Protocol

Treatment of primary irresectable, locally advanced pancreatic cancer.

The S-LAPC trial

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Background:

Due to diffuse symptoms pancreatic cancer is diagnosed in 80% or more when it is already too late for a primary resection. For those patients with a resectable cancer the 5 year survival is about 20% compared to <5% in all pancreatic cancers and the median survival after a radical resection is about 21 months compared to 6 months if no resection is done. Patients with incomplete tumor clearance after resection (R2) is probably not much better off compared to inoperable locally advanced pancreatic cancer. Margin resection status seems to be of great importance regarding the prognosis. It is therefore of great value to diagnose those patients where there is a reasonable chance to resect the tumor with a negative margin even though there is vascular involvement.

The traditional two main parameters used for evaluating tumor vessel encasement are; the grade of the circumferential involvement and the length that the tumor is in contact with the vessel. The importance of both grade and length of such encasements probably differs from arteries to veins in the pancreatic region. For instance a <50% circumferential involvement in a short vein segment is easy to deal with for the trained surgeon, whereas corresponding involvement of arteries makes it less likely to achieve a R0 resection. It is possible that also periarterial stranding has to be taken into account. Moreover, venous narrowing or complete obstruction might jeopardize surgical resection.
About 30-40% of the patients have locally advanced pancreatic cancer (LAPC) at the time of diagnosis, with extensive tumor growth over the adjacent organs, and particularly due to vascular involvement of the tumor – venous and/or arterial, but without evidence of distant metastases. These tumors are usually considered unresectable due to the fact that complete surgical excision with negative pathologic margins is not possible using standard surgical procedures, with a survival no different than that in metastatic disease. In many of these patients, however, radical (R0) resection could be achieved if simultaneous venous and/or arterial en-block resection and reconstruction is performed after neoadjuvant downstaging oncologic therapy (most often chemoradiotherapy).

The best diagnostic tool at present time is the latest multislice multiphase contrast enhanced computed tomography (CT) with software for 3-D reconstruction. Through a joint effort between dedicated radiologists and pancreatic surgeons at Karolinska University Hospital the following system has been launched and evaluated, to preoperatively categorize the pancreatic tumors according to the CT findings:

**A1** Resectable tumor status when the tumor is not reaching the SMA/hepatic arteries/celiac trunk or SMV/portal vein (PV)

**A2** Resectable tumor status when there is ≤ 50% tumor encasement directly against the SMV/PV for <2 cm in length and no deformity. No abutment to main arteries but so called spikes reaching the artery may be accepted.

**B1** Resectable tumor status necessitating venous resection when >50% encasement of SMV/portal vein or deformity/occlusion is seen extending <2 cm. No involvement of main arteries, except for an isolated spiking towards the vessel, can be accepted.

**B2** Resectable tumor status without neoadjuvant treatment, if an anomalous artery (e.g. right hepatic artery originating from SMA with tumor involvement, i.e. “unlucky” anatomy where a normal artery anatomy otherwise would have graded the patient as A2 or B1. The same is true for a tumor extension (spike<) towards the common hepatic artery (such as at the origin of the gastroduodenal artery), requiring a limited resection of the artery and end to end anastomosis.

**C** represents a borderline resectable tumor status, when either the tumor encase SMV/portal vein >50% and ≥2 cm of length but where reconstruction is technically possible including grafts if judged necessary. To this category contain also patients with a tumor status as above and/or involvement of SMA/CHA and/or the celiac trunk of ≤50% and <2 cm, again offering where it is technically possible to carry out a straightforward en bloc vessel resection and reconstruction. Due to the locally advanced tumor status neoadjuvant treatment is
recommended whereupon an exploration with curative intent is recommended if the tumor volume-status is radiologically stable or reduced upon treatment.

D tumors are defined as locally advanced tumors that have reached a more advanced arterial encasement (> 50-100 %). These tumors are today considered incurable and are usually offered only palliative treatment. However, these tumors may allegedly be divided into two sub-categories depending on whether reconstruction of arteries or veins is technically possible (D1) or not (D2). Involvement of veins or arteries in the mesenteric root (“kvasten”) as well as the aortic wall as represent a situation, together with encasement the hepatic arteries beyond the proper hepatic artery (except when the right hepatic artery stems from the SMA), are all definitely regarded as signs of irresectability i.e. these tumors may be regarded as D2-tumor. The remaining D-tumors are those with an advanced arterial encasement of the superior mesenteric artery or celiac trunk length, but where anatomical circumstances offer a chance for proper arterial reconstruction (often together with adjacent portal-mesenteric vein segments) after neoadjuvant treatment (D1).

