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Intraoperative Radiotherapy for Borderline Resectable Pancreatic Cancer: A Retrospective Analysis

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Abstract

To evaluate the feasibility and effect of intraoperative radiotherapy on patients with borderline resectable pancreatic cancer, Seventy-two consecutive patients who had undergone resection with/without the addition of intraoperative radiotherapy between 2013 and 2017 at our single institution were included and analyzed. Thirty-four patients (47.2%) received additive low-energy photon IORT with 17.4 Gy median radiation dose. With a median follow-up of 20.0 months (range, 6.0-40.0), the media overall survival time and the media progression-free survival time of all patients was 18.1 months and 11.2 months, respectively. Univariate analyses showed that not receiving IORT retained significance with regard to both PFS (HR, 1.74; p=0.02) and OS (HR, 1.79; p=0.02). In the multivariate analysis, not receiving IORT was associated with a lower probability of PFS (HR, 2.13; p<0.01) and OS (HR, 2.05; p<0.01). After resection combined with intraoperative radiotherapy, 20 (86%) of patients treated with surgery with intraoperative radiotherapy completely relieved the abdominal/waist pain, while 11 (44%) of patients of the control group relieved the pain (p=0.01). Thus, IORT can prolong survival and also improve the quality of life, and it can provide an adjunct to resection in patients with borderline resectable pancreatic cancer.

Keywords: Pain; Pancreatic Cancer; Radiotherapy; Survival

Abbreviations

IORT	:	Intraoperative Radiotherapy
BRPC	:	Borderline Resectable Pancreatic Cancer
PDAC	:	Pancreatic Ductal Adenocarcinoma
PC	:	Pancreatic Cancer
OS	:	Overall Survival
PFS	:	Progression-Free Survival

Introduction

Pancreatic Cancer (PC) is the fourth leading cause of cancer-related deaths in America with an overall 5-year survival rate of 7% [1], and is likely to be the second cancer cause of death by 2030 [2]. Surgery still remains the most effective treatment at present. However, only 15-20% of the patients were diagnosed in potentially resectable stages, and the rest were locally advanced or metastatic. There is a distinct subset of pancreatic cancer patients named as "Borderline Resectable Pancreatic Cancer (BRPC)", which was characterized by reconstructable venous involvement of the superior mesenteric vein or portal vein, along with abutment but not encasement of arterial structures or removable retroperitoneal structures [3].

Different with resectable PC, patients with BRPC act as the imprecise continuum between straightforwardly resectable and technically unresectable stage, for some degree of vascular involvement that may jeopardize a margin- negative (R0) resection [4]. For this reason, part of the BRPC patients choose to downstage by neoadjuvant therapy. However, some research

show that only 24%-46% BRPC patients obtain the opportunity to curative surgical treatment after neoadjuvant therapy [5,6]. In China, the conversion of successful resection rate was lower due to the fact that most of chinese patients could not tolerate the side effects of neoadjuvant therapy, and many patients tend to choose the traditional Chinese medicine rather than chemotherapy when a tumor cannot be removed surgically. In this case, a surgery-first strategy was very common in China and the final determination of whether a tumor is able to be resected with negative margins has customarily been made by the surgeon undertaking a trial dissection. So, combined a new technology to help achieving a margin-negative (R0) resection is essential.

The development of Intraoperative Radiotherapy (IORT) offers a hope to transform the R1 margin to R0 margin through killing the residual cancer cells in positive surgical margin with a high-dose radiation. INTRABEAM® PRS500 system (Carl Zeiss, Oberkochen, Germany) is the most widely used mobile intraoperative radiotherapy device to date, and the effect in resectable and locally advanced or unresectable pancreatic cancer has been reported. However, the researches focusing on the role of INTRABEAM IORT for BRPC patients, are unclear. In the current study, we reviewed a retrospective single-institutional series of BRPC patients who received surgical resection combining with/without sequential IORT. To determine the role of IORT in patient with BRPC, clinicopathological characteristics and survival information from 72 patients with BRPC matching the condition were collected and analyzed.

