Letter to the Editor



# Neoadjuvant chemoradiotherapy for pancreatic cancer is beneficial, but schedules should be improved

**Geertjan van Tienhoven[1], Eva Versteijne[1], Marc G. Besselink[2], Johanna W. Wilmink[2], Anna M. Bruynzeel[4]**

[1]Department of Radiation Oncology, Cancer Center Amsterdam, AmsterdamUMC, University of Amsterdam, Amsterdam, The Netherlands; [2]Department of Surgery, Cancer Center Amsterdam, AmsterdamUMC, University of Amsterdam, Amsterdam, The Netherlands; [3]Department of Medical Oncology, Cancer Center Amsterdam, AmsterdamUMC, University of Amsterdam, The Netherlands; [4]Department of Radiation Oncology, Cancer Center Amsterdam, AmsterdamUMC, Free University, Amsterdam, The Netherlands

*Correspondence to:* Geertjan van Tienhoven, MD, PhD. AMC, Department of Radiation Oncology, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. Email: g.vantienhoven@amsterdamumc.nl.

*Response to:* Chuong MD, Tchelebi LT, Tuli R. Neoadjuvant chemoradiation for resectable and borderline resectable pancreatic cancer: is there a benefit? Dig Med Res 2020. doi: 10.21037/dmr-20-41.

Received: 29 June 2020; Accepted: 14 July 2020; Published: 30 September 2020.
doi: 10.21037/dmr-20-99
**View this article at:** http://dx.doi.org/10.21037/dmr-20-99

First of all, we thank Chuong *et al.* (1) for their positive comments and their critical appraisal of our PREOPANC trial (2). We fully agree that we are in the middle of a paradigm shift from surgery as only potentially curative option via surgery followed by adjuvant therapy towards neoadjuvant therapy, if possible followed by surgery. This is a shift towards a truly multidisciplinary management. Perhaps the United States are ahead in this shift, since the neoadjuvant approach is strongly advocated, at least for borderline resectable pancreatic cancer (BRPC), while this is not yet the case in Europe (3,4).

The potential advantage of neoadjuvant treatment over immediate surgery followed by adjuvant therapy has long been obscure because of selection differences. Studies of neoadjuvant treatment typically include patients immediately after being diagnosed with resectable pancreatic cancer (RPC) or BRPC. A proportion of these patients fails before or during neoadjuvant treatment, at exploratory surgery, or in the first months after surgery because of the aggressiveness of the disease. Postoperative adjuvant treatment studies typically include patients who have had a successful resection and are fit enough to undergo the adjuvant treatment within 3 months thereafter. This excludes the relatively large group of patients failing before or at exploratory surgery or shortly thereafter. Due to this different selection, neoadjuvant studies report median survival rates between 12 and 23 months (5), whereas adjuvant studies typically report median survival rates of 25 up to 54 months (6). To overcome these selection differences we performed a systematic review of studies reporting the upfront surgery and/or the neoadjuvant approach by intention-to-treat and this indeed suggested that a neoadjuvant approach was better (7).

We agree with Chuong *et al.* about the challenges of the upfront surgery approach for RPC and BRPC and also agree with the potential advantages of the neoadjuvant approach: improving radical resection rate and other pathological outcomes of resections, potential (early) treatment of micrometastatic disease, and preventing patients with biologically aggressive tumours from undergoing futile surgery. In addition, compliance with chemoradiotherapy is better in the neoadjuvant setting. We also agree that the above mentioned consensus/ guidelines, and reviews are insufficient to prove the concept and that randomized evidence is warranted. Apart from our own PREOPANC trial, 5 other randomized trials have been performed so far. Two of these were prematurely closed for lack of accrual. One study was closed early because the interim analysis turned out positive, and one was published as a conference abstract only (2,8-12). A recent meta-analysis of these six trials confirms an overall survival benefit of the neoadjuvant approach, not only overall but also in the subsets of patients with RPC and BRPC separately (13).

This meta-analysis may be considered "proof of

principal" evidence for the neoadjuvant approach. However, as Chuong *et al.* already pointed out, the treatment schedules used in the various studies are heterogeneous and fairly old-fashioned. All schedules were gemcitabine based, two trials used chemotherapy only and four used chemoradiotherapy. When the PREOPANC trial protocol was written, most chemoradiotherapy schedules consisted of a full dose of radiation (about 50 Gy) combined with a low dose chemotherapy (5-fluorouracil or gemcitabine). At the same time, some European studies showed inferior results of chemoradiotherapy compared to (full dose) chemotherapy alone. Therefore, in the PREOPANC trial we deliberately chose a schedule that had a full dose of gemcitabine and an adapted dose of radiation, that was already established in a phase 1 study, escalating the dose of radiotherapy, and showed promising results in a subsequent phase 2 study (14,15).

Indeed, more contemporary schedules of both chemotherapy and radiotherapy should be applied and may further improve the results of neoadjuvant treatment. FOLFIRINOX is a good candidate, likely more effective than gemcitabine alone, currently used in our PREOPANC-2 trial and compared to the chemoradiotherapy of PREOPANC. Another frequently used chemotherapeutic option is gemcitabine-nab-paclitaxel. We do believe that radiation should play a role by improving the local tumour situation before explorative surgery. Stereotactic Body Radiation Therapy (SBRT) with daily online image guidance improves the precision and accuracy of treatment delivery and is a promising technique combining extremely high doses of radiation with little toxicity and a high local disease control (16). With SBRT, five fractions of 8 Gy can be applied within 2 weeks and it can be combined with FOLFIRINOX. To allow for an optimal locoregional effect this hould be scheduled early during the neo adjuvant treatment. Indeed, in various reviews and epidemiological studies SBRT coupled to multi agent chemotherapy is suggested to be superior, even in terms of overall survival, to conventionally fractionated radiation therapy and chemotherapy alone (17,18). Remarkably, this even seems the case in primary resectable pancreatic cancer (19).

To conclude, we do agree that the paradigm is shifting towards a neoadjuvant approach for RPC and BRPC, and that our PREOPANC trial, together with five other randomized trials amounts increasing evidence for that. Further research should include more contemporary forms of chemotherapy such as FOLFIRINOX or gemcitabine-nab-paclitaxel, probably combined with stereotactic radiation therapy. Currently, we are including patients in the PREOPANC-2 trial that compares totally neoadjuvant FOLFIRINOX (eight courses) with the neoadjuvant schedule of the PREOPANC trial. If, indeed, FOLFIRINOX appears to be superior, the addition of SBRT, added early in the neo adjuvant treatment should next be investigated.

## Acknowledgments

We acknowledge all the patients that participate in our DPCG trials PREOPANC and PREOPANC-2, without whom our clinical research would have been impossible.
*Funding:* The PREOPANC trial was supported by the Dutch Cancer Society (KWF; grant No. UVA 2012-5696), which funded the data management (central and local) and onsite monitoring of the trial. KWF did not influence the design or analysis of the study.

## 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:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr-20-99). AMB reports personal fees from ViewRay Inc., outside the submitted work. The other 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 work are appropriately investigated and resolved.

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doi: 10.21037/dmr-20-99

**Cite this article as:** van Tienhoven G, Versteijne E, Besselink MG, Wilmink JW, Bruynzeel AM. Neoadjuvant chemoradiotherapy for pancreatic cancer is beneficial, but schedules should be improved. Dig Med Res 2020;3:33.