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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Adjuvant Radiotherapy in the Treatment of Invasive Intraductal Papillary Mucinous Neoplasm of the Pancreas: an Analysis of the Surveillance, Epidemiology, and End Results Registry

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ABSTRACT

Background. Management and outcomes of patients with invasive intraductal papillary mucinous neoplasm (IPMN) of the pancreas are not well established. We investigated whether adjuvant radiotherapy (RT) improved cancer-specific survival (CSS) and overall survival (OS) among patients undergoing surgical resection for invasive IPMN.

Methods. The Surveillance, Epidemiology, and End Results (SEER) registry was used in this retrospective cohort study. All adult patients with resection of invasive IPMN from 1988 to 2007 were included. CSS and OS were analyzed using Kaplan–Meier curves. Unadjusted and propensity-score-adjusted Cox proportional-hazards modeling were used for subgroup analyses.

Results. 972 patients were included. Adjuvant RT was administered to 31.8% ($n = 309$) of patients. There was no difference in overall median CSS or OS in patients who received adjuvant RT (5-year CSS: 26.5 months; 5-year OS: 23.5 months) versus those who did not (CSS: 28.5 months, $P = 0.17$; OS: 23.5 months, $P = 0.23$). Univariate predictors of survival were lymph node (LN) involvement, T4-classified tumors, and poorly differentiated tumor grade (all $P < 0.05$). In the propensity-score-adjusted analysis, adjuvant RT was associated with improved 5-year CSS [hazard ratio (HR): 0.67, $P = 0.004$] and 5-year OS (HR: 0.73, $P = 0.014$) among all patients with LN involvement, though further analysis by T-classification demonstrated no survival differences among patients with T1/T2 disease; patients with T3/T4-classified tumors had improved CSS (HR: 0.71, $P = 0.022$) but no difference in OS (HR: 0.76, $P = 0.06$).

Conclusion. On propensity-score-adjusted analysis, adjuvant RT was associated with improved survival in selected subsets of patients with invasive IPMN, particularly those with T3/T4 tumors and LN involvement.

The prevalence of invasive intraductal papillary mucinous neoplasm (IPMN) has been estimated to be approximately 26/100,000.[1] In a national series of nearly 20,000 patients with pancreatic cancer, 95% had sporadic adenocarcinoma whereas 5% patients had invasive IPMN.[2] The World Health Organization (WHO) defines IPMN as an intraductal mucin-producing lesion that contains tall, columnar mucin-containing epithelium communicating with pancreatic ducts.[3,4] Absence of ovarian stroma in IPMN distinguishes it from other mucin-producing cystic neoplasms of the pancreas, such as mucinous cystadenoma and cystadenocarcinoma.[3,4] Although IPMN is a well-characterized pancreatic neoplasm, the optimal strategy for definitive treatment, especially the role of adjuvant radiotherapy (RT) after surgical resection, is still debatable.

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Resection of noninvasive IPMN is associated with favorable prognosis, whereas invasive IPMN has much poorer outcome.[5–11] Unfortunately, approximately 25% of all resected IPMNs are invasive.[12] Malignant transformation of IPMN from adenomatous stage to noninvasive and subsequently invasive IPMN is similar to the development of pancreatic ductal adenocarcinoma from pancreatic intraepithelial neoplasia, though, unlike pancreatic adenocarcinoma, the natural history of invasive IPMN remains poorly defined.[13,14] Recent evidence suggests that invasive IPMN in the setting of lymph node involvement, advanced tumor stage and grade, tumor size >2 cm, and positive resection margins is associated with poor outcomes comparable to pancreatic adenocarcinoma.[15,16]

