomy/appleby with IORT ($N = 31$) (%)	Combined resection with IORT ($N = 86$) (%)	IORT alone ($N = 46$) (%)
12	98.1	100	98.8	97.8
24	79.4	78.6	79.2	49.1
48	43.3	54.7	47.3	13.1
60	31.6	20.5	27.8	8.7

(12.7%) (Table 4). Local recurrence was seen in 25% of the patients who progressed, which represented 12.7% of all resection with IORT patients. In patients with R0 resection ($N = 72$), 57% had no evidence of disease progression. When patients developed distant metastases, the liver (17%) was again the most common site. Local recurrence represented 11% of recurrences. Of patients and major complications were seen in 15% with no perioperative or postoperative deaths.

For the 64 patients that received IORT alone following NAT, the average length of stay was 6 days (± 6.2 days) with a 30-day readmission rate of 6.3% (Table 5). The overall complication rate 20.3%, and the rate of Clavien-Dindo III/IV complications was 4.7%. There was one death

TABLE 4 Progression data following IORT for *FOLFIRINOX* treated patients at study follow-up ($N = 132$)

	Progression	Liver	Lung	Local	Peritoneal/pelvis
All resection with IORT (N = 86)	51% ($N = 44$)	19.7% ($N = 17$)	12.7% ($N = 11$)	12.7% ($N = 11$)	5.8% ($N = 5$)
R0 resection with IORT ($N = 72$)	43% ($N = 31$)	17% ($N = 12$)	11% ($N = 8$)	11% ($N = 8$)	4% ($N = 3$)
R1 resection with IORT ($N = 14$)	93% ($N = 13$)	36% ($N = 5$)	21.5% ($N = 3$)	21.5% ($N = 3$)	14% ($N = 2$)
IORT alone ($N = 46$)	67% ($N = 31$)	30% ($N = 14$)	15% ($N = 7$)	15% ($N = 7$)	7% ($N = 3$)

TABLE 5 Post-operative outcomes by treatment method for *all* NAT BR/LA PDAC patients ($N = 158$)

Procedure	Average length of stay (days)	30-Day readmission rate (%)	Overall complication rate (%)	Clavien-Dindo III/IV complication rate (%)	Rate of DGE
Whipple or total pancreatectomy with IORT ($N = 60$)	7.65 (± 3.9)	10	26.7	12	5%
Distal pancreatectomy or Appleby with IORT ($N = 34$)	5.8 (± 2.5)	5.9	23.5	15	N/A
IORT alone ($N = 64$)	6 (± 6.2)	6.3	20.3	4.7	6.3%

due to renal failure in the setting of spontaneous bacterial peritonitis (Table 5). The rate of DGE was 6.3%. All complications from the resection with IORT and IORT alone cohorts are described in Table 6.

DISCUSSION

Widespread use of IORT for intra-abdominal solid tumors began in the late 1970s after a survival benefit was identified for patients with advanced stage gastric cancer. IORT emerged for the treatment of pancreatic cancer after several retrospective studies demonstrated better locoregional control and improved survival.[11–18] For pancreatic cancer patients in the era of neoadjuvant chemo- and radiation therapy, a study performed by Keane et al.[8] described that BR/LA PDAC patients undergoing surgery and IORT had improved OS compared to patients who did not receive IORT. In conjunction with these findings, our data further exemplifies the robust effect of multimodal therapy in treating BR/LA PDAC.