Many studies have shown that resection of pancreatic tumor with venous resection have equal morbidity/mortality compared to when no venous resection is done, at least in experienced hands. The case for arterial reconstructions is not that unanimous but several authors have shown case series that this is a feasible option for longer survival in the right patient, as long as the margin is clear of tumor involvement. The prognosis is worse compared to resections without the necessity to reconstruct the SMA, the celiac trunk or hepatic artery. There is also heterogeneity in the literature regarding the definition of borderline resectability and locally advanced (incurable) pancreatic cancer. Another aspect is that former CT generations seem to slightly overestimate vascular involvement of the tumor but remain accurate regarding the retroperitoneal fat tissue infiltration.

Few if any prospective studies have been completed where arterial reconstructions are performed as part of a predefined study protocol particularly so when taking the advantage of the most updated CT technology.

During recent years promising improvements in CT scanning have emerged and enhance our possibility to accurately delineate the tumor from adjacent healthy tissue. To this can be added the introduction and evaluation of novel chemotherapy regimens with or without the addition of radiotherapy. Moreover translational research has opened up a new therapeutic principle, in the form of immune modulating treatment. All these options are of great importance for patients suffering from pancreatic cancer due to its dismal prognosis. Even small
improvements could be of importance for these patients. There are a number of studies ongoing in resectable tumor stages and the neoadjuvant therapeutic concept has been met with great expectations. In parallel with these therapeutic endeavors those patients with locally advanced tumor stages mandate special attention. One of the problems with these tumor stages is that very few data are available from prospective controlled clinical trials to guide future study design in terms of fundamentally important issues such as; safety, tolerability and feasibility. In the field of GI surgical oncology it can be argued that until proven otherwise, the therapeutic concept which should be prevailing is that the original anatomical extent of the tumor growth should determine the extent of en bloc resection even in a situation where a stable disease or regression has been observed as a response to neoadjuvant therapy. The process aimed at developing the future therapeutic concepts in locally advanced pancreatic cancer requires a number of pivotal prerequisites.

- The definition and separation of primary irresectable from resectable pancreatic cancers(category C/D) with wider definitions of what is traditionally recognized, specifically on the arterial side, has to be agreed upon.
- Tumors originating in the head- neck and body regions of the pancreas harbor the greatest demands in terms of vascular involvement and subsequent challenges concerning the quality of reconstruction.
- Tumors originating in the distal body and tail of the gland are when locally advanced, often mandating only multivisceral resections without special requirements for advanced vascular reconstructions.
- The latest technology in computerized tomography with 3-D software should give a more distinctive description of the tumor-vascular relation.
- A national forum-platform (MDT platform) has to be established where these patients can be carefully evaluated.
- These patients should surgically be treated at a highly specialized center with the latest diagnostic facilities, MDT-conferences and where large volumes of patients with pancreatic cancer are diagnosed and treated, and where advanced vascular resections are standard procedure.
- Combined arterial and venous en bloc resections and reconstructions are complex and rare cases which demands centralization within the country to one unit.
Objectives:

- To study whether patients with pancreatic head cancers of categories C and D1 and/or locally advanced pancreatic tail cancer can be offered and tolerate neoadjuvant therapy followed by advanced en bloc resection including major vessels and/or multiple organs adjacent to the gland.

Patients and methods:

Eligible Patients:

- Pancreatic cancer of category C/D1 (with a wider anatomical categorization, see below) where the initial assessment and anatomical tumor invasion allows for en bloc resection and even complex vascular reconstruction.
- Potentially resectable mass in the pancreatic head as defined by MDCT criteria.
- Histologically or cytologically proven pancreatic ductal adenocarcinoma (including variants).
- Able to undergo biliary stenting.
- 18-75 years
- WHO performance status 0, 1 or 2.
- Platelets >100 x 10^9/l; WBC > 3 x 10^9/l; neutrophils > 1.5 x 10^9/l, serum bilirubin < 50 mol/l, serum creatinine < 180 mol/l.
- Patient able to comply with protocol requirements and deemed fit for surgical resection.
- Written informed consent.