Adjuvant chemoradiotherapy has been recommended for many patients with pancreatic adenocarcinoma due to a survival advantage compared with treatment with surgical resection alone, though results from the European Study Group for Pancreatic Cancer (ESPAC) ESPAC-1 trial suggested that adjuvant RT may not be of benefit.[17–23] However, the role of adjuvant RT in the treatment of invasive IPMN has not been well studied. In a recent retrospective series of 98 patients with invasive IPMN, adjuvant chemoradiotherapy was not associated with a survival benefit. It is difficult to draw conclusions from this study, however, as it was limited by small sample size; only 37 patients received adjuvant chemotherapy or chemoradiation.[12] Using the population-based Surveillance, Epidemiology, and End Results (SEER) cancer registry, we thus tested the hypothesis that adjuvant RT in patients with invasive IPMN of the pancreas following surgical resection was associated with improved CSS and OS. In addition, we performed propensity-score-adjusted analyses to account for the nonrandomized allocation of patients receiving adjuvant RT. Given the low prevalence of invasive IPMN, prospective comparative trials are unlikely to be performed, and small retrospective series are limited in the quality of evidence. We felt, therefore, that a population-based study using SEER and advanced statistical analyses using propensity-scoring methods had the potential to provide the highest level of evidence possible for guiding therapy.

METHODS

We obtained Institutional Review Board approval for this study. We conducted a secondary data analysis of SEER, the largest, population-based cancer registry in the USA. Patient data in SEER are currently collected prospectively in 17 different geographic regions and represent 28% of the US population. In 2007, more than 350,000 cancer cases were recorded.[24,25] We restricted our analysis to a 20-year time period spanning from 1988 to 2007.

We used SEER*Stat 6.6.2 to extract IPMN cases from the SEER registry.[26] We primarily identified our patient cohort through the "SEER Site Recode" using the term "pancreas." Patients with IPMN were then identified using the variable "Histologic Type ICD-O-3" (International Classifications of Diseases for Oncology, 3rd edition) with the following codes for IPMN: 8050, 8260, 8450, 8453, 8471, 8480, 8481, and 8503 and the label "malignant."[2,16] We only included patients aged 18 years or older who underwent surgical resection of invasive IPMN. We then identified all patients who did or did not receive postoperative adjuvant external-beam RT. Patients undergoing neoadjuvant (with or without adjuvant RT), intraoperative, or unknown RT were excluded.

The primary outcome was 5-year survival measured in months. The last available date in SEER for all patients was collected. Patients alive at this time point were right-censored in the survival analysis. The primary predictor in our analysis was provision of postoperative external-beam RT. To evaluate the effect of postoperative RT for different patient groups, we performed subgroup analyses according to available demographic variables in addition to characteristics describing the extent and grade of the resected tumor. Though tumor–node–metastasis (TNM) stage according to AJCC for pancreatic cancer is not provided in SEER for every year of our analysis, it is, in most cases, possible to recode the AJCC stage manually using SEER variables regarding the extent of disease.[27,28] We added a combined T1/T2 primary tumor classification group, since 32 patients with <T3 disease had missing tumor size and thus could not be more accurately categorized as being either T1 or T2.

Available demographic characteristics including age, sex, race, marital status, and presence of a single reportable tumor were collected for all patients. Additionally, tumor characteristics were included in the analysis: tumor location (head of pancreas versus other location), primary tumor (T1–T4, T1/T2, missing), regional lymph node status (N0, N1, unknown), distant metastasis status (M0, M1, unknown), tumor stage (stage 1–4, unknown), and tumor size (<2 cm, ≥2 cm, unknown). In the SEER registry, tumor size represents the size of the primary tumor and is typically the largest known dimension or diameter of the tumor (e.g., from pathology or operative reports) prior to adjuvant therapy. Only the invasive component of the IPMN is recorded in SEER; data regarding cystic components, IPMN adenomas, or in situ carcinoma are unavailable.[25] To account for variation in measurement techniques, we dichotomized tumor size (<2 cm versus ≥2 cm) in our analysis. Data regarding classification of IPMN as main duct, branch duct, or mixed type were unavailable in SEER. The type of surgical procedure was grouped into four categories: partial/localized resection,

total pancreatectomy, pancreatoduodenectomy (Whipple procedure), and all others.

