

Neoadjuvant Radiotherapy After (m)FOLFIRINOX for Borderline Resectable Pancreatic Adenocarcinoma: A TAPS Consortium Study

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ABSTRACT

Background: The value of neoadjuvant radiotherapy (RT) after 5-fluorouracil with leucovorin, oxaliplatin, and irinotecan, with or without dose modifications [(m)FOLFIRINOX], for patients with borderline resectable (BR) pancreatic ductal adenocarcinoma (PDAC) is uncertain. **Methods:** We conducted an international retrospective cohort study including consecutive patients with BR PDAC who received (m)FOLFIRINOX as initial treatment (2012–2019) from the Trans-Atlantic Pancreatic Surgery Consortium. Because the decision to administer RT is made after chemotherapy, patients with metastases or deterioration after (m)FOLFIRINOX or a performance score ≥ 2 were excluded. Patients who received RT after (m)FOLFIRINOX were matched 1:1 by nearest neighbor propensity scores with patients who did not receive RT. Propensity scores were calculated using sex, age (≤ 70 vs > 70 years), WHO performance score (0 vs 1), tumor size (0–20 vs 21–40 vs > 40 mm), tumor location (head/uncinate vs body/tail), number of cycles (1–4 vs 5–8 vs > 8), and baseline CA 19-9 level (≤ 500 vs > 500 U/mL). Primary outcome was overall survival (OS) from diagnosis. **Results:** Of 531 patients who received neoadjuvant (m)FOLFIRINOX for BR PDAC, 424 met inclusion criteria and 300 (70.8%) were propensity score–matched. After matching, median OS was 26.2 months (95% CI, 24.0–38.4) with RT versus 32.8 months (95% CI, 25.3–42.0) without RT ($P=.71$). RT was associated with a lower resection rate (55.3% vs 72.7%; $P=.002$). In patients who underwent a resection, RT was associated with a comparable margin-negative resection rate (> 1 mm) (70.6% vs 64.8%; $P=.51$), more node-negative disease (57.3% vs 37.6%; $P=.01$), and more major pathologic response with $< 5\%$ tumor viability (24.7% vs 8.3%; $P=.006$). The OS associated with conventional and stereotactic body RT approaches was similar (median OS, 25.7 vs 26.0 months; $P=.92$). **Conclusions:** In patients with BR PDAC, neoadjuvant RT following (m)FOLFIRINOX was associated with more node-negative disease and better pathologic response in patients who underwent resection, yet no difference in OS was found. Routine use of RT cannot be recommended based on these data.

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Background

Pancreatic ductal adenocarcinoma (PDAC) represents one of the most aggressive solid tumors. Localized PDAC is classified into radiographic stages as potentially resectable (PR), borderline resectable (BR), or locally advanced disease, based on the extent of venous and arterial involvement.^{1,2} Although several staging criteria are currently used, patients with BR PDAC are generally considered technically resectable, but with increased risk of a microscopic margin-positive (R1) resection. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pancreatic Adenocarcinoma recommend neoadjuvant therapy for patients with BR PDAC to increase the likelihood of a microscopically radical (R0) resection.² Moreover, a neoadjuvant approach allows for early treatment of occult micrometastatic disease and ensures systemic treatment of all patients without the risk of postoperative complications precluding adjuvant treatment.³ Last, it allows tumor biology to declare itself for patients with elevated tumor markers, thereby improving patient selection for surgery.⁴

In the current NCCN Guidelines (Version 2.2021), neoadjuvant chemotherapy may be followed by radiotherapy

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(RT), without clear specification on when this may be considered.² Cohort studies reported that neoadjuvant RT is associated with better locoregional control compared with chemotherapy alone. However, a benefit in overall survival (OS) has not been clearly demonstrated.^{5–8} The long-term results of the PREOPANC trial found better OS with neoadjuvant chemoradiotherapy compared with upfront surgery in patients with BR and PR PDAC.^{9,10} However, this study did not directly compare neoadjuvant chemotherapy with or without RT. Moreover, the PREOPANC trial used gemcitabine alone, which was shown to be inferior to FOLFIRINOX (5-fluorouracil/leucovorin/irinotecan/oxaliplatin) in the metastatic and adjuvant setting.^{11,12} Through extrapolation of these results, the NCCN Guidelines has included neoadjuvant FOLFIRINOX, with or without dose modifications [(m)FOLFIRINOX] as one of the preferred first-line treatments for patients with BR PDAC and good performance status.² Several retrospective studies have already shown promising results using neoadjuvant (m)FOLFIRINOX with or without additional RT.^{13–16}

