学位論文

Efficacy and Safety of Neoadjuvant Chemoradiation Therapy Administered for 5 Versus 2 Weeks for Resectable and Borderline Resectable Pancreatic Cancer

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Efficacy and Safety of Neoadjuvant Chemoradiation Therapy Administered for 5 Versus 2 Weeks for Resectable and Borderline Resectable Pancreatic Cancer

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Objectives: Indications of preoperative treatment for resectable (R-) or borderline resectable (BR-) pancreatic ductal adenocarcinoma (PDAC) are unclear, and the protocol remains to be standardized.

Methods: Included 65 patients with R- and BR-PDAC with venous involvement (V-) received neoadjuvant chemoradiotherapy with S-1 and 50 Gy of radiation as the 5-week regimen. The outcomes of this group were compared with those of 52 patients who underwent S-1 and 30 Gy of radiation as the 2-week regimen, previously collected as our prospective phase II study.

Results: Compared with the 2-week regimen, there were no significant differences in the rate of protocol completion, adverse events, mortality and morbidity, or R0 resection in the 5-week regimen. In subgroup analyses of R-PDAC, there were no significant differences in overall survival and recurrence-free survival between the groups. In contrast, the 5-week regimen had significantly better overall survival and recurrence-free survival than the 2-week regimen for BRV-PDAC. Similar results were observed after propensity score matching analysis.

Conclusions: The 5-week regimen of neoadjuvant chemoradiotherapy has good clinical efficacy and safety for R- and BRV-PDAC. The 5-week regimen could achieve better outcomes than the 2-week regimen for BRV-PDAC. In contrast, both regimens achieved similar outcomes for R-PDAC.

Key Words: neoadjuvant therapy, pancreatic cancer, chemotherapy, chemoradiation, pancreatectomy

(*Pancreas* 2022;51: 269–277)

Pancreatic adenocarcinoma (PDAC) is associated with poor prognosis and a low resection rate. Both local and systemic recurrences are common even after curative resection, and long-term survival remains limited. Patients undergoing curative resection alone survive a median of 18 to 20 months, and the 5-year survival rate is 10%.[1,2] This evidence highlights that resection alone is an inadequate therapy for pancreatic cancer, and multimodality treatment is required to improve long-term survival. Although postoperative adjuvant chemotherapy has become the standard treatment for resected PDAC based on findings from the results of the Charité Onkologie-001 and the Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC) 01 studies,[1,3] the optimal neoadjuvant treatment protocol and its impact on patient prognosis remain unclear.[4]

According to the National Comprehensive Cancer Network (NCCN) 2020 guidelines,[5] the value of neoadjuvant treatment for resectable- (R-) PDAC remains unclear. Nevertheless, the guidelines advise to consider neoadjuvant treatment in patients with high-risk characteristics, including imaging consistent with advanced metastatic disease, significantly elevated carbohydrate antigen 19-9 (CA 19-9) levels, large primary tumors or regional lymph nodes, excessive weight loss, and notable pain. Preferably, such patients should be treated in a clinical trial setting. Recent reports have demonstrated that neoadjuvant treatment decreases the rate of recurrence and improves the prognosis of patients with R-PDAC.[6–9] Concurrently, neoadjuvant treatment is recommended for borderline resectable (BR-) PDAC, with therapeutic options including multiagent chemotherapy such as a combination of leucovorin, 5-fluorouracil (FU), oxaliplatin, and irinotecan (FOLFIRINOX) or gemcitabine with nab-paclitaxel, either with or without subsequent chemoradiotherapy. The JASPAC-05 study,[10] which was a multicenter, single-arm, phase II trial of neoadjuvant chemoradiotherapy (NACRT) with S-1 and radiation (50.4 Gy in 28 fractions), reported that the rates of pathological complete resection (R0), 2-year overall survival (OS), and median OS at 63%, 58%, and 30.8 months, respectively, in patients with BR-PDAC.

Most previous studies on neoadjuvant treatment for R- and BR-PDAC have focused on the evaluation of therapeutic effects of each regimen. However, few studies have focused on regimen-dependent differences in the efficacy and safety of neoadjuvant treatment. We have previously completed a phase II clinical trial of NACRT with 30 Gy of radiation therapy administered as a 2-week regimen in patients with R- and BR-PDAC, and reported the efficacy, safety, and tolerability of this regimen.[6] Subsequently, we extended the duration of NACRT to 5 weeks with 50 Gy of radiation therapy (5-week regimen) and conducted a new clinical trial for R and BR with venous involvement (BRV-) PDAC. The present study aimed to compare the outcomes of 5- and 2-week regimens to examine the efficacy and safety of NACRT for R- and BRV-PDAC patients.

MATERIALS AND METHODS

Study Design and Subject

This was a single-center, prospective, phase II trial of patients diagnosed with R- or BRV-PDAC (University Hospital Medical Information Network Clinical Trials Registry number 000035232).

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Received for publication July 2, 2021; accepted March 24, 2022.
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The authors declare no conflict of interest.
Supplemental digital contents are available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pancreasjournal.com).

DOI: 10.1097/MPA.0000000000002011

The study was approved by the institutional review board of Kagawa University (H26-16). Informed consent was obtained from all patients according to the institutional protocol of our hospital before study initiation. A total of 65 consecutive patients with histologically confirmed PDAC, classified as R- or BRV-PDAC according to the NCCN guidelines,[5] who met the eligibility criteria underwent a 5-week regimen of NACRT. The eligibility criteria included patients with R- and BRV-PDAC (based on the NCCN guidelines),[5] performance status 0 to 1, age 20 to 85 years, adequate bone marrow reserve, and organ function (defined by hemoglobin levels ≥9 g/dL, absolute neutrophil count of ≥2 × 10^3/L, platelet count ≥100 × 10^9/L, total bilirubin levels of ≥6 mg/dL, serum transaminase ≥3 times the upper normal limit, and creatinine clearance rate of ≥60 mL/min). The exclusion criteria were a history of chemotherapy within 6 months; prior radiation in the abdominal field; myocardial infarction within the last 3 months; a history of unstable angina pectoris, interstitial pneumonia, fibroid lung, or severe emphysema; concurrent active malignancy; uncontrolled infection; and pregnancy or lactation.

The regimen consisted of 50 Gy of radiation therapy plus S-1 for a period of 5 weeks between June 2016 and December 2019 in our hospital, with intention to curative resection. The primary end point was the R0 rate. The secondary end points included the safety of NACRT, pathological response to NACRT, and OS and recurrence-free survival (RFS) estimates.

