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Neoadjuvant radiotherapy following (m)FOLFIRINOX for borderline resectable pancreatic adenocarcinoma – a TAPS Consortium study

Quisette P. Janssen, MD[1,2], **Jacob. L. van Dam, MD**[2], **Laura R. Prakash, MD**[3], **Deesje Doppenberg, MD**[4], **Christopher H. Crane, MD**[5], **Casper H.J. van Eijck, MD PhD**[2], **Susannah G. Ellsworth, MD**[6], **William R. Jarnagin, MD**[1], **Eileen M. O'Reilly, MD**[7], **Alessandro Paniccia, MD**[8], **Marsha Reyngold, MD PhD**[5], **Marc G. Besselink, MD PhD**[4], **Matthew H.G. Katz, MD**[3], **Ching-Wei Tzeng, MD**[3], **Amer H. Zureikat, MD**[8], **Bas Groot Koerkamp, MD PhD**[2,*], **Alice C. Wei, MD**[1,*],

Trans-Atlantic Pancreatic Surgery (TAPS) Consortium

[1]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA;

[2]Department of Surgery, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands;

[3]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;

[4]Department of Surgery, Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands;

[5]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA;

[6]Department of Radiation Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA;

Corresponding Author: Alice C. Wei, MD, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave, C-886A, New York, NY, 10065, Phone: 212.639.5643, weia@mskcc.org.

*These authors contributed equally.

Author contributions: QJ: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, validation, visualization, writing – original draft, writing – review and editing. JvD: Data curation, formal analysis, methodology, validation, writing – review and editing. LP: Data curation, investigation, project administration, validation, writing – review and editing. DD: Data curation, investigation, validation, writing – review and editing. CC: Conceptualization, validation, writing – review and editing. CvE: Conceptualization, supervision, validation, writing – review and editing. SE: Conceptualization, validation, writing – review and editing. WJ: Conceptualization, validation, writing – review and editing. EO: Conceptualization, validation, writing – review and editing. AP: Conceptualization, validation, writing – review and editing. MR: Conceptualization, methodology, validation, writing – review and editing. MB: Conceptualization, supervision, validation, writing – review and editing. MK: Conceptualization, supervision, validation, writing – review and editing. CWT: Conceptualization, supervision, validation, writing – review and editing. AZ: Conceptualization, supervision, validation, writing – review and editing. BGK: Conceptualization, formal analysis, funding acquisition, methodology, supervision, validation, writing – review and editing. AW: Conceptualization, formal analysis, methodology, supervision, validation, writing – review and editing.

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[7]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA;

[8]Department of Surgery, Division of Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA.

Abstract

BACKGROUND—The value of neoadjuvant radiotherapy following (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. Since the decision for radiotherapy is made after chemotherapy, patients with metastases or deterioration after (m)FOLFIRINOX or a performance score ≥2 were excluded. Patients who received radiotherapy following (m)FOLFIRINOX were matched 1:1 by nearest neighbor propensity scores with patients who did not. Propensity scores were calculated using sex, age (≤70 versus >70), performance score (0 versus 1), tumor size (0–20 versus 21–40 versus >40mm), tumor location (head/uncinate versus body/tail), number of cycles (1–4 versus 5–8 versus >8), and baseline carbohydrate antigen (CA) 19–9 (≤500 versus >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% confidence interval [CI]: 24.0–38.4) with radiotherapy versus 32.8 months (95% CI: 25.3–42.0) without radiotherapy (p=0.71). Radiotherapy was associated with a lower resection rate (55.3% versus 72.7%, p=0.002). In patients who underwent a resection, radiotherapy was associated with a comparable margin-negative resection rate (>1mm) (70.6% versus 64.8%, p=0.51), more node-negative disease (57.3% versus 37.6%, p=0.01), and more major pathologic response with <5% tumor viability (24.7% versus 8.3%, p=0.006). The OS of conventional and stereotactic body radiation approaches was similar (median OS: 25.7 versus 26.0 months, p=0.92).