Exclusion criteria:

- Distant metastatic disease.
- History of previous or concurrent malignancy diagnoses (except curatively-treated basal cell carcinoma of skin, carcinoma in situ of cervix).
- Serious medical or psychological condition precluding neoadjuvant treatment and surgical resection.
- Previous chemotherapy or chemoradiotherapy.
- Pregnancy.
- WHO status 3 or 4.
- New York Heart Association Classification Grade III or IV.

**Radiology:**

All CT examinations were performed on a 64-channel MDCT scanner (LightSpeed VCT or LightSpeed VCT XT, GE Healthcare, Milwaukee, WI). Intravenous contrast media was administered followed by saline flush. A triple phase protocol, with a non-contrast phase (NCP), a pancreatic parenchymal phase (PPP) and a portal venous phase (PVP), was used. To reduce patient-to-patient variability, SmartPrep (GE Healthcare, Milwaukee, WI) real-time tracking of contrast in the aorta was used at the level of the first lumbar vertebra, and the scan start threshold was set at 160 Hounsfield units (HU) for obtaining the PPP. The PVP was obtained after further 30 seconds delay. All contrast-enhanced images were reconstructed in 0.6 mm slices that were reformatted in the transversal, coronal and sagittal planes with 5 mm slice thickness and 2.5 mm interval. Another set of images, with thinner sections (3 mm) and interval (1.5 mm), and a smaller field-of-view (focused on the pancreas), were in addition created in all three planes. From the CT scanning a pre op 3-D reconstructed layered venous and arterial “tree” with its connection to tumor tissue is mandatory for proper planning of the vascular resection/reconstruction.

**Table 1. CT protocol**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Fasting for 4 hours</th>
</tr>
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<tbody>
<tr>
<td>Oral contrast</td>
<td>1000ml water, 30min prior to examination</td>
</tr>
<tr>
<td>Intravenous contrast</td>
<td>Iomeron 400 or Visipaque 320,</td>
</tr>
<tr>
<td>a. Dose</td>
<td>0.75g l/kg body weight (+/- 10%)</td>
</tr>
<tr>
<td>b. Injection time</td>
<td>25 seconds</td>
</tr>
<tr>
<td>c. Flushing</td>
<td>50 ml NaCl – 25 sec</td>
</tr>
<tr>
<td>Scan range</td>
<td>Upper abdomen</td>
</tr>
<tr>
<td>a. NCP</td>
<td>Upper abdomen</td>
</tr>
<tr>
<td>b. PPP</td>
<td>Upper abdomen + small pelvis</td>
</tr>
<tr>
<td>c. PVP</td>
<td></td>
</tr>
<tr>
<td>Scanning parameters</td>
<td></td>
</tr>
<tr>
<td>a. (section)collimation</td>
<td>0.625 mm</td>
</tr>
<tr>
<td>b. (table)increment</td>
<td>0.6 mm</td>
</tr>
</tbody>
</table>
Reconstructions
  a. slice thickness
  b. interval

<table>
<thead>
<tr>
<th>c. tube current</th>
<th>120kV</th>
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<td></td>
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</table>

Axial, coronal and sagittal

5 mm (and 3mm with smaller FOV focused on the pancreas)

2.5 mm (and 1.5 mm with smaller FOV focused on the pancreas)

NCP, non contrast phase; PPP, Pancreatic parenchymal phase; PVP, Portal venous phase

Table 2. Grading of vascular involvement

<table>
<thead>
<tr>
<th>1. Vessel circumference (%)</th>
<th>2. Vessel length (cm)</th>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1-24</td>
</tr>
<tr>
<td>3</td>
<td>25-49</td>
</tr>
<tr>
<td>4</td>
<td>50-74</td>
</tr>
<tr>
<td>5</td>
<td>≥ 75</td>
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</table>

<table>
<thead>
<tr>
<th>1. Vessel circumference (%)</th>
<th>2. Vessel length (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1-0.9</td>
</tr>
<tr>
<td>3</td>
<td>1.0-1.9</td>
</tr>
<tr>
<td>4</td>
<td>2.0-2.9</td>
</tr>
<tr>
<td>5</td>
<td>≥ 3</td>
</tr>
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</table>
### The used classification

