Author’s response to reviews

Title: Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT)) - Study protocol for a national, multicentre randomized controlled trial

Authors:
Knut Jørgen Labori (kjlabori@gmail.com;uxknab@ous-hf.no)
Kristoffer Lassen (krlass@ous-hf.no)
Dag Hoem (dag.hoem@helse-bergen.no)
Jon Grønbech (jon.e.gronbech@ntnu.no)
Jon Søreide (jonarne.soreide@uib.no)
Kim Mortensen (Kim.Erlend.Mortensen@unn.no)
Rune Smaaland (rune.smaaland@sus.no)
Halfdan Sørbye (halfdan.sorbye@helse-bergen.no)
Caroline Verbeke (c.s.verbeke@medisin.uio.no)
Svein Dueland (svedue@ous-hf.no)

Version: 2 Date: 07 Jul 2017

Author’s response to reviews:

Dear Editor
BMC Surgery

Thank you for reviewing our manuscript “Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1)) – Study protocol for a national multicentre randomized controlled trial”.

We are grateful to the reviewers for their valuable comments and suggestions. Please find below our detailed point-by-point reply.
Reviewer 1:

1. In some cases pathological examination might reveal that the resected tumor is not optimal target for this study, such as intra-ductal papillary mucinous neoplasm or neuroendocrine neoplasms, even though the cytological confirmation was obtained before enrollment. How will you manage such cases?

It is highly unlikely that IPMN, a cystic lesion, should be missed or misdiagnosed as pancreatic cancer on preoperative imaging. A small IPMN in association or concomitant with invasive ductal adenocarcinoma that was invisible on preoperative imaging but detected on pathology examination of the resection specimen does not represent a reason for exclusion of the case. Neuroendocrine tumours of the pancreas are likely to be correctly diagnosed on preoperative imaging and can be discerned from pancreatic ductal adenocarcinoma by preoperative cytology (including immunocytochemistry).

2. Why do you use non-equal (3:2) randomization? Please explain and add the reason.

An estimated one-third of patients in the NT group will not be available for evaluation regarding the primary endpoint of the study for the following reasons: (i) development of distant metastasis or local progression under neoadjuvant treatment, and (ii) failure to achieve adequate reduction of bilirubin levels (below 50 µmol/L) within 4 weeks after randomization. These patients will thus not be available for evaluation per protocol and those who do not reach resection at all will not be analyzable with regard to the primary endpoint. While the exact incidence of these adverse events is not known, a 3:2 randomization was deemed appropriate to counterbalance and ensure approximately equally sized groups at primary endpoint. While this was discussed in the paragraph: “Sample-size calculation” of the original version of the manuscript, the following paragraph “Handling cross-over, drop-outs and exclusion” has now been added to the revised manuscript:

“Post-randomisation exclusion is to be avoided at “all costs”. While patients are offered to withdraw without giving any reason, this is not considered very likely as both groups provide standard treatment of today, albeit at reversed sequence for some (Group 2). Patients who for some reason cannot fulfil neoadjuvant chemotherapy (Group 2) but are still considered
candidates for resection will be offered resection according to standard criteria. The reasons for this might be:

- Inability to achieve adequate reduction of bilirubin levels by drainage within 4 weeks
- Massive adverse reactions to first cycle chemotherapy

These patients are considered cross-over provided no single cycle was completed, but remain under analysis by intention-to-treat. They are not excluded from the trial. Patients who suffer other incidents post-randomisation but prior to any treatment are still analysed under intention-to-treat.”

3. You estimated one-third of the NT group would not reach resection. However previous reports you cited showed that the resection rate of resectable tumor was 87% in ref.16 and 75% in ref.17. Please explain why you estimate the resection rate of your cohort such low.

Thank you for this specific comment. An estimated 25 % will not reach resection due to development of distant metastasis, locoregional progression or poor performance status during neoadjuvant chemotherapy (25.4 % in reference 16). This is in accordance with the results from an Italian study showing that 22 % of the patients with resectable pancreatic cancer could not be offered surgery after neoadjuvant chemoradiotherapy (R. Casadei et al. J Gastrointest Surg 2016, 9:1802–1812). We choose to err on the side of including a few patients too many than too few in a completely unselected cohort where exact prediction is impossible. Please, see also the reply to comment 2.

4. Do you have any stratification factors to balance the randomization such as radiological tumor size or value of serum tumor marker after biliary drainage? You mentioned that randomization would be balanced only by each centers.
The study has no stratification factors such as radiological tumour size or values of tumour markers. However, as stated in the protocol, randomization is stratified for each centre and will be generated in blocks of unknown and varying size (4-6 patients per block) to ensure that groups are balanced at all centres, irrespective of the final number of patients recruited. Thus, at each centre this will ensure a balanced number of patients being randomized to either surgery first or neoadjuvant chemotherapy. In our opinion, tumour size stratification is not necessary, because all patients included in the study have a tumour that fulfills the NCCN definition of resectability. However, radiological tumour size and CA19-9 values in the two groups will be included in the data set and study analysis.

5. When the patient with obstructive jaundice and randomized to NT group efficacy of drainage must influence and (in some cases) it might break down the randomization (Figure 1). Randomization should be performed after appropriate biliary drainage.

I am afraid that we disagree on this point and argue that randomization must be performed at the time of tissue diagnosis and before appropriate biliary drainage to avoid unnecessary ERCP/PTC and biliary drainage in the surgery-first group. In patients randomized to surgery-first, biliary drainage is only undertaken if there is a clinical indication.

6. Is the adjuvant treatment of both arms in the protocol of this study? If so, please describe how and how long the agents will be administered. Safety evaluation should be described.

Adjuvant chemotherapy is described in detail in the paragraph “Treatment” of the original manuscript version. To address the safety issue, the following paragraph has been added to the paragraph “Safety”:

“The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authority and Ethics Committee after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated. All other suspected
serious unexpected adverse reactions will be reported to the Competent Authority concerned and to the Ethics Committee concerned as soon as of first knowledge by the sponsor.”

Reviewer 2:

1. This is a very timely study and scientifically valid, except that you have added potential bias by making Time 0 from the beginning of treatment (there might be delays in either arm, probably more in SF). I would suggest Time 0 at the time of tissue diagnosis. (Obviously, marking survival from time of resection provides a lead time bias of months in favor of SF (in your secondary end points)).

Time 0 for the primary endpoint in this study (overall mortality at one year for patients who undergo resection) is set at the time of commencement of allocated treatment (date of first cycle of neoadjuvant chemotherapy in Group 1 and date of surgery in Group 2) and expected to be about 2 weeks after tissue diagnosis in both arms. For the most important secondary endpoint (intention-to-treat analysis), time 0 is set at the date of randomization, which will be performed immediately after the tissue diagnosis has been confirmed.

2. It will be very important to record and follow ALL patients from time of entry onto the trial, as there will be those dropping out from each arm (distant metastases, toxicity, failed resection for whatever reason) and these will be of great importance and interest. Similarly, for the primary end point, you look at only those having resections. Those that fail to have resections (distant metastases, local irresectability, complications from NT) will also be of great importance.

We fully agree. All patients entered into the trial will be recorded, followed and analysed for overall survival after the date of randomization (intention-to-treat), overall survival at 3 and 5 years, feasibility of neoadjuvant and adjuvant chemotherapy (Common Terminology Criteria for Adverse Events, grade 3-5, dose reduction, dose delay), completion rates of all parts of multimodal treatment, quality of life (EORTC QLQ-30), performance status (ECOG) compared
to baseline values, and exploratory translational research. This important issue was already stated in the original version of the manuscript in the section “Secondary end points”.

Furthermore we will record and follow up all eligible patients not entering the trial and present these patients in a Consort flow diagram.

3. The method of determining the biologic response to the NAT should be detailed, such as in Chatterjee et al. Cancer 118:3182-90, 2012. This response correlates strongly with overall survival.

As stated in the manuscript in the section “Pathology examination”, tumour regression grading will be performed according to guidelines of the College of American Pathologists (CAP) (Reference 33; Washington K et al. Protocol for the examination of specimens from patients with carcinoma of the exocrine pancreas. College of American Pathologists, available from: http://www.cap.org). However, there are concerns regarding the robustness and reproducibility of existing tumour regression grading systems, incl. those proposed by CAP and Chatterjee et al. (Please see reference 32: Verbeke C et al. Cancer Treatment Rev 2015;41:17-26), and therefore central pathology review of tumour regression grading will be undertaken and alternative scoring systems will be tested.

4. Is there central Radiology review? This would be important to assure equality of the groups, as would initial CA19-9 values and those CA19-9 values after the completion of NAT.

A central radiology review is not planned. This was not deemed necessary, because the inclusion criteria follow the NCCN guidelines that allow stringent definition of a resectable tumour and exclusion of borderline resectable tumours (definition of a resectable tumor: 1) No tumour contact with the superior mesenteric vein or portal vein or ≤ 180 ° contact without vein contour irregularity, 2) No arterial tumour contact (coeliac axis, common hepatic artery or mesenteric superior artery), 3) No distant metastasis). CA19-9 values are recorded before inclusion, after completion of neoadjuvant chemotherapy and during follow-up, and these data will be included in the study analysis.
5. You will receive complaints, particularly if the arms show better 1 year survival in the NAT group, that the chemo treatments are not equivalent and thus favor the NAT arm. Unless your findings are striking, another trial with exactly the same chemo arms may be in order.

We agree that this complaint may be raised. However, for this trial only the most effective neoadjuvant chemotherapy regimen was deemed appropriate (FOLFIRINOX), while the regimen that in Norway is currently standard of care was chosen for adjuvant chemotherapy (Gem-Cap).

Editor

If the revision work would generate any difference in the protocol that have been approved by the ethics committee, you need to seek further approval from the committee to allow the modification. Certificate from the ethics committee that allow the change of the protocol should be accompany with the revision work.

The revision has not generated any differences in the protocol that would require renewed approval by the ethics committee.

With kind regards

Knut Jørgen Labori

Oslo July 1, 2017