This study aimed to assess the effectiveness of neoadjuvant RT after (m)FOLFIRINOX in patients with BR PDAC. In the absence of published phase III trials, we performed a propensity score–matched analysis of a large observational cohort to minimize known confounding biases.¹⁷

Methods

Study Design and Patients

The international Trans-Atlantic Pancreatic Surgery (TAPS) Consortium includes 5 PDAC referral centers from the United States (University of Pittsburgh Medical Center, MD Anderson Cancer Center [MDACC], and Memorial Sloan Kettering Cancer Center) and the Netherlands (Amsterdam UMC and Erasmus MC University Medical Center). All participating centers obtained ethical approval from local Institutional Review Boards. Because of the retrospective nature of the study, the requirement to obtain informed consent was waived. This study followed the STROBE reporting guideline, modified for reporting propensity score analysis.¹⁷

The consortium centers aggregated a consecutive cohort of patients diagnosed with clinically localized PDAC between 2012 and 2019, who started with (m)FOLFIRINOX as initial treatment. Radiographic stage was based on the MDACC classification system⁴ or the NCCN criteria applicable at time of diagnosis (the other 4 centers). For patients from the Netherlands, stage according to NCCN criteria was reconstructed based on the exact extent of vascular contact with and possible occlusion of surrounding vasculature after radiologic review of the CT scan prior to start of treatment.

For the present study, all patients diagnosed with BR PDAC were identified from the TAPS total cohort of 1,835 patients. Because the decision for RT is generally made after completion of chemotherapy, patients were excluded if they had metastatic disease or clinical decline at restaging after (m)FOLFIRINOX, or a baseline WHO performance score of ≥ 2 . Furthermore, patients were excluded if it was unknown whether they had received neoadjuvant RT. The decision to proceed with and the type of neoadjuvant RT was based on discussions at each institution's local multidisciplinary meeting. RT options included conventional regimens (typically 30 Gy in 10 fractions or 50.4 Gy in 28 fractions, often with concurrent chemotherapy) or stereotactic body RT (SBRT) regimens of ≥ 5 Gy per fraction in 5 fractions.

Data Collection and Definitions

Prespecified data on patient demographics, tumor characteristics, treatment details, and clinical and pathologic outcomes were collected locally and merged after deidentification. OS was defined from date of tissue diagnosis to date of death, with censoring at the date of last follow-up for patients with no event. The date of final analysis for the cohort was December 31, 2020. The 8th edition of the *AJCC Cancer Staging Manual* was used for TNM staging,¹⁸ the 1-mm definition was used to determine resection margin status,¹⁹ and pathologic response was categorized as major/complete ($< 5\%$ tumor viability) or not ($\geq 5\%$).²⁰ One biweekly treatment of (m)FOLFIRINOX was considered one cycle.

Statistical Analysis

Clinicopathologic characteristics were presented based on treatment (RT vs no RT) using descriptive statistics. Chi-square test was used to compare categorical variables and the Mann-Whitney *U* test for continuous variables. To minimize confounding biases, propensity score matching was performed using 1:1 nearest neighbor matching. Propensity scores were calculated using a logistic regression model including known prognostic factors that may determine subsequent treatment; sex, age at diagnosis (≤ 70 vs > 70 years), WHO performance score (0 vs 1), tumor size (0–20 vs 21–40 vs > 40 mm), tumor location (head/uncinate vs body/tail), baseline CA 19-9 level (≤ 500 vs > 500 U/mL), and number of neoadjuvant (m)FOLFIRINOX cycles (1–4 vs 5–8 vs > 8). Sampling without replacement was used, and only patients with complete data on the matching factors were included. After matching, a standardized difference of < 0.10 was considered an insignificant and acceptable imbalance.^{21,22} The primary endpoint was OS for the matched cohort, assessed using Kaplan-Meier estimates. The difference in OS between the treatment groups was tested using the log-rank test. The treatment effect

was estimated using a Cox proportional hazards model and expressed as a hazard ratio (HR) with corresponding 95% confidence interval. Secondary endpoints included differences in pathologic outcomes between the matched treatment groups.

A subgroup analysis separately evaluated patients from the matched cohort who did or did not undergo a resection, comparing the treatment groups. A second subgroup analysis compared patients receiving conventional RT and SBRT.

All tests were 2-sided and a P value $<.05$ was considered statistically significant. Analyses were performed using R version 3.4.3 (R Foundation for Statistical Computing). The MatchIt package was used to create the matched sample.

