



Neoadjuvant chemoradiotherapy is not superior to upfront surgery in pancreatic adenocarcinoma

Diana L. Xinaxtle, Leonardo S. Lino-Silva

Gastrointestinal Surgical Pathology, Instituto Nacional de Cancerología (INCan), Tlalpan, Mexico City, Mexico

Correspondence to: Leonardo S. Lino-Silva, MD, MSc, M.Ed. Anatomic Pathology Professor, Gastrointestinal Pathology, Instituto Nacional de Cancerología de México (Mexico's National Cancer Institute), Av. San Fernando # 22, Sección XVI, Tlalpan, Mexico City, Mexico.

Email: saul.lino.sil@gmail.com.

Comment on: Versteijne E, Suker M, Groothuis K, *et al.* Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. *J Clin Oncol* 2020. doi:10.1200/JCO.19.02274.

Received: 28 April 2020; Accepted: 18 May 2020; Published: 30 December 2020.

doi: 10.21037/dmr-20-57

View this article at: <http://dx.doi.org/10.21037/dmr-20-57>

Ductal carcinoma of the pancreas is the 8th most frequent neoplasm in women and the 9th in men, it represents 3% of new cases but it has a high lethality and an aggressive clinical course (1), where 80% of patients present in unresectable stages and from the 20% of resectable cases, only a quarter of them will have a negative margin (2). Due to this poor prognosis and knowing that neoadjuvant chemoradiotherapy (NCRT) has theoretical advantages based on data obtained from other types of cancers, such as directly treating radiographically occult metastatic disease, delaying surgery during NCRT allows re-staging before surgery and improves complete resection rates, and even improve overall survival (OS). Thus, its usefulness in pancreatic ductal carcinoma has been studied, showing in a systematic review with meta-analysis (derived from non-randomized studies) that NCRT prolongs OS from 14.8 to 18.8 months compared to upfront surgery (3).

This year [2020] the results of a randomized clinical trial (RCT), the PREOPANC study, are published, which objective was to determine if NCRT has better OS than upfront surgery in patients with carcinoma of the pancreas (4). The Median of OS was superior in the NCRT group (16.0 *vs.* 14.3 months), a difference not statistically significant. Interestingly, their results show that the complete resection (R0) rate was superior in the NCRT group (71% *vs.* 40%) and the patients with R0 had better overall survival (hazard ratio 0.47; 95% confidence interval, 0.31–0.72; $P < 0.001$). In addition, their results suggest a potential benefit of NCRT in disease-free survival, locoregional failure-

free interval, lower rate of lymph node metastasis, and less perineural/venous invasion. However, these data are derived from sub-analyzes of secondary objectives.

Although these results seem promising, they are difficult to interpret, as there are important sources of bias; some of them are explained by the inherent complexity of performing and completing an RCT in aggressive tumors with scarce patients who are candidates for surgery.

We find the following sources of bias. (I) The definition of a resectable borderline tumor in ductal carcinoma of the pancreas is debatable and the criteria for defining it are different in places other than the Netherlands. Also, the definition of high-volume centers is not clear, it is not defined in the study or protocol (5), and there is little published evidence in this regard. In a population registry-based study ($n=42,202$) is defined that a high-volume center is that performing 36 or more pancreaticoduodenectomies/year, medium-volume that performing 10–36, and low-volume that performing 1–9 (6). These (II) the groups at the time of randomization are slightly unbalanced (120 *vs.* 128 patients) and, if, as the methodology suggests, the randomization was 1:1, what is the explanation for this imbalance? Information on how the randomization process went (for example, by blocks, clusters, centers, etc.) could clarify this. (III) Most importantly, there are baseline characteristics in the groups that are clearly associated with a better prognosis for the group that received NCRT. Although the authors mention in the results section that the groups are balanced, based on the data from the

Table 1 Ongoing randomized clinical trials (updated on April 2020) comparing preoperative chemoradiotherapy/chemotherapy *vs.* upfront surgery in resectable or borderline resectable pancreatic adenocarcinoma

Trial name/country	Population (n)	Preoperative schema (number of cycles)	Surgery arm (number of cycles of adjuvance)	Primary outcome	Start date
ESPAC-5F ISRCTN89500674, European Union (9)	85, borderline resectable	a. FOLFIRINOX [4] b. Gemcitabine [1]+capecitabine	Surgery + adjuvant gemcitabine [6] or 5-FU [6]	R0 resection rate	April 2014
NEONAX NCT02047513, Germany (10)	127, resectable	Gemcitabine/nabpaclitaxel [2+4]	Surgery + adjuvant gemcitabine/nabpaclitaxel [6]	Disease free survival	April 2015
NORPACT-1 NCT02919787, Norway (11)	90, resectable	FOLFIRINOX [4] + Adjuvant gemcitabine-capecitabine [4]	Surgery + adjuvant gemcitabine-capecitabine [4]	Overall survival at 1 year	September 2016
PANACHE01- PRODIGE48 NCT02959879, France (12)	160, resectable	a. FOLFIRINOX [4] + adjuvant chemotherapy [8] b. FOLFOX [4] + adjuvant chemotherapy [8]	Surgery + adjuvant chemotherapy [12]	Overall survival at 1 year	March 2017
ALLIANCE A021806, USA (13)	Resectable	mFOLFIRINOX	Surgery + adjuvant mFOLFIRINOX	Overall survival	2020

comparative table, it is clear that the group with NCRT has a higher proportion of cases with good functional status (58% *vs.* 39%) and lower proportion of patients with WHO performance status 1 (41% *vs.* 61%) ($P=0.0018$). Also, the NCRT group had fewer cases with presentation in the head of the pancreas (82% *vs.* 92%, $P=0.013$), which translates that in the surgery group the procedures were more complex; and finally, the group with NCRT had a lower proportion of patients with suspicious nodes (77.3% *vs.* 66.9%, $P=0.038$), which indicates that, at least clinically, the patients had a lower clinical stage (P values are based on χ^2 test at two tails, and were calculated with Stata 14.1, College Station, Texas, USA).