Treatment Protocol

The chemoradiation schedule consisted of external-beam radiotherapy (50 Gy in 25 fractions) with concurrent S-1 given 5 d/wk for 5 weeks and subsequent 4 weeks rest before pancreatectomy. S-1 is an oral fluoropyrimidine consisting of tegafur, a prodrug of fluorouracil, and 2 biochemical modulators. It is characterized by the inhibition of dihydropyrimidine dehydrogenase activity by gimeracil, the maintenance of a high concentration of fluorouracil, and the suppression of fluorouracil's phosphorylation in the gastrointestinal tract by oteracil potassium, which reduces gastrointestinal toxicity. S-1 has reportedly shown a higher response rate and noninferiority in terms of OS than gemcitabine for patients with advanced pancreatic cancer.[11] Radiotherapy consisted of 50 Gy, with a daily dose of 2 Gy delivered with ≥6-MV x-rays.

Responses to NACRT

All adverse events experienced during the study were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Physical examination, toxicity assessment, and blood examination with respect to complete blood cell count and serum chemistry profile were performed at least once weekly during the treatment period. Radiological responses in patients who underwent neoadjuvant chemoradiation were evaluated via computed tomography (CT) scanning according to the Response Evaluation Criteria in Solid Tumors (RECIST). The RECIST evaluation was performed by at least 2 experienced radiologists. The pathological response to NACRT was evaluated considering the residual tumor load according to the classification reported by Evans et al.[12–14] This grading scheme consists of a 4-tiered system for assessing the percentage of viable cells remaining in the lesion, with the lowest grade (grade I) representing little or no response (<10%) and the highest grade (grade IV) representing the greatest response (no viable tumor cells or acellular pools of mucin); grades II and III represent a spectrum of tumor cell destruction from 10% to 90% (10 < IIA ≤ 50%, 50 < IIB ≤ 90%) and ≥90% of tumor cells destroyed, respectively. The findings were histologically examined by at least 2 experienced pathologists.

Surgery

All surgeries in this study (pancreaticoduodenectomy [PD], distal pancreatectomy [DP], and total pancreatectomy [TP]) were performed via an open approach. Pancreaticoduodenectomy or TP was performed according to the Whipple procedure, and the reconstruction after PD was performed with pancreaticojejunostomy. The pancreatic remnant after DP was managed with a stapler. The surgical margin was defined as either the stump of the pancreas or the bile duct, or the dissected plane around the pancreas.[15] If viable cancer cells were detected microscopically at the tip of any of these sites, the surgical margin was determined as positive.

Postoperative Adjuvant Chemotherapy and Follow-Up

Adjuvant chemotherapy was initiated within 2 months postoperatively in all patients eligible for this treatment. Patients received S-1, as recommended.[3] S-1 was administered every 6 weeks for up to 4 cycles (6 months). Follow-up examinations were performed every 3 months for 2 to 3 years and every 6 months thereafter until the disease progression. Enhanced CT scanning was performed every 6 months. The examination date moved forward and added magnetic resonance imaging or fluorodeoxyglucose positron emission tomography (FDG-PET) scanning was added, as required.

Comparative Study

To examine the differences in the efficacy and safety profiles of the NACRT regimens, patients with R- and BRV-PDAC who underwent the 2-week regimen of NACRT in our previous prospective phase II study (September 2009 and May 2016; University Hospital Medical Information Network Clinical Trials Registry number 000026438)[6] were included as a comparison group in the present study. The chemoradiation schedule consisted of hypofractionated external-beam radiotherapy (30 Gy in 10 fractions) with concurrent S-1 given 5 d/wk for 2 weeks and a subsequent 2-week rest before pancreatectomy.

Except for the duration and total dose of each NACRT, the comparison groups were similar with respect to the eligibility criteria that applied, relevant adverse events observed during the treatment period, surgical procedure, attending surgical team, and postoperative follow-up protocol. Although gemcitabine was administered to 2 of 38 (5%) patients who received postoperative adjuvant chemotherapy in the 2-week regimen group, the remaining 36 (95%) patients received S-1, as also given in the 5-week regimen group. Gemcitabine was administered every 4 weeks for up to 6 cycles (6 months), as recommended.[1]

Statistical Analysis

Survival was estimated by generating Kaplan-Meier survival curves and was compared between the groups using the log-rank test. Safety and efficacy analyses were conducted using the intention-to-treat (ITT) population, defined as all study patients who received either the 5-week regimen or the 2-week regimen. Categorical data were presented as frequencies with percentages. To evaluate baseline differences between the 2 different regimen groups, the Mann-Whitney U test was used for continuous variables, and the Fisher exact test or χ^2 test was used for categorical variables. Overall survival was defined as the interval from initial treatment to death from any cause or to the last follow-up. For patients who underwent resection, RFS was defined as the time from the initial treatment to the time of first recurrence (local, distant, or both) or death, whichever occurred first. "Recurrence" was defined by definitive evidence of recurrence, that is, a mass and/or

biopsy-based confirmation. P values <0.05 were considered significant. We also performed 1:1 case matching using a propensity score incorporating 6 factors: age, sex, body mass index, primary tumor location, resectability, completion of NACRT, and resection rate. Nearest-neighbor matching without replacement, with a caliper set at 0.02 of a standard deviation of the logit of the propensity score. All statistical analyses were performed using SPSS Statistics 25.0 for Windows software program (SPSS, Inc, Armonk, NY).

RESULTS

The 5-week regimen group included 51 (78%) patients with R-PDAC and 14 (22%) with BRV-PDAC. The patient characteristics are shown in Table 1. The total treatment completion rate for protocol treatment was 89% (58 of 65). Seven patients failed to complete the 5-week regimen of NACRT protocol because of cholangitis (n = 4), neutropenia (n = 2), and multiple liver metastases found on CT (n = 1). There were no significant differences with respect to age, sex, body mass index, primary tumor location, resectability, or NACRT completion between the 5-week regimen and 2-week regimen groups. However, the resection rate in the 5-week regimen group was significantly lower than that in the 2-week regimen group (85% vs 96%, $P = 0.041$) because of a high rate (15%) of liver metastases in the 5-week regimen group. To correct selection biases and confounding factors, propensity score matching was performed at a 1:1 ratio. After matching, 46 patients were included in each group. Table 1 summarizes the baseline characteristics before and after propensity score matching.

The treatment responses to NACRT are shown in Table 2. The median complete blood cell counts, including white blood cells, neutrophils, lymphocytes, and serum albumin levels, in the 5-week regimen group were similar to those in the 2-week regimen group. Meanwhile, the CA 19-9 levels and the median maximum standardized uptake values (SUVmax) in FDG-PET scan after the 5-week regimen of NACRT were significantly lower than those after the 2-week regimen ($P = 0.002$ and $P < 0.001$, respectively). In addition, both RECIST parameters and pathological response (resected cases) measured according to the Evans classification were significantly different between the 2 groups ($P = 0.003$ and $P = 0.025$, respectively). Adverse events (grade 3 or 4) during the 5-week regimen occurred in 13 (20%) patients, at a rate similar to that observed in the 2-week regimen. In the analysis after propensity score matching, the results about treatment responses to NACRT were almost the same as before the matching (Supplemental Table 1, http://links.lww.com/MPA/A932).

The perioperative variables and pathological outcomes of the 55 resected cases in the 5-week regimen group and of the 50 resected cases in the 2-week regimen group are shown in Table 3. There were no significant differences in perioperative variables with respect to surgical procedure, operation time, intraoperative blood loss volume and transfusion rate, frequency of portal vein resection, mortality (within 90 days) and morbidity rates (≥grade 3b), clinically relevant pancreatic fistula rate, or TNM stages. Meanwhile, R0 resection was achieved in 53 of 55 (96%) in the 5-week regimen group, which was a rate similar to that observed in the 2-week regimen group. The induction and completion rates of postoperative adjuvant chemotherapy were also similar for both groups. In the analysis after propensity score matching, the results of perioperative variables and pathological outcomes were almost the same as before the analysis (Supplemental Table 2, http://links.lww.com/MPA/A932).

In the overall analysis of patients in the 5-week regimen group, the median OS was 43.0 months and the 3-year survival rate was 59.2%. There was no significant difference in OS compared with the 2-week regimen group ($P = 0.795$; Fig. 1A). In resected cases (after excluding 2 mortality cases), there were no

TABLE 1. Comparison of Baseline Characteristics Between the 5-Week Regimen and 2-Week Regimen of NACRT Groups Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
Parameter	**5-wk Regimen (n = 65)**	**2-wk Regimen (n = 52)**	***P***	**5-wk Regimen (n = 46)**	**2-wk Regimen (n = 46)**	***P***
Age, median (IQR, range), y	73 (70–77, 58–84)	71 (67–77, 44–83)	0.327	73 (66–74, 58–84)	73 (67–79, 54–83)	0.293
Sex, n (%)			0.528			1.000
Male	40 (62)	29 (56)		24 (52)	24 (52)	
Female	25 (38)	23 (44)		22 (48)	22 (48)	
BMI, median (IQR, range), kg/m^2	22.4 (19.8–24.0, 15.2–28.6)	22.4 (21.0–23.7, 14.0–27.7)	0.963	22.7 (19.5–24.3, 15.2–28.6)	22.4 (21.2–23.8, 14.0–27.7)	0.907
Primary tumor location, n (%)			0.092			0.482
Head or neck	42 (65)	41 (79)		32 (70)	35 (76)	
Body or tail	23 (35)	11 (21)		14 (30)	11 (24)	
Resectability*, n (%)			0.073			0.643
R	51 (78)	33 (63)		34 (74)	32 (70)	
BRV	14 (22)	19 (37)		12 (26)	14 (30)	
Completion of NACRT protocol, n (%)	58 (89)	45 (87)	0.656	41 (89)	40 (87)	0.748
Resection rate, n (%)	55 (85)	50 (96)	0.041	42 (91)	44 (96)	0.398

*According to the NCCN guideline 2021.[5]
BMI indicates body mass index; IQR, interquartile range.

TABLE 2. Comparison of Response to NACRT Between the 5- and 2-Week Regimen

Parameter	5-wk Regimen (n = 65)	2-wk Regimen (n = 52)	P
White blood cell count, median (IQR, range), /μL			
Pre-NACRT	5290 (4330–6190, 2680–11,560)	4980 (4575–5650, 3370–12,900)	0.510
Post-NACRT	3810 (3080–4870, 1690–8650)	3940 (3285–4835, 1920–6910)	0.651
Neutrophil count, median (IQR, range), /μL			
Pre-NACRT	3076 (2635–4134, 1528–7768)	2877 (2576–3638, 1614–10,578)	0.698
Post-NACRT	2627 (1856–3439, 1029–5625)	2649 (2053–3390, 989–6046)	0.318
Lymphocyte count, median (IQR, range), /μL			
Pre-NACRT	1399 (1112–1628, 398–3167)	1466 (1110–1736, 668–2750)	0.720
Post-NACRT	770 (480–908, 266–2370)	745 (556–955, 275–2510)	0.677
Albumin, median (IQR, range), g/dL			
Pre-NACRT	3.7 (3.5–4.1, 2.2–4.7)	3.7 (3.3–4.1, 2.4–4.6)	0.623
Post-NACRT	3.9 (3.5–4.3, 1.8–4.9)	3.8 (3.3–4.0, 2.6–4.7)	0.106
CA 19-9 level, median (IQR, range), U/mL			
<37 at diagnosis, n (%)	11 (17)	17 (33)	0.047
Pre-NACRT*	340 (141–813, 42–70,555)	116 (154–1257, 56–18,159)	0.367
Post-NACRT*	76 (37–243, 4–52,480)	213 (80–728, 10–8100)	0.002
SUVmax level in FDG-PET, median (IQR, range)			
<3 at diagnosis, n (%)	9 (14)	5 (10)	0.484
Pre-NACRT†	7.90 (4.69–10.32, 3.07–30.49)	7.36 (5.69–10.66, 3.29–45.71)	0.617
Post-NACRT†	3.10 (2.27–5.01, 0–9.44)	5.86 (3.96–8.34, 0–47.57)	<0.001
RECIST‡, n (%)			0.003
Partial response	13 (20)	3 (6)	
Stable disease	43 (66)	48 (92)	
Progressive disease	9 (14)	1 (2)	
Evans classification (105 resected cases), n (%)			0.025
I	1 (2)	8 (16)	
IIa	29 (53)	27 (54)	
IIb	18 (33)	14 (28)	
III	5 (9)	0 (0)	
IV	2 (4)	1 (2)	
Adverse events§ during NACRT, ≥grade 3, n (%)	13 (20)	7 (13)	0.351
Anorexia	5 (8)	3 (6)	0.682
Neutropenia	3 (5)	1 (2)	0.426
Leukopenia	2 (5)	1 (2)	0.695
Hyponatremia	2 (3)	2 (4)	0.820
Nausea	1 (2)	2 (4)	0.433
Anemia	1 (2)	0 (0)	0.369
Thrombopenia	1 (2)	0 (0)	0.369
Diarrhea	1 (2)	0 (0)	0.369

*Excluding 14 patients with no accumulation of SUVmax level (<3) in FDG-PET at diagnosis.
†Excluding 28 patients with normal CA 19-9 level (<37 U/mL) at diagnosis.
‡According to RECIST.
§According to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0).
IQR indicates interquartile range.

significant differences in either OS or RFS estimates between the groups ($P = 0.297$ and $P = 0.059$, respectively; Figs. 1B, C). Likewise, no significant differences were found in OS of ITT, OS of resected cases, or RFS between the 2 groups in the analysis after propensity score matching ($P = 0.925$, $P = 0.586$, and $P = 0.400$, respectively; Figs. 1D–F).