Statistical Analysis

Empiric Analysis and Kaplan–Meier Estimates Demographic and tumor-related characteristics were compared according to the provision of adjuvant RT using *t*-test for continuous data and chi-square test for categorical data. Since our primary objective is to evaluate the role of adjuvant RT, we left-censored patients who survived less than 3 months after diagnosis. The rationale for this censoring is that it mitigates the potential for selection bias resulting from inclusion of patients with adverse short-term perioperative outcomes and also those who did not survive long enough to complete a therapeutic regimen of RT.[21,29] Patients with cause of death other than pancreatic etiology were right-censored for the CSS analysis to obtain specific estimates of pancreatic-disease-related survival.[30] We restricted the analysis to a 5-year survival period. Unadjusted survival analyses were performed according to the method of Kaplan and Meier. The resulting survival curves were compared using the log-rank test. In addition, unadjusted Cox proportional-hazard models were performed to obtain unadjusted hazard ratios (HR) with corresponding confidence intervals for the entire patient population as well as for important subgroups. Estimates for grade 4 tumors were not calculated, since none of these patients received RT.

Propensity Score Creation/Adjusted Survival Analysis Since the focus of our study is establishing a causal inference regarding the association between adjuvant RT and patient outcomes, we used a propensity score methodology. Propensity scores calculate the conditional probability of receiving a treatment (e.g., adjuvant RT) given all potential confounders measured. In providing such adjustments, propensity scores approximate the results of nonrandomized studies to their randomized counterparts.[31] The selection of variables for our study included in the propensity score calculation was based on the potential association with CSS and OS as well as on the likelihood of receipt of adjuvant RT.[32] These variables were chosen prior to estimating survival. We included the following variables in the propensity score calculation: year of operation, age, sex, marital status, race, tumor location, tumor size, tumor grade, presence of single reportable tumor, type of surgery, primary tumor classification, regional lymph node status, and presence of distant metastasis. The propensity score was calculated through a multivariate logistic regression model using the provision of adjuvant RT as the dependent variable and the listed confounders as independent variables. The propensity score was then used to perform survival analysis using Cox proportional-hazard models and the technique of stratification over the propensity score. HR and 95% confidence intervals were calculated for all estimates.

Sensitivity Analyses We performed two sets of sensitivity analyses. First, we performed the propensity-score-adjusted survival analysis using Cox proportional-hazard models without left-censoring of the first 3 months. Second, due to the relatively high proportion of patients with distant metastases who did not receive adjuvant RT (24.4%, versus 6.8% who did receive adjuvant RT), we repeated the analyses excluding from both comparison groups patients with distant metastases.

SAS software (version 9.2; SAS Institute, Cary, NC, USA) was used for all analyses.

RESULTS

A total of 972 patients with invasive IPMN of the pancreas were included in our analysis, of whom 476 (49.0%) were female (Table 1). The mean age of our patient cohort was 64.9 years (range 18–94 years). Most patients ($n = 821$, 84.5%) were White, while 74 (7.6%) were Black and 77 (7.9%) were of indeterminate race/ethnicity. Postoperative adjuvant RT was administered to 309 (31.8%) patients. Median follow-up for patients undergoing adjuvant RT was 18 months (range: 0–180 months) versus 12 months (range: 0–213 months) in patients not receiving adjuvant RT. More tumors were located in the head of the pancreas in patients receiving adjuvant RT compared with in those who did not receive RT (70.6% versus 54.4%, $P < 0.001$). The TNM tumor characteristics were different between the two groups: adjuvant RT was more commonly administered to patients with T3 tumors (59.9%, versus 37.1% in patients with no adjuvant RT, $P < 0.001$), lymph node involvement (58.6% versus 38.0%, $P < 0.001$), and in the absence of metastatic disease (92.6% versus 74.2%, $P = 0.003$). Univariate predictors of survival were lymph node involvement, T4-classified tumors, and poorly differentiated tumor grade (all $P < 0.05$).

