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Does Intraoperative Radiation Therapy Improve Local Tumor Control in Patients Undergoing Pancreaticoduodenectomy for Pancreatic Adenocarcinoma? A Propensity Score Analysis

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Abstract

Background: Locoregional recurrence (LRR) is an important factor after pancreaticoduodenectomy (PD) for pancreatic cancer. IORT administered to the resection bed may improve local tumor control.

Methods: We performed a retrospective analysis of patients who underwent PD at Thomas Jefferson University Hospital (TJUH) between 1995 and 2005 to identify patients who underwent resection with and without intraoperative radiation therapy (IORT). Data collected included age, gender, complications, margin status, stage, survival, and recurrence. Unadjusted analyses of the IORT and non-IORT groups were performed using Fisher's chi-square method for discrete variables and Wilcoxon Rank Sum test for continuous variables. To account for biases in patient selection for IORT, a propensity score was calculated for each patient and adjusted statistical analyses were performed for survival and recurrence outcomes.

Results: Between January 1995 and November 2005, 122 patients underwent PD for perimpullary tumors, including 99 pancreatic cancers. Of this group, 37 patients were treated with IORT, and there was adequate follow-up information for a group of 46 patients who underwent PD without IORT. The IORT group contained a higher percentage of Stage IIB or higher tumors (65%) than in the non-IORT group (39.1%), though differences in stage did not reach significance ($p = 0.16$). There was a non-significant decrease in the rate of LRR in patients who had IORT (39% non-IORT vs. 23% IORT, $p = 0.19$). The median survival time of patients who received IORT was 19.2 months, which was not significantly different than patients managed without IORT, 21.0 months (p=0.78). In the propensity analyses, IORT did not significantly influence survival or recurrence after PD.

Conclusions: IORT can be safely added to management approaches for resectable pancreatic cancer, with acceptable morbidity and mortality. IORT did not improve loco-regional control and did not alter survival for patients with resected pancreatic cancer. IORT is an optional component of adjuvant chemoradiation for pancreatic cancer. In the future, IORT may be combined with novel therapeutic agents in the setting of a clinical trial in order to attempt to improve outcomes for patients with pancreatic cancer.

Surgical resection is an essential component in the therapeutic approach to patients with localized pancreatic cancer. Despite refinements in surgical technique, local and distant recurrences are common. Long-term survival rates are low for patients with resectable tumors, with 15-20% 5-year survival reported among patients who undergo pancreaticoduodenectomy (PD) alone.[1,2] In a review of resection margins of 72 patients who underwent PD, Willett *et al.* detected a positive margin in 51% of cases; this factor was associated with inferior survival and local control when compared with those patients with negative surgical margins.[2] Although there is controversy regarding the appropriate components of adjuvant management of resected pancreatic cancer,[3-7] outcomes achieved after surgery alone continue to be poor; therefore, the need remains for adjuvant therapy to improve local control and survival.[3-8] In the United States, adjuvant chemoradiotherapy (CRT) is performed as part of the standard therapeutic paradigm, based on the recurrence patterns of pancreatic cancer after surgery.[8,9]

Intraoperative radiation therapy (IORT), the delivery of a single, large dose of irradiation at the time of surgery, was developed in order to administer higher doses of irradiation while displacing or shielding adjacent normal tissue structures from radiation exposure.[10] In pancreatic cancer, IORT has been offered for unresectable tumors to provide local tumor control and palliation of pain,[11-16] and for resectable tumors in an effort to improve local control and survival after PD.[11-19] Although a definitive survival benefit has not been observed, improvement of local control by IORT at the time of PD for resectable pancreatic cancer is supported by retrospective data, as well as by a prospective, randomized trial conducted at the National Cancer Institute (NCI).[19-21]

