Concurrent Nab-paclitaxel and Radiotherapy

**Novel Radiosensitization for Borderline Resectable or Unresectable Pancreatic Cancer**

William T. Arscott, MD,*† Kevin T. Nead, MD, MPhil,*‡ Adham Bear, MD,*§ Srijan Venigalla, MD,* Jacob Shabason, MD,* John N. Lukens, MD,* John P. Plastaras, MD, PhD,* Andrzej Wojcieszyński, MD,* James Metz, MD,* Mark O’Harra, MD,* Kim A. Reiss, MD,* Ursina Teitelbaum, MD,* Arturo Loaiza-Bonilla, MD,§¶ Jeffrey Drebin, MD,¶†# Major K. Lee IV, MD, PhD,¶|| Stuti G. Shroff, MD, PhD,** and Edgar Ben-Josef, MD*+

Purpose: This study evaluates the toxicity and tumor response with concurrent nab-paclitaxel chemoradiotherapy (CRT) compared with standard (5-fluorouracil or gemcitabine) CRT.

Materials and Methods: Fifty patients with borderline resectable or unresectable pancreatic adenocarcinoma from 2014 to 2017 were divided into 2 groups: concurrent nab-paclitaxel (100 to 125 mg/m² weekly) CRT (median: 2.1 Gy fraction size and 52.5 Gy total) or standard CRT (median: 1.8 Gy fraction size, 54.5 Gy total). The primary endpoint was toxicity, and secondary endpoints were local failure and conversion to resectability. Comparisons were made using rank-sum or Fisher exact test and multivariable competing risk regression for the cumulative incidence of local failure.

Results: There were 28 patients in the nab-paclitaxel CRT group and 22 in the standard CRT group; 88% had the unresectable disease. The median follow-up was 18 months. The median duration of chemotherapy before concurrent CRT was 1.9 and 2.3 months in the nab-paclitaxel and standard CRT groups (P = 0.337), and radiotherapy dose was 52.5 Gy (range, 52.5 to 59.4 Gy) and 54.5 Gy (range, 45.0 to 59.4 Gy), respectively. There were no statistically significant grade ≥2 toxicities. The nab-paclitaxel CRT group experienced a nonstatistically significant lower incidence of local failure (hazard ratio = 0.91, 95% confidence interval: 0.27-3.03, P = 0.536). More patients in the nab-paclitaxel CRT group proceeded to surgery (9/28 compared with 3/22 in the standard CRT, P = 0.186), of which 6 (25%) in the nab-paclitaxel CRT and 2 (10%) in the standard CRT groups were initially unresectable.

Conclusions: Nab-paclitaxel CRT had similar toxicity compared with standard CRT in the treatment of borderline resectable or unresectable pancreatic cancer. Its use was associated with an arithmetically lower cumulative incidence of local failure and an arithmetically higher conversion to resectability, both of which were not statistically significant.

Key Words: pancreatic cancer, chemoradiation, resection, nab-paclitaxel, abraxane

(Ann J Clin Oncol 2021;44:469–474)

Pancreatic cancer is one of the most aggressive malignancies with a similar annual incidence and survival rate of around 50,000 cases per year for each.¹ Surgical resection continues to be the only chance for cure, however, only a minority of patients present with resectable disease. In unresectable patients, a general approach is to provide upfront chemotherapy for several weeks, followed by reassessment for resectability. Newer chemotherapy regimens demonstrating survival benefit in the metastatic setting such as FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and 5-fluorouracil [5-FU]) and combination gemcitabine/nab-paclitaxel² have been recently introduced as neoadjuvant options for nonmetastatic patients. The role of external beam radiotherapy (RT) in unresectable cases has been debated, with some trials demonstrating an overall survival (OS) benefit,³ while others show a local control benefit without a concomitant improvement in OS.⁴ Importantly, however, there is wide agreement that chemoradiotherapy (CRT) improves local disease control, which may be important in this disease where local progression is associated with substantial morbidity.⁵,⁶