Median OS of all patients without left-censoring for invasive IPMN of the pancreas was 19.5 months (CI: 16.5–21.5 months) with a 5-year OS rate of 24.1% (CI: 21.1–27.3%). After left-censoring the first 3 months of follow-up as described earlier, the median OS of all patients was 23.5 months (CI: 21.5–26.5 months). The median OS for patients who received adjuvant RT was 23.5 months (CI: 20.5–26.5 months), which was similar compared with patients without adjuvant RT (23.5 months, CI: 19.5–27.5 months, $P = 0.23$). The median CSS for patients who received adjuvant RT was 26.5 months (CI: 22.5–29.5 months) compared with 28.5 months (CI: 23.5–36.5 months) for patients who did not receive adjuvant

TABLE 1 Demographics of patients with invasive IPMN of the pancreas (1988–2007)

	Adjuvant RT ($n = 309$, 31.8%)	No adjuvant RT ($n = 663$, 68.2%)	*P*-Value
Age (mean, SD), years	62.9 (11.2)	65.8 (12.8)	0.001
Female (*n*, %)	135 (43.7)	341 (51.4)	0.025
Race			0.92
White	262 (84.8)	559 (84.3)	
Black	22 (7.1)	52 (7.8)	
Others/unknown	25 (8.1)	52 (7.8)	
Marital status			0.073
Married	213 (68.9)	418 (63.0)	
Other	96 (31.1)	245 (37.0)	
Tumor location			<0.001
Head of pancreas	218 (70.6)	361 (54.4)	
Other	91 (29.4)	302 (45.6)	
Primary tumor (T)			<0.001
T1	14 (4.5)	63 (9.5)	
T2	49 (15.9)	145 (21.9)	
T3	185 (59.9)	246 (37.1)	
T4	51 (16.5)	163 (24.6)	
Unknown	3 (1.0)	21 (3.2)	
T1/T2	7 (2.3)	25 (3.8)	
Regional lymph nodes (N)			<0.001
N0	118 (38.2)	364 (54.9)	
N1	181 (58.6)	252 (38.0)	
Unknown	10 (3.2)	47 (7.1)	
Distant metastasis (M)			<0.001
M0	286 (92.6)	492 (74.2)	
M1	21 (6.8)	162 (24.4)	
Unknown	2 (0.6)	9 (1.4)	
Stage			<0.001
Stage 1	39 (12.6)	177 (26.7)	
Stage 2	210 (68.0)	279 (42.1)	
Stage 3	36 (11.7)	24 (3.6)	
Stage 4	21 (6.8)	162 (24.4)	
Unknown	3 (1.0)	21 (3.2)	
Tumor grade			0.001
G1 (well)	58 (18.8)	120 (18.1)	
G2 (moderate)	128 (41.4)	223 (33.6)	
G3 (poor)	67 (21.7)	111 (16.7)	
G4 (undifferentiated)	0	11 (1.7)	
Unknown	56 (18.1)	198 (29.9)	
Tumor size			<0.001
<2 cm	45 (14.6)	99 (14.9)	
≥2 cm	228 (73.8)	396 (59.7)	
Unknown	36 (11.7)	168 (25.3)	
Single reportable tumor (*n*, %)	254 (82.2)	538 (81.1)	0.69
Type of surgery			<0.001
Partial/localized	38 (12.3)	101 (15.2)	
Total pancreatectomy	25 (8.1)	69 (10.4)	
Pancreatoduodenectomy	230 (74.4)	380 (57.3)	
Other	16 (5.2)	113 (17.0)	
Cause of death			0.16
Alive	83 (26.9)	198 (29.9)	
Pancreas	192 (62.1)	371 (56.0)	
Other cause of death	34 (11.0)	94 (14.2)	

Values are counts and % if not otherwise indicated

RT ($P = 0.17$). Cause of death was similarly distributed between the two groups ($P = 0.16$).