<table>
<thead>
<tr>
<th>Vein</th>
<th>Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 None</td>
<td>None</td>
</tr>
<tr>
<td>A2 SMV/PV&lt; 50%</td>
<td>None</td>
</tr>
<tr>
<td>B1 SMV/PV &gt; 50% and&lt;2cm</td>
<td>None</td>
</tr>
<tr>
<td>B2 None or SMV/PV &lt; 50% and</td>
<td>HA &lt; 50% and&lt;2cm, right HA originating from SMA passing through the tumor mass</td>
</tr>
<tr>
<td>C SMV/PV &gt; 50% and&gt; 2cm</td>
<td>and/or CAor/andSMA&lt; 50% and&lt;2cm</td>
</tr>
<tr>
<td>D1 An advanced arterial encasement of the superior mesenteric artery or celiac trunk length, but where anatomical circumstances offer a chance for proper arterial reconstruction after neoadjuvant treatment and resection of the native tumor margins.</td>
<td>and/or Prox. HA or CA or SMA&gt; 50% and/or&gt; 2cm without encasement of mesenteric branching</td>
</tr>
<tr>
<td>D2 Involvement of veins or arteries in the mesenteric root (“kvasten”) as well as the aortic wall as well a situation with encasement the hepatic arteries beyond the proper hepatic artery (except when the right hepatic artery stems from the SMA) is definitely regarded as a sign of irresectability Prox. HA or CA or SMA&gt; 50% and&gt; 2cm and encasement of mesenteric branching</td>
<td></td>
</tr>
</tbody>
</table>

SMV, superior mesenteric vein; PV, portal vein; HA, hepatic artery; CA, celiac artery; SMA, superior mesenteric artery

### Arteries with borderline resectability:
- **Superior mesenteric artery (SMA)**: ≤50% circumferential tumor abutment of ≤2 cm axial length.
- **Celiac trunk**: Up to 100% circumferential encasement not engaging the aortic wall making it possible to divide the trunk flush against the aorta with clearance from the tumor (R0). Patch repair of the aortic origin of the trunk is accepted.
- **Common hepatic artery (CHA) and the proper hepatic artery (PHA)**: Up to 100%
circumferential encasement but no tumor growth onto left and right hepatic artery can be accepted, with the exception when the right hepatic artery stems from the SMA.

**Veins with borderline resectability:**
- Portal vein (PV) and the superior mesenteric vein (SMV): Tumor engagement of the portal bifurcation and not peripheral to the division of the SMV into jejunal branches are considered to be signs of irresectability. Only a short total occlusion ($\leq 2$cm) can be accepted where the portal vein above and SMV below are of adequate size for a safe anastomosis.

Tumor encasement of the anterior part ($\leq 25\%$) of the caval vein is considered to be compatible with resectability including the confluence of the left renal vein and the caval vein. In similar situation it may be necessary to apply a temporary veno-venous by-pass

**Neoadjuvant treatment:**

The available therapeutic options to manage LAPC are systemic chemotherapy (CT) alone or chemoradiotherapy (CRT) but the choice of one or the other of these treatments is controversial. Moreover, it is difficult to have a clear opinion because in most series, patients with LAPC and metastatic carcinomas have not been studied separately. The administration of CRT as a first line treatment in patients with cancer of the pancreas has the following drawbacks: it is administered in certain cases to patients in poor condition at diagnosis, who cannot tolerate an aggressive treatment. It is also well known that metastases may rapidly occur ($< 3$-4 months) in 20%-30% of patients receiving preoperative CT.

A different strategy has been proposed containing initial treatment with CT for three months and if the tumour is controlled (partial response or stabilization), administration of CRT to finalize treatment. This strategy was tested in the recently reported randomised controlled LAP 07 (ASCO 2013), where systemic gemcitabine was given followed by CRT in patients with stable or responding tumours. A survival benefit for this strategy could not be demonstrated compared with continued systemic therapy only (ASCO 2013).

