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.

**Editorial Commentary**

**Neoadjuvant chemoradiotherapy is not superior to upfront surgery in pancreatic adenocarcinoma**

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Provenance and Peer Review: This article was commissioned by the Editorial Office, *Digestive Medicine Research*. The article did not undergo external peer review.


Received: 28 April 2020; Accepted: 18 May 2020.

doi: 10.21037/dmr-20-57

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

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Although the authors mention in the results section that the groups are balanced, based on the data from the 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 $\chi^2$ 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 wait the results of ongoing trials to establish the usefulness of NCRT.

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

<table>
<thead>
<tr>
<th>Trial name/country</th>
<th>Population (n)</th>
<th>Preoperative schema (number of cycles)</th>
<th>Surgery arm (number of cycles of adjuvance)</th>
<th>Primary outcome</th>
<th>Start date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLIANCE A021806, USA (13)</td>
<td>Resectable</td>
<td>mFOLFIRINOX</td>
<td>Surgery + adjuvant mFOLFIRINOX</td>
<td>Overall survival</td>
<td>2020</td>
</tr>
</tbody>
</table>

Acknowledgments

Funding: None.
Footnote

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.

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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.