Materials and Methods

Patients

We retrospectively collected all of cases of patients with pancreatic cancer since January 1, 2013 to June 30, 2017 at the Sun Yat-sen Memorial Hospital of Sun Yat-sen University matching the following standards: 1). BRPC was defined to include one or more of the after radiographic findings: Tumor abutment (>180° of the circumference of the vessel) of the Superior Mesenteric Artery (SMA) or celiac axis; tumor abutment or encasement (>180° of the circumference of the vessel) of a short segment of the hepatic artery, short-segment occlusion of the Superior Mesen-Teric Vein (SMV), Portal Vein (PV), or SMV–PV confluence amenable to vascular resection and reconstruction [7]; 2). Pancreatic ductal adenocarcinoma was pathologically identified; 3). All patients postoperatively received gemcitabine-based combination chemotherapy. Exclusion criteria was those combining with other types of tumor like islet cell tumor and mucinous cystadenocainoma or metastasis. Finally, we sorted out 72 patients to further analyze the survival and the quality of life, in which 34 patients treated with surgery combined with IORT, while 38 patients treated with surgery only. The study protocol was approved by the institutional ethic committee. Written informed consent on intra-operative radiotherapy was obtained from patients treated with IORT prior to operation.

Procedures

Among of IORT group/non-IORT group, 25/26 patients with tumor in the head of pancreas received pancreatoduoenectomy, and 9/12 patients with tumor in the body or tail of pancreas received distal pancreatectomy combined with splenectomy, respectively. In IORT group, the operations were carried out at an operating room equipped with an intraoperative low-energy photon applicator (Carl Zeiss Intrabeam, X-ray source 50 kV, German) (Figure 1A). Patients immediately received the intraoperative radiation after tumor removal (Figure 1B) and before digestive anastomosis (Figure 1C). The protocol using the intra-operative radiotherapy method in this study was described in previous reports [8]. The target area was 5 mm away from source applicator with a 5cm efficient diameter. The radial field included the tumor bed with approximate 1-cm to 3-cm margin, comprising the retroperitoneum, vascular structures, and tumor bed extending from the transected bile duct superiorly to the right kidney laterally and to the pancreatic remnant medially. Prior to irradiation, lead shielding was used to cover the surrounding radiosensitive organs like small bowel in order to avoid unnecessary damage. The IORT dose was prescribed to 90% isodose and the media dose was 17.4 Gy (range 10 to 20 Gy). The radiation dose depended on the vessel number of tumor involvement, the vessel range of tumor encasement and the possibility and extent of tumor residue after resection. The dose would be reduced to 10 Gy for R0 margins confirmed by frozen section. For larger tumors or tumors involving with main vessels, 20 Gy was preferred. After IORT, surgeons continued to rebuild the digestive tract and finished the operation. All of patients postoperatively received six courses of gemcitabine monotherapy after rest for 4-6 weeks.