CONCLUSIONS—In patients with BR PDAC, neoadjuvant radiotherapy 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 radiotherapy cannot be recommended based on these data.

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Neoadjuvant radiotherapy following (m)FOLFIRINOX was not associated with improved OS in patients with BR PDAC. Routine use of radiotherapy cannot be recommended based on these data.

Lay summary:

In this international retrospective cohort study, 150 patients with BR PDAC who received radiotherapy following (m)FOLFIRINOX were 1:1 propensity score matched to 150 patients who received (m)FOLFIRINOX alone. After matching, median OS was 26.2 months (95% CI: 24.0–38.4) with radiotherapy versus 32.8 months (95% CI: 25.3–42.0) without radiotherapy (p=0.71). Radiotherapy was associated with fewer resections (55.3% vs. 72.7%, p=0.002), comparable margin-negative resection rates (70.6% vs. 64.8%, p=0.51), more node-negative disease (57.3%

vs. 37.6%, p=0.01), and more major pathologic response (24.7% vs. 8.3%, p=0.006). In conclusion, **n**eoadjuvant radiotherapy following (m)FOLFIRINOX was not associated with improved OS in patients with BR PDAC.

Keywords

pancreatic neoplasms* / therapy; radiation; propensity score; pancreatectomy; survival analysis

1. INTRODUCTION

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 (LA) 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 National Comprehensive Cancer Network (NCCN) guideline recommends 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 micro-metastatic disease and ensures systemic treatment for 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 guideline, neoadjuvant chemotherapy may be followed by radiotherapy, without clear specification on when this may be considered.[2] Cohort studies reported that neoadjuvant radiotherapy 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 radiation. Moreover, the PREOPANC trial used gemcitabine alone that was shown inferior to FOLFIRINOX (i.e. 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin) in the metastatic and adjuvant setting.[11,12] By extrapolation of these results, the NCCN guideline has included neoadjuvant (m)FOLFIRINOX as one of the preferred first-line treatments for patients with BR PDAC with a good performance status.[2] Several retrospective studies have already shown promising results using neoadjuvant (m)FOLFIRINOX with or without additional radiotherapy.[13–16]

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

2. METHODS

2.1 Study design and patients

The international Trans-Atlantic Pancreatic Surgery (TAPS) Consortium includes five PDAC referral centers from the United States (University of Pittsburgh Medical Center; MD Anderson Cancer Center; Memorial Sloan Kettering Cancer Center) and the Netherlands (Amsterdam UMC; Erasmus MC University Medical Center). All participating centers obtained ethical approval from local Institutional Review Boards. Due to the retrospective nature of the study, the requirement to obtain informed consent was waived. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (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 system[4] or the NCCN criteria applicable at time of diagnosis (the other four 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 1835 patients. Since the decision for radiotherapy is generally made after completion of chemotherapy, patients were excluded in case of metastatic disease or clinical decline at restaging following (m)FOLFIRINOX, or in case of a baseline World Health Organization (WHO) performance score of ≥2. Furthermore, patients were excluded if it was unknown whether they had received neoadjuvant radiotherapy. The decision to proceed with and the type of neoadjuvant radiotherapy was based on the discussions at each institution's local multidisciplinary meeting. Radiotherapy options included conventional regimens (typically 30 Gy in 10 fractions or 50.4 Gy in 28 fractions, often with concurrent chemotherapy) or stereotactic body radiation therapy (SBRT) regimens of ≥ 5 Gy per fraction in 5 fractions.

2.2 Data collection and definitions

Prespecified data on patient demographics, tumor characteristics, treatment details, and clinical and pathological outcomes were collected locally and merged after de-identification. 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 31st, 2020. The 8th edition of the American Joint Committee on Cancer Staging (AJCC) Manual was used for tumor-node-metastasis (TNM) staging,[18] the 1mm definition for resection margin status,[19] and pathologic response was categorized as major/complete (<5% tumor viability) or not (≥5%).[20] One biweekly treatment of (m)FOLFIRINOX was considered one cycle.

2.3 Statistical analysis

Clinicopathological characteristics were presented based on treatment (radiotherapy vs. no radiotherapy) 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), performance score (WHO 0 vs. WHO 1), tumor size (0–20 vs. 21–40 vs. >40 mm), tumor location (head/uncinate vs. body/tail), baseline CA 19–9 (≤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 (CI). Secondary endpoints included differences in pathological 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 radiotherapy and SBRT.

All tests were two-sided and a p-value <0.05 was considered statistically significant. Analyses were performed using R software, version 3.4.3. The MatchIt package was used to create the matched sample.

3. RESULTS

3.1 Patient and treatment characteristics

Between 2012 and 2020, 531 patients with BR PDAC who received at least one cycle of neoadjuvant (m)FOLFIRINOX as initial treatment were extracted from the total TAPS cohort of 1835 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 radiotherapy. Overall, patients received a median of six cycles (IQR 4–8) of neoadjuvant (m)FOLFIRINOX (Table 1).

3.2 Radiotherapy regimens

Of the 195 patients with BR PDAC who received neoadjuvant radiotherapy, 128 patients (65.6%) received conventional radiotherapy and 63 patients (32.3%) received SBRT. For four patients, radiotherapy treatment specifics were unknown. For the patients receiving conventional radiotherapy, concurrent chemotherapy was given as radiosensitizer in 115/128 patients (89.8%) (Supplementary Table 1).

3.3 Propensity score matching

Baseline characteristics and treatment details before and after propensity score matching are summarized in Table 1. Before matching, patients in the radiotherapy group had worse performance scores (p<0.001) and received more neoadjuvant cycles of (m)FOLFIRINOX (p=0.001). With propensity score matching, 150 patients from the radiotherapy group (77%) were matched to 150 patients from the no radiotherapy 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.

3.4 Survival analysis

After a median follow-up time of 36.5 months, 253/424 patients (59.7%) had died. The median OS in the unmatched cohort was 25.7 months (95% CI: 23.7–31.8) with radiotherapy versus 29.1 months (95% CI: 23.2–35.0) without radiotherapy (HR 0.99, 95% CI: 0.77–1.26, p=0.91) (Figure 2a). After matching, the median OS was 26.2 months (95% CI: 24.0–38.4) with radiotherapy versus 32.8 months (95% CI: 25.3–42.0) without radiotherapy (HR 1.06, 95% CI: 0.78–1.43, p=0.71) (Figure 2b). The 5-year OS was comparable (27 vs. 26%).

3.5 Surgical exploration and resection in the matched cohort

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

Surgical exploration was recommended for the remaining 99 patients (66.0%) in the radiotherapy group and 135 patients (90.0%) in the no radiotherapy group (p<0.001). The median time from diagnosis to surgery was 229 days (IQR 189 – 268) in the radiotherapy group and 146 days (IQR 125 – 175) in the no radiotherapy group (p<0.001). In total, 83 patients (55.3%) underwent a resection in the radiotherapy group versus 109 patients (72.7%) in the no radiotherapy group (p=0.002). The resection rate of patients recommended for surgery was comparable (83.8% vs. 80.7%, p=0.54). A vascular resection was performed in 43 patients (51.8%) in the radiotherapy group versus 45 patients (42.1%) in the no radiotherapy group (p=0.23). Only one patient died within 30-days following resection, who was included in the no radiotherapy group. Adjuvant chemotherapy was started in 33 patients (39.8%) in the radiotherapy versus 85 patients (78.0%) in the no radiotherapy group (p<0.001). Palliative treatment was started in a comparable number of patients (52.0% vs. 51.3%, p=0.62).

Figure 2c shows the OS curves for both treatment groups, separately for the resection and non-resection cohort. For patients who underwent a resection, the median OS was 46.9 months (95% CI: 38.4–83.9) with radiotherapy versus 42.3 months (95% CI: 35.4–56.2) without radiotherapy (HR 0.87, 95% CI: 0.58–1.32, p=0.53). With resection, the 5-year OS

was 44% (95% CI: 32–61%) with radiotherapy versus 34% (95% CI: 24–49%) without radiotherapy. For patients who did not undergo a resection, the median OS was 17.5 months (95% CI: 16.0–24.4) with radiotherapy versus 16.4 months (95% CI: 13.9–19.8) without radiotherapy (HR 0.77, 95% CI: 0.49–1.20, p=0.25). Without resection, the 5-year OS was 10% (95% CI: 4–26%) with radiotherapy versus 3% (95% CI: 1–24%) without radiotherapy.

3.6 Pathological outcomes in the matched cohort

Patients in the radiotherapy group had a similar R0 resection rate (70.6% vs. 64.8%, p=0.53), more node-negative disease (ypN0: 57.3% vs. 37.6%, p=0.01), and more often had a major or complete pathologic response (24.7% vs. 8.3%, p=0.01) (Table 2).

3.7 Conventional radiotherapy 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 radiotherapy (HR 1.02, 95% CI: 0.69–1.52, p=0.92) (Figure 3).

4. 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 radiotherapy compared with 32.8 months without radiotherapy (HR 1.06, 95% CI: 0.78–1.43, p=0.71). In addition, no difference in survival was found between the treatment groups when separately analyzing the resection and non-resection cohort. In those patients who underwent surgical resection, neoadjuvant radiotherapy 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 directly comparing neoadjuvant multi-agent chemotherapy with or without radiotherapy.[23,24] The ALLIANCE A021501 trial compared neoadjuvant mFOLFIRINOX (8 cycles) to mFOLFIRINOX (7 cycles) followed by SBRT (33–40 Gy in 5 fractions) or HIGRT (25 Gy in 5 fractions). After inclusion of 56 patients, the radiotherapy arm was closed due to futility regarding the R0 resection rate. At final analysis, OS in the radiotherapy arm (median OS: 17.1 months) was not better compared to historical data (18–23 months) and lower compared to mFOLFIRINOX without radiotherapy (31.0 months). Median OS without radiotherapy 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 LA PDAC.[25–27] In the present study, we found similar survival between SBRT and conventional radiotherapy for BR PDAC.

In a meta-analysis including 512 patients with BR or PR PDAC from 15 small single arm studies, neoadjuvant radiotherapy following (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 PDAC[29] also found no difference in OS with and without radiotherapy. Four studies found better survival with neoadjuvant radiotherapy following multi-agent

chemotherapy regimens.[16,30–32] Three of these four studies, however, only included the selected subgroup of patients who underwent a resection, thereby introducing selection bias. In the no radiotherapy group, a patient who undergoes a resection might be diagnosed with liver metastases three months after surgery; in the radiotherapy group, the same patient would be diagnosed with liver metastases at restaging after radiotherapy and would therefore not end up in the resection cohort. We found that 12.7% of patients in the radiotherapy group had developed metastatic disease at restaging after radiotherapy, 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 radiotherapy. Consequently, a resection is avoided in the radiotherapy group in about 1 in 8 patients who would have developed early recurrent disease without a period of radiotherapy. In the present study, patients in the radiotherapy group also had higher risk of locally advanced (i.e., unresectable) disease at radiologic restaging (20.0% vs. 10.0%). Despite propensity matched analysis, patients in the radiotherapy group may have had more extensive vascular involvement at baseline within the spectrum of BR PDAC or less local response to (m)FOLFIRINOX (i.e., residual confounding).

In patients who underwent a resection in the matched cohort, radiotherapy was associated with a higher frequency of node-negative disease and major pathologic response, which is consistent with literature.[5–7,30,31,33] This may be explained by the locoregional effect of radiotherapy, although it may also be partly explained by selecting out patients with progressive disease during the prolonged treatment time for radiotherapy. No difference in R0 resection rate was found between the radiotherapy and no radiotherapy 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 following neoadjuvant therapy due to its cytoreductive effect, although consensus on the optimal assessment of margin status in this setting is lacking.[36] Since the main effect of radiotherapy 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 radiotherapy may increase postoperative complications. Two recent studies, however, have found no difference in postoperative complications between patients with and without preoperative radiotherapy. Moreover, the rate of postoperative pancreatic fistula was lower in patients who received preoperative radiotherapy.[37,38]

Currently, three randomized trials assess the role of neoadjuvant radiotherapy for BR PDAC. The 3-arm BRPCNCC-1 trial compares neoadjuvant gemcitabine plus nab-paclitaxel with or without SBRT to S1 plus nab-paclitaxel with SBRT in 150 patients.[39] The PANDAS-PRODIGE44 trial (NCT02676349) compares neoadjuvant mFOLFIRINOX with or without conventional chemoradiotherapy (50.4 Gy in 28 fractions) in 90 patients. Last, the PREOPANC-2 trial compares neoadjuvant FOLFIRINOX to 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

radiotherapy for BR PDAC. Only a large randomized controlled trial (i.e. 500–1000 patients) directly comparing multi-agent systemic treatment with or without radiotherapy could definitively adjudicate whether the improved locoregional control of radiotherapy translates into a clinically relevant survival benefit.

Within the context of these data, routine use of radiotherapy for all BR PDAC patients may not be justified. Improved pathology outcomes in the radiotherapy group suggest that radiotherapy can benefit a subgroup of patients, but this subgroup remains to be identified. Selected radiotherapy 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 radiotherapy group. On the other hand, guarantee-time bias was an advantage for the radiotherapy 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 (i.e. locoregional or distant) were not available. Last, treatment protocols (e.g., selection for radiotherapy, type of radiotherapy, 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 two different countries.

In conclusion, neoadjuvant radiotherapy following (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 radiotherapy 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 radiotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

AJCC	American Joint Committee on Cancer
BR	Borderline resectable
CA 19-9	Carbohydrate antigen 19-9
CI	Confidence interval
(m)FOLFIRINOX	5-Fluorouracil with leucovorin, oxaliplatin, and irinotecan, with or without dose modifications
HIGRT	Hypofractionated image guided radiation therapy
HR	Hazard ratio
IQR	Interquartile range
MDACC	MD Anderson Cancer Center
NCCN	National Comprehensive Cancer Network
PDAC	Pancreatic ductal adenocarcinoma
SBRT	Stereotactic body radiation therapy
TAPS	Trans-Atlantic Pancreatic Surgery
TNM	Tumor, node, metastasis
WHO	World Health Organization

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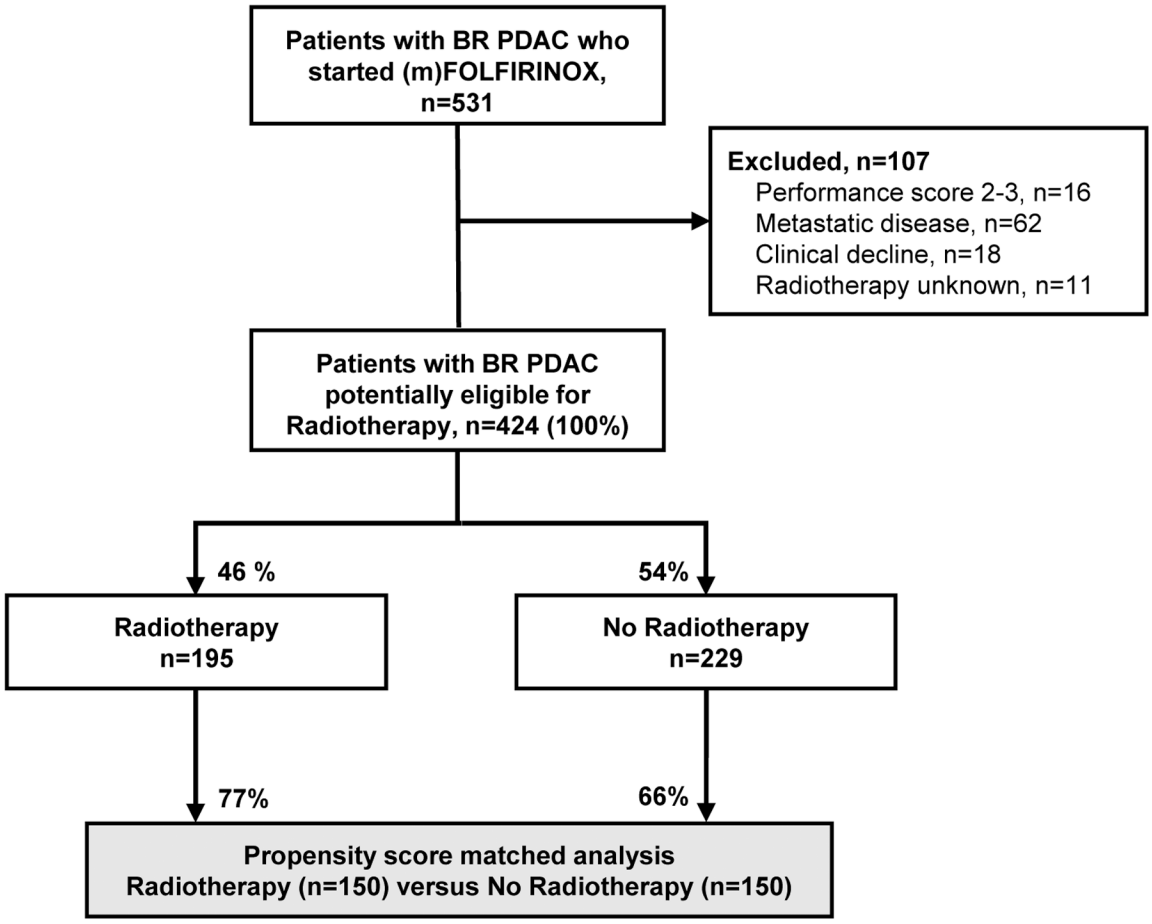

Figure 1.
Flow diagram of patient enrollment.

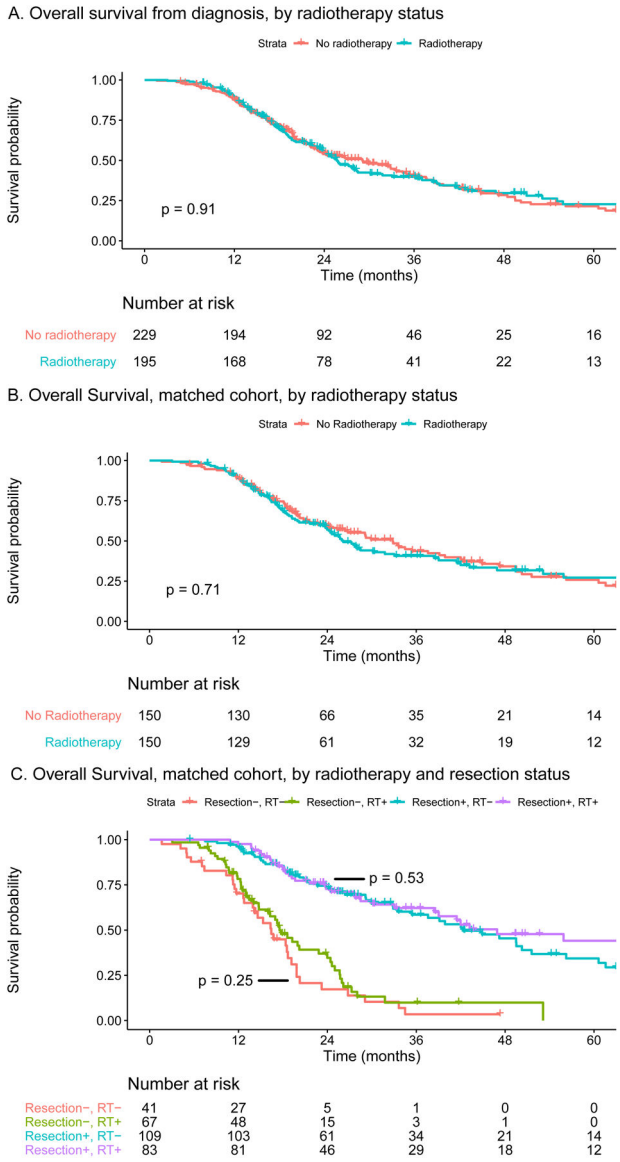

Figure 2. Overall survival from diagnosis for patients who did or did not receive neoadjuvant radiotherapy after (m)FOLFIRINOX, (a) in the unmatched cohort, (b) in the propensity score matched cohort, (c) in the propensity score matched cohort for patients who did or did not undergo a resection.

One-to-one matching based on sex, age at diagnosis (≤70 vs. >70 year), performance score (WHO 0 vs. WHO 1), tumor size (0–20 vs. 21–40 vs. >40 mm), tumor location (head/uncinate vs. body/tail), baseline CA 19–9 (≤500 vs. >500), and number of neoadjuvant cycles of (m)FOLFIRINOX (1–4 vs. 5–8 vs. >8).

Abbreviations: CA, carcinogen antigen; RT, radiotherapy; WHO, World Health Organization.

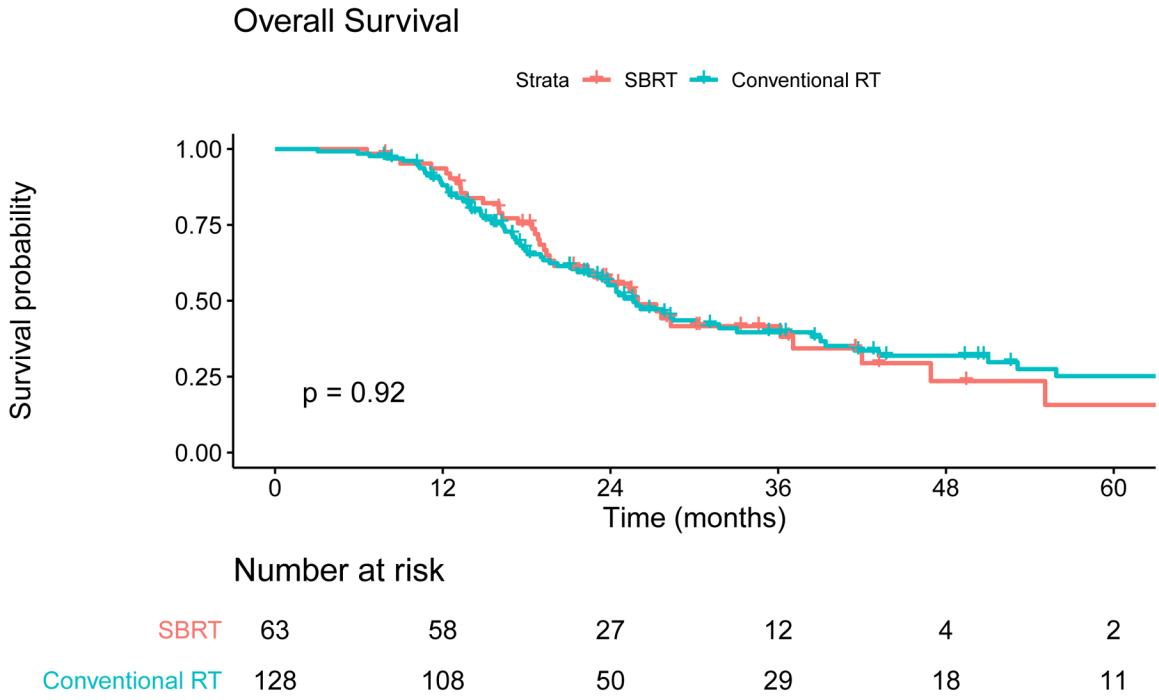

Figure 3.

Overall survival from diagnosis for patients with BR PDAC who received neoadjuvant radiotherapy after (m)FOLFIRINOX, comparing stereotactic body radiation therapy (SBRT) with conventional radiotherapy (RT).

Table 1.

Baseline characteristics and treatment details, unmatched and matched cohort.

	Unmatched cohort				Matched cohort			
	Overall	**No radiotherapy**	**Radiotherapy**	**P-value**	**Overall**	**No radiotherapy**	**Radiotherapy**	**P-value**
	n = 424	**n = 229**	**n = 195**		**n = 300**	**n = 150**	**n = 150**	
Female, n (%)	189 (44.6)	92 (40.2)	97 (49.7)	0.06	147 (49.0)	72 (48.0)	75 (50.0)	0.82
Age, years (median [IQR])	64 [57, 70]	64 [58, 69]	64 [57, 70]	0.85	64 [57, 70]	65 [58, 70]	64 [57, 70]	0.57
Performance status, n (%)				<0.001 *				0.91
WHO 0	222 (52.4)	139 (60.7)	83 (42.6)		150 (50.0)	76 (50.7)	74 (49.3)	
WHO 1	202 (47.6)	90 (39.3)	112 (57.4)		150 (50.0)	74 (49.3)	76 (50.7)	
BMI, kg/m^2 (median [IQR])	26 [23, 29]	26 [23, 30]	26 [24, 29]	0.78	26 [24, 30]	26 [23, 30]	26 [24, 29]	0.77
Tumor location: Head/uncinate, n (%)	335 (79.0)	184 (80.3)	151 (77.4)	0.54	229 (76.3)	117 (78.0)	112 (74.7)	0.59
Tumor size on CT, mm (median [IQR])	34 [26, 41]	33 [26, 41]	34 [27, 43]	0.29	34 [27, 41]	34 [26, 41]	34 [27, 41]	0.58
Pre-treatment CA 19–9, U/mL (median [IQR])	196 [48, 653]	178 [42, 578]	232 [75, 706]	0.13	198 [46, 653]	157 [30, 582]	238 [73, 710]	0.14
Number of cycles, n (%)				0.001 *				0.88
1–4 cycles	142 (33.5)	95 (41.5)	47 (24.1)		92 (30.7)	48 (32.0)	44 (29.3)	
5–8 cycles	230 (54.2)	109 (47.6)	121 (62.1)		172 (57.3)	84 (56.0)	88 (58.7)	
>8 cycles	52 (12.3)	25 (10.9)	27 (13.8)		36 (12.0)	18 (12.0)	18 (12.0)	

* = significant p-value <0.05.

Abbreviations: BMI, body mass index; CA 19-9, carbohydrate antigen 19-9; CT, computed tomography; IQR, interquartile range; n, number; WHO, World Health Organization. Missing data: BMI (n=6), tumor size (n=12), CA 19-9 (n=31).

Table 2.

Pathological outcomes of patients who underwent a resection in the matched cohort.

	Matched cohort			
	Overall	**No radiotherapy**	**Radiotherapy**	**P-value**
	n = 192	**n = 109**	**n = 83**	
Tumor size, mm (median [IQR])	25 [18, 33]	25 [20, 30]	25 [17, 36]	0.83
T stage[a], n (%)				0.13
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[a], n (%)				0.01*
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], n (%)				0.53
R0	118 (67.0)	70 (64.8)	48 (70.6)	
R1	58 (33.0)	38 (35.2)	20 (29.4)	
Tumor differentiation, n (%)				0.01*
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)	
Perineural invasion, n (%)	147 (77.4)	84 (77.8)	63 (76.8)	1
Lymphovascular invasion, n (%)	101 (53.4)	64 (59.3)	37 (45.7)	0.09
Pathologic response, n (%)				0.01*
<5% tumor viability	28 (15.8)	8 (8.3)	20 (24.7)	
≥5% tumor viability	149 (84.2)	88 (91.7)	61 (75.3)	

[a] 8th edition of American Joint Committee on Cancer Staging.

[b] 1mm definition of Royal College of Pathologists.

* = significant p-value <0.05. Abbreviations: G, grade; IQR, interquartile range; n, number; yp, pathological outcome after neoadjuvant treatment. Missing data: tumor size (n=2), ypT (n=1), ypN (n=1), resection margin (n=16), tumor differentiation (n=19), perineural invasion (n=2), lymphovascular invasion (n=3), pathologic response (n=15)