The optimal concurrent chemotheraphy to administer with external beam radiation continues to be evaluated. It has been previously shown that pathologic response following CRT can be an independent predictor of survival,⁷ demonstrating that aggressive combined modality therapy allowing for resection can improve outcomes. We recently completed a phase I study evaluating nab-paclitaxel administered concurrently with RT.⁸ Nab-paclitaxel was selected based on its favorable outcomes in the metastatic setting when combined with gemcitabine,² likely due to improved uptake of the albumin-bound formulation of paclitaxel by pancreatic tumor cells and the associated stroma.⁹

From the Departments of *Radiation Oncology; †Medical Oncology; **Pathology; ‡Surgery, University of Pennsylvania; ¶Cancer Treatment Centers of America, Philadelphia, PA; ††Compass Oncology, Tigard, OR; ‡‡The University of Texas MD Anderson Cancer Center, Houston, TX; ‡§Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, W.T.A. and K.T.N. are joint first authors. K.T.N.; is responsible for statistical analyses. Presented in part at the American Society for Radiation Oncology 2017 Annual Meeting in Boston, MA.

A.L.-B. reports personal fees from Celgene outside the submitted work. The other authors declare no conflicts of interest.

Correspondence: Edgar Ben-Josef, MD, Department of Radiation Oncology, Perelman Center for Advanced Medicine, University of Pennsylvania, 4 West, Room 316, 3400 Civic Center Boulevard, Philadelphia, PA 19104. E-mail: edgar.ben-josef@pennmedicine.upenn.edu.

Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 0277-3732/21/4409-0469

DOI: 10.1097/COC.0000000000000854

American Journal of Clinical Oncology • Volume 44, Number 9, September 2021 www.amjclinicaloncology.com | 469
In addition, preclinical work demonstrated radiosensitization in mouse xenograft models without increased gastrointestinal toxicity.10

The phase I study by Shabason et al8 demonstrated acceptable toxicity of the concurrent regimen with no grade ≥ 3 toxicity, and 4 of 9 patients were able to undergo curative-intent resection. Given the tolerability of nab-paclitaxel in this setting, additional patients were treated in a similar fashion off-protocol at our institution. While there are published trials combining nab-paclitaxel and radiation in other malignancies, including head and neck cancer11 and non–small-cell lung cancer,12 there are no other published studies evaluating this combination in pancreatic cancer.

Therefore, we retrospectively reviewed patients treated with concurrent nab-paclitaxel and RT following a similar treatment paradigm as those included in the recently published study,8 using matched patients receiving concurrent standard CRT to compare outcomes.

MATERIALS AND METHODS

Study Patients

Patients with locally advanced pancreatic ductal adenocarcinoma (PDAC) consecutively treated at a single institution between 2014 and 2017 were selected under an institutional review board approved protocol. Patients had to have (1) histologically confirmed PDAC, (2) radiographic evidence of unresectable or borderline resectable disease, and (3) received neoadjuvant chemotherapy (any number of cycles), followed by concurrent CRT. Criteria defining unresectable and borderline resectable disease were based on the National Comprehensive Cancer Network (NCCN) Guidelines (v 1.2018, page PANC-B).13 Patients could receive any neoadjuvant chemotherapy regimen, and were divided into 2 groups based on the chemotherapy regimen administered concurrently with RT: nab-paclitaxel (100 to 125 mg/m²) or standard chemotherapy—5-FU-based chemotherapy (infusional 5-FU or oral capecitabine, standard dosing) or gemcitabine (800 to 1000 mg/m²). Patients receiving upfront surgery and those without complete records for review were excluded from the analysis. RT treatment volumes were defined as follows: the gross tumor volume as visualized on the computed tomography scan, a 0.5 cm to create a clinical target volume, an additional margin for breathing-related tumor excursion as defined by the 4-dimensional computed tomography scan, and a 0.5 cm in all directions to create a planning target volume to account for daily set-up error.