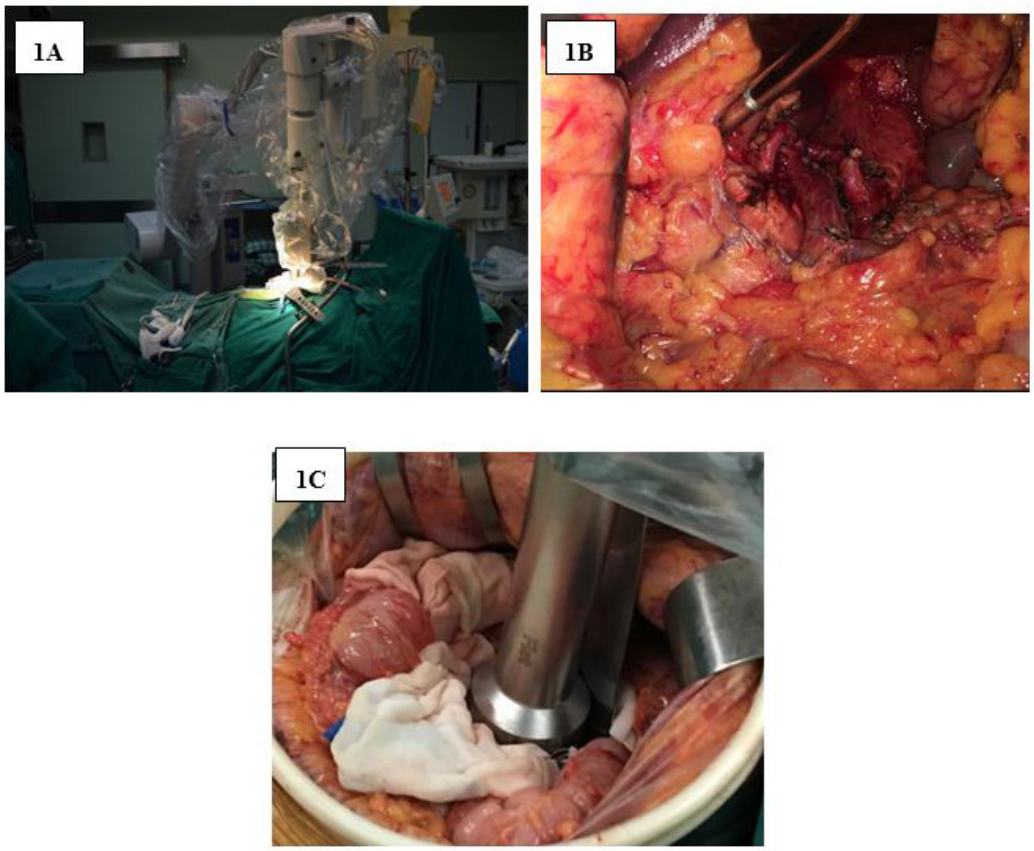

Figure 1: A: The low-energy photon intrabeam: The application was movable and feasible to a proper position in different size and bevel angles. The target area was 5mm away from source applicator with a 5cm efficient diameter. A single dose was 10 to 20 Gy. **B:** The condition after the removal of tumor **C:** The application of electron beam was placed in the bed

Data Collection

Patient demographics (age and gender), jaundice status, pain, CA 19-9, tumor site, tumor stage (the pathological TNM staging system issued by 8th edition of AJCC), Lymph Node (LN) invasion, vascular invasion, perineural invasion，pathological differentiation was obtained. Margin resection status, Visual Analogue Scale (VAS) at the preoperation and the first postoperative follow-up and postoperation complication were collected. Acute and chronic toxicities were evaluated using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer score.

Follow-Up

The researchers would follow up all of patients every month after operation for the initial 1 year and every 3 months for the next year and every 6 months for 3 additional years thereafter. Patients were restaged routinely every 3 to 6 months with blood tests, ultrasound and Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of the upper abdomen. Progression was defined as identification of suspicious imaging finding or biopsy-proven tumor in the tumor bed, regional LN area or distant area. Overall survival (OS) was defined as the duration from the date of operation until death or the last follow-up. Progression-Free Survival (PFS) was defined as the duration from the date of operation until the date when tumor progression was diagnosed or the last follow-up. The last follow-up was completed on June 30 2018.

Statistical Analysis

SPSS version 24 software (SPSS Inc, Chicago, IL, USA) was used to analyze the data. The primary endpoints of the analysis were OS and PFS. Potential associations were assessed in univariate and multivariate analyses using the Cox proportional hazards model (2-tailed p test 0.05). As for the contrast of pain. patients were divided into four subgroups: the mild group (VAS=1-3), severe group (VAS=4-6), extreme severe group (VAS=7-10) and no-pain

group (VAS=0) and were analyzed with the nonparametric text.

Results

Patient characteristics

Median follow-up time for the entire group of patients was 20.0 months (range: 6.0-40.0 months). No patients were lost to follow-up. Baseline characteristics of patients are shown in (Table 1). The median age of all patients was 57.9years (range: 28.0-82.0 years). Taken altogether, 48 (66.7%) patients had abdominal pain. 51 patients (70.8%) had tumors located at the head of pancreas more than tumors in the body or tail (29.2%) of pancreas. The mean tumor diameter was 3.2 cm ± 0.8 cm. According to the pathological reports, 43 (59.7%) patients were in stage T3, 16(22.3%) patients in stage T4, 69(95.8%) patients in stage N1, and 17(23.6%) patients were diagnosed with poor differentiation, 41(56.9%) with moderate differentiation and 14 (19.4%) with well differentiation. In total, 55.6% (n=40) of patients had R0 resection margin and 44.4% (n=32) had R1 resection margin. There were no significant differences on patient characteristics between the IORT group and non-IORT group.

Characteristic		IOERT group (n=34)	Non-IOERT group (n=38)	p value
Age(years)	Median	59.85	56.18	
Gender	Male	17	27	0.067
	Female	17	11	
CA19-9	≥500	14	14	0.706
	<500	20	24	
Obstructive jaundice	Yes	14	17	0.686
	No	20	20	
Pain	Yes	23	25	0.738
	No	11	13	
Tumor site	Head	23	28	0.574
	body or tail	11	10	
Clinical stage	Ⅱb	14	17	0.761
	Ⅲ	20	21	
Staging cT	cT2	5	8	0.627
	cT3	20	23	
	cT4	9	7	
Staging cN	N0	1	2	0.829
	N1	31	33	
	N2	2	3	
Margin resection status	R0	19	21	0.958
	R1	15	17	
Perineural invasion	Yes	13	16	0.738
	No	21	22	
LN invasion	Yes	33	36	0.623
	No	1	2	
Vascular invasion	Yes	9	10	0.958
	No	25	27	
Differentiation	Poorly differentiated	8	9	0.081
	Moderately differentiated	23	18	
	Well differentiated	3	11	
Post-operation complication	No complication	20	24	0.875
	Intestinal obstruction	1	1	
	Intestinal fistula	0	0	
	Digestive tract bleeding	0	0	
	Pancreatic leakage	7	8	
	Abdominal infection	4	4	
	Bile leakage	3	2	
Vascular resection	Yes	10	12	0.842
	No	24	26	

Table 1: Patient, tumor, and treatment characteristics.