At our institution, IORT has been offered since 1986 in a dedicated operating suite located in the radiotherapy department for patients with either resectable or unresectable pancreatic cancer. IORT was considered for all patients undergoing PD at our institution until 1998. Since then, IORT has been reserved for patients with larger tumors with higher risk of positive margins, as visualized by the surgeon on preoperative imaging. Prior reports from our institution have described outcomes of patients who received IORT for resectable and unresectable pancreatic cancer prior to 1995.[13, 22] The current study evaluates outcomes for patients who received treatment for resectable pancreatic cancer from 1995 to 2005. As a result of physician bias for the use of IORT in more advanced-stage pancreatic cancer at our institution, it was not possible to identify a comparative group of patients for use in a matched pair analysis. Therefore, in order to account for the biases inherent in the nonrandom treatment assignment for patients in the current study, analyses of survival and recurrence were adjusted using propensity scoring.[23] In this way, we attempted to minimize the influence of confounding patient- and tumor-related variables in order to assess the contribution of IORT to local tumor control and survival of patients with localized, resectable pancreatic cancer treated at our institution.

Materials & Methods

A prospective tumor registry database was searched to identify all patients who underwent PD at Thomas Jefferson University during 1995-2005. The study was performed with approval of the institutional review board at Thomas Jefferson University. These patients were further divided into those who did and did not receive IORT. We collected data regarding age, gender, margin status, stage, survival and recurrence. Loco-regional recurrence (LRR) was defined as recurrence within the tumor bed or regional lymph nodes. Systemic recurrence (SR) consisted of recurrence in the liver, peritoneum, lungs, bone, or other distant site. Overall survival (OS) and time to LRR were measured from the date of surgery. Given the institutional bias towards IORT for larger tumors during much of the study period, a difference between treatment groups was anticipated in the statistical analysis. A propensity score, a statistical method to adjust for nonrandom treatment decisions in observational studies, was also calculated for each patient using a logistic regression model.[23]

Treatment Policy

All patients were treated according to institutional treatment policies during 1995-2005. As a general rule, IORT was considered for all patients prior to 1998 and subsequently for patients with larger tumors based on review of preoperative imaging by the attending surgeon. For these patients, surgery was performed in an operating room located in the radiation oncology department, an arrangement selected to facilitate IORT delivery. IORT was delivered using 6-15 MeV electrons and cone sizes selected in order to deliver a dose of 10-20 Gy to a field encompassing the pancreatic tumor bed within the 90% isodose line. Regional lymph nodes were not included in the target volume for most cases. The cone size, treatment set-up, and immobilization were selected in order to treat the target volume while minimizing exposure of adjacent normal tissue structures. The standard dose, 15 Gy, was reduced to 10 Gy for either large treatment volumes or margins that were clearly negative. For larger tumors, 20 Gy was often prescribed. In cases where adjuvant external beam radiation therapy (RT) was also delivered, a dose of 45-50.4 Gy was prescribed using a conformal, four-field radiation technique.

Statistical Analysis

Simple descriptive statistics were generated, and unadjusted associations with IORT were determined using Fisher's Chi Square test for categorical variables and using the Wilcoxon rank sum test for continuous variables. The propensity score, which was calculated for all patients included in the analysis using a logistic regression model, included resection status, AJCC Stage, differentiation, age, race, and sex. Propensity scores were incorporated as a categorical variable in the statistical analyses based on quartiles. The association of IORT with the primary outcome of survival was determined using a Cox proportional hazards model. The Cox proportional hazards model included IORT, the propensity score (by quartile), adjuvant chemotherapy, and adjuvant radiotherapy. Association of IORT with the secondary outcomes of any recurrence, loco-regional recurrence, and systemic recurrence was determined using logistic regression models. Included in the logistic regression models for adjusted analyses of recurrence were IORT, the propensity score (by quartile), adjuvant chemotherapy, and adjuvant radiotherapy.