In subgroup analyses of CSS comparing patients who received versus did not receive adjuvant RT, there was a significant unadjusted survival benefit in patients with lymph-node-positive disease [median survival: 21 (CI: 16–26) versus 12 (CI: 10–15) months, respectively, $P < 0.001$; Fig. 1], T4-classified tumors [median survival: 16 (CI: 10–25) versus 7 (CI: 6–9) months, $P = 0.012$], and poorly differentiated tumors [median survival: 15 (CI: 12–28) versus 12 (CI: 10–15) months, $P = 0.022$]. In addition, patients who received adjuvant RT with T3 or

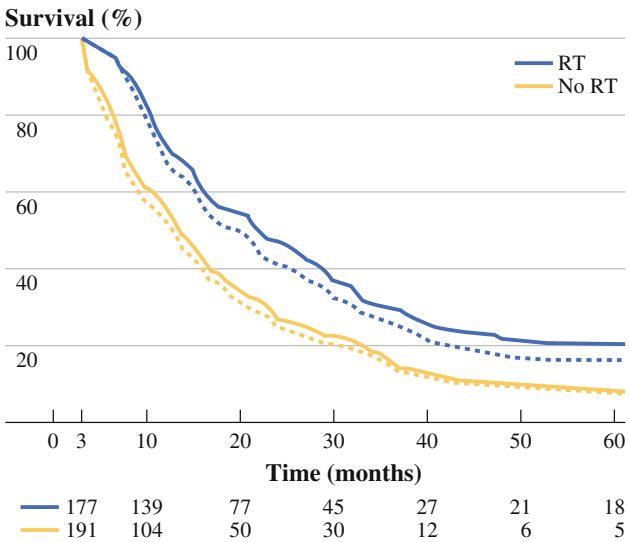

FIG. 1 Kaplan–Meier curves comparing CSS (straight lines, $P < 0.001$) and OS (dotted lines, $P < 0.001$) for patients with lymph-node-positive (N1) invasive IPMN who received adjuvant RT versus those who did not. In the first 3 months, 4 patients were left-censored in the RT group and 61 were left-censored in the non-RT group

TABLE 2 Effect of adjuvant RT on 5-year CSS and OS calculated using unadjusted and propensity-score-adjusted stratified multivariate Cox proportional-hazard modeling