Contrast for overall survival

OS for all patients at 1 year, 2 years and 3 years was 54.2%, 27.8% and 11.1%, respectively (Figure 2A). The median overall survival of the IORT group is 22.0 mouths (range: 7.9 to 40.1),

while the median overall survival of the non-IORT group is 14.8 mouths (range: 5.7 to 40.1) (p<0.01). Both the univariate and multivariate Cox proportional hazard analyses showed that R0 resection (Table 2, p <0.01; Table 3, p <0.01) (Figure 2B) and IORT (Table 2, p =0.02; Table 3, p <0.01) (Figure 2C) were associated with a higher probability of OS consistently.

Contrast for Progression-free survival

PFS for the study population at 1 year, 2 years and 3 years was 34.7%, 11.1% and 0 (Figure 2D). The median PFS of the IORT group/the non-IORT group is 11.7 months (range: 4.7 to 28.4)/8.9 months (range: 1.9 to 33.8) (p<0.01). Univariate analyses revealed a significantly higher risk of R1 resectio (Table 2; p<0.01) (Figure 2E) and non-IORT (Table 2, p=0.02) (Figure 2F). The multivariate Cox proportional hazard analyses showed R1 resection (Table 3; p<0.01) and IORT (Table 3; p<0.01) retained significance with regard to PFS.