Study Methods

Patient demographics, treatment characteristics, toxicity data, chemotherapy dose reductions during CRT, response to therapy, and laboratory values were extracted from the electronic medical record. Toxicity was recorded according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Templated toxicity questionnaires completed routinely during nursing symptom assessment in our department were used.

Statistics Analysis

The primary endpoint was the difference in toxicity during CRT between groups. Secondary endpoints were cumulative incidence of local treatment failure, radiographic response to therapy, conversion to resectable disease, rate of R0 resection, pathologic response, and OS. We compared treatment characteristics, toxicity, radiographic and pathologic response using a rank-sum (continuous) or Fisher exact (categorical) test. We examined the odds of radiographically decreased, stable, or progressive disease among those undergoing gemcitabine/nab-paclitaxel versus FOLFIRINOX using ordinal logistic regression adjusting for the total number of chemotherapy cycles. We compared the cumulative incidence of local, distant, and any (local or distant) failure according to treatment group using a multivariable-adjusted competing risk regression, with death as the competing risk, according to the method of Fine and Gray. We compared 1- and 2-year OS in the nab-paclitaxel versus standard CRT groups by comparing Kaplan-Meier survival curves using the log-rank test. We additionally examined survival using multivariable-adjusted Cox proportional hazards regression models. Cox proportional hazards regression assumptions were evaluated by Schoenfeld residuals tests. Tests were considered significant with a 2-sided P-value < 0.05. Analyses were performed using Stata, version 15.1 (StataCorp.).

RESULTS

Patient and Treatment Characteristics

Fifty patients with initially unresectable or borderline resectable PDAC meeting inclusion criteria were identified (Table 1). Nine patients were included from a phase I study performed at the same institution.8 Thirty-five patients (70%) were male with a median age of 66 years (range, 47 to 86 y). Twenty-eight patients received nab-paclitaxel with RT (herein referred to as nab-paclitaxel CRT), and 22 patients received standard CRT (19 with 5-FU and 3 with gemcitabine-based concurrent therapy). The median follow-up time was 16.9 months in the nab-paclitaxel CRT group and 18.8 months in the standard CRT group. The median duration of neoadjuvant chemotherapy before CRT was similar, 1.9 months (range, 0.9 to 6.4 mo) versus 2.3 months (range, 0.6 to 8.7 mo) in the nab-paclitaxel and standard CRT groups, respectively (P = 0.337), with a similar median time from diagnosis to start of CRT between the groups of 3.8 months (range, 2.3 to 15.5 mo) and 4.6 months (range, 2.3 to 11.2 mo), respectively (P = 0.054). The most common neoadjuvant chemotherapy regimens were dual-agent gemcitabine and nab-paclitaxel (86% vs. 64%), and the multiagent regimen FOLFIRINOX (oxaliplatin, leucovorin, irinotecan, and 5-FU; 11% vs. 32%) for nab-paclitaxel CRT and standard CRT, respectively (P = 0.063 for interaction by Fisher exact test). The median size of tumors treated were similar between the 2 groups (3.3 cm [range, 1.0 to 8.0 cm] in nab-paclitaxel CRT vs. 4.0 cm [range, 2.8 to 4.5 cm] in standard CRT, P = 0.162). There was no difference in radiation dose (median: 52.5 Gy [range, 52.5 to 59.4 cm] vs. 54.5 Gy [range, 45 to 59.4 Gy], P = 0.482), modality (proton, photon, or mixed, P = 0.781), though there was a difference in median fraction size (2.1 Gy/fraction [range, 1.8 to 2.1 Gy/fraction] vs. 1.8 Gy/fraction [range, 1.8 to 2.5 Gy/fraction], P = 0.001) for nab-paclitaxel CRT and standard CRT, respectively.