	Cancer-specific survival (CSS)				Overall survival (OS)			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Overall	0.95 (0.79–1.14)	0.56	0.92 (0.75–1.14)	0.43	1.11 (0.93–1.33)	0.24	1.00 (0.82–1.22)	0.96
Age								
<65 years	1.25 (0.95–1.66)	0.11	0.87 (0.63–1.20)	0.38	1.21 (0.93–1.58)	0.15	0.86 (0.63–1.16)	0.30
≥65 years	1.07 (0.82–1.39)	0.60	0.94 (0.70–1.26)	0.66	1.06 (0.84–1.35)	0.60	0.99 (0.75–1.29)	0.92
Sex								
Female	1.24 (0.94–1.63)	0.12	0.88 (0.64–1.23)	0.45	1.22 (0.95–1.58)	0.12	0.90 (0.68–1.19)	0.46
Male	1.07 (0.82–1.40)	0.62	0.92 (0.68–1.24)	0.58	1.03 (0.80–1.32)	0.82	0.98 (0.72–1.33)	0.88
Race								
White	1.13 (0.92–1.38)	0.24	0.95 (0.75–1.20)	0.66	1.09 (0.90–1.31)	0.39	0.96 (0.77–1.18)	0.67
Black	0.92 (0.45–1.89)	0.82	0.56 (0.18–1.79)	0.32	0.92 (0.47–1.78)	0.80	0.60 (0.22–1.68)	0.32
Marital status								
Married	1.10 (0.79–1.53)	0.22	0.99 (0.77–1.28)	0.94	1.17 (0.94–1.46)	0.15	1.01 (0.80–1.29)	0.92
Other	1.15 (0.91–1.46)	0.57	0.77 (0.51–1.17)	0.22	1.01 (0.75–1.36)	0.95	0.86 (0.59–1.25)	0.42
Tumor location								
Head of pancreas	1.00 (0.79–1.27)	0.98	0.79 (0.60–1.02)	0.06	1.02 (0.82–1.27)	0.87	0.82 (0.64–1.05)	0.11
Other	1.40 (1.01–1.96)	0.042	1.45 (0.99–2.14)	0.05	1.32 (0.98–1.79)	0.064	1.36 (0.97–1.92)	0.073
Primary tumor (T)								
T1	2.10 (0.70–6.27)	0.18	1.17 (0.35–3.97)	0.80	1.80 (0.68–4.77)	0.23	1.21 (0.40–3.73)	0.73
T2	1.47 (0.85–2.52)	0.16	1.16 (0.63–2.12)	0.63	1.32 (0.81–2.16)	0.25	1.08 (0.62–1.87)	0.78
T3	1.01 (0.77–1.31)	0.96	0.85 (0.63–1.14)	0.26	1.02 (0.79–1.30)	0.90	0.89 (0.68–1.18)	0.41
T4	0.64 (0.43–0.93)	0.017	0.75 (0.44–1.27)	0.27	0.63 (0.44–0.91)	0.01	0.72 (0.43–1.23)	0.22
T1/T2	1.62 (1.00–2.63)	0.048	1.11 (0.67–1.87)	0.67	1.45 (0.94–2.24)	0.09	1.10 (0.69–1.76)	0.69
T3/T4	0.81 (0.65–1.00)	0.049	0.87 (0.69–1.11)	0.25	0.82 (0.67–1.01)	0.05	0.92 (0.73–1.15)	0.46
Regional lymph nodes (N)								
N0	1.50 (1.09–2.07)	0.012	1.35 (0.95–1.91)	0.089	1.38 (1.03–1.85)	0.029	1.26 (0.92–1.74)	0.14
N1	0.59 (0.46–0.76)	<0.001	0.67 (0.51–0.89)	0.004	0.63 (0.50–0.81)	<0.001	0.73 (0.56–0.94)	0.014
Distant metastasis (M)								
M0	1.43 (1.16–1.78)	0.001	0.91 (0.72–1.15)	0.42	1.39 (1.14–1.69)	0.001	0.94 (0.76–1.18)	0.61
M1	0.80 (0.47–1.34)	0.38	0.62 (0.33–1.18)	0.14	0.76 (0.46–1.25)	0.27	0.60 (0.32–1.10)	0.091
Tumor grade								
G1 (well)	1.94 (1.19–3.17)	0.007	1.55 (0.87–2.75)	0.13	1.78 (1.13–2.79)	0.011	1.54 (0.90–2.64)	0.11
G2 (moderate)	1.01 (0.75–1.36)	0.96	0.88 (0.60–1.27)	0.47	1.03 (0.78–1.37)	0.81	0.91 (0.64–1.29)	0.59
G3 (poor)	0.63 (0.42–0.96)	0.027	0.74 (0.47–1.18)	0.20	0.67 (0.46–0.98)	0.035	0.79 (0.51–1.22)	0.28
T-classification T1/T2								
N0	1.64 (0.82–3.30)	0.16	1.28 (0.60–2.76)	0.51	1.25 (0.65–2.39)	0.49	1.19 (0.59–2.43)	0.62
N1	0.73 (0.36–1.47)	0.37	0.78 (0.34–1.79)	0.55	0.86 (0.46–1.63)	0.64	0.73 (0.32–1.64)	0.43
T-classification T3/T4								
N0	1.09 (0.75–1.59)	0.64	1.22 (0.78–1.91)	0.37	1.08 (0.76–1.52)	0.68	1.25 (0.82–1.88)	0.29
N1	0.57 (0.43–0.75)	<0.001	0.71 (0.52–0.96)	0.022	0.61 (0.47–0.79)	<0.001	0.76 (0.56–1.02)	0.06

The reference group is those patients who did not receive adjuvant RT. Propensity score calculation based on: year of operation, age, sex, marital status, race, tumor location, tumor size, tumor grade, single reportable tumor, type of surgery, primary tumor (T), regional lymph nodes (N), and distant metastasis (M)