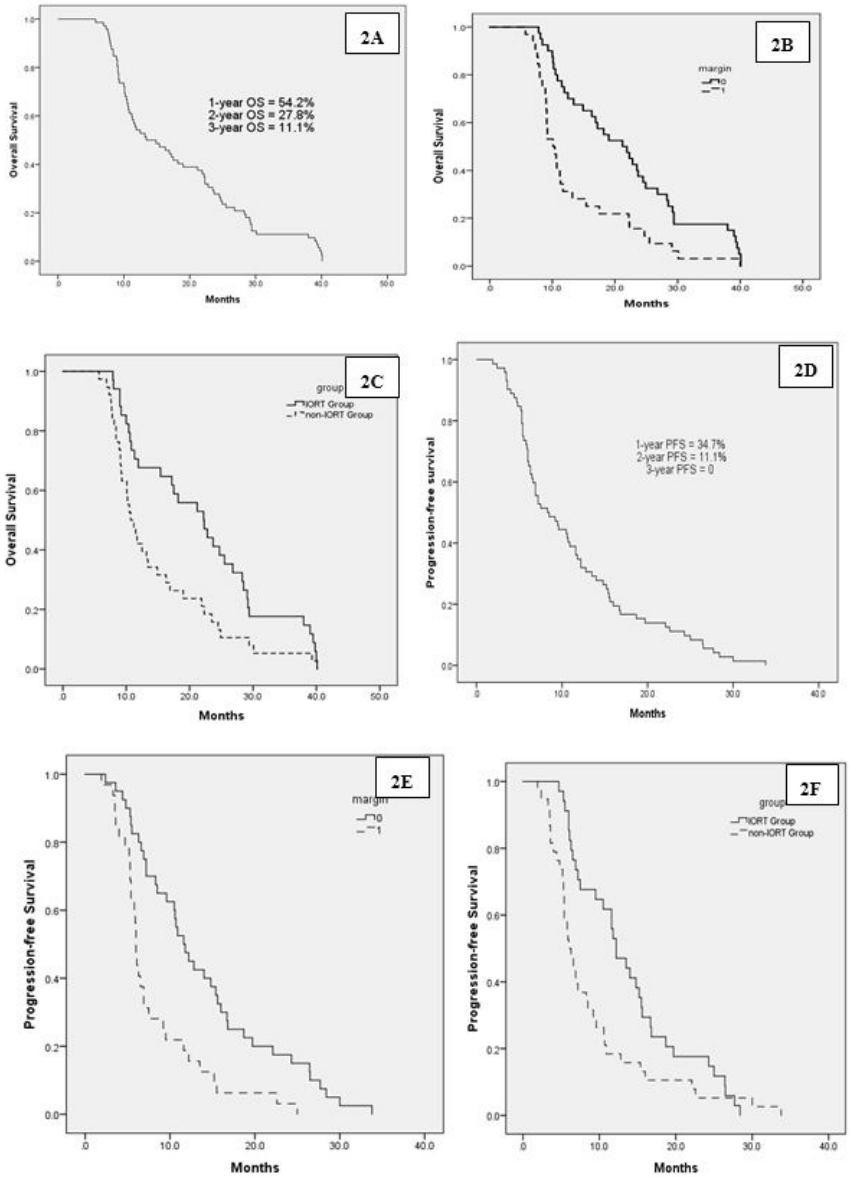

Figure 2: Kaplan-Meier curves for all 72 patients **A:** overall survival **B**：OS according to the margin resection status **C:** OS according to the group **D:** progression-free survival **E:** PFS according to the margin resection status **F:** PFS according to the group. (Abbreviations：OS: Overall survival; PFS: Progression-free survival.)

		Disease-free survival	Overall survival
	variable	**HR 95%CI P value**	**HR 95%CI P value**
Patient variables			
Age(years)	<=60	1.00 0.52-1.34 0.45	1.00 0.58-1.47 0.74
	>60	0.83	0.92
Gender	Male	1.00 0.63-1.66 0.92	1.00 0.759-1.981 0.41
	Female	1.03	1.23
CA19-9	<500	1.00 0.61-1.63 0.99	1.00 0.78-2.05 0.34
	≥500	1	1.26
Obstructive jaundice	No	1.00 0.81-2.14 0.27	1.00 0.87-2.26 0.17
	Yes	1.31	1.4
Pain	No	1.00 0.82-2.13 0.25	1.00 0.765-2.02 0.38
	Yes	1.32	1.24
Preoperative staging			
Tumor site	Head	1.00 0.70-1.97 0.55	1.00 0.63-1.77 0.83
	Body or Tail	1.17	1.06
Clinical stage	Ⅱb	1.00 0.62-1.60 0.98	1.00 0.61-1.59 0.96
	Ⅲ	1	1
Staging cT	cT1-cT3	1.00 0.52-1.37 0.50	1.00 0.63-1.65 0.93
	cT4	0.85	1.02
Staging cN	N0-N1	1.00 0.24-2.45 0.65	1.00 0.19-1.91 0.38
	N2	0.76	0.6
Vascular invasion	No	1.00 0.66-1.94 0.65	1.00 0.70-2.05 0.51
	Yes	1.13	1.2
Microscopic surgical specimen			
Differentiation	III	1.00 0.49-1.48 0.57	1.00 0.53-1.60 0.77
	I-II	0.85	0.92
Perineural invasion	No	1.00 0.90-2.39 0.17	1.00 0.81-2.13 0.27
	Yes	1.46	1.32
Margin resection status	R0	1.00 1.48-4.00 <0.01	1.00 1.33-3.47 <0.01
	R1	2.44	2.15
IORT	No	1.00 1.08-2.80 0.02	1.00 1.12-2.87 0.02
	Yes	1.74	1.79

Table 2: Univariate analysis of associations between the patient, tumor and pathologic characteristics and survival.

		Disease-free survival	Overall survival
	variable	**HR 95%CI P value**	**HR 95%CI P value**
Clinical stage	Ⅱb	**1.00 0.53-1.41 0.57**	**1.00 0.40-1.26 0.24**
	Ⅲ	**0.86**	0.9
Margin resection status	R0	1.00 1.71-4.78 <0.01	1.00 1.46-3.89 <0.01
	R1	2.86	2.39
IOERT	No	1.00 1.29-3.52 <0.01	1.00 1.25-3.37 <0.01
	Yes	2.13	2.05
Differentiation	III	1.00 0.32-1.05 0.07	1.00 0.40-1.26 0.24
	I-II	0.58	0.71

Table 3: Factors associated with disease-free survival, and overall survival in the multivariate analysis.

Waist/abdominal pain

In pre-operation, the number of the mild group, severe group, extreme severe group and no-pain group of the IORT group were 9(26.4%), 10(29.4%), 4(11.8%) and 11(32.4%). Correspondingly, the number of the non-IORT group were 11(28.9%), 9(23.7%), 5(13.2%), 13(34.2%), respectively. The Kruskal-Wallis Test analyses showed no difference between the two groups (Table 4; p =0.82). In postoperation, 20(86%)of the IORT group obtained complete remission of pain vs. 11(44%) of the non-IORT group obtained complete remission of pain. The Kruskal-Wallis Test analyses showed that the difference of pain control between the two groups of pain control makes sense (Table 4; p =0.01).

	IOERT group (n=34)	Non-IOERT group (n=38)	p value
preoperative VAS			0.82
0	11	13	
1	9	11	
2	10	9	
3	4	5	
postoperative VAS			0.01
0	31	24	
1	2	10	
2	1	4	
3	0	0	
Complete response	20(86%)	11(44%)	

Table 4: The Kruskal-Wallis Test analyses of the waist/abdominal pain.

Complication

In all patients, the rate of operative complications was approximately 57%. The operative complications include bile leakage (n=5), pancreatic leakage (n=15) and abdominal infection (n=8), but no digestive tract bleeding, intestinal fistula or digestive tract bleeding. After conservative therapy like enhanced peritoneal lavage, all patients survived from the post-operative complications. Of all patients, there were no long-term complications such as radiation enteritis and pancreatitis. The short-term post-operative complications like bile leakage and pancreatic leakage are quite common for pancreaticoduodenectomy. And there were no significant differences between the IORT group and non-IORT group.

Discussion

Our relevant research can be summarized as follows. First, we found that patients who did not received IORT had a higher probability of disease progression and poor outcomes. Second, we observed that IORT can effectively alleviate cancerous pain. Finally, there was no significant increase in additional complications in IORT patients.

Pancreatic cancer is characterized by the extremely malignant biological characteristics. Even in nowadays, there is only 20% of tumors can be resected at diagnosis, in which approximately 10-35% of patients may occur isolated local recurrences [7-9], likely associated with positive microscopic resection margins. Our research shows that R1 margin status leads to the increased probability of overall progression and death. As Sugiura et. reported, R1 margins are indicative of biologically aggressive tumors [10]. Borderline resectable pancreatic cancer is in betweenness from resectability to technical unresectability, which is suffering with a higher recurrence rate for a fewer R0 ratio. So, it is necessary to stress the importance of attempting to achieve microscopically negative margins for curative intent. It should be mentioned that although several definitions have been projected for BRPC for example ASCO, we still selecting the NCCN CPG definition for its clearer criteria for tumor resection in contrast with ASCO [11].

Available data in patients receiving IORT after pancreaticoduodenectomy suggest an improvement in local control. Alfieri et al. noted IORT in resectable pancreatic cancer increased local control and they found that local control was 58% in the IORT group vs. 29% in the group that did not receive IORT ($p < 0.01$) [12]. Reni et al reported that 127 patients of resectable pancreatic cancer surgically treated with curative intent combined with IORT was compared with 76 patients treated with surgery, in which median time to local failure treated with surgery alone or with IORT were 11 months and 14 months, respectively (p =0.02) [13]. In our research, the median PFS of IORT group is 13.7 months while the median PFS of IORT group is 8.9 months($p<0.01$), suggusted that IORT combimed with surgery improves local control not only in resectable pancreatic cancer but also in borderline resectable pancreatic cancer. What's more, an Italian series evaluated 43 patients receiving IORT in addition to surgical resection whereas 47 underwent resection alone. Results revealed local recurrence in the group receiving IORT was 27% compared with 56% in the group receiving surgical resection alone ($P <0.01$). However, 1-year, 2-year and 3-year survival rates were respectively 71%, 24%, and 7% in IORT group and 49%, 16%, and 10% in non-IORT group (P was not significant), and there are no differences in overall survival [14]. The National Cancer

Institute reported an experience evaluating 24 additional patients randomized to receive IORT (20 Gy). Excluding 7 perioperative deaths, an improvement in median survival was seen in the patients who received IORT (OS 18 vs. 12 months; P ¼ 0.01) [15]. Our research shows the OS in BRPC patients is 22.0 months in IORT group vs.14.8 months in non-IORT group (p<0.01). Whether the IORT can benefit the survival of patients in pancreatic cancer need to be further verified, but our study shows that IORT does improve the prognois of BRPC patients.

Many studies have documented pain control with IORT in locally advanced or unresectable pancreatic cancer, resulting in complete pain resolution in 75%-90% of cases [16]. Another research from China evaluated 43 patients with advanced pancreatic cancer who received IORT combined with EBRT. This approach was shown to alleviate pain, improve quality of life [12]. In our study, the rate of complete remission of pain in IORT group reaches to 86%, higher than the non-IORT group. The contrast showed IORT can control local pain in BRPC at same with locally advanced or unresectable pancreatic cancer. What is more, our research shows that no matter whether radical excision, patients improve the quality of life, away from the side-effects of opioid painkillers. In our study, patients accept IORT with the INTRABEAM® PRS500 system (Carl Zeiss Surgical, Oberkochen, Germany), which is a compact mobile X-ray source originally developed for intracranial stereotaxy in the early 1990s. is widely used in breast cancer nowadays. An analysis of 208 women who underwent IORT with INTRABEAM® during breast conserving surgery (BCS) shows rare postoperative complications and the low immediate toxicity low without any grade 3/4 acute toxicity [17]. In resectable pancreatic adenocarcinoma, A larger series of 127 patients treated with potentially curative surgery and IORT comparing with a cohort of 76 patients who received surgery alone show no additional operative morbidity or mortality was seen with the addition of IORT [18]. In our study in borderline pancreatic adenocarcinoma, the application of radiotherapy with the Intrabeam® device in selected patients has not resulted in increased perioperative morbidity or mortality.

For patients who present with border line resectable disease, neoadjuvant treatment strategies would be a better choice to enhance the odds of cure by improving rates of R0 resection. Research notes that neoadjuvant therapy would potentially benefit the BRPC patients [19]. Despite the encouraging clinical results of the neoadjuvant treatment for BRPC, there are also some problems we need to face with. On the one hand, it may cause radioactive enteritis and tissue edema surrounding tumor, therefore increase the odd of combined vascular resection and operation difficulty of some patients. On the other hand, part of patients with poor sensitivity would be failing to control the progression and delay the surgical treatment [20]. What is worth mentioning is, in order to exclude the effect of chemotherapy on the prognosis postoperatively, we deliberately selected patients receiving the gemcitabine-based combination chemotherapy.

In comparison with neoadjuvant treatment strategies aimed at borderline resectable disease, the results from this study suggest that IORT affords similar, if not better, outcomes. It is suitable for patients who are not willing to accept neoadjuvant chemotherapy in China especially. For most of patients with BRPC, surgical resection combined with IORT will help to achieve progression-free survival benefit and improve their quality of life. The addition of IORT after surgery did not increase rates of perioperative mortality, postoperative complications and in-hospital deal significantly. In our institution, the radiation dose was similar to the dose of most of IORT for pancreatic cancer in the worldwide. The cost of the addition of IORT is much cheaper than the cost of neoadjuvant therapy like neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy [21-32].

Conclusion

In conclusion, receiving IORT after surgical pancreaticoduodenectomy shows a high rate of R0 resection, improves local control and prolongs survival. This modality was relatively safe and cost-effective. What is more, it could relief the abdominal/waist pain of BRPC patients, keep patients away from the by-effects of opioid painkillers and improve the quality of life. This study supports the design of III prospective RCT trial for borderline pancreatic cancer. In our institution, IORT has routinely been used in the management of part of patients with BRPC.

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Conflict of Interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

References

1. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics, 2016. CA: a cancer journal for clinicians 66: 7-30.

2. Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, et al. (2014) Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 155: 977-988.

3. National Comprehensive Cancer Network 2018.

4. Ryan DP, Hong TS, Bardeesy N (2014) Pancreatic adenocarcinoma. The New England journal of medicine 371: 1039-1049.

5. Landry J, Catalano PJ, Staley C, Harris W, Hoffman J, et al. (2010) Randomized phase II study of gemcitabine plus radiotherapy versus gemcitabine, 5-fluorouracil, and cisplatin followed by radiotherapy and 5-fluorouracil for patients with locally advanced, potentially resectable pancreatic adenocarcinoma. Journal of surgical oncology 101: 587-592.

6. McClaine RJ, Lowy AM, Sussman JJ, Schmulewitz N, Grisell DL, et al. (2010) Neoadjuvant therapy may lead to successful surgical resection and improved survival in patients with borderline resectable pancreatic cancer. HPB : the official journal of the International Hepato Pancreato Biliary Association 12: 73-79.

7. Yokoyama Y, Ebata T, Igami T, Sugawara G, Takahashi Y, et al. (2012) [Borderline resectable pancreatic cancer - a definition and effective treatment strategy]. Gan to kagaku ryoho Cancer & chemotherapy 39: 337-341.

8. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, et al. (2007) Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. Jama 297: 267-277.

9. Hishinuma S, Ogata Y, Tomikawa M, Ozawa I, Hirabayashi K, et al. (2006) Patterns of recurrence after curative resection of pancreatic cancer, based on autopsy findings. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 10: 511-518.

10. Sugiura T, Uesaka K, Mihara K, Sasaki K, Kanemoto H, et al. (2013) Margin status, recurrence pattern, and prognosis after resection of pancreatic cancer. Surgery 154: 1078-1086.

11. Zheng Suli, Zhang Taiping (2017) Consensus and controversy about resectable and possibly resectable pancreatic cancer between ASCO and NCCN clinical practice guideline. Chinese Journal of General Surgery 26: 1085-1088.