Toxicity and Tolerability

Concurrent nab-paclitaxel CRT was well-tolerated with comparable rates of toxicity compared with standard CRT. Rates of grade ≥ 2 toxicity of any kind was 71% in the nab-paclitaxel group and 68% in the standard CRT groups (P = 1.0) (Table 2). There was a nonstatistically significant increase in grade 3 hematologic toxicity in the nab-paclitaxel CRT group (25% vs. 5%, P = 0.116), and overall there was no statistical difference in the rates of neurological, gastrointestinal, or hematologic toxicity between the groups (all P > 0.1, Table 2).
Response to Therapy

The radiographic response following initial chemotherapy and chemoradiation was evaluated (Table 3). Regarding initial therapy, there was a nonstatistically significant reduction in the odds of progression among those undergoing gemcitabine/nab-paclitaxel versus FOLFIRINOX when adjusting for a total number of cycles given (0.62, 95% confidence interval [CI]: 0.13-2.99, \( P = 0.553 \)). Following CRT, progression was seen in 2 patients in the nab-paclitaxel and 1 patient in the standard CRT groups, and there was a similar number of patients who showed stable disease (50% vs. 55%) or decreased disease volume (43% vs. 36%), though there was no significant difference between the 2 groups (\( P = 0.765 \)).

Rate of conversion to resectable disease was also evaluated (Table 4). In the standard CRT group, 1 patient with borderline resectable disease and 2 patients with unresectable disease successfully underwent curative-intent surgery, while in the nab-paclitaxel CRT group, 3 patients with the borderline resectable disease and 6 patients with the unresectable disease were taken to surgery. Overall, 3 (13%) patients in the standard CRT group were taken to surgery, compared with 9 (32%) patients in the nab-paclitaxel CRT group. Unadjusted Fisher exact test was non-significant (\( P = 0.186 \)) and remained nonsignificant when adjusted for age and performance status (\( P = 0.109 \)). Two patients in the nab-paclitaxel CRT group had pathologic complete responses (CRs), and none were seen in the standard CRT group. In those who underwent surgical resection, the median percent viable cells were 15% (range, 0% to 30%) in the nab-paclitaxel CRT group and 5% (range, 3% to 10%) in the standard CRT group. High rates of negative margins were achieved with nab-paclitaxel CRT (\( n = 7 \), 78%) and standard CRT (\( n = 3 \), 100%).
Survival Outcomes

The risk of progression and OS are illustrated in Figure 1. The standardized hazard ratios for local, distant, or any progression was 0.91 (95% CI: 0.27-3.03), 0.89 (95% CI: 0.41-1.92), and 0.86 (95% CI: 0.42-1.78), respectively, comparing nab-paclitaxel CRT to standard CRT, though the differences were not significant (all \( P > 0.1 \)). OS at 1 and 2 years was 80% (95% CI: 58%-91%) and 71% (95% CI: 47%-86%) in the nab-paclitaxel CRT group, and 71% (95% CI: 47%-86%) and 22% (95% CI: 4%-48%) in the standard CRT group, respectively, though the differences were not significant (log-rank \( P = 0.320 \)). For patients able to be converted to resectable disease, median OS was 29.0 months (resected) versus 17.0 months (nonresected).

DISCUSSION

Novel therapies are needed for patients with borderline and unresectable PDAC as current options are limited, and these patients have high rates of local and distant progression. This retrospective review evaluated the tolerability of concurrent nab-paclitaxel CRT compared with standard CRT (5-FU or gemcitabine-based), as well as several outcome measures. The postulated mechanism of increased radiosensitivity with nab-paclitaxel is through the Cav-1 receptor (Al-Batran and colleagues\(^9,10\) and unpublished literature) suggesting a higher rate of nab-paclitaxel uptake in cancer cells than with paclitaxel and with higher specificity. While we hypothesized that nab-paclitaxel concurrent with RT would be better tolerated due to this preferential uptake in pancreatic cancer cells, there were similar rates of neurological, hematologic, and gastrointestinal toxicity between the nab-paclitaxel CRT and standard CRT groups. Progression-free survival (PFS) and OS were similar with either concurrent regimen, while we observed arithmetically different rates of surgery, surgical resection, and pathologic CR favoring the nab-paclitaxel CRT versus standard CRT group, these results are not significantly different, and our trial was not adequately powered to allow meaningful conclusions about these differences. It is possible that these apparent differences should be hypothesis-generating for future studies regarding both optimal chemotherapy regimen and optimal fractionation size for RT in this clinical context.

The role of neoadjuvant chemotherapy for patients with borderline or locally advanced, unresectable PDAC continues to evolve, and the optimal regimen is not currently defined.\(^{14}\) With the goal of attaining objective clinical responses that may transition patients from unresectable to resectable disease, data is often extrapolated from the treatment of patients with metastatic pancreatic cancer in selecting an appropriate neoadjuvant

### TABLE 4. Adjusted Odds of Undergoing Resection Following Chemoradiation Among Those Treated With Nab-paclitaxel Versus Standard Chemoradiation

|                                      | OR (95% CI)         | \( P \)  |
|--------------------------------------|---------------------|---------|
| Nab-paclitaxel CRT                   | 3.58 (0.75-17.10)   | 0.109   |
| Age                                  | 0.99 (0.91-1.08)    | 0.857   |
| ECOG at initiation of CRT            | 0.44 (0.13-1.51)    | 0.193   |

CI indicates confidence interval; CRT, chemoradiation; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio.

FIGURE 1. Survival outcomes. A, Overall survival. B, Local progression risk. C, Distant progression risk. D, Any progression risk. CRT indicates chemoradiotherapy, RT, radiotherapy.
regimen. In 2 landmark studies demonstrating increased OS in patients with metastatic pancreatic cancer treated with FOLFIRINOX or combination gemcitabine/nab-paclitaxel compared with gemcitabine alone, patients experience objective response rates of 31.6% and 22.9%, respectively.1,5 The largest systematic review and patient-level meta-analysis regarding FOLFIRINOX for locally advanced pancreatic cancer reported that in 12 studies, 91 (28%) of 325 patients underwent resection after FOLFIRINOX.6 In the adjuvant setting, FOLFIRINOX has taken a major role as the preferred regimen given its survival advantage over gemcitabine as per the PRODIGE (Partenariat de Recherche en Oncologie Digestive) 24 trial results.7 However, the international phase 3 study evaluating adjuvant therapy with nab-paclitaxel in combination with gemcitabine versus gemcitabine alone for patients with surgically resected pancreatic cancer8 did not achieve the primary endpoint of improvement in disease-free survival, as confirmed by independent radiologic review, compared with gemcitabine alone. In the neoadjuvant setting, no randomized controlled trial directly comparing these 2 regimens has been performed. Therefore, the superiority of either regimen cannot be determined, and the choice of regimen is left to provider discretion based on treatment practice and perceived patient tolerance.

The use of concurrent chemoradiation for locally advanced PDAC has been questioned. The LAP07 trial demonstrated no survival advantage with the use of adjuvant 5-FU based CRT following neoadjuvant chemotherapy over adjuvant chemotherapy alone.4 However, the trial was designed before the advent of more aggressive chemotherapy regimens (ie, nab-paclitaxel/gemcitabine and FOLFIRINOX), and its relevance has come into question as a result. A recent retrospective cohort study evaluated combined-agent chemotherapy followed by CRT or chemoradiation alone and found improvements in time to local failure, PFS and OS with the use of adjuvant CRT.9 This highlights the importance of effective “lead-in” chemotherapy to select optimal patients for CRT. A recent phase 2 study by Murphy et al10 used a similar approach (chemotherapy > CRT > surgery) in borderline resectable patients. An adaptable RT plan was used depending on the extent of response to chemotherapy: accelerated RT (5 Gy ×5) if resolution of vascular involvement after chemotherapy versus long-course RT with a simultaneous integrated boost to 55.5 Gy for persistent vascular involvement, using 5-FU based chemoradiation concurrent with RT. This trial demonstrated favorable outcomes in terms of R0 resection and survival, with median PFS in resected patient of 48.5 months and a 2-year OS of 72%. While these results lend support to this approach, it is interesting to note that in this study, no patient experienced a pathologic CR, whereas in our study, we observed 2 patients (7% of all patients; 22% of patients taken to surgery) with pathologic CR in the nab-paclitaxel CRT group (none in those receiving standard CRT). As no patients in our study cohort received short-course RT, this finding could be a result of insufficient time to achieve a CR in patients receiving short-course RT, but certainly suggests that concurrent nab-paclitaxel may augment the response to RT in this group of patients and improve rates of pathologic CR. Last, advances in RT delivery including protons and adaptive planning with the advent of the MR-Linac, have potential to safely escalate the dose to the gross tumor, which may further improve outcomes in this population irrespective of concurrent chemotherapy used.21