The new triplet combination chemotherapy FOLFIRINOX (oxaliplatin 85 mg/m$^2$, irinotecan 180 mg/m$^2$, leucovorin 400 mg/m$^2$, and 5-fluorouracil (400 mg/m$^2$) given as a bolus followed by 2,400 mg/m$^2$ administered as a 46-h continuous infusion q 2 weeks) has been shown to be
more effective than single therapy with gemcitabine in patients with metastatic disease or locally advanced cancers in terms of response rate (32% vs 9%) and overall survival (11.1 vs 6.8 months)

In patients with primarily resectable pancreatic cancers 6 months of adjuvant systemic therapy with either 5-Fu/lv or gemcitabine increases the median survival, viz. to 24 months, and the 5 year overall survival by 10-15% compared with surgical resection alone

In this protocol we therefore test if a more intensified pre-operative systemic chemotherapy, viz. 10 weeks of FOLFIRINOX, can convert a clinically significant rate of patients with initially unresectable LAPC resectable, i.e. 30%. Furthermore, patients undergoing R_{0-1} will receive 3 months of post-operative 5-Fu/lv as adjuvant therapy. The goal with respect to median overall survival for the entire cohort will be 24 months. The latter median overall survival is identical with earlier reports on the effect of adjuvant chemotherapy in patients with primarily resectable cancers

Non-responding patients will be managed according to local investigators’ standard of care regimen which may include a switch of systemic therapies, CRT, or best supportive care only.

In the event of predefined toxic events, protocol specified treatment modifications were permitted. If the granulocyte count decreased to 500 to 999 per cubic millimeter or if the platelet count was 50,000 to 100,000 per cubic millimeter and/or in case of grade 2, 3, or 4
neutropenia or thrombocytopenia, FOLFIRINOX administration will be delayed until recovery and doses will then be reduced according to clinical routine.

Grading of toxicities to neoadjuvant and adjuvant chemotherapy is done using the “Common Terminology Criteria for Adverse Events” version 3 based on the worst toxicity observed after the last treatment (http://ctep.cancer.gov/forms/CTCAEv3.pdf)

Toxicity

Myelosuppression +++

Emesis +++

Alopecia ++

Mucositis ++

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
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<tbody>
<tr>
<td>Fluorouracil</td>
<td>Palmar-plantar erythrodysesthesia, diarrhoea, chest pain</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Acute cholinergic syndrome, diarrhoea (may be delayed)</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Peripheral neuropathy (cumulative), acute laryngopharyngeal dysasthesia (increase duration of infusion)</td>
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Anemia of any grade does not require dose modifications. A neutrophil count of greater than 1000/μl and a platelet count greater than 100’000/μl are required for full dose. If on the day of planned treatment neutrophil counts between 500 and 1000/μl or platelet counts between 75’000 and 100’000/μl are found, the doses are reduced to 75% of the starting dose. The treatment is withheld in case of a neutrophil count below 500/μl or a platelet count below 75’000/μl.
For those toxicities considered by the investigator to be unlikely to become serious or life-threatening and which do not result in a delay or interruption of therapy (e.g. alopecia), treatment will be continued at the same dose without reduction or interruption.

Treatment can be restarted as soon as neutrophil and platelet counts are greater than 1000/μl and 100’000/μl, respectively.

If patients experience nausea/vomiting after treatment despite routine use of 5-HT-blockers and steroids (dexamethason dose may be increased up to 20mg iv. or po.), metoclopramide and/or domperidone is recommended. Other drugs such as aprepitant or palonosetron may be used. When nausea and vomiting occur despite prophylaxis, intensified and effective symptomatic treatment has to be initiated immediately.

At the start of every cycle, the patient’s status will be assessed according to his or her medical history, complete physical examination by a physician, ECOG performance status, and complete blood counts and blood chemical tests. Baseline evaluations also included measurement of the serum carbohydrate antigen 19-9 level, a computed tomographic (CT) evaluation, and assessment of the patient’s quality of life with the use of the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (QLQ-C30, version 3.0)

**Termination (discontinuation) of neoadjuvant chemotherapy**

Neoadjuvant chemotherapy is terminated on a patient’s request or if a dose limiting toxicity requires a treatment delay of more than 14 days (interval between two treatments > 28 days). Also, treatment can be terminated upon the recommendation of the investigator due to other relevant medical conditions (e.g. myocardial infarction, pulmonary embolism, etc) which interfere with the study treatment (chemotherapy or surgery).

**Patient’s withdrawal criteria**

- Disease progression during treatment.
- Limiting toxicity
- Patient refusal
- Investigator’s decision
- Lost to follow up
- Treatment delays of more than 28 days for patients receiving FOLIRINOX

**Definition of Response**

The modified Response Evaluation Criteria in Solid tumors (RECIST) criteria will be used for this trial for objective tumor response assessment; details are given in Appendix 4, also see the Trial Plan for timing of the assessments. RECIST will be utilized during the treatment period but the formula will be used for rules of reintroduction.