12. Alfieri S, Morganti AG, Di Giorgio A, Valentini V, Bossola M, et al. (2001) Improved survival and local control after intraoperative radiation therapy and postoperative radiotherapy: a multivariate analysis of 46 patients undergoing surgery for pancreatic head cancer. Archives of surgery 136: 343-347.

13. Reni M, Panucci MG, Ferreri AJ, Balzano G, Passoni P, et al. (2001) Effect on local control and survival of electron beam intraoperative irradiation for resectable pancreatic adenocarcinoma. International journal of radiation oncology, biology, physics 50: 651-658.

14. Zerbi A, Fossati V, Parolini D, Carlucci M, Balzano G, et al. (1994) Intraoperative radiation therapy adjuvant to resection in the treatment of pancreatic cancer. Cancer 73: 2930-2935.

15. Sindelar WF, Kinsella TJ (1999) Studies of intraoperative radiotherapy in carcinoma of the pancreas. Annals of oncology : official journal of the European Society for Medical Oncology 4: 226-230.

16. Valentini V, Balducci M, Tortoreto F, Morganti AG, De Giorgi U, et al. (2002) Intraoperative radiotherapy: current thinking. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 28: 180-185.

17. Tuschy B, Berlit S, Romero S, Sperk E, Wenz F, et al. (2013) Clinical aspects of intraoperative radiotherapy in early breast cancer: short-term complications after IORT in women treated with low energy x-rays. Radiation oncology (London, England) 8: 95.

18. Ma HB, Di ZL, Wang XJ, Kang HF, Deng HC, et al. (2004) Effect of intraoperative radiotherapy combined with external beam radiotherapy following internal drainage for advanced pancreatic carcinoma. World journal of gastroenterology 10: 1669-1771.

19. Papavasiliou P, Chun YS, Hoffman JP (2013) How to define and manage borderline resectable pancreatic cancer. The Surgical clinics of North America 93: 663-674.

20. XU CB, LI F (2016) The research progress of neoadjuvant treatment strategies in borderline resectable pancreatic cancer. The World Clinical Medicine 2: 117-118.

21. Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE, et al. (2008) Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. Journal of the American College of Surgeons 206: 833-846.

22. Krempien R, Roeder F (2017) Intraoperative radiation therapy (IORT) in pancreatic cancer. Radiation oncology (London, England) 12: 8.

23. Rau BM, Moritz K, Schuschan S, Alsfasser G, Prall F, et al. (2012) R1 resection in pancreatic cancer has significant impact on long-term outcome in standardized pathology modified for routine use. Surgery 152: S103-111.

24. Kooby DA, Lad NL, Squires MH, 3rd, Maithel SK, Sarmiento JM, et al. (2014) Value of intraoperative neck margin analysis during Whipple for pancreatic adenocarcinoma: a multicenter analysis of 1399 patient. Annals of surgery 260: 494-501.

25. Calvo FA, Sole CV, Atahualpa F, Lozano MA, Gomez-Espi M, et al. (2013) Chemoradiation for resected pancreatic adenocarcinoma with or without intraoperative radiation therapy boost: Long-term outcomes. Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al] 13: 576-582.

26. Klauss M, Stiller W, Fritz F, Kieser M, Werner J, et al. (2012) Computed tomography perfusion analysis of pancreatic carcinoma. Journal of computer assisted tomography 36: 237-242.

27. Golcher H, Brunner TB, Witzigmann H, Marti L, Bechstein WO, et al. (2015) Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al] 191: 7-16.

28. Versteijne E, van Eijck CH, Punt CJ, Suker M, Zwinderman AH, et al. (2016) Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC trial): study protocol for a multicentre randomized controlled trial. Trials 17: 127.

29. Keane FK, Wo JY, Ferrone CR, Clark JW, Blaszkowsky LS, et al. (2018) Intraoperative Radiotherapy in the Era of Intensive Neoadjuvant Chemotherapy and Chemoradiotherapy for Pancreatic Adenocarcinoma. American journal of clinical oncology 41: 607-612.

30. Katz MH, Marsh R, Herman JM, Shi Q, Collison E, et al. (2013) Borderline resectable pancreatic cancer: need for standardization and methods for optimal clinical trial design. Annals of surgical oncology 20: 2787-2795.

31. Huguet F, Mornex F, Orthuon A (2016) [Radiation therapy of pancreatic cancer]. Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique 20: S169-73.

32. Khorana AA, Mangu PB, Berlin J, Engebretson A, Hong TS, et al. (2017) Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 35: 2324-2328.