Surgical resection is generally considered the only curative intervention for PDAC,22 and there is a clear survival benefit for initially resectable patients.23,24 In borderline resectable or unresectable disease, data supports a survival benefit when an R0 resection can be achieved.3,25,26 A recent meta-analysis found that approximately one third of initially unresectable patients (including both borderline resectable and unresectable patients) ultimately underwent surgical resection, and this was associated with an estimated improvement in OS from 10.2 months (intact) to 20.5 months (resected).25 In the Murphy et al’s study discussed above, median OS was 37.7 months in all patients and was not reached in those that underwent resection at the time of publication (median follow-up was 18 mo). Our analysis demonstrates that patients who underwent resection had a median OS of 29.0 versus 17.0 months in those remaining intact. One must consider the likely impact of selection bias on this observation as patients undergoing surgical resection must experience prolonged survival, maintain performance status, and exhibit objective response to neoadjuvant therapy.

Our analysis has several important limitations. First, regarding neoadjuvant chemotherapy, there was heterogeneity in the chemotherapy type and duration before CRT between groups, though none reached statistical significance. Also, the median duration of neoadjuvant chemotherapy was 1.9 to 2.3 months, shorter than current practice, and this may have impacted outcomes, including conversion to resectable disease and/or tolerance to CRT regimens. Second, those receiving concurrent gemcitabine included in the standard CRT group were the minority, and gemcitabine-based CRT has shown encouraging preliminary results in unresectable patients with regard to local control and conversion to resectable disease.27 Third, the small number of patients in the study is likely one reason a significant difference in outcomes could not be seen, particularly for the conversion to resectable disease. Resectability is also a subjective endpoint, which could vary based on institutional practice, radiologist evaluating imaging, or surgeon determining appropriateness for the operation. Fourth, toxicity data is best collected in a prospective setting (though hematologic toxicity was based on discrete laboratory values). However, templated toxicity questionnaires are standard as part of our nursing symptom assessment and were used in our evaluation of toxicity during CRT. Last, there may be selection bias in patients referred for RT, based on the treating physician’s opinion on whether CRT would provide a benefit (particularly in light of the conflicting data), and/or patients may have elected for nonsurgical management of their disease for a variety of reasons, and thus were underrepresented in one of our cohorts.

These limitations notwithstanding, we demonstrate that concurrent CRT with nab-paclitaxel was well-tolerated, allowed more patients to undergo resection, and resulted in pathologic CRs. Nab-paclitaxel given concurrently with RT seems to be fairly equivalent to standard CRT and may provide clinicians another reasonable regime to use when 5-FU or gemcitabine-based regimens cannot be administered, though further evaluation of its safety in clinical trials are necessary.

REFERENCES
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7–30.
2. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:1691–1703.
3. Loehrer PJ Sr, Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group Trial. J Clin Oncol. 2011;29:4105–4112.
4. Hammel P, Huguet F, van Laethem JL, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with...
locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. JAMA. 2016;315:1844–1853.

5. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. J Clin Oncol. 2009;27:1806–1813.

6. Poruk KE, Wolfgang CL. Palliative management of unresectable pancreas cancer. Surg Oncol Clin N Am. 2016;25:327–337.

7. Katz MH, Shi Q, Ahmad SA, et al. Preoperative modified FOLFIRINOX treatment followed by capcitabine-based chemoradiation for borderline resectable pancreatic cancer: alliance for Clinical Trials in Oncology Trial A021101. JAMA Surg. 2016;151:e161137.

8. Shabason JE, Chen J, Apisarnthanarax S, et al. A phase I dose escalation trial of nab-paclitaxel and fixed dose radiation in patients with unresectable or borderline resectable pancreatic cancer. Cancer Chemother Pharmacol. 2018;81:609–614.

9. Al-Batran SE, Geissler M, Seufferlein T, et al. Nab-paclitaxel for metastatic pancreatic cancer: clinical outcomes and potential mechanisms of action. Oncol Res Treat. 2014;37:128–134.

10. Wiedenmann N, Valdecasas D, Hunter N, et al. 130-nm albumin-bound paclitaxel enhances tumor radioirradiability and therapeutic gain. Clin Cancer Res. 2007;13:1868–1874.

11. Fury MG, Sherman EJ, Rao SS, et al. Phase I study of weekly nab-paclitaxel+weekly cetuximab+intensity-modulated radiation therapy (IMRT) in patients with stage III-IVB head and neck squamous cell carcinoma (HNSCC). Ann Oncol. 2014;25:689–694.

12. Hasegawa T, Futamura Y, Horiba A, et al. A phase II study of nab-paclitaxel plus carboplatin in combination with thoracic radiation in patients with locally advanced non-small-cell lung cancer. J Radiat Res. 2016;57:50–54.

13. National Comprehensive Cancer Network. Pancreatic adenocarcinoma (v.1.2018). 2018. Available at: www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed May 3, 2020.

14. Hosein PJ, Macintyre J, Kamawara C, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline- resectable locally advanced pancreatic adenocarcinoma. BMC Cancer. 2012;12:199.

15. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817–1825.

16. Suker M, Beumer BR, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol. 2016;17:801–810.

17. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379:2395–2406.

18. Tempero MA, Cardin DB, Goldstein D, et al. APACT: Phase III randomized trial of adjuvant treatment with nab-paclitaxel (nab-P) plus gemcitabine (Gem) versus Gem alone in patients (pts) with resected pancreatic cancer (PC). J Clin Oncol. 2016;34:TPS473.

19. Choi Y, Oh DY, Kim K, et al. Concurrent chemoradiotherapy versus chemotherapy alone for unresectable locally advanced pancreatic cancer: a retrospective cohort study. Cancer Res Treat. 2016;48:1045–1055.

20. 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.

21. Reyngold M, Parikh P, Crane CH. Ablative radiation therapy for locally advanced pancreatic cancer: techniques and results. Radiat Oncol. 2019;14:95.

22. Bachmann J, Michalski CW, Martignoni ME, et al. Pancreatic resection for pancreatic cancer. HPB (Oxford). 2006;8:346–351.

23. Chakraborty S, Singh S. Surgical resection improves survival in pancreatic cancer patients without vascular invasion- a population based study. Ann Gastroenterol. 2013;26:346–352.

24. Yamamoto T, Yagi S, Kinoshita H, et al. Long-term survival after resection of pancreatic cancer: a single-center retrospective analysis. World J Gastroenterol. 2015;21:262–268.

25. Gillen S, Schuster T, Meyer Zum Buschenfelde C, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med. 2010;7:e1000267.

26. Bockhorn M, Urunoglu FG, Adham M, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2014;155:977–988.

27. Ben-Josef E, Schipper M, Francis IR, et al. A phase III trial of intensity modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 2012;84:1166–1171.