- Complete Response (CR): disappearance of all target lesions;
- Partial Response (PR): at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter;
- Progression Disease (PD): at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions;
- Stable disease (SD): neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

**MDT conference:**

All patients are presented and discussed at national MDT conference, which is held every week in order to make a final judgment of the diagnostic work up and to decide if the
candidates can be enrolled. After completion of the induction therapy every patient is presented to the same board where the final decision of if and when the surgery will be completed.

**Re-staging:**

All patients recover for 4-6 weeks after neoadjuvant therapy and undergo MDCT. Within that time slot a renewed staging (see above) has to be completed. If the patient has not developed metastases or unresectable locally advanced disease, they will undergo surgical exploration for resection.

**Surgery:**

- Total pancreatic resection with or without multivisceral resections and ± islet auto-transplantation is the procedure of choice to minimize the risk of pancreatic fistula exposing the vascular reconstruction to enhanced risk. When the trunk is resected and the left gastric artery cannot be reconnected, total gastrectomy has to be done.

In a situation with a tumor originating in the body and tail of the pancreas, leaving the SMA and hepatic arteries intact but having a proximal involvement of the celiac trunk, the gastroduodenal artery together with the intact pancreatic arcade can secure the hepatic arterial supply without additional vascular reconstructions.

**Arterial reconstruction:** If possible tension-free end-to-end anastomosis with or without graft preferably using the splenic artery, internal iliac artery, gonad vein or saphenous vein. (e.g. the splenic artery dissected free to the left, divided, angled to the right and anastomosed to the proper hepatic artery or using the gonad vein/saphenous vein between the infra-renal aorta or right renal artery to an anastomosis with the hepatic arteries). If autologous vessel graft is impossible to use, the externally strengthened ePTFE 6, 8 or 10 mm graft could be contemplated, but as the operating area is contaminated, there is a high risk of graft infection. Blood flow is checked before reconstruction (for reference) and after anastomosis with Doppler. The warm ischemia time is recorded.

**Venous reconstruction:** Mobilizing the mesentery when needed according to the Cattell-Braasch maneuver for a tension-free venous anastomosis. If this is not enough, the triangular
ligament of the liver can be cut to mobilize the liver slightly downward to even further reduce tension over the anastomosis. If only a smaller part of the venous wall is infiltrated by tumor, tangential resections with or without venous patch (no significant stricture should be allowed) could be done.

SMV/portal resections down to immediately proximal of SMV jejunal branching with direct end to end anastomosis. If the gap is > 5cm interpositions grafting may be necessary using internal jugular vein, left renal vein or the major saphenous vein. It is important to have a graft of similar diameter. The saphenous vein could be sutured together to the double diameter if necessary. The internal jugular and left renal veins often have the right diameter. The venous anastomosis is accomplished using continuous Prolene/ProNova (5-0) and to reduce the risk of stricture the knot is tightened with a “growth factor”, i.e. the knot is constructed about 1/2 of the venous diameter away from the vein wall according to Starzl. The splenic vein could be included in the anastomosis but if difficult it could just be ligated if the gastrica brevis vessels and/or the inferior mesenteric vein (IMV) (if it flows into the splenic vein) are spared.

Vena cava wall resections can often be sutured directly as long as the vessel diameter after reconstruction still is >50%, otherwise patch grafting should be used. Preferably using autologous vein patch and ePTFE as second choice.

Portal clamping time is recorded.

**Portal vein arterialization (PVA):** A possibility to increase oxygenized blood to the liver to enhance liver recovery and reduce the risk of liver absceses after ischemic events such as after failing to reconstruct for example a right or left hepatic artery. The gastro-duodenal artery could be anastomosed to the portal vein (end-to-side), the ileocolic artery or a peripheral jejuna artery could be connected (side-to-side) with a SMV vein.

**Per op flow measure:** During the operation Doppler measurement of flow before and after arterial/venous reconstruction should be performed. If the arteries are constricted after manipulation, bathing the area with smooth muscle relaxant for a couple of minutes (e.g. nitroglycerin) could give a more realistic flow values.

**Drains:** Standard is 2 Blake drains (passive) not too near the vascular anastomosis or graft.

**Post operative surveillance and therapy:**
**First 5 days after surgery:**
Routine post operative care asa for all pancreatic resections including daily sampling of blood tests regarding hemoglobin, albumin, pancreