I've read with great interest the paper of Machairas et al. (1) which is of great interest for the oncological and surgical community.

Pancreatic adenocarcinoma (PDAC) is still considered a malignancy with an extremely poor prognosis, being currently the 4th cause of death for cancer and, according to the Global Cancer Statistics in the next decade, it may ascend up to the third cause of death (2). During the last decades, there have been great efforts to improve survival of potentially resectable pancreatic cancer through several improvements. Firstly, the selection of patients: newer preoperative studies have been able to select those patients that might really benefit from resection. Secondly, the surgical procedure itself improved its outcome: proper mesopancreatic dissection and lymphadenectomy, superior mesenteric artery approach and vascular resection have been able to enhance the R0 resection rate with acceptable morbidity (3). Finally, newer chemotherapies regimens have been introduced, as well, with relevant survival improvement (4).

The standard treatment for patients with resectable pancreatic cancer is surgery followed by adjuvant chemotherapy with the chance of long-term survival up to 20–25% (5).

In 2011, the new regimens Gem-Nab-Paclitaxel and FOLFIRINOX with the MPACT and ACCORD11, respectively, have showed for the first time a remarkable improved survival in metastatic and locally advanced pancreatic cancer (LA-PDAC) (6,7). In 2012, these regimens have been implemented with the PRODIGE24 for the first time as adjuvant treatment for resectable pancreatic cancer, showing an increased mean survival up to 54.4 months, compared with the 34.8 months of the previous standard Gemcitabine regimen (8).

In the last decade, neoadjuvant treatment (NAT) strategies are showing a crucial role in solid organ cancers such as breast, rectal, gastric cancer and pancreatic cancer, as well (9). Currently, several trials, such as the PRODIGE 48, 44 and 56 and NEOPAN are investigating with optimism the benefit of these regimens as NAT for potentially resectable pancreatic cancer (5). In this regard, NAT in borderline resectable (BR) or even resectable (R) PDAC has gained wide acceptance lately based on the results of several multicentric randomized clinical trials carried out in highly selected centers such as the PREOPANC, JANG and ESPAC-5F (5,10). The main potential claimed benefit of NAT is to improve the OS by increasing the R0 resections, treating micrometastasis, delivering chemotherapy to all patients, and making an adequate selection of patients who are likely to benefit from a pancreatectomy (11). To that purpose, portal venous resection (PVR) is an essential surgical maneuver to achieve R0 resection in many cases of BL-PDAC or LA-PDAC (12). Many studies showed the feasibility and safety of venous resection during pancreateoduodenectomy for PDAC; however, although short-term postoperative outcomes are acceptable, existing evidence on long-term survival on this topic is still limited (12). Therefore, it is essential to address the impact
of these so-called NAT regimens in PDAC with PVR not only focusing on surgical outcomes but also on overall and disease-free survival, as it is done in this study (1).

The article that comments this editorial, Machairas et al. reports the largest study to date including more than 1000 patients to address pancreaticoduodenectomy (PD) with concomitant PVR in an international setting (1). This is a retrospective, single cohort, multicenter including 23 high volume centers of pancreatic surgery, which included all consecutive patients with R/BR-PDAC undergoing PD with PVR with the aim to assess the impact of NAT on long-term oncological outcomes. The median OS for the NAT group was 28 months compared to 21 months in the non-neoadjuvant group (95% CI: 25–34 vs. 95% CI: 19–23; P<0.001) and in a subsequent sub-analysis was even showed improved survival when adding chemoradiotherapy in NAT regimen. This finding is also confirmed by the multivariate analyses being NAT an independent factor related to better survival. As secondary end-points the patients receiving NAT also had lower rates of PV involvement on final histology [(31.5%) vs. (49.3%); P<0.001] and higher R0 rates (57.5% vs. 46.6%, P=0.004). The overall conclusion of the study is the beneficial impact of NAT in terms of complete surgical margin resection and OS.

Despite the retrospective design of the study the authors deserve much credit as this is the largest PD with PVR cohort published to date giving a lot of insight into such an actual topic as the NAT in PADC. However, its inherent limitations as retrospective study precludes answering some open questions.

First of all, the authors chose to use the overall survival (OS) as primary end-point instead of disease-free survival or local recurrence. Considering the large sample population of the study, to mitigate bias of the non-randomly assignment, it might have been interesting to perform a propensity score matching study since the difference in OS within groups could also be explained by the fact that the groups were not comparable in terms of baseline characteristics.

Second, currently in literature there is a lack of homogeneity with regard to the definition of R/BR-PADC. There is no international consensus regarding the local staging classification of the PADC, since the NCCN first defined BR-PADC in 2006 (13). From a pragmatically point of view, the authors, in the limitation section, assume that PD with PVR is a surrogate of BR assessment; however, over 52% of the resections (Supplementary material) (1) were tangential resections, i.e., <180° grades, which leads to deem whether half of the patients could have been considered as R from the beginning and undergone upfront surgery. Nevertheless, as most of the available randomized trials on this topic (11,14,15), with the exception perhaps of PREOPANC (16), the spectrum of R-to-BR-PADC it is not so well defined, it is acceptable to accept the author's assumption.

Third, this large study cohort covers a 10 years period of time (from 2009–2018) in which the chemotherapy regimens have importantly evolved, taking for example the introduction of FOLFIRINOX in 2011 (7) as a milestone in PDAC treatment. However, the authors are not able to specify whether the majority of the patients received FOLFIRINOX or gemcitabine-based therapies with or without concomitant Nab-Placlitaxel. This would have been an important information to have, as randomized studies to date, such as PREOPANC (16) or Jang et al. (15) conclude that gemcitabine-based NAT do not improve OS compared to upfront surgery whereas it seems that there it is a trend towards improved OS when using Gemcitabine-capcitabine in combination or FOLFIRINOX according to the preliminary outcomes reflected in ESPAC-5F study presented at the ASCO 2020 meeting (17). Early results of this study showed one-year survival rate of 40% for immediate surgery and 77% for the NAT group, even if it remains unclear whether those are data from the 3-arms or specifically for FOLFIRINOX arm (17).

In the setting of NAT, the total number of chemotherapy cycles is important, as well, and few data are available in the literature concerning its relation with OS (14). However, with such great population, the number of chemotherapy cycles have not been investigated in this study (1).

In conclusion, this is a valuable paper that may permit to get a picture of OS of patients affected by PDAC after NAT with PVR. It might be interesting to take advantage from the recorded database of Machairas et al. group, enlarge this multicenter collaboration and further analysis some missing data.

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