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Intraoperative Radiotherapy for Resectable Pancreatic Cancer Using a Low-Energy X-Ray Source: Postoperative Complications and Early Outcomes

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Purpose: We evaluated the safety, feasibility, and early treatment outcomes of intraoperative radiotherapy (IORT) using a low-energy X-ray source.
Materials and Methods: Patients with resectable pancreatic cancer were enrolled in this single-institution, prospective, single-arm, phase II trial. Patients underwent surgery and IORT with 10 Gy prescribed at a 5-mm depth from the tumor bed using a 50 kV X-ray source (Intrabeam, Carl Zeiss). Six cycles of adjuvant gemcitabine-based chemotherapy were administered 8–12 weeks after surgery.
Results: A total of 41 patients were included. Thirty-one patients (75.6%) underwent wide R0 resection, while 5 (12.2%) underwent R1 resection and 5 (12.2%) underwent narrow R0 resection (retroperitoneal margin <1 mm). Grade 3 postoperative complications were reported in only one patient (4.9%) who needed additional surgery due to ulcer perforation. At a median follow-up of 9 months, four patients showed local-only recurrence, nine had distant metastases, and two showed both local and distant recurrence. The 1-year local control rate was 76.4%.
Conclusion: Our preliminary report suggests that IORT is well-tolerated and feasible in patients with resectable pancreatic cancer. Further follow-up is needed to confirm the clinical benefits of IORT in terms of local control and overall survival.
Trial Registration: Clinical trial registration No. (NCT03273374).

Key Words: Pancreatic neoplasms, radiotherapy, postoperative complications, x-ray therapy, recurrence

INTRODUCTION

Curative surgery followed by adjuvant chemotherapy is the standard treatment for patients with resectable pancreatic cancer. However, despite appropriate treatment, survival rates are low, and local recurrence after curative resection is not uncommon.[1] The main reason for the high rate of recurrence is that pancreatic cancer patients often have microscopic residual disease.[2] Therefore, postoperative external beam radiotherapy (EBRT) has been proposed as a method to improve local control in resectable pancreatic cancer patients.[3]

Although previous studies have examined the potential therapeutic benefits of EBRT in an adjuvant setting, its use remains limited.[4] The delivery of high-dose radiotherapy (RT) to the pancreas is extremely challenging, as there are several radiosensitive abdominal organs around the pancreas. Recent advanced RT techniques, such as intensity-modulated RT, image-guided RT, magnetic resonance-guided RT, and particle therapy, have shown favorable outcomes in pancreatic cancer patients.[5,6] Most of these treatments have been administered to patients with unresectable or borderline resectable pancreatic cancer, and the potential clinical use of these treatments in an adjuvant setting has not yet been established.

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The use of intraoperative radiotherapy (IORT) for pancreatic cancer was first reported in Japan in the 1980s for patients with locally advanced pancreatic cancer. During a surgical procedure, IORT can be used to deliver a single fraction of high-dose radiation to the tumor bed after the tumor has been removed. IORT has the potential to improve the efficacy of RT for pancreatic cancer by reducing the radiation dose delivered to the adjacent organs and by allowing radiation dose escalation to the tumor bed, thus improving local control of the disease.

The majority of cases in which IORT has been used for the pancreas has involved the administration of electron beams. However, IORT involving electron beams needs to be delivered in an appropriately shielded room, and transferring patients from the operating room to a shielded radiation room increases the risk of contamination and can undermine patient safety. We have been conducting a phase II study assessing the use of IORT in patients with resectable pancreatic cancer using a 50 kV X-ray source (Intrabeam, Carl Zeiss, Germany) and a study protocol that has been previously described.[7] Since Intrabeam employs a miniaturized low-energy X-ray source, it can be used to administer IORT in an operating theater. In this preliminary report, we investigated acute postoperative complications and reviewed the early oncologic outcomes of patients with resectable pancreatic cancer undergoing IORT using a low-energy X-ray source.

MATERIALS AND METHODS

Patient selection

This single-institution prospective phase II study was approved by our Institutional Review Board (protocol number: 3-2015-0102) in 2017 and registered at ClinicalTrials.gov (NCT 03273374). Patients diagnosed with pancreatic cancer were recruited between August 2017 and September 2019. The eligibility criteria were as follows: 1) age 20 years or older; 2) histologically or clinically confirmed pancreatic carcinoma; 3) Eastern Cooperative Oncology Group (ECOG) performance status scores of 0–2; 4) resectable disease defined as the absence of distant metastases, absence of direct involvement of the inferior vena cava or aorta, and clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery; 5) stage I–III disease as per the 7th edition of the American Joint Committee on Cancer (AJCC); 6) good bone marrow function (hemoglobin level >10 g/dL, absolute neutrophil count >1500/mm^3, platelet count >100000/mm^3); and 7) adequate renal function (serum creatinine level <1.4 mg/dL, blood urea nitrogen level <20 mg/dL). Patients who 1) had previously received RT to the abdominal area; 2) had a tumor bed that could not be adequately covered by the IORT field as defined by a radiation oncologist; 3) had received neoadjuvant chemotherapy; 4) had synchronous distant metastasis; 5) were pregnant or nursing; or 6) had any condition rendering them unsuitable for IORT (at the discretion of a physician) were excluded from this study.

Treatment scheme

Patients who fulfilled the inclusion criteria and provided written informed consent were assigned to the protocol. Details on the treatment protocol have been described in a previously published study.[7] The patients were subjected to curative resection, either pylorus-preserving pancreaticoduodenectomy (PPPD), distal pancreatectomy, or total pancreatectomy. A mobile 50-kV X-ray source was used for IORT. The target volume included the tumor bed, the celiac and superior mesenteric arteries, the mesenteric root, and the portal vein; any areas deemed at risk by the surgeon and radiation oncologist were included as well. A spherical applicator with a diameter of 3.5 cm was used. An additional shielding device was attached to the spherical applicator, leaving only the bottom surface unshielded from which the X-ray beam was delivered to the tumor bed (Fig. 1). The percentage depth dose curve of the shielded applicator is shown in Supplementary Fig. 1 (only online).

The target volume was irradiated with a single dose of 10 Gy, prescribed at a 5-mm depth into the tumor bed, resulting in a surface dose of approximately 16 Gy, referring to previous literature.[8-10] Eight to 12 weeks following surgery, the patients received six cycles of adjuvant gemcitabine-based chemotherapy every 4 weeks. Each chemotherapy cycle consisted of three weekly gemcitabine doses.

Follow-up and analysis

Acute postoperative complications were the primary endpoint of this study; any toxicity occurring within 3 months of surgery was considered an acute toxicity. Delayed gastric emptying was defined and graded according to the International Study Group of Pancreatic Surgery consensus,[11] while postoperative pancreatic fistula was defined and graded according to the International Study Group on Pancreatic Fistula consensus.[12] Other acute postoperative complications were evaluated using the

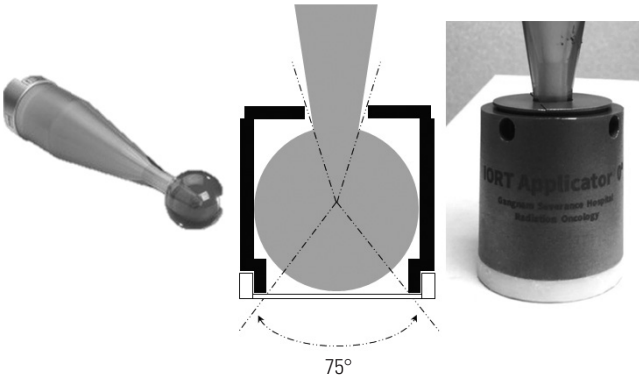

Fig. 1. Shielding device of the spherical applicator. Only the bottom surface of the applicator is covered with plastic, while all other parts are shielded by steel use stainless steel.

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Clavien-Dindo classification.

Early oncologic outcomes were also investigated. We defined local failure as any failure around the superior mesenteric artery and celiac trunk, including the tumor bed, remnant pancreas, and regional nodes.[13] Failures other than local failure were considered as distant failures. Patient survival was determined from the day of surgery.