Results

Patient and Treatment Characteristics

Between 2012 and 2020, 531 patients with BR PDAC who received at least 1 cycle of neoadjuvant (m)FOLFIRINOX as initial treatment were extracted from the total TAPS cohort of 1,835 patients. Of those, 107 patients (20.2%) were excluded for reasons shown in Figure 1. Of the remaining 424 patients, 195 (46.0%) received neoadjuvant

RT. Overall, patients received a median of 6 cycles (interquartile range [IQR], 4–8 cycles) of neoadjuvant (m)FOLFIRINOX (Table 1).

RT Regimens

Of the 195 patients with BR PDAC who received neoadjuvant RT, 128 (65.6%) received conventional RT and 63 (32.3%) received SBRT. For 4 patients, RT treatment specifics were unknown. For the 128 patients receiving conventional RT, concurrent chemotherapy was given as radiosensitizer in 115 (89.8%) (supplemental eTable 1, available with this article at JNCCN.org).

Propensity Score Matching

Baseline characteristics and treatment details before and after propensity score matching are summarized in Table 1. Before matching, patients in the RT group had worse performance scores ($P<.001$) and received more neoadjuvant cycles of (m)FOLFIRINOX ($P=.001$). With propensity score matching, 150 patients from the RT group (77%) were matched to 150 patients from the no RT group (66%). After matching, the absolute standardized differences for the unbalanced variables were low (range, 1%–5%), resulting in comparable patient, tumor, and treatment characteristics.

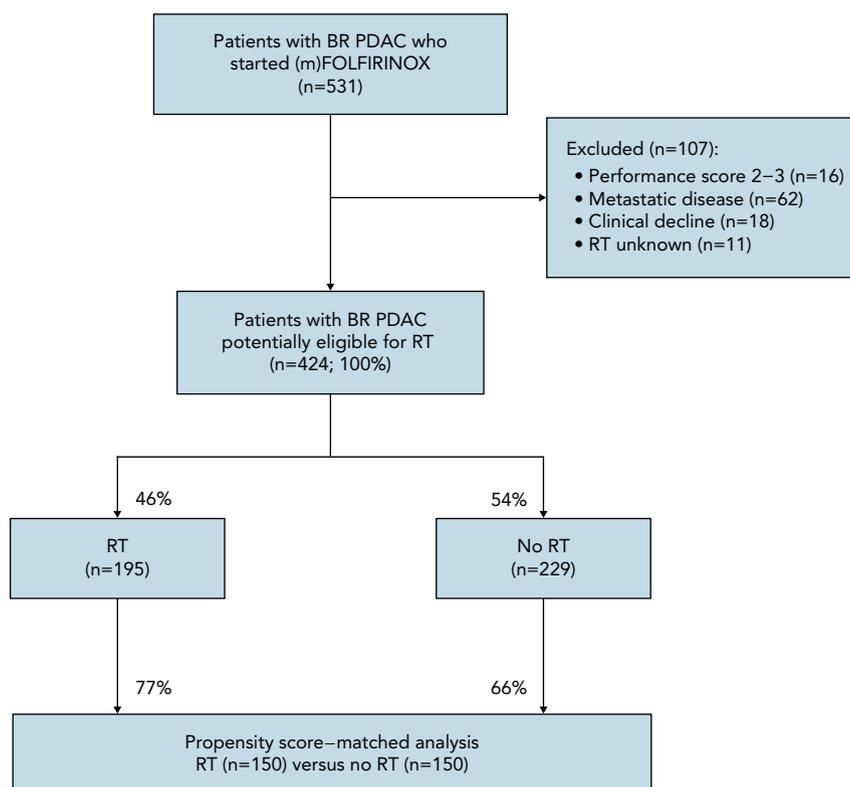


Figure 1. Flow diagram of patient enrollment.

Abbreviations: BR, borderline resectable; (m)FOLFIRINOX, 5-fluorouracil/leucovorin/oxaliplatin/irinotecan, with or without dose modifications; PDAC, pancreatic ductal adenocarcinoma; RT, radiotherapy.

Table 1. Baseline Characteristics and Treatment Details

	Unmatched Cohort				Matched Cohort			
	Overall n (%)	No RT n (%)	RT n (%)	P Value	Overall n (%)	No RT n (%)	RT n (%)	P Value
Total, n	424	229	195		300	150	150	
Female	189 (44.6)	92 (40.2)	97 (49.7)	.06	147 (49.0)	72 (48.0)	75 (50.0)	.82
Age, median (IQR), y	64 (57–70)	64 (58–69)	64 (57–70)	.85	64 (57–70)	65 (58–70)	64 (57–70)	.57
WHO PS				<.001 ^a				.91
0	222 (52.4)	139 (60.7)	83 (42.6)		150 (50.0)	76 (50.7)	74 (49.3)	
1	202 (47.6)	90 (39.3)	112 (57.4)		150 (50.0)	74 (49.3)	76 (50.7)	
BMI, median (IQR), kg/m ²	26 (23–29)	26 (23–30)	26 (24–29)	.78	26 (24–30)	26 (23–30)	26 (24–29)	.77
Tumor location: head/uncinate	335 (79.0)	184 (80.3)	151 (77.4)	.54	229 (76.3)	117 (78.0)	112 (74.7)	.59
Tumor size on CT, median (IQR), mm	34 (26–41)	33 (26–41)	34 (27–43)	.29	34 (27–41)	34 (26–41)	34 (27–41)	.58
Pretreatment CA 19-9, median (IQR), U/mL	196 (48–653)	178 (42–578)	232 (75–706)	.13	198 (46–653)	157 (30–582)	238 (73–710)	.14
Number of cycles				.001 ^a				.88
1–4	142 (33.5)	95 (41.5)	47 (24.1)		92 (30.7)	48 (32.0)	44 (29.3)	
5–8	230 (54.2)	109 (47.6)	121 (62.1)		172 (57.3)	84 (56.0)	88 (58.7)	
>8	52 (12.3)	25 (10.9)	27 (13.8)		36 (12.0)	18 (12.0)	18 (12.0)	

Missing data: BMI (n=6); tumor size (n=12); CA 19-9 (n=31).

Abbreviations: BMI, body mass index; IQR, interquartile range; PS, performance status; RT, radiotherapy.

^aSignificant P value <.05.

Survival Analysis

After a median follow-up time of 36.5 months, 253 of 424 patients (59.7%) had died. Median OS in the unmatched cohort was 25.7 months (95% CI, 23.7–31.8) with RT versus 29.1 months (95% CI, 23.2–35.0) without RT (hazard ratio [HR], 0.99; 95% CI, 0.77–1.26; $P=.91$) (Figure 2A). After matching, the median OS was 26.2 months (95% CI, 24.0–38.4) with RT versus 32.8 months (95% CI, 25.3–42.0) without RT (HR, 1.06; 95% CI, 0.78–1.43; $P=.71$) (Figure 2B). The 5-year OS was comparable (27% vs 26%).

Surgical Exploration and Resection in the Matched Cohort

At multidisciplinary evaluation after completion of (m)FOLFIRINOX and RT in the RT group, 30 patients (20.0%) had developed locally unresectable disease, 19 (12.7%) had metastatic disease that became manifest at restaging after RT, and 2 (1.3%) had clinically declined precluding surgery. In the no RT group, 15 patients (10.0%) had developed locally unresectable disease after completion of (m)FOLFIRINOX alone. As noted, patients with metastatic disease at restaging after (m)FOLFIRINOX were already excluded from the analyses.

Surgical exploration was recommended for the remaining 99 patients (66.0%) in the RT group and 135 (90.0%) in the no RT group ($P<.001$). The median time from diagnosis to surgery was 229 days (IQR, 189–268 days) in the RT group and 146 days (IQR, 125–175 days) in the no RT group ($P<.001$). In total, 83 patients

(55.3%) underwent a resection in the RT group versus 109 (72.7%) in the no RT group ($P=.002$). The resection rate of patients recommended for surgery was comparable (83.8% vs 80.7%; $P=.54$). A vascular resection was performed in 43 patients (51.8%) in the RT group versus 45 (42.1%) in the no RT group ($P=.23$). Only one patient died within 30 days after resection, who was included in the no RT group. Adjuvant chemotherapy was started in 33 patients (39.8%) in the RT versus 85 (78.0%) in the no RT group ($P<.001$). Palliative treatment was started in a comparable number of patients (52.0% vs 51.3%; $P=.62$).

Figure 2C shows the OS curves for both treatment groups, separately for the resection and nonresection cohort. For patients who underwent a resection, median OS was 46.9 months (95% CI, 38.4–83.9) with RT versus 42.3 months (95% CI, 35.4–62.2) without RT (HR, 0.87; 95% CI, 0.58–1.32; $P=.53$). With resection, the 5-year OS was 44% (95% CI, 32%–61%) with RT versus 34% (95% CI, 24%–49%) without RT. For patients who did not undergo a resection, median OS was 17.5 months (95% CI, 16.0–24.4) with RT versus 16.4 months (95% CI, 13.9–19.8) without RT (HR, 0.77; 95% CI, 0.49–1.20; $P=.25$). Without resection, the 5-year OS was 10% (95% CI, 4%–26%) with RT versus 3% (95% CI, 1%–24%) without RT.