Results

From January 1995 to November 2005, 122 patients underwent PD for periampullary tumors, including 99 pancreatic cancers. We identified 37 patients with pancreatic cancer who were treated with IORT. Among the remaining 62 patients with pancreatic cancer treated without IORT, adequate follow-up data could be obtained for 46 patients, who comprised the non-IORT group used in the statistical analyses. The median patient age in the IORT group was 64 years (inter-quartile range, 55-70 years); in the non-IORT group, the median age was 67 years (inter-quartile range, 59-74 years). The IORT group demonstrated non-significant trends toward more advanced stage tumors (p=0.16) and a higher rate of positive margins (p=0.26). A higher proportion of patients received adjuvant chemotherapy after PD with IORT than after PD alone (p=0.05) (Table 1). There were 2 perioperative deaths in the IORT group (5.4%) and none in the non-IORT group (p=0.20). Rates of perioperative complications were similar, 46% in the IORT group versus 40% in the non-IORT group. The median follow-up among surviving patients was 21 months.

Recurrence and Survival

Recurrence data were available for 80% of all patients, including 30 IORT patients (81%) and 36 non-IORT patients (78%). Rates of loco-regional recurrence (LRR) (Figure 1) or any recurrence (Figure 2) were not significantly different between the IORT and non-IORT groups. Among non-IORT patients, there was loco-regional recurrence (LRR) in 39%, systemic recurrence (SR) in 50%, and any recurrence in 69%. In the IORT group, LRR in 23%, SR in 57% of patients, with, and recurrence was observed in 67% (Table 2). Liver metastases were the most common form of SR. LRR in the absence of SR was observed in 2 patients (7%) in the IORT group and in 7 patients in the non-IORT group (19%). LRR was not significantly different between the IORT and non-IORT groups (p=0.20). The median survival time of patients undergoing IORT was 19.2 months, which was not significantly different than patients managed without IORT, 21.0 months (p=0.49) (Figure 3).

Propensity Score Analysis

In the adjusted, propensity score analysis of the association of IORT with survival, IORT was not associated with significant improvement of survival time (Table 3). The Cox regression model for survival included IORT status with propensity score (by quartile), as well as adjuvant RT and chemotherapy. The propensity score-adjusted analyses of the association

Table 1. Tumor- and treatment-related characteristics for 37 IORT patients and 46 non-IORT patients with resected pancreatic cancer.

Factor		PD + IORT [n (%)]	PD (No IORT) [n (%)]	*p* value
Stage	I	7 (19)	16 (35)	0.16
	IIA	6 (16)	12 (26)	
	≥IIB	24 (65)	18 (39)	
Margin Status	RO	21 (57)	32 (70)	0.26
	R1/R2	16 (43)	14 (30)	
Grade (n=81)	Well	7 (19)	8 (18)	0.91
	Moderate	21 (58)	25 (56)	
	Poor	8 (22)	12 (27)	
Adjuvant Chemotherapy (n=79)	Yes	26 (84)	27 (63)	0.05
	No	5 (16)	16 (37)	
Adjuvant EBRT (n=75)	Yes	23 (74)	29 (66)	0.44
	No	8 (26)	15 (34)	

of IORT with LRR, with SR, and with any recurrence were conducted using logistic regression models (Table 4). After adjusting for propensity score quartile and for adjuvant therapies, IORT did not influence recurrence rates after PD for pancreatic cancer. A non-significant trend towards higher rates of any recurrence was noted for propensity scores in the third (OR 9.66, $p = 0.14$) or fourth quartile (OR 9.64, $p = 0.15$).

Discussion

Local control was not significantly different between the two groups, IORT and non-IORT, evaluated in the current series. Although the current study is limited by its retrospective design and institution bias towards treating more advanced tumors with IORT, an attempt was made to account for nonrandom allocation of patients into the IORT and non-IORT groups by using propensity score values in adjusted statistical analyses of the association of IORT with survival and recurrence. Adjuvant chemotherapy was administered to more patients in the IORT group. Although information concerning decision-making was not available, the increased rate of chemotherapy may be related to the presence of more advanced tumors in the IORT group. Despite the trends toward more advanced-stage tumors and positive resection margins in the IORT group, similar local control rates were observed.

Table 2. Location of first recurrence. Thirty patients in the IORT group and 36 patients in the non-IORT group were included in the recurrence analysis, based on availability of data to determine site of recurrence.