While the literature supports that many BR/LA PDAC patients with radiographically unresectable disease following NAT are indeed resectable,[12,19] unrecognized microscopic residual disease may remain following a challenging dissection. In these situations, IORT potentially serves as a valuable therapeutic tool. In our study, 94 patients underwent pancreatectomy with IORT, and because of the tumor's proximity to the major vasculature

TABLE 6 Complications by Clavien-Dindo Classification for *all* NAT BR/LA PDAC patients ($N = 158$)

	Whipple procedure and total pancreatectomy with IORT ($N = 60$)	Distal pancreatectomy and appleby with IORT ($N = 34$)	IORT alone ($N = 64$)
Clavien-Dindo I/II	New medication or antibiotic (6) Transfusion (1) DGE (3)	New medication or antibiotic (3)	New medication or antibiotic (8) DGE (4)
Clavien-Dindo III/IV	Endoscopy for gastrointestinal bleed (1) Return to operating room for dehiscence (1) IR procedure for non-gastrointestinal bleed (GIB) (3) ICU admission after iInterventional rRadiology procedure for gastrointestinal bleed (GIB) (2)	Interventional Radiology procedure for non-gastrointestinal bleed (3) ICU admission after OR after leak (2)	Endoscopy for gastrointestinal bleed (GIB) (1) ICU admission for sepsis (1)
Clavien-Dindo V			Death from spontaneous bacterial peritonitis (SBP) (1)

DGE delayed gastric emptying, *ICU* intensive care, *IR* Interventional Radiology, *OR* operating room

or retroperitoneum, 80 received IORT despite a negative microscopic margin. Incorporating IORT into the treatment algorithm for BR/LA disease therefore provides an additional safeguard in the event of undetected microscopic disease. IORT was also given to 14 patients who had positive intraoperative margins because of tumor extension into the SMA, the hepatic artery, or the celiac trunk. In these scenarios, the utility of combined resection and IORT with or without proven positive margins is underscored by the median overall survival of 46 months and local recurrence rate of 12.7%.

While pancreatectomy is possible for many BR/LA PDAC patients after neoadjuvant therapies, there is a subset of patients who are explored and deemed unresectable despite the absence of distant metastases. In these patients, IORT also serves as a potentially valuable therapeutic adjunct for its ability to arrest tumor progression. In long-term IORT only survivors, the tumor was re-biopsied at the time of laparotomy and confirmed to be malignant, excluding complete pathological response as a cause for their long-term survival. These findings are consistent with a growing body of literature which suggests that ablative doses of radiation can result in long-term survival in pancreatic cancer.[20,21] This approach was first described by Krishnan et al.,[20] who treated patients with dose-escalated intensity modulated radiation therapy (IMRT). Additional studies have supported this approach given improved 2-year OS rates using MR-guided techniques with similar doses.[21] In our cohort, the current regimen of 58.8 Gy in 28 fractions followed by a 15-Gy IORT boost yields a biologic equivalent dose of approximately 90 Gy. While other adjunct therapies such as stereotactic body radiation therapy (SBRT) and irreversible electroporation (IRE) are also available for the treatment of BR/LA PDAC, our series highlights both the safety and efficacy derived from an intraoperative radiation boost.[17,22]

Our study does have limitations related to its retrospective nature. Ideally, we would like to perform a prospective study of patients with BR/LA PDAC that received neoadjuvant therapy, surgery, and IORT versus patients that do not receive IORT, to fully elucidate its benefit. We also hope in future series to better identify the long-term survivors and any common clinical features that may suggest their unique response despite unresectable disease. Last, our study does not comment on preoperative functional status, which may help identify those patients most likely to benefit from IORT.

In conclusion, current management of non-metastatic pancreatic cancer requires a multimodality approach. While surgical resection plays a central role, there is consensus that all patients need chemotherapy, and in those with BR/LA disease, a neoadjuvant approach is preferable. IORT combined with surgical resection appears to be associated with good survival with minimal morbidity in patients with close or positive margins. IORT is also associated with improved survival in patients with unresectable, non-metastatic pancreatic cancer and may encourage providers to explore a greater number of patients with suspected localized unresectable disease.

DISCLOSURE There are no sources of support or funding for any of the listed authors to disclose aside from: Motaz Qadan discloses his role as a former Olympus consultant (2018). Theodore Hong discloses research support from Astra-Zeneca, BMS, IntrOp, Taiho, Tesaro, an advisory position to Merck Corporation, and consulting for Synthetic Biologics.

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