Based on these facts, we believe that there is a clear bias in favor of the NCRT group, making it difficult to support the true value of the secondary outcomes presented in this study that favors NCRT.

Two other RCTs have compared NCRT against initial surgery, none of them was concluded. The first was discontinued due to low recruitment after the inclusion of 73 (29%) patients, so no difference in OS could be demonstrated (7). The second, a phase II-III trial in Korea, was suspended for superiority. The latter compared a group that received gemcitabine-based NCRT (45 Gy in 25 fractions and 9 Gy in 5 fractions) against a group that received upfront surgery + adjuvant chemoradiotherapy with the same scheme as the NCRT group. This study

found in the interim analysis ($n=50$) a higher median OS (21 *vs.* 12 months, $P=0.028$), higher 2-year cumulative survival (41% *vs.* 26%), and a higher R0 resection (52% *vs.* 26%, $P=0.004$) in the NCRT group (8).

As is clear, there is little conclusive evidence on the real advantage of the NCRT, so it is, therefore, essential to wait for the results of ongoing RCT (*Table 1*) (9-13). Only a direct comparison of NCRT against upfront surgery in a well-conducted RCT avoid biases. Despite the limited number of RCTs available, patients with resectable and borderline resectable pancreatic carcinomas appear to be beneficiaries of NCRT regarding the proportion of R0 resection. Furthermore, OS is at least the same in patients with NCRT compared to upfront surgery.

Ongoing and future RCTs will investigate the true value of NCRT in OS, the optimal number and type of NCRT cycles and the optimal selection for surgery. There is no doubt that we must await the results of ongoing trials to establish the usefulness of NCRT.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned

by the Editorial Office, *Digestive Medicine Research*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at: <http://dx.doi.org/10.21037/dmr-20-57>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the manuscript are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7-30.
2. Tummers WS, Groen JV, Sibinga Mulder BG, et al. Impact of resection margin status on recurrence and survival in pancreatic cancer surgery. *Br J Surg* 2019;106:1055-65.
3. 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;105:946-58.
4. Versteijne E, Suker M, Groothuis K, et al. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. *J Clin Oncol* 2020. doi:10.1200/JCO.19.02274.
5. Versteijne E, van Eijck CH, Punt CJA, et al. Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC trial): study protocol for a multicentre randomized controlled trial. *Trials* 2016;17:127.
6. Panni RZ, Liu J, Fields RC, et al. Defining “high volume center” for pancreaticoduodenectomy. *HPB* 2019;21:S65-6.
7. Golcher H, Brunner TB, Witzigmann H, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. *Strahlenther Onkol* 2015;191:7-16.
8. Jang JY, Han Y, Lee H, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. *Ann Surg* 2018;268:215-22.
9. Current Controlled Trials [Internet]. London: BioMed Central. [2014 Mar 31]. ISRCTN89500674, ESPAC-5F: European Study Group for Pancreatic Cancer - Trial 5F Four arm, prospective, multicentre, randomised feasibility trial of immediate surgery compared with neoadjuvant chemotherapies and neoadjuvant chemoradiotherapy. 2020 Apr 30 [cited 2020 Apr 30]; Available online: <http://www.controlled-trials.com/ISRCTN13256080>
10. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 Jan 28. Identifier NCT02047513, Neoadjuvant Plus Adjuvant or Only Adjuvant Nab-Paclitaxel Plus Gemcitabine for Resectable Pancreatic Cancer (NEONAX); [cited 2020 Apr 30]; [about 4 screens]. Available online: clinicaltrials.gov/ct2/show/NCT02047513
11. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2016 Sep 29. Identifier NCT02919787, Norwegian Pancreatic Cancer Trial (NorPACT) - 1; [cited 2020 Apr 30]; [about 4 screens]. Available online: clinicaltrials.gov/ct2/show/NCT02919787
12. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2016 Nov 9. Identifier NCT02959879, Neo-adjuvant FOLF(IRIN)OX for Resectable Pancreatic Adenocarcinoma (PANACHE01); [cited 2020 Apr 30]; [about 4 screens]. Available online: clinicaltrials.gov/ct2/show/NCT02959879
13. Katz MHG, Ou FS, Herman JM, et al. Alliance for clinical trials in oncology (ALLIANCE) trial A021501: Preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas. *BMC Cancer* 2017;17:505.

doi: 10.21037/dmr-20-57

Cite this article as: Xinaxtle DL, Lino-Silva LS. Neoadjuvant chemoradiotherapy is not superior to upfront surgery in pancreatic adenocarcinoma. *Dig Med Res* 2020;3:103.