In a subgroup analysis of R-PDAC patients, there was no significant difference in OS between the 5-week regimen (n = 51) and the 2-week regimen (n = 33) groups ($P = 0.148$; Fig. 2A). Similarly, there were no significant differences in either OS or RFS estimates among resected cases with R-PDAC between the groups ($P = 0.400$ and $P = 0.609$, respectively; Figs. 2B, C). In contrast, in a subgroup of patients with BRV-PDAC, patients in the 5-week regimen group (n = 14) had significantly better OS than did those in the 2-week regimen group (n = 19; $P = 0.030$; Fig. 3A). Moreover, patients who underwent resection in the 5-week regimen group had significantly better OS and RFS estimates than did those in the 2-week regimen group also in resected cases ($P = 0.005$ and $P = 0.011$, respectively; Figs. 3B, C). Similar results were observed after propensity score matching. In a

TABLE 3. Comparison of Perioperative and Pathological Outcomes Between the 5- and 2-Week Regimen of NACRT Groups (Resected Cases)

Parameter	5-wk Regimen (n = 55)	2-wk Regimen (n = 50)	P
Surgical procedure, n (%)			0.332
PD	32 (58)	36 (72)	
DP	16 (29)	10 (20)	
Total pancreatectomy	7 (13)	4 (8)	
Operation time, median (IQR, range), min	484 (359–525, 225–733)	484 (416–569, 231–816)	0.142
Blood loss, median (IQR, range), mL	958 (626–1744, 53–5060)	1444 (759–2171, 118–9268)	0.080
Transfusion, n (%)	20 (36)	16 (32)	0.638
Portal vein resection, n (%)	19 (35)	26 (52)	0.071
Mortality, within 90 d, n (%)	1 (2)	1 (2)	0.946
Morbidity*, ≥grade 3b, n (%)	6 (11)	4 (8)	0.612
Pancreatic fistula†, grade B or C, n (%)	9 (19)	6 (13)	0.450
TNM stage‡			0.380
0	2 (4)	1 (2)	
IA	19 (35)	10 (20)	
IB	10 (18)	13 (26)	
IIA	3 (5)	3 (6)	
IIB	20 (36)	18 (36)	
III	1 (2)	3 (6)	
IV	0 (0)	2 (4)	
Resection status, n (%)			0.615
R0	53 (96)	49 (98)	
R1	2 (4)	1 (2)	
Induction rate of adjuvant chemotherapy, n (%)	46 (84)	38 (76)	0.329
Completion of adjuvant chemotherapy, ≥6 mo, n (%)	30 (55)	26 (52)	0.794

*Clavien-Dindo classification[16] ≥grade IIIb.

†According to the International Study Group of Pancreatic Surgery classification[17] and excluding to 11 patients who received TP.

‡According to the Union for International Cancer Control TNM classification, eighth edition.[18]

IQR indicates interquartile range.

subgroup analysis of R-PDAC, no significant differences were found in OS of ITT, OS of resected cases, or RFS between the 2 groups ($P = 0.092$, $P = 0.228$, and $P = 0.525$, respectively; Figs. 2D–F). Meanwhile, in a subgroup of patients with BRV-PDAC, patients in the 5-week regimen group had significantly better OS of ITT, OS of resected cases, and RFS than did those in the 2-week regimen group ($P = 0.014$, $P = 0.007$, and $P = 0.005$, respectively; Figs. 3D–F).

DISCUSSION

In this single-arm, prospective, phase II trial of neoadjuvant S-1 with concurrent 50-Gy radiotherapy in patients with R- and BRV-PDAC, the R0 rate, which was the primary end point of this study, was 96%. The median OS was 43.0 months. The present study protocol was well tolerated, with a completion rate of 89% and an adverse event rate of 20%. In addition, the subsequent pancreatic resection rate of 85% was satisfactory. Collectively, these results demonstrate the considerable efficacy and feasibility of this multimodality treatment that incorporates neoadjuvant S-1 with radiation for a period of 5 weeks and radical resection for R- and BRV-PDAC.

No difference in morbidity or mortality rates has been previously reported in studies comparing between neoadjuvant treatment and upfront surgery.[19–21] In addition, some reports also revealed[19,20,22] that NACRT was associated with a lower risk of pancreatic fistula, which might be related to the development of pancreatic fibrosis. In the present study, there was no significant difference in operation time, blood loss volume, transfusion rate, or morbidity and mortality rates between 2 NACRT regimens. The clinically relevant pancreatic fistula rate was also comparable between the groups and was <20% (19% and 13%) in both groups.

Whether neoadjuvant treatment may impair the induction rate of postoperative adjuvant chemotherapy remains an important question. Data from the Netherlands Cancer Registry[23] have demonstrated that the induction rate of postoperative adjuvant chemotherapy after pancreatoduodenectomy was only 54% because of toxicity and patient age, among others. Furthermore, according to the results from the American College of Surgeons National Surgical Quality Improvement Program and the National Cancer Database, 2047 patients from 149 hospitals underwent pancreatic resection for PDAC, of which 23.2% had at least 1 serious complication, with the overall postoperative adjuvant chemotherapy receipt being 57.7%. This study concluded that postoperative complications were associated with the induction of adjuvant chemotherapy.[24] In Japanese populations, postoperative adjuvant chemotherapy with S-1 significantly extended OS of patients with resected PDAC compared with gemcitabine, as reported in the JASPAC01 study.[3] Based on this evidence, adjuvant chemotherapy with S-1 has become the standard of care for curatively resected PDAC in Japan. In this study, presumably because of relatively lower toxicity risk associated with S-1, the induction rate of postoperative adjuvant chemotherapy in the 5-week regimen group was 84%, similar to that

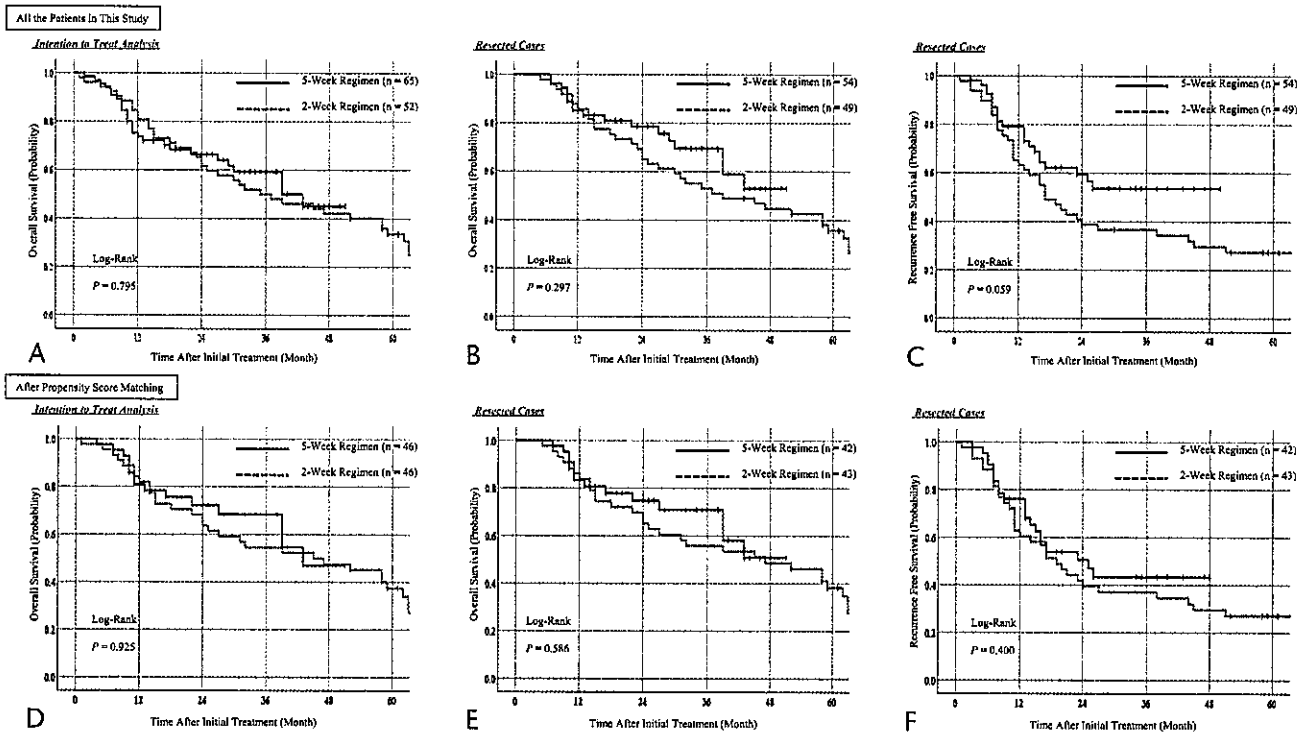

FIGURE 1. A, Intention-to-treat analyses of OS. B, Overall survival estimates for patients who underwent resection, excluding 2 mortality cases. C, Recurrence-free survival estimates for patients who underwent resection, excluding mortality cases. D, Intention-to-treat analyses of OS after propensity score matching. E, Overall survival estimates for patients who underwent resection after propensity score matching, excluding 2 mortality cases. F, Recurrence-free survival estimates for patients who underwent resection after propensity score matching, excluding 2 mortality cases. Comparisons between NACRT regimens administered for 5 weeks versus 2 weeks.

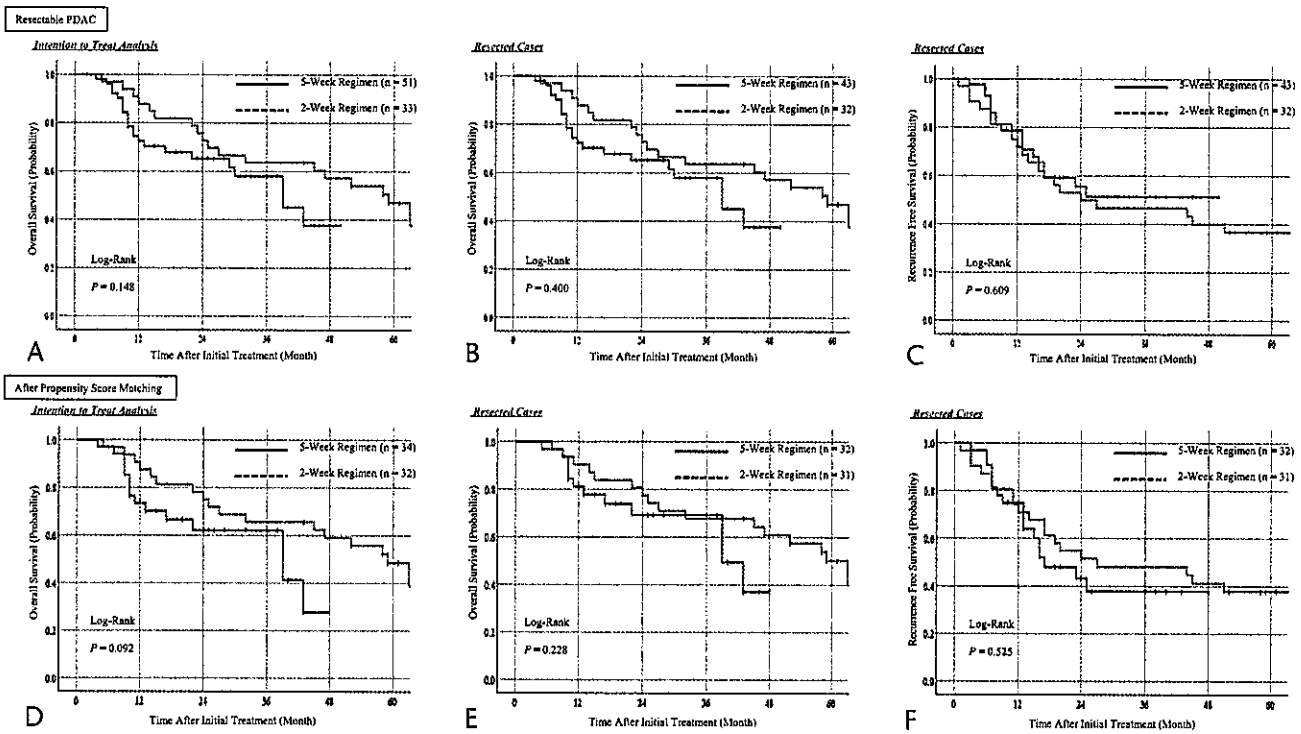

FIGURE 2. Subgroup analysis of patients diagnosed with resectable pancreatic ductal adenocarcinoma. A, Intention-to-treat analyses of OS. B, Overall survival estimates for patients who underwent resection, excluding 2 mortality cases. C, Recurrence-free survival estimates for patients who underwent resection, excluding 2 mortality cases. D, Intention-to-treat analyses of OS after propensity score matching. E, Overall survival estimates for patients who underwent resection after propensity score matching, excluding 2 mortality cases. F, Recurrence-free survival estimates for patients who underwent resection after propensity score matching, excluding 2 mortality cases. Comparisons between NACRT regimens administered for 5 weeks vs 2 weeks.

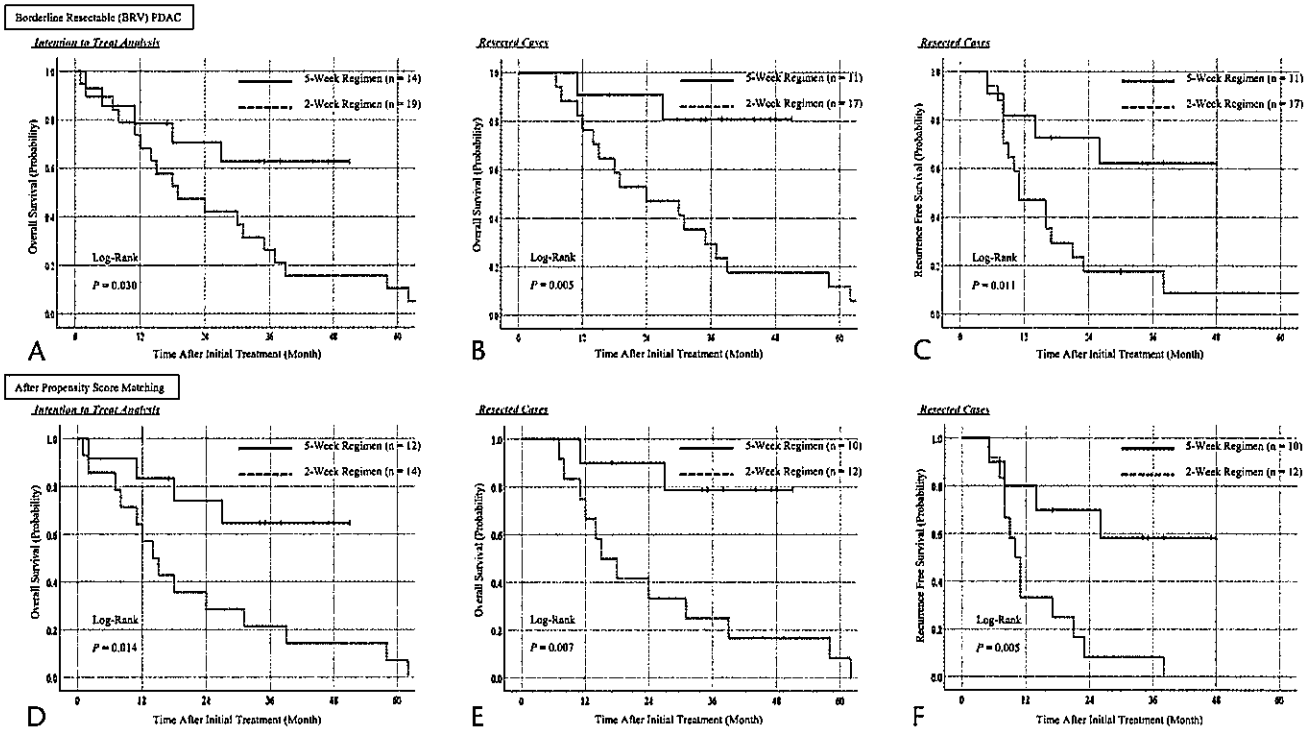

FIGURE 3. Subgroup analysis of patients diagnosed with borderline resectable pancreatic ductal adenocarcinoma. A, Intention-to-treat analyses of OS. B, Overall survival estimates for patients who underwent resection. C, Recurrence-free survival estimates for patients who underwent resection. D, Intention-to-treat analyses of OS after propensity score matching. E, Overall survival estimates for patients who underwent resection after propensity score matching. F, Recurrence-free survival estimates for patients who underwent resection after propensity score matching. Comparisons between NACRT regimens administered for 5 weeks versus 2 weeks.

observed in the 2-week regimen group (76%). These rates were higher than those reported previously. Neither of these treatment regimens affected patient safety, including the induction and completion rates of postoperative adjuvant chemotherapy.

Several studies have demonstrated the feasibility and safety of neoadjuvant treatment for patients with R-PDAC.[6–9,13,25–38] Systematic reviews and meta-analyses of patients with localized PDAC have also suggested the survival benefit of neoadjuvant treatment in patients with R-PDAC.[39–41] The result of phase II-III Preop-02/JSAP-05 trial was a large collaboration study of 57 centers in which 364 patients with R-PDAC were randomly allocated to either neoadjuvant chemotherapy or upfront surgery. The results, presented at the 2019 American Society of Clinical Oncology congress, showed superior survival after neoadjuvant treatment, with a median OS of 37 versus 27 months (hazard ratio, 0.72; 95% confidence interval, 0.55–0.94; $P = 0.015$).[42] Thus, we considered the enrollment of R-PDAC patients in our trials to be well justified.

In 2016, the MD Anderson Cancer Center reported[43] that hypofractionated chemoradiotherapy (30 Gy in 10 fractions) was associated with margin-negative resection rates, treatment effects, and OS rates similar to those associated with standard fractionated chemoradiotherapy (50.4 Gy in 28 fractions) in patients with R- and BR-PDAC patients. However, in the Center's retrospective study, patient baseline characteristics differed between the groups. The present single-center study compared the results from 2 prospective phase II trials with different NACRT regimens (30 Gy in 10 fractions vs 50 Gy in 25 fractions, both with concurrent S-1) for R- and BRV-PDAC patients. Despite similar patient characteristics in both study groups, there were no significant differences in margin-negative resection rates, OS estimates in ITT analysis, or OS or RFS estimates of resected cases in the whole sample or R-PDAC subgroup analysis. These findings are consistent with those of the MD Anderson Cancer Center group. Overall, these findings suggest that the 2-week regimen of hypofractionated chemoradiotherapy with S-1 might be sufficient as an NACRT for R-PDAC.

In sharp contrast, the patients with BRV-PDAC who received the 5-week regimen of NACRT had significantly better OS in ITT analysis, and OS and RFS estimates among resected cases than did those who received the 2-week regimen in the present study. Several multicenter studies[10,44,45] have previously revealed the efficacy of neoadjuvant treatment for BR-PDAC. Neoadjuvant treatment is recommended for BR-PDAC by the NCCN 2020 guidelines,[5] although a standard treatment regimen for BR-PDAC remains to be established. In the JASPAC-05 study,[10] patients received S-1 orally at 40 mg/m^2 twice daily on the day of irradiation, and 50.4 Gy was delivered in 28 fractions over a 5.5-week period. In the present study, the SUVmax in FDG-PET scan and CA 19-9 levels after the 5-week regimen were significantly lower than those after the 2-week regimen. In addition, RECIST parameters and pathological response in the 5-week regimen group were better than those observed in the 2-week regimen group. A few previous studies demonstrated[46,47] that outstanding local response to neoadjuvant therapy resulted in prolonged survival in PDAC. Moreover, Yamamoto et al[48] concluded that preoperative SUVmax of FDG-PET scans of >6 was a significant predictor of early recurrence and poor survival after surgery. These results suggest that the 2-week regimen of NACRT might be insufficient for BRV-PDAC.

In the present study, the resection rate of the 5-week regimen group was 85%, which was comparable to that of some previous reports. However, it was significantly lower than that of the 2-week regimen group (85% vs 96%, $P = 0.041$). Although the shorter protocol involved in the 2-week regimen might have contributed to a higher resection rate, a notable point was that 10 patients in the

5-week regimen group were excluded from the indication for surgery because of liver metastases. It is likely that this negatively influenced OS estimates in the 5-week regimen group and countervailed the stronger antitumor effect of this regimen in analyses of the entire sample and R-PDAC subgroup. Some previous reports revealed[49,50] that radiotherapy promoted distant metastasis by inducing cancer cell migration. Although there have been no reports showing any association between NACRT for PDAC and distant metastases, there might be effects from the 2-week regimen of 30 Gy to the 5-week regimen of 50 Gy.

The present study has some limitations. This study was not a randomized controlled trial, but a prospective phase II study and a comparative study with another phase II study, both of which were conducted at a single institution. The sample size was small, and a historical backdrop existed. Because the present study was small, it may preclude definitive conclusions about the examined protocols. However, this is the first study to examine the differences in efficacy, safety, and feasibility of different NACRT regimens of different duration in analysis stratified by PDAC resectability. Studies with larger sample sizes are required to validate the present findings.

In conclusion, this prospective analysis demonstrated that the 5-week regimen of NACRT with S-1 showed outstanding clinical efficacy and safety for patients diagnosed with R- and BRV-PDAC. The 5-week regimen of NACRT could be more effective than the 2-week regimen against BRV-PDAC. In contrast, these 2 regimens had similar effects on R-PDAC.

ACKNOWLEDGMENTS

The authors are grateful to all the patients who contributed data to this study. The authors would like to thank Editage (https://www.editage.jp) for the English language review.

REFERENCES

1. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA*. 2013;310:1473–1481.
2. Ueno H, Kosuge T, Matsuyama Y, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. *Br J Cancer*. 2009;101:908–915.
3. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet*. 2016;388:248–257.
4. Verma V, Li J, Lin C. Neoadjuvant therapy for pancreatic cancer: systematic review of postoperative morbidity, mortality, and complications. *Am J Clin Oncol*. 2016;39:302–313.
5. NCCN Guidelines®. Pancreatic adenocarcinoma (Version 2.2021, February 25, 2021). Available at: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 26, 2022.
6. Okano K, Suto H, Oshima M, et al. A prospective phase II trial of neoadjuvant S-1 with concurrent hypofractionated radiotherapy in patients with resectable and borderline resectable pancreatic ductal adenocarcinoma. *Ann Surg Oncol*. 2017;24:2777–2784.
7. Endo Y, Kitago M, Aiura K, et al. Efficacy and safety of preoperative 5-fluorouracil, cisplatin, and mitomycin C in combination with radiotherapy in patients with resectable and borderline resectable pancreatic cancer: a long-term follow-up study. *World J Surg Oncol*. 2019;17:145.
8. Nakano Y, Kitago M, Shinoda M, et al. Clinical predictive factors of long-term survival after curative resection of pancreatic cancer: a retrospective study. *Cancer Med*. 2017;6:2278–2286.
9. Eguchi H, Takeda Y, Takahashi H, et al. A prospective, open-label, multicenter phase 2 trial of neoadjuvant therapy using full-dose gemcitabine and S-1 concurrent with radiation for resectable pancreatic ductal adenocarcinoma. *Ann Surg Oncol*. 2019;26:4498–4505.
10. Takahashi S, Ohno I, Ikeda M, et al. Neoadjuvant S-1 with concurrent radiotherapy followed by surgery for borderline resectable pancreatic cancer: a phase II open-label multicenter prospective trial (JASPAC05). *Ann Surg*. 2020 Oct 15. [Online ahead of print].
11. Ueno H, Ioka T, Ikeda M, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol*. 2013;31:1640–1648.
12. Evans DB, Pisters PW, Lee JE, et al. Preoperative chemoradiation strategies for localized adenocarcinoma of the pancreas. *J Hepatobiliary Pancreat Surg*. 1998;5:242–250.
13. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol*. 2008;26:3496–3502.
14. Evans DB, Rich TA, Byrd DR, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg*. 1992;127:1335–1339.
15. Staley CA, Cleary KR, Abbruzzese JL, et al. The need for standardized pathologic staging of pancreaticoduodenectomy specimens. *Pancreas*. 1996;12:373–380.
16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
17. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. *Surgery*. 2017;161:584–591.
18. Brierley JD, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours*. 8th ed. Oxford, United Kingdom/Hoboken, NJ: John Wiley and Sons; 2017.
19. Cooper AB, Parmar AD, Riall TS, et al. Does the use of neoadjuvant therapy for pancreatic adenocarcinoma increase postoperative morbidity and mortality rates? *J Gastrointest Surg*. 2015;19:80–86; discussion 86–87.
20. Denbo JW, Bruno ML, Cloyd JM, et al. Preoperative chemoradiation for pancreatic adenocarcinoma does not increase 90-day postoperative morbidity or mortality. *J Gastrointest Surg*. 2016;20:1975–1985.
21. Araujo RL, Gaujoux S, Huguet F, et al. Does pre-operative chemoradiation for initially unresectable or borderline resectable pancreatic adenocarcinoma increase post-operative morbidity? A case-matched analysis. *HPB (Oxford)*. 2013;15:574–580.
22. Ishikawa O, Ohigashi H, Imaoka S, et al. Concomitant benefit of preoperative irradiation in preventing pancreas fistula formation after pancreatoduodenectomy. *Arch Surg*. 1991;126:885–889.
23. Bakens MJ, van der Geest LG, van Putten M, et al. The use of adjuvant chemotherapy for pancreatic cancer varies widely between hospitals: a nationwide population-based analysis. *Cancer Med*. 2016;5:2825–2831.
24. Merkow RP, Bilimoria KY, Tomlinson JS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. *Ann Surg*. 2014;260:372–377.
25. Sho M, Akahori T, Tanaka T, et al. Importance of resectability status in neoadjuvant treatment for pancreatic cancer. *J Hepatobiliary Pancreat Sci*. 2015;22:563–570.
26. Boone BA, Steve J, Zenati MS, et al. Serum CA 19-9 response to neoadjuvant therapy is associated with outcome in pancreatic adenocarcinoma. *Ann Surg Oncol*. 2014;21:4351–4358.
27. Papalezova KT, Tyler DS, Blazer DG 3rd, et al. Does preoperative therapy optimize outcomes in patients with resectable pancreatic cancer? *J Surg Oncol*. 2012;106:111–118.

28. Barbier L, Turrini O, Grégoire E, et al. Pancreatic head resectable adenocarcinoma: preoperative chemoradiation improves local control but does not affect survival. *HPB (Oxford)*. 2011;13:64–69.
29. Takai S, Satoi S, Yanagimoto H, et al. Neoadjuvant chemoradiation in patients with potentially resectable pancreatic cancer. *Pancreas*. 2008;36: e26–e32.
30. Fujii T, Satoi S, Yamada S, et al. Clinical benefits of neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreatic head: an observational study using inverse probability of treatment weighting. *J Gastroenterol*. 2017;52:81–93.
31. Tzeng CW, Balachandran A, Ahmad M, et al. Serum carbohydrate antigen 19-9 represents a marker of response to neoadjuvant therapy in patients with borderline resectable pancreatic cancer. *HPB (Oxford)*. 2014;16: 430–438.
32. Calvo FA, Matute R, García-Sabrido JL, et al. Neoadjuvant chemoradiation with tegafur in cancer of the pancreas: initial analysis of clinical tolerance and outcome. *Am J Clin Oncol*. 2004;27:343–349.
33. O'Reilly EM, Perelshteyn A, Jarnagin WR, et al. A single-arm, nonrandomized phase II trial of neoadjuvant gemcitabine and oxaliplatin in patients with resectable pancreas adenocarcinoma. *Ann Surg*. 2014;260: 142–148.
34. Kim EJ, Ben-Josef E, Herman JM, et al. A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. *Cancer*. 2013;119: 2692–2700.
35. Small W Jr, Mulcahy MF, Rademaker A, et al. Phase II trial of full-dose gemcitabine and bevacizumab in combination with attenuated three-dimensional conformal radiotherapy in patients with localized pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2011;80:476–482.
36. Turrini O, Ychou M, Moureau-Zabotto L, et al. Neoadjuvant docetaxel-based chemoradiation for resectable adenocarcinoma of the pancreas: new neoadjuvant regimen was safe and provided an interesting pathologic response. *Eur J Surg Oncol*. 2010;36:987–992.
37. Le Scodan R, Mornex F, Girard N, et al. Preoperative chemoradiation in potentially resectable pancreatic adenocarcinoma: feasibility, treatment effect evaluation and prognostic factors, analysis of the SFRO-FFCD 9704 trial and literature review. *Ann Oncol*. 2009;20:1387–1396.
38. Casadei R, Di Marco M, Ricci C, et al. Neoadjuvant chemoradiotherapy and surgery versus surgery alone in resectable pancreatic cancer: a single-center prospective, randomized, controlled trial which failed to achieve accrual targets. *J Gastrointest Surg*. 2015;19:1802–1812.
39. Andriulli A, Festa V, Botteri E, et al. Neoadjuvant/preoperative gemcitabine for patients with localized pancreatic cancer: a meta-analysis of prospective studies. *Ann Surg Oncol*. 2012;19:1644–1662.
40. D'Angelo F, Antolino L, Farcomeni A, et al. Neoadjuvant treatment in pancreatic cancer: evidence-based medicine? A systematic review and meta-analysis. *Med Oncol*. 2017;34:85.
41. Versteijne E, Vogel JA, Besselink MG, et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. *Br J Surg*. 2018;105:946–958.
42. Motoi F, Kosuge T, Ueno H, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). *Jpn J Clin Oncol*. 2019;49:190–194.
43. Cloyd JM, Crane CH, Koay EJ, et al. Impact of hypofractionated and standard fractionated chemoradiation before pancreatoduodenectomy for pancreatic ductal adenocarcinoma. *Cancer*. 2016;122:2671–2679.
44. Katz MH, Shi Q, Ahmad SA, et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: Alliance for Clinical Trials in Oncology Trial A021101. *JAMA Surg*. 2016;151:e161137.
45. Murphy JE, Wo JY, Ryan DP, et al. Total neoadjuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for borderline resectable pancreatic adenocarcinoma: a phase 2 clinical trial. *JAMA Oncol*. 2018;4:963–969.
46. Lee SM, Katz MH, Liu L, et al. Validation of a proposed tumor regression grading scheme for pancreatic ductal adenocarcinoma after neoadjuvant therapy as a prognostic indicator for survival. *Am J Surg Pathol*. 2016;40: 1653–1660.
47. Mellon EA, Jin WH, Frakes JM, et al. Predictors and survival for pathologic tumor response grade in borderline resectable and locally advanced pancreatic cancer treated with induction chemotherapy and neoadjuvant stereotactic body radiotherapy. *Acta Oncol*. 2017;56:391–397.
48. Yamamoto T, Sugiura T, Mizuno T, et al. Preoperative FDG-PET predicts early recurrence and a poor prognosis after resection of pancreatic adenocarcinoma. *Ann Surg Oncol*. 2015;22:677–684.
49. Lee SY, Jeong EK, Ju MK, et al. Induction of metastasis, cancer stem cell phenotype, and oncogenic metabolism in cancer cells by ionizing radiation. *Mol Cancer*. 2017;16:10.
50. Al-Assar O, Demiciorglu F, Lunardi S, et al. Contextual regulation of pancreatic cancer stem cell phenotype and radioresistance by pancreatic stellate cells. *Radiother Oncol*. 2014;111:243–251.