Site of First Recurrence	PD + IORT [n (%)]	PD (No-IORT) [n (%)]
Locoregional	7 (23)	14 (39)
Tumor Bed	6 (20)	8 (22)
Lymph Node	4 (13)	10 (28)
Locoregional-Only	2 (7)	7 (19)
Systemic	17 (57)	18 (50)
Liver	11 (37)	11 (31)
Lung/Pleura	4 (13)	7 (19)
Systemic-Only	14 (47)	11 (31)

The disparities in stage and margin status in the current study may have obscured any potential local control benefit of IORT, as these factors have been reported to negatively influence survival for patients with resected pancreatic cancer.[24, 25] Prior retrospective, single-institution reports suggest that IORT improves local control after PD by approximately 30%.[19, 21] In this study, LRR was 50% less in the IORT group. In the prospective, randomized trial conducted at the NCI, local control improved from 0% to 33% with the addition of IORT.[20] In a recent series

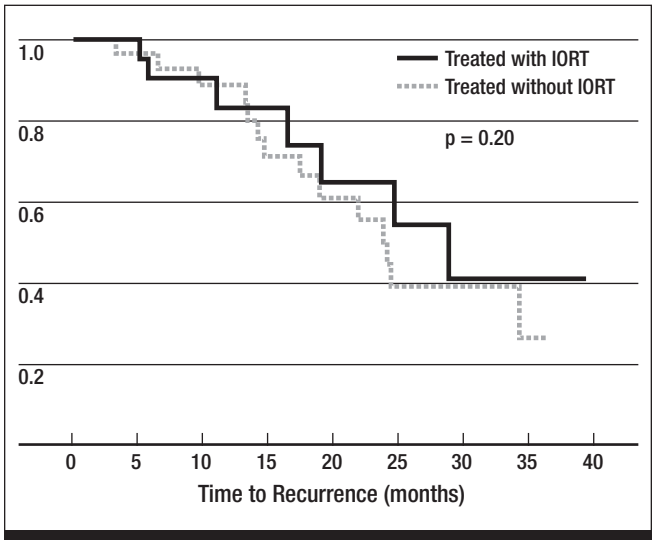

Figure 1. Kaplan-Meier plot of locoregional failure for patients treated with (*solid line*) and without (*dashed line*) IORT ($p = 0.20$).

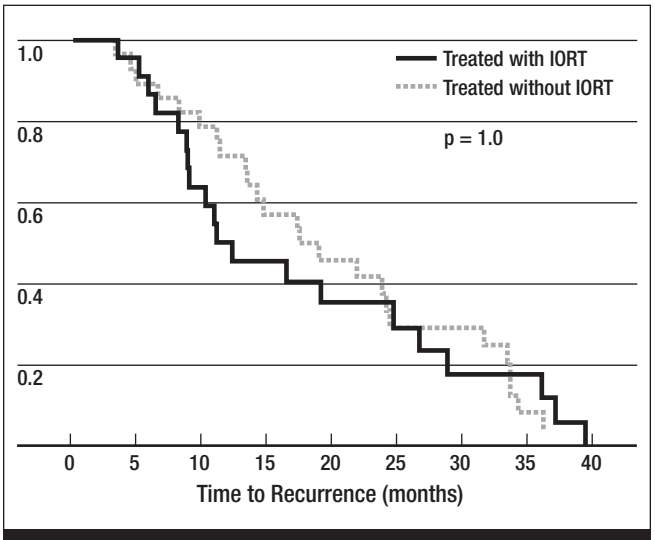

Figure 2. Kaplan-Meier plot of recurrence (any site) for patients treated with (*solid line*) and without (*dashed line*) IORT ($p = 1.0$).

Table 2. Location of first recurrence. Thirty patients in the IORT group and 36 patients in the non-IORT group were included in the recurrence analysis, based on availability of data to determine site of recurrence.