Pathologic Outcomes in the Matched Cohort

Patients in the RT group had a similar R0 resection rate (70.6% vs 64.8%; $P=.53$), more node-negative disease

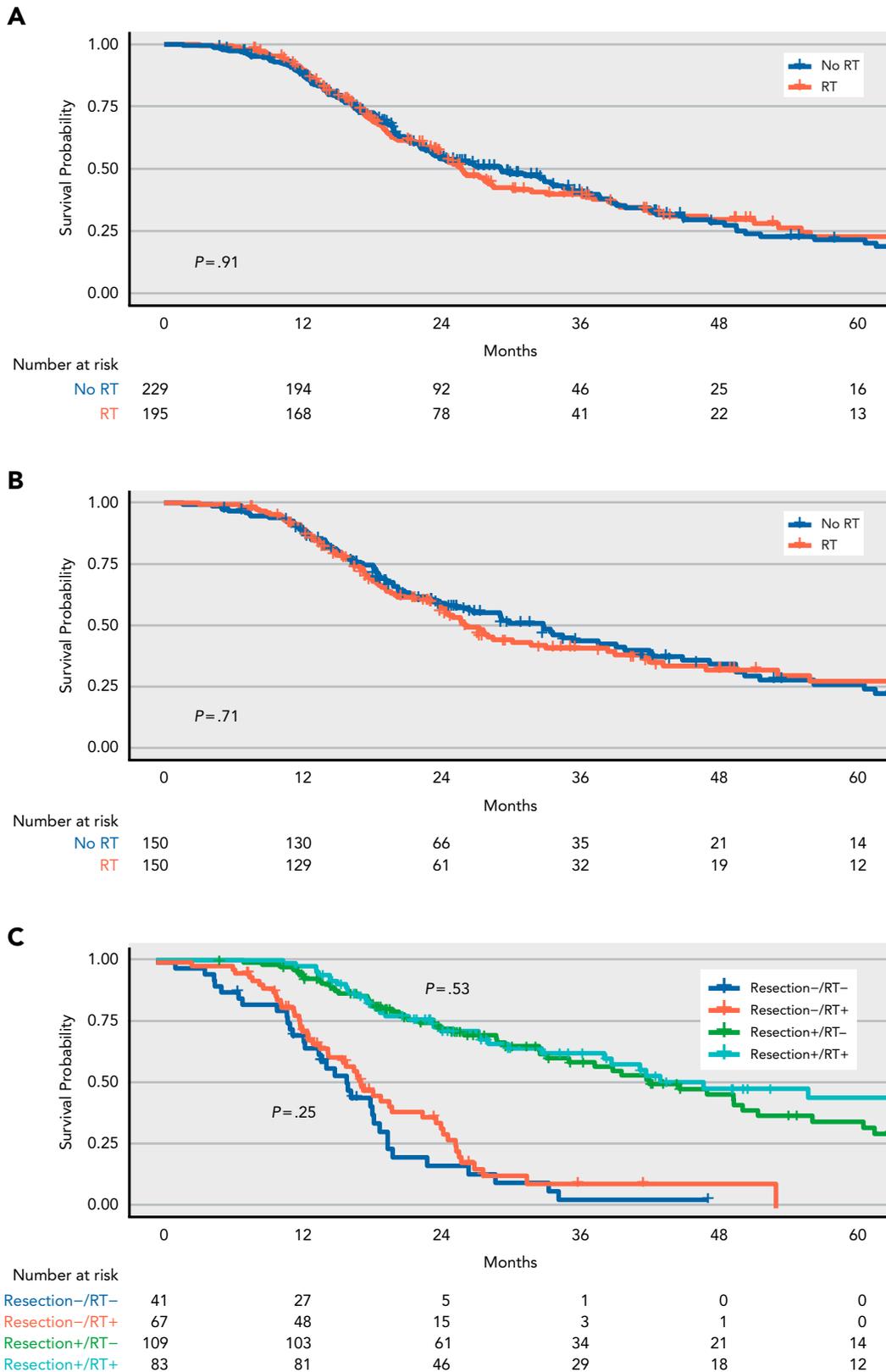


Figure 2. Overall survival from diagnosis for patients who did (+) or did not (-) receive neoadjuvant RT after (m)FOLFIRINOX in **(A)** the unmatched cohort, **(B)** the propensity score-matched cohort, and **(C)** the propensity score-matched cohort for patients who did (+) or did not (-) undergo a resection. One-to-one matching based on sex, age at diagnosis (≤ 70 vs > 70 years), WHO performance score (0 vs 1), tumor size (0–20 vs 21–40 vs > 40 mm), tumor location (head/uncinate vs body/tail), baseline CA 19-9 level (≤ 500 vs > 500 U/mL), and number of neoadjuvant cycles of (m)FOLFIRINOX (1–4 vs 5–8 vs > 8). Abbreviations: (m)FOLFIRINOX, 5-fluorouracil/leucovorin/oxaliplatin/irinotecan with or without dose modifications; RT, radiotherapy.

(ypN0, 57.3% vs 37.6%; $P=.01$), and more often had a major or complete pathologic response (24.7% vs 8.3%; $P=.01$) (Table 2).

Conventional RT Versus SBRT

The median OS was 26.0 months (95% CI, 22.4–42.0) for the 63 patients receiving SBRT versus 25.7 months (95% CI, 22.5–38.4) for the 128 patients receiving conventional RT (HR, 1.02; 95% CI, 0.69–1.52; $P=.92$) (Figure 3).

Discussion

This multicenter propensity score–matched analysis of 300 patients with BR PDAC who received (m)FOLFIRINOX as initial treatment showed a median OS of 26.2 months with RT compared with 32.8 months without RT (HR, 1.06; 95% CI, 0.78–1.43; $P=.71$). In addition, no difference in survival was found between the treatment groups when separately

analyzing the resection and nonresection cohorts. In patients who underwent surgical resection, neoadjuvant RT was associated with more node-negative disease and better pathologic response. The OS of conventional and stereotactic body radiation approaches was similar.

To date, only one randomized phase II trial has been presented that directly compared neoadjuvant multiagent chemotherapy with or without RT.^{23,24} The ALLIANCE A021501 trial compared neoadjuvant mFOLFIRINOX (8 cycles) versus mFOLFIRINOX (7 cycles) followed by SBRT (33–40 Gy in 5 fractions) or hypofractionated image-guided RT (25 Gy in 5 fractions). After inclusion of 56 patients, the RT arm was closed due to futility regarding the R0 resection rate. At final analysis, OS in the RT arm (median OS, 17.1 months) was not better compared with historical data (18–23 months) and lower compared with mFOLFIRINOX without RT (31.0 months). Median OS without RT was similar between the ALLIANCE trial and the present study. In the ALLIANCE trial, SBRT rather than conventional RT was used, based on promising results in patients with locally advanced PDAC.^{25–27} In the present study, we found similar survival between SBRT and conventional RT for BR PDAC.

In a meta-analysis including 512 patients with BR or PR PDAC from 15 small single-arm studies, neoadjuvant RT after (m)FOLFIRINOX was not associated with a difference in OS.²⁸ Retrospective series evaluating neoadjuvant chemotherapy regimens other than (m)FOLFIRINOX^{5–8} and the randomized LAP-07 trial for patients with locally advanced PDAC²⁹ also found no difference in OS with and without RT. Four studies found better survival with neoadjuvant RT after multiagent chemotherapy regimens^{16,30–32}; 3 of these studies, however, only included the selected subgroup of patients who underwent a resection, thereby introducing selection bias. In the no RT group, a patient who undergoes a resection might be diagnosed with liver metastases 3 months after surgery; in the RT group, the same patient would be diagnosed with liver metastases at restaging after RT and would therefore not end up in the resection cohort. We found that 12.7% of patients in the RT group had developed metastatic disease at restaging after RT, illustrating this selection bias in studies that only report the cohort who underwent a resection. These patients had an additional period for metastatic disease to become overt at restaging after RT. Consequently, a resection is avoided in the RT group in approximately 1 in 8 patients who would have developed early recurrent disease without a period of RT. In the present study, patients in the RT group also had higher risk of locally advanced (ie, unresectable) disease at radiologic restaging (20.0% vs 10.0%). Despite propensity matched analysis, patients in the RT group may have had more extensive vascular involvement at baseline within the spectrum of BR PDAC or less local response to (m)FOLFIRINOX (ie, residual confounding).

Table 2. Pathologic Outcomes of Patients Who Underwent a Resection in the Matched Cohort

	Overall n (%)	No RT n (%)	RT n (%)	P Value
Total, n	192	109	83	
Tumor size, median (IQR), mm	25 (18–33)	25 (20–30)	25 (17–36)	.83
T stage ¹⁸				.13
ypT0	8 (4.2)	2 (1.8)	6 (7.3)	
ypT1–2	145 (75.9)	87 (79.8)	58 (70.7)	
ypT3–4	38 (19.9)	20 (18.3)	18 (22.0)	
N stage ¹⁸				.01 ^a
ypN0	88 (46.1)	41 (37.6)	47 (57.3)	
ypN1	67 (35.1)	41 (37.6)	26 (31.7)	
ypN2	36 (18.8)	27 (24.8)	9 (11.0)	
Resection margin status ^b				.53
R0	118 (67.0)	70 (64.8)	48 (70.6)	
R1	58 (33.0)	38 (35.2)	20 (29.4)	
Tumor differentiation				.01 ^a
Well (G1)	5 (2.9)	5 (5.0)	0 (0.0)	
Moderate (G2)	125 (72.3)	77 (77.0)	48 (65.8)	
Poor (G3)	43 (24.9)	18 (18.0)	25 (34.2)	
PNI	147 (77.4)	84 (77.8)	63 (76.8)	1.0
LVI	101 (53.4)	64 (59.3)	37 (45.7)	.09
Pathologic response				.01 ^a
<5% TV	28 (15.8)	8 (8.3)	20 (24.7)	
≥5% TV	149 (84.2)	88 (91.7)	61 (75.3)	

Missing data: tumor size (n=2); ypT (n=1); ypN (n=1); resection margin (n=16); tumor differentiation (n=19); PNI (n=2); LVI (n=3); pathologic response (n=15).

Abbreviations: G, grade; IQR, interquartile range; LVI, lymphovascular invasion; PNI, perineural invasion; RT, radiotherapy; TV, tumor viability; yp, pathologic outcome after neoadjuvant treatment.

^aSignificant P value < .05.

^bOne millimeter definition of Royal College of Pathologists.¹⁹

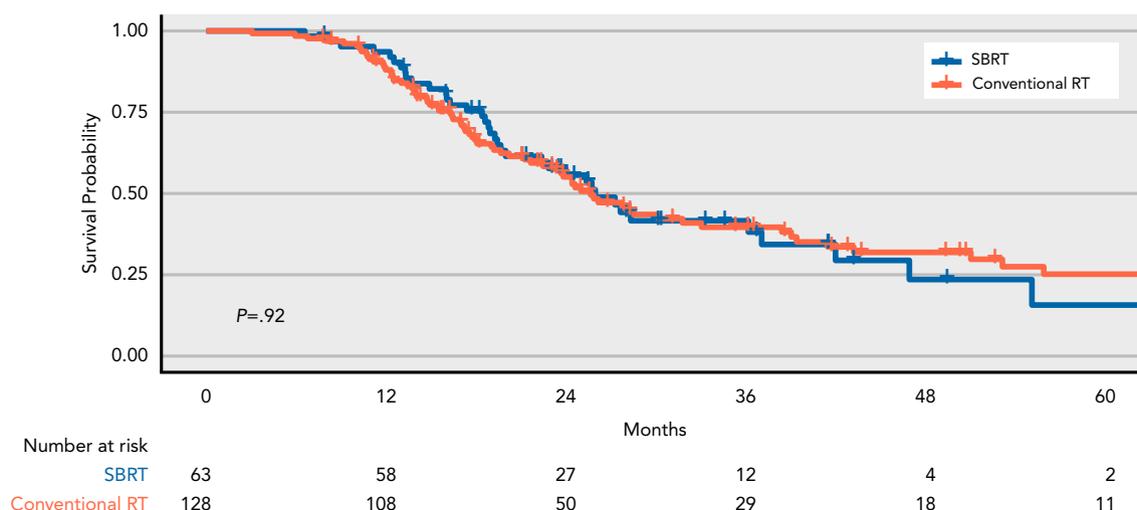


Figure 3. Overall survival from diagnosis for patients with BR PDAC who received neoadjuvant SBRT versus conventional RT after (m)FOLFIRINOX.

Abbreviations: BR, borderline resectable; (m)FOLFIRINOX, 5-fluorouracil/leucovorin/oxaliplatin/irinotecan, with or without dose modifications; PDAC, pancreatic ductal adenocarcinoma; RT, radiotherapy; SBRT, stereotactic body radiation therapy.

In patients who underwent a resection in the matched cohort, RT was associated with a higher frequency of node-negative disease and major pathologic response, which is consistent with the literature.^{5–7,30,31,33} This may be explained by the locoregional effect of RT, although it may also be partly explained by selecting out-patients with progressive disease during the prolonged treatment time for RT. No difference in R0 resection rate was found between the RT and no RT group. Other studies show conflicting data on this outcome.^{6,7,24,28,30,31} Differences in the definition of R0 and pathology grossing techniques hamper the comparability of margin status across studies.^{19,34,35} Of note, the conventional definition of an R0 resection based on 1-mm clearance may not be adequate after neoadjuvant therapy due to its cytoreductive effect, although consensus on the optimal assessment of margin status in this setting is lacking.³⁶ Given that the main effect of RT seems to be improved locoregional control, future studies should try to identify those patients for whom survival is mainly defined by their local tumor.