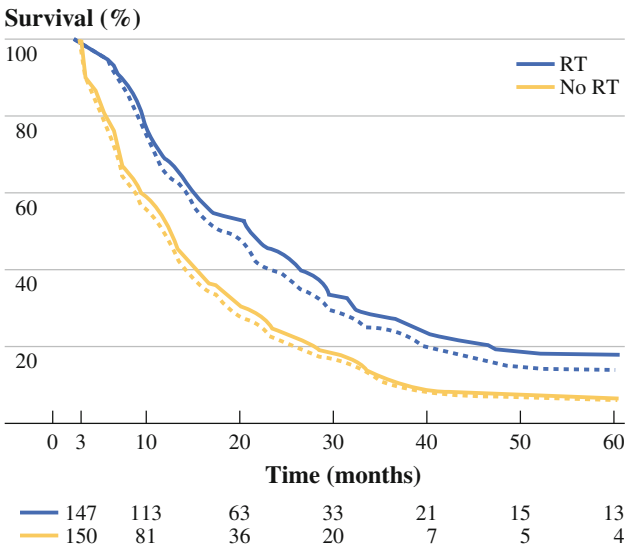

FIG. 2 Kaplan–Meier curves comparing CSS (straight lines, $P < 0.001$) and OS (dotted lines, $P < 0.001$) for patients with T3/T4, lymph-node-positive (N1), invasive IPMN who received adjuvant RT versus those who did not. In the first 3 months, 3 patients were left-censored in the RT group and 51 were left-censored in the non-RT group

T4 tumors and positive lymph nodes demonstrated a median CSS of 20 months (CI: 15–25 months) compared with 12 months (CI: 10–14 months, $P < 0.001$) for patients not receiving adjuvant RT (Fig. 2).

Given the above findings, we performed Cox proportional-hazard model analysis stratified over propensity score to account for nonrandomized provision of adjuvant RT. We compared outcomes for patients who received versus did not receive adjuvant RT. There was no overall CSS or OS difference after propensity score adjustment (Table 2). In subgroup analyses, patients with lymph node involvement who received adjuvant RT demonstrated improved CSS (HR: 0.67, CI: 0.51–0.89, $P = 0.004$) and OS (HR: 0.73, CI: 0.56–0.94, $P = 0.014$). In patients with T3/T4-classified tumors with lymph node positivity, adjuvant RT was associated with improved CSS (HR: 0.71, CI: 0.52–0.96, $P = 0.022$), though there was no difference in OS (HR: 0.76, CI: 0.56–1.02, $P = 0.06$). There was no survival difference among patients with T1/T2 tumors and positive lymph nodes. There was no significant difference in CSS or OS in patients with negative lymph nodes. All other subgroup analyses demonstrated no statistically significant differences. Unadjusted and adjusted HR for CSS and OS are presented in Table 2.

When the analysis was performed without left-censoring, there were no significant changes compared with the primary analysis. Furthermore, excluding patients with distant metastasis in the propensity-score-adjusted analyses also did not significantly change the results of the primary analysis [CSS (HR: 0.61, CI: 0.45–0.82, $P < 0.001$) and OS (HR: 0.67, CI: 0.50–0.89, $P = 0.005$) comparing patients with lymph-node-positive disease who received versus did not receive RT], though patients with T3/T4-classified tumors and positive lymph nodes had improved CSS and, additionally, an OS benefit with adjuvant RT (HR: 0.58, CI: 0.41–0.82, $P = 0.001$ and HR: 0.65, CI: 0.47–0.91, $P = 0.009$, respectively).

DISCUSSION

IPMN has potential for malignant transformation to pancreatic adenocarcinoma, but, unlike pancreatic adenocarcinoma, the role of adjuvant therapy is not well studied. In this retrospective cohort study of the SEER cancer registry from 1998 to 2007, we examined whether adjuvant RT following surgical resection was associated with a survival benefit compared with no adjuvant RT. We used SEER to address sample size limitations of prior studies and to examine subgroup differences in survival outcomes.[6,9,12,33] Our findings demonstrate a significant survival benefit in patients with lymph-node-positive invasive IPMN who received adjuvant RT, though further analysis suggests this benefit is limited to those patients with T3/4 tumors. As with pancreatic adenocarcinoma, adjuvant RT may have an important role in treatment of invasive IPMN, especially in selected patients with lymph-node-positive disease.[34,35]

IPMN accounts for nearly 5% of all resected malignant pancreatic neoplasms, but there is a paucity of data investigating the role of adjuvant therapy in patients with invasive IPMN.[2] Many patients presently receive adjuvant therapy based on clinical evidence generated for treatment of pancreatic ductal adenocarcinoma. An emerging body of evidence suggests that IPMN and pancreatic adenocarcinoma, in fact, have a different natural history and prognosis.[6,9,10,15,16,36–39] Most studies to date of adjuvant RT have been single-center and pooled multisite series of adjuvant chemotherapy (with or without RT) in a limited number of patients with invasive pancreatic IPMN.[6,9,12] Using SEER, we were able to identify a large cohort of cases and, accordingly, achieve sufficient statistical power to estimate subgroup differences according to provision of adjuvant RT. In this nonrandomized observational dataset, we used propensity-score-adjusted analysis to mitigate the effects of confounders.

Patients with invasive IPMN have poor prognosis: the 5-year OS is estimated to be 22–46%.[6,7,9,10,12,15,16,33,37,38] In our population-based study of 972 patients, the 5-year OS for patients with and without adjuvant RT was 24%, which is on the lower end of previously reported survival. Our findings, however, suggest that certain subgroups may benefit from RT following surgical resection. Lymph node

involvement was highly predictive of worsened survival: the 5-year OS for lymph-node-positive invasive IPMN in the present study was 12% (published range: 0–45%) compared with 42% for patients with node-negative tumors (40–85%).[5–9,12,36] The difference in OS between patients with versus without lymph node involvement is consistent with previous reports.

In the present study, the survival benefit associated with adjuvant RT was limited to patients with positive regional lymph nodes, though further analyses suggested this was limited to patients with advanced T stage (T3/T4) and positive regional lymph nodes. It is likely that patients with such tumors have higher probability of positive resection margins and/or residual positive lymph nodes, and are thus more likely to benefit from adjuvant RT. It should be noted, however, that the SEER registry does not contain information regarding surgical margin status, thus limiting our conclusions.

We acknowledge several other potential limitations of the present study. First, retrospective secondary data analyses are impacted by selection bias. Propensity score adjustment is one means to mitigate such bias. Nonetheless, propensity score adjustment itself can only take into account what is explicitly known through the SEER registry. The propensity score calculation thus lacks several patient (e.g., body mass index, comorbidities), tumor (e.g., resection margin), and hospital characteristics (e.g., hospital volume) that are unavailable in SEER but which potentially influence both survival as well as the probability of receiving adjuvant RT. Second, data regarding the details of external-beam RT (e.g., technique, dose) are not available in SEER. Third, data regarding adjuvant chemotherapy administration are unavailable in the SEER registry. We are therefore unable to identify patients who may have also received adjuvant chemotherapy. No guidelines presently exist for adjuvant therapy for invasive IPMN; it is likely that many therapeutic regimens include a combined approach using adjuvant chemoradiotherapy. This is supported by Turrini et al., who did not report any patients receiving adjuvant RT alone in a retrospective analysis of two major centers in the USA.[12] Fourth, the identification of invasive IPMN in the SEER registry is based on ICD-O-3 codes. The nature of administrative, de-identified databases does not allow for verification of coded pathological diagnoses. Though unlikely, we acknowledge the possibility of misclassification of these tumors. Lastly, *p*-values approaching 0.05 should be interpreted with caution due to multiple testing related to the subgroup analyses.

In essence, the results from our study demonstrate that, in the setting of lymph-node-positive disease and advanced T stage, adjuvant RT in patients with invasive IPMN is associated with an improvement in 5-year CSS. Further studies are needed to investigate the role of adjuvant therapy in the treatment of invasive IPMN, particularly the role of single-modality and combined chemoradiotherapy approaches. Nevertheless, the suggested benefit of adjuvant RT in select patients with invasive IPMN is encouraging.

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