Site of First Recurrence		PD + IORT [n (%)]	PD (No-IORT) [n (%)]
Locoregional		7 (23)	14 (39)
	Tumor Bed	6 (20)	8 (22)
	Lymph Node	4 (13)	10 (28)
	Locoregional-Only	2 (7)	7 (19)
Systemic		17 (57)	18 (50)
	Liver	11 (37)	11 (31)
	Lung/Pleura	4 (13)	7 (19)
	Systemic-Only	14 (47)	11 (31)

from the City of Hope National Medical Center, isolated local recurrences were reduced from 33% to 5% with the addition of IORT, which is comparable to the rate of isolated LRR in the current report (7%).[24] Reni *et al*. reported a similar alteration of recurrence patterns, with 15% local-only recurrences with IORT versus 33% without IORT.[26] The cumulative evidence, including one prospective randomized trial and a few prospective studies, supports a local control benefit for IORT in resectable pancreatic cancer. An improvement in local control has not been shown to translate into a clinical benefit in survival outcomes, including in this study. Although a propensity score analysis was performed in the current study to evaluate the influence of IORT on recurrence rates after PD, the limited size of the patient population may have restricted our ability to detect a significant positive effect.

The survival rates were not different between the IORT and non-IORT groups in the current series, which is consistent with the results of the prospective NCI study.[20] Given the propensity of pancreatic cancer towards distant metastatic recurrence, it is not surprising that a measurable increase in local control did not produce a corresponding improvement of survival.[27] Although some authors report a survival benefit from IORT for resectable pancreatic tumors at their institutions, the literature does not consistently support this claim, and detection of a potential small survival benefit would require a large trial.[19, 22, 24, 26, 28, 29] Regardless of the absence of improved survival, the problem of locoregional control does leave open a place for radiation therapy after PD, and IORT is an effective technique to boost radiation dose around the resection bed while displacing sensitive adjacent organs.[8, 10, 17, 30] A recent analysis of the Surveillance, Epidemiology, and End Results database revealed a survival benefit to the addition of adjuvant radiotherapy after PD, and radiation therapy remains an important component of adjuvant strategies in the United States.[25] Results recently published from the Radiation Therapy Oncology Group (RTOG) trial 9704, the first cooperative group study to require prospective quality assurance of radiotherapy, suggest a benefit to the addition of gemcitabine to adjuvant CRT after PD. The rates of first relapse in local and regional sites in the experimental arm of RTOG 9704 were 23% and 7%, respectively.[31]

Table 3. Cox proportional survival hazard model for the association of IORT, propensity score, and other factors with survival time in months.

	Estimate	Standard Error	Chi-Square	Hazard Ratio	*p*
IORT	-0.34	0.35	0.94	0.71	0.33
Adjuvant Chemo-therapy	0.51	0.73	0.48	1.66	0.49
Adjuvant Radiotherapy	-1.05	0.68	2.39	0.35	0.12
Propensity Score (vs. 1st Quartile)					
2nd Quartile	-0.68	0.45	2.35	0.50	0.13
3rd Quartile	0.55	0.49	1.26	1.73	0.26
4th Quartile	0.58	0.47	1.56	1.79	0.21

Table 4. Logistic regression models of the association of IORT, propensity score, and other factors, with the outcomes of any recurrence, locoregional occurrence, and systemic recurrence.

	Odds Ratio	95% CI	*p*
Any Recurrence			
IORT	0.77	(0.19, 5.20)	0.72
Adjuvant Chemotherapy	1.69	(0.15, 19.29)	0.67
Adjuvant Radiotherapy	1.11	(0.11, 11.68)	0.93
Propensity Score (vs. 1st Quartile)			
2nd Quartile	1.22	(0.33, 4.52)	0.76
3rd Quartile	9.66	(0.47, 197.40)	0.14
4th Quartile	9.64	(0.46, 203.31)	0.15
Locoregional Recurrence			
IORT	0.41	(0.10, 10.30)	0.23
Adjuvant Chemotherapy	0.49	(0.02, 11.37)	0.65
Adjuvant Radiotherapy	1.74	(0.86, 35.51)	0.72
Propensity Score (vs. 1st Quartile)			
2nd Quartile	0.39	(0.02, 7.47)	0.53
3rd Quartile	5.13	(0.73, 36.03)	0.10
4th Quartile	3.32	(0.46, 23.93)	0.23
Systemic Recurrence			
IORT	0.99	(0.28, 3.52)	0.99
Adjuvant Chemotherapy	0.40	(0.03, 6.42)	0.52
Adjuvant Radiotherapy	1.30	(0.10, 16.96)	0.84
Propensity Score (vs. 1st Quartile)			
2nd Quartile	1.11	(0.23, 5.40)	0. 90
3rd Quartile	0.91	(0.16, 5.13)	0.91
4th Quartile	0.59	(0.10, 3.50)	0.56