Some surgeons have raised concerns that preoperative RT may increase postoperative complications. Two recent studies, however, have found no difference in postoperative complications between patients with and without preoperative RT. Moreover, the rate of postoperative pancreatic fistula was lower in patients who received preoperative RT.^{37,38}

Currently, 3 randomized trials are assessing the role of neoadjuvant RT for BR PDAC. The 3-arm BRPCNC-1 trial is comparing neoadjuvant gemcitabine plus nab-paclitaxel with or without SBRT with S1 plus nab-paclitaxel with SBRT in 150 patients.³⁹ The PANDAS-PRODIGE44 trial

(ClinicalTrials.gov identifier: NCT02676349) is comparing neoadjuvant mFOLFIRINOX with or without conventional chemoradiotherapy (50.4 Gy in 28 fractions) in 90 patients. Last, the PREOPANC-2 trial is comparing neoadjuvant FOLFIRINOX with neoadjuvant gemcitabine-based chemoradiotherapy in 368 patients with BR and PR PDAC.⁴⁰ It is unlikely, however, that these studies will completely resolve the debate on the added value of neoadjuvant RT for BR PDAC. Only a large randomized controlled trial (ie, 500–1,000 patients) directly comparing multiagent systemic treatment with or without RT could definitively adjudicate whether the improved locoregional control of RT translates into a clinically relevant survival benefit.

Within the context of these data, routine use of RT for all BR PDAC patients may not be justified. Improved pathology outcomes in the RT group suggest that RT can benefit a subgroup of patients, but this subgroup remains to be identified. Selected RT prior to surgery may be indicated in patients with threatened margins or for vascular preservation to avoid the need for arterial resection.

The findings reported in this study should be interpreted with some limitations in mind. First, confounding by indication may have occurred, with more advanced tumors (within the definition of BR PDAC) in the RT group. On the other hand, guarantee-time bias was an advantage for the RT group.⁴¹ These biases were addressed with propensity score-matched analysis, but residual bias from unmeasured factors may still be present. Second, data on the exact extent of vascular involvement within the spectrum of BR PDAC and data on disease recurrence (ie, locoregional or distant) were not available. Last, treatment

protocols (eg, selection for RT, type of RT, and subsequent adjuvant and palliative treatment) differed across centers and over time. However, a cohort in which similar patients received different treatments is a requirement for propensity score matching. Moreover, this reflects real-world protocol variations in experienced treatment centers. Strengths of this study include the large sample size, the uniform use of (m)FOLFIRINOX chemotherapy, and the inclusion of patients from experienced referral centers from 2 different countries.

Conclusions

Neoadjuvant RT after (m)FOLFIRINOX for BR PDAC was not associated with improved OS despite some benefits in node-negative disease and pathologic response in those patients who underwent surgical resection. Routine use of neoadjuvant RT for all patients cannot be recommended based on these data. Future studies are needed to assess whether specific subgroups of patients with BR PDAC would benefit from neoadjuvant RT.

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Neoadjuvant Radiotherapy After (m)FOLFIRINOX for Borderline Resectable Pancreatic Adenocarcinoma: A TAPS Consortium Study

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eTable 1: Radiotherapy Treatment

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	Overall	Conventional RT	SBRT
Total, n	195 ^a	128	63
RT dose, median (IQR), Gy	40.0 (36.0–50.4)	50.4 (36.0–50.4)	36.0 (36.0–40.0)
Number of fractions, median (IQR)	12.0 (5.0–28.0)	25.0 (12.0–28.0)	5.0 (3.0–5.0)
Concurrent chemotherapy, n (%)			
Capecitabine	90 (47.1)	90 (70.3)	0
Gemcitabine	23 (12.0)	23 (18.0)	0
Other	2 (1.0)	2 (1.6)	0
Unknown	6 (3.1) ^a	2 (2.3)	0
No concurrent chemotherapy	74 (37.9)	11 (8.6)	63 (100.0)

Missing data: type (n=4); dose (n=8); fractions (n=8); concurrent chemotherapy (n=4).

Abbreviations: IQR, interquartile range; RT, radiotherapy; SBRT, stereotactic body radiation therapy.

^aFor 4 patients, RT treatment specifics were unknown, therefore these could not be categorized.