Kaplan-Meier survival analysis was conducted to evaluate local and distant control. Univariate and multivariate analyses of factors related to local and distant control and overall survival (OS) were conducted using the Cox proportional hazards model. Variables with $p<0.1$ in univariate analysis were included in the multivariate analysis. *P*-values<0.05 were considered statistically significant.

RESULTS

Patients and disease characteristics

Between November 2017 and August 2019, a total of 53 patients were screened for eligibility. However, nine patients did not fulfill the inclusion criteria: three patients showed peritoneal seeding or liver metastasis during surgery, four underwent superior mesenteric vein or portal vein resection and reconstruction, and two patients' condition deteriorated during surgery. Thus, a total of 44 patients was initially enrolled in the study. After excluding three patients whose final pathology revealed neoplasms that did not originate from the pancreas, a total of 41 patients was finally included for analysis (Fig. 2).

The patient and disease characteristics of the 41 patients included in our analysis are shown in Table 1. The median age of the patients was 66 years (range, 42–84 years), and the cohort consisted of 56.1% male patients and 43.9% female patients. The majority of tumors were located in the pancreatic head or the uncinate process (63.4%). The median serum concentration of carbohydrate antigen 19-9 (CA19-9) was 86 U/mL, and preoperative assessment showed that the median tumor size was 3.0 cm (range, 1.0–8.0 cm). Fifteen (36.6%) patients were pathologically confirmed to have pancreatic cancer be-

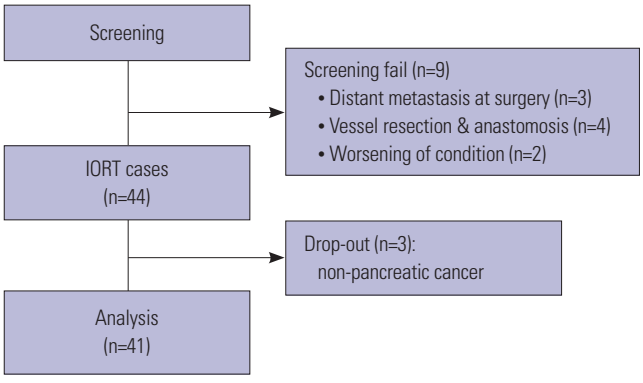

Fig. 2. Patients selection for this analysis. IORT, intraoperative radiotherapy.

Table 1. Patient and Disease Characteristics (n=41)

Variables	Value
Age (yr)	66 (42–84)
<70	23 (56.1)
≥70	18 (43.9)
Sex	
Male	23 (56.1)
Female	18 (43.9)
Location	
Head/uncinated process	26 (63.4)
Body/tail	15 (36.6)
CEA (ng/mL)	3.2 (0.8–144.8)
CA19-9 (U/mL)	86 (0.08–15698.3)
Tumor size (clinical, cm)	3.0 (1.0–8.0)
Pathologic confirm before surgery	
No	26 (63.4)
Yes	15 (36.6)
Types of surgery	
PPPD	26 (63.4)
Distal pancreatectomy	13 (31.7)
Total pancreatectomy	2 (4.9)
Pathological T stage	
T1	1 (2.4)
T2	23 (56.1)
T3	17 (41.5)
Pathological N stage	
N0	15 (36.6)
N1	16 (39.0)
N2	10 (24.4)
AJCC stage (8th)	
I	9 (22.0)
II	22 (53.7)
III	10 (24.4)
Histology	
Adenocarcinoma	39 (95.1)
Others	2 (4.9)
LVI	
No	22 (53.7)
Yes	19 (46.3)
PNI	
No	6 (14.6)
Yes	35 (85.4)
Margin status	
Negative	36 (87.8)
Positive	5 (12.2)
Degree of resection	
Wide R0	31 (75.6)
Narrow R0	5 (12.2)
R1	5 (12.2)

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; PPPD, pylorus-preserving pancreaticoduodenectomy; AJCC, American Joint Committee on Cancer; LVI, lymphovascular invasion; PNI, perineural invasion.
Data are presented as median (range) or n (%).

fore surgery. PPPD, distal pancreatectomy, and total pancreatectomy were performed in 26, 13, and 2 patients, respectively.

For our analysis, we used the tumor staging system devised by the AJCC 8th edition. More than 40% of patients had tumors larger than 4 cm (T3), and 63.4% of patients had regional lymph node metastasis. Most patients were diagnosed with adenocarcinoma; however, two patients had acinic cell carcinoma of the pancreas. Lymphovascular invasion and perineural invasion were observed in 46.3% and 85.4% of patients, respectively. Resection margins were positive in five patients. Regarding the degree of resection, we defined resections with a retroperitoneal margin of <1 mm as "narrow R0 resections"; five patients underwent R1 resection and five underwent narrow R0 resection.

Perioperative conditions and postoperative complications

The duration of the operation depended on the type of surgery. Distal pancreatectomy had a relatively shorter duration than the other surgeries (Table 2). The average IORT time was

Table 2. Details on Perioperative Conditions

Variables	Value
Postop complications	12 (29.3)
ICU stays	18 (43.9)
APACHE-II score	12 (9–18)
Predicted hospital mortality, %	13.4 (6.2–33.2)
Hospital stays after surgery, days	10 (7–36)
Operating time, min	
PPPD	409 (249–536)
Distal pancreatectomy	244 (161–309)
Total pancreatectomy	449 (449–570)

PPPD, pylorus-preserving pancreaticoduodenectomy; ICU, intensive care unit; APACHE-II, Acute Physiology, Age, Chronic Health Evaluation II.
Data are presented as median (range) or n (%).

Table 3. Postoperative Complications (n=41)

Checklist	Grade	n (%)
Delayed Gastric emptying*	A	1 (2.4)
	B	4 (9.8)
Postoperative pancreatic fistula†	A	1 (2.4)
	B	1 (2.4)
Chyle leakage	2	2 (4.9)
Duodenal ulcer perforation	3b	1 (2.4)

Other acute postoperative complications were evaluated using Clavien-Dindo classification.
*Delayed gastric emptying was graded according to the International Study Group of Pancreatic Surgery consensus definition; †We use the consensus of International Study Group on Pancreatic Fistula (ISGPF) for the definition and grading of postoperative pancreatic fistula.

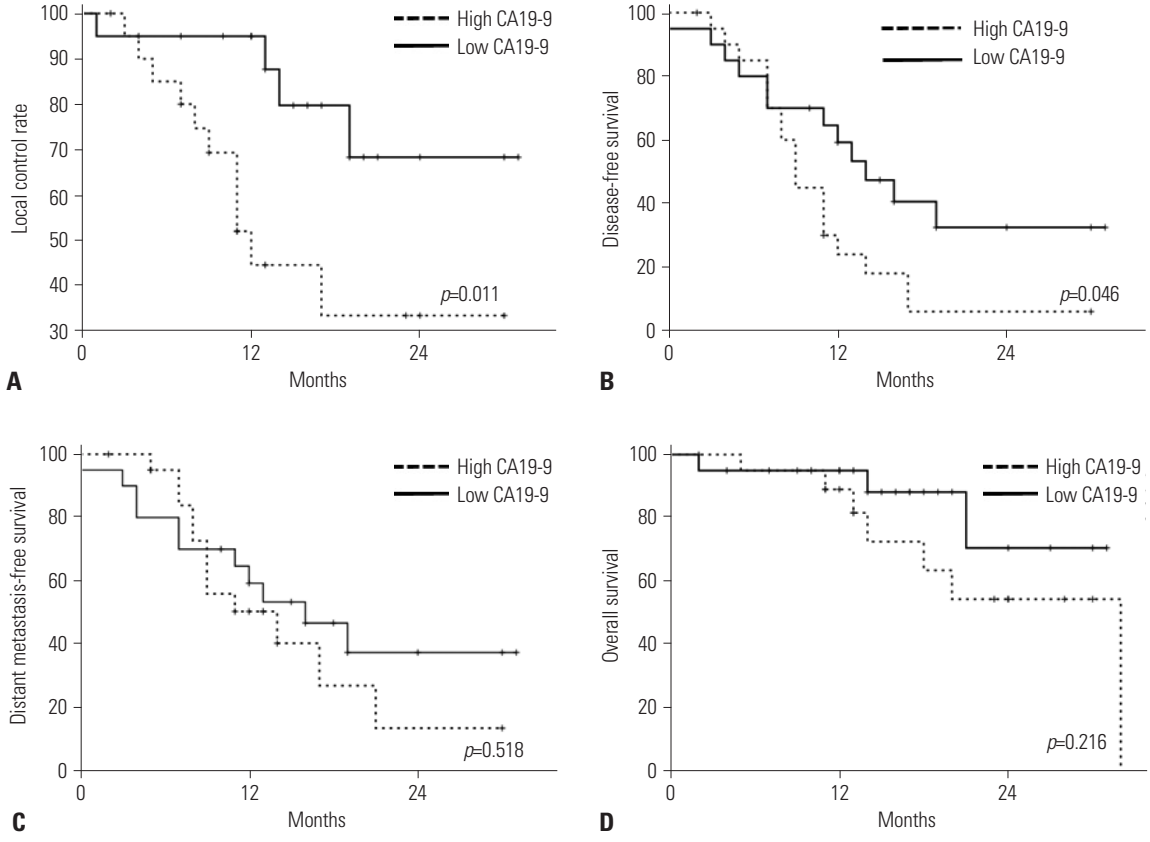

Fig. 3. Kaplan-Meir survival analysis according to the initial CA19-9 level. (A) Local control rate. (B) Disease-free survival. (C) Distant metastasis-free survival. (D) Overall survival. CA19-9, carbohydrate antigen 19-9.

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35 minutes and 29 seconds. Eighteen patients, all of whom had undergone PPPD, needed to stay in the intensive care unit for 2 days. In these patients, the median Acute Physiology, Age, Chronic Health Evaluation II (APACHE-II) score was 12 (range, 9–18), which has a predicted hospital mortality rate of 13.4% (range, 6.2–33.2%).

Ten patients (24.4%) experienced postoperative complications, the details of which are listed in Table 3. The most common complication was delayed gastric emptying, experienced by five patients (13.2%); four of these cases were classified as grade B. Other postoperative complications included postoperative pancreatic fistula, chyle leakage, and duodenal ulcer perforation; most of the postoperative complications were tolerable with conservative management. However, one patient required drainage for postoperative pancreatic fistula of grade B, and one patient needed additional surgery due to duodenal ulcer perforation (G3b). These two patients received PPPD, and they were of old age, 75 and 84 years old, respectively.

Two patients did not receive adjuvant gemcitabine chemotherapy at our institution (4.8%): one patient was in a poor condition due to early liver metastases, and the other required reconstructive surgery due to ulcer perforation and received chemotherapy at another hospital. Two patients started receiving adjuvant chemotherapy 13 weeks after the surgery due to their general conditions, while the remaining patients started receiving adjuvant chemotherapy between 8 and 12 weeks after the surgery as per the treatment protocol.

Treatment outcomes

The median follow-up duration was 9 months (range, 1–21 months). Twenty (47.6%) patients had a follow-up duration shorter than 9 months, and 14 (33.3%) had a follow-up duration shorter than 6 months. Five patients died less than a year after treatment, resulting in a 1-year OS rate of 94.1%. The patterns of the first recurrence were as follows: four patients, local-only failure (9.8%); nine, distant-only failure (22.0%); and two, both local and distant failure (4.8%). The 1-year local control and distant control rates were 76.4% and 55.7%, respectively. The survival analysis according to the initial CA19-9 level (with a median CA19-9 of 86 U/mL, high CA19-9 ≥86 U/mL vs. low CA19-9 <86 U/mL) were shown in Fig. 3. Patients characteristics (Supplementary Table 1, only online) and patterns of failure (Supplementary Table 2, only online) according to the CA19-9 level was described in supplementary data.

The prognostic factors for local and distant failure and OS are listed in Table 4. Pathologic N2 stage was significantly associated with local failure in multivariate analysis [hazard ratio (HR) 6.51; 95% confidence interval (CI) 1.23–34.46; p=0.027]. Lymphovascular invasion was identified as a prognostic factor for distant metastasis in the multivariate analysis (HR, 3.89; 95% CI, 1.28–11.82; p=0.016). Only LVI was significantly associated with OS

Table 4. Prognostic Factors for Local, Distal Failure, and Overall Survival

		Local failure						Distant failure						Overall survival					
		Univariate			Multivariate			Univariate			Multivariate			Univariate			Multivariate		
		HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	≥70 (vs. <70)	0.84	0.30–2.35	0.732										1.08	0.29–4.05	0.903			
Location	Others (vs. head)	1.32	0.46–3.75	0.607										2.54	0.67–9.60	0.169			
Initial CA19-9	≥86 (vs. <86)	1.03	1.26–12.85	0.019	4.12	1–17.04	0.050	2.05	0.97–4.332	0.060				2.17	0.54–8.76	0.275			
pT	T3 (vs. T1, 2)	2.85	1.01–8.03	0.048	2.51	0.75–8.44	0.135	7.10	2.75–18.36	<0.001	1.79	0.80–4.00	0.159	1.06	0.28–3.98	0.929			
pN	N2 (vs. N0, 1)	4.06	1.13–14.65	0.032	6.51	1.23–34.46	0.027	3.35	1.47–7.65	0.004	2.40	0.93–6.23	0.071	70.62	0.30–1653.98	0.126			
LVI	Positive (vs. negative)	3.60	1.22–100.64	0.020	1.64	0.46–5.33	0.445	7.10	2.75–18.36	<0.001	3.89	1.28–11.82	0.016	7.31	1.47–36.25	0.015			
PNI	Positive (vs. negative)	28.84	0.12–705.75	0.230				32.88	0.87–1442.20	0.059				26.54	0.01–588.60	0.401			
Degree of resection	R1 or narrow R0 (vs. wide R0)	2.71	0.79–9.30	0.112				2.55	1.07–6.09	0.035	1.37	0.51–0.37	0.538	2.86	0.54–15.17	0.218			

HR, hazard ratio; CI, confidence interval; CA19-9, carbohydrate antigen 19-9; LVI, lymphovascular invasion; PNI, perineural invasion.

in univariate analysis; therefore, multivariate analysis for OS was not conducted.

DISCUSSION

IORT using a low-energy 50-kV X-ray source was well-tolerated in pancreatic cancer patients. Even though our study included a large number of patients older than 70 years who underwent high-risk surgery, the mortality rate was 0%, and most postoperative complications were classified as grade 2 or less. These results are concordant with those of previous studies on IORT using electron beams that reported that IORT did not increase perioperative morbidity.[14,15]

Most pancreatic cancer patients undergo surgical resection as a part of disease management. However, one-third of the patients experience at least one postoperative complication, and complications of grade 3 or higher occur in up to 20% of patients.[16] Although recent large-scale studies have demonstrated that postoperative mortality rates are less than 6%, pancreatectomy is one a high-risk surgery that often results in poor patient outcomes.[17,18] In particular, postoperative complications may result in omission of or delay in adjuvant treatment.[19] A previous study also demonstrated that complications of grade 3 or higher after pancreatectomy have a substantial impact on long-term survival.[20] Therefore, establishment of treatment strategies that improve local control without increasing postoperative complications is of high priority. Although adjuvant chemotherapy was delayed in two patients in this study, the majority of patients (90.5%) started receiving chemotherapy between 8 and 12 weeks after surgery.

There were only two cases of local-only recurrence in our preliminary data, and the patients showed a 1-year local control rate of 76.4%. Ogawa, et al.[21] used IORT in a Japanese multicenter retrospective trial; the 2-year local control rate was 83.7%, which is superior to that reported herein. However, in our preliminary data, one-third of the patients had a follow-up duration shorter than 6 months. Thus, the Kaplan-Meier survival analysis results should be interpreted with caution and after careful consideration of the impact of censored data. Further follow-up of our patients might lead to outcomes similar to those in the Japanese report.

Additionally, 30% of patients included in the Japanese study of Ogawa, et al.[21] received EBRT as an adjuvant treatment. Other studies on pancreatic IORT also involved preoperative or postoperative EBRT.[22,23] Whether additional EBRT could improve oncologic outcomes remains unclear. In some cases, residual tumors could not be covered sufficiently with IORT due to a rapid decrease in the dose of X-ray or electrons. Moreover, the surface of the tumor bed was irregular; thus, there is a possibility that the applicator did not cover the whole tumor bed. We found that high CA19-9 levels, lymph node metastasis, and narrow R0/R1 resection were significantly associated with local recurrence even after IORT. In these cases, the addition of EBRT to the treatment strategy may overcome the limitations of IORT. Moreover, neoadjuvant chemoradiotherapy has been found to improve oncologic outcome in several studies.[24-26] A further prospective study assessing the potential benefits of adding preoperative or postoperative EBRT should be conducted.

There is no clear evidence regarding the safety of IORT using kV X-rays, and the optimal radiation dose has not been established. In a previous study involving the use of an orthovoltage X-ray beam, only an average of 11.1 Gy was delivered: the study reported that three patients (13% of all patients, n=23) experienced treatment-related complications of grade 3 or higher.[9] Our preliminary results indicate that IORT with 10 Gy at a 5-mm depth does not increase postoperative complications. Establishment of an optimal radiation dose in X-ray IORT through dose-escalation studies is essential, as this could improve local control rates.

Additionally, neoadjuvant treatment has been suggested even for resectable tumors to improve disease control.[27,28] A recent randomized phase II/III trial showed a significant survival benefit for neoadjuvant gemcitabine-S1 treatment in resectable pancreatic cancer patients.[28] A combination of neoadjuvant chemotherapy with IORT might improve local control and OS. A prospective trial assessing the clinical benefit of neoadjuvant chemotherapy followed by IORT for resectable pancreatic cancer will be conducted at our institution in the near future.

Among the patients who agreed to receive IORT, four underwent vessel resections and reconstructions, and IORT was not delivered to these patients at the discretion of the physicians. It has been reported that postoperative RT does not increase morbidity in terms of stability after vessel reconstruction or wound healing.[29] However, in most studies, EBRT was administered several weeks after surgery, and currently, there is no report on the safety of RT immediately following vessel reconstruction. Therefore, we decided not to administer IORT to these patients. Additional local treatment may be helpful in such cases since patients requiring vessel resection often have locally advanced disease.[30]

There are several limitations to this study. First, due to the short-term follow-up duration, the late toxicities of IORT using kV X-rays could not be evaluated. Previous studies have reported late toxicity in only 3% of patients and reported that IORT with doses of approximately 25 Gy are generally well tolerated.[21,31] Additionally, due to the short-term follow-up, it is difficult to draw reliable and valid conclusions with regard to the treatment outcomes. Second, since we did not perform a randomized control study comparing patients undergoing IORT and surgery with patients undergoing surgery alone, we could not reach a conclusion on the potential superiority of IORT plus surgery over surgery only in terms of postoperative complications or treatment outcomes. Moreover, since most patients in this study received adjuvant chemotherapy, it is difficult to judge

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whether IORT has brought about benefits from this study alone. Therefore, in subsequent studies, we plan to compare the results with the further follow-up of the treatment outcomes of patients who received only postoperative adjuvant chemotherapy, which was not included in this study. However, to the best of our knowledge, the current study is the first prospective study to report early outcomes of IORT using kV X-ray for pancreatic cancer, providing a reference for future studies to establish proper protocols of IORT for resectable pancreatic cancer.

In conclusion, this preliminary report demonstrated that IORT is well-tolerated and feasible in patients with resectable pancreatic cancer and does not cause significant postoperative complications. Our results also suggested that IORT using kV X-rays might yield favorable outcomes, concordant with the results of previous studies involving IORT with electron beams. Future prospective randomized trials comparing the current standard of care for pancreatic cancer with or without IORT are required.

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AUTHOR CONTRIBUTIONS

Conceptualization: Ik Jae Lee, Joon Seong Park, and Jun Won Kim. Data curation: Yeona Cho and Hyung Sun Kim. Formal analysis: Yeona Cho. Methodology: Yeona Cho and Hyung Sun Kim. Project administration: Jun Won Kim, Joon Sung Park, and Ik Jae Lee. Writing—original draft: Yeona Cho and Jun Won Kim. Writing—review & editing: Jun Won Kim. Approval of final manuscript: all authors.

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