Importantly, the addition of IORT after PD did not increase perioperative complication rates significantly in the current series, which is consistent with the earlier experience from our institution.[22] Although late complications have been reported after IORT for pancreatic cancer, our results and other reports suggest that IORT may be delivered safely in combination with surgical resection.[24, 26, 28, 32, 33-37] Selection of

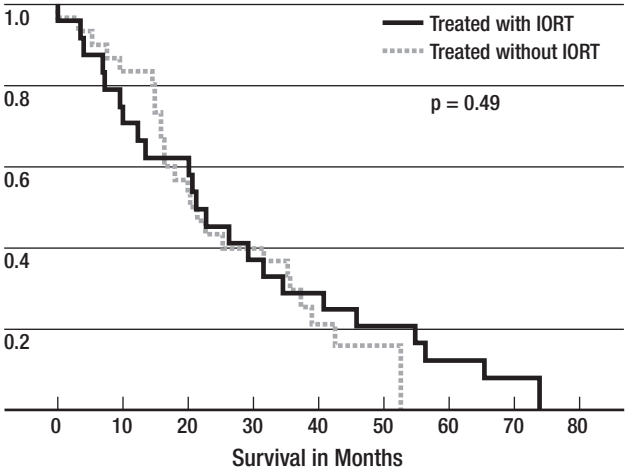

Figure 3. Cox proportional hazards model for overall survival of patients treated with (*solid line*) and without (*dashed line*) IORT after PD ($p = 0.49$).

radiation doses for IORT was influenced by seminal, preclinical canine experiments performed at the National Cancer Institute that provided an understanding of normal tissue tolerances, including surgically-manipulated tissues, for IORT.[38,39] These studies created a foundation for the rational delivery of IORT in humans, so it should not be surprising that clinical studies have shown these RT doses to be safe and feasible.

Based on recent practice changes at our institution, IORT will be offered infrequently for patients with localized pancreatic tumors, in favor of alternate adjuvant strategies after surgical resection. Novel adjuvant therapy combinations tested in recent institutional and cooperative group trials have focused on systemic treatments aimed at reducing metastatic recurrences after PD, as distant dissemination is a dominant cause of mortality for patients with pancreatic cancer.[27, 40] However, adjuvant external beam radiation therapy remains an important component of management, based on recognition of the parallel importance of preventing local recurrence.[2, 25] Although the current study does not support its continued use, it is reasonable that IORT is considered as a potential component of adjuvant RT strategies. Should adjuvant systemic therapies for resected pancreatic cancer improve in the future, LRR may become a more significant concern. IORT may become a more important tool for maximizing loco-regional control in that situation.

In summary, the current study demonstrates that IORT is a safe addition to PD and standard adjuvant therapies, with the intention of improving local control after PD for patients with resectable pancreatic cancer. Although local control was not significantly improved with the addition of IORT in the current study, the significantly higher number of more advanced stage tumors and a trend towards more positive surgical margins in the IORT patients may have influenced the results of our comparative analyses. We cannot currently recommend routine use of IORT in the adjuvant setting for patients with resected pancreatic cancer. Future clinical trials with novel therapeutic agents may include IORT in combination with resection, adjuvant external beam radiotherapy, and systemic agents in order to improve outcomes for patients with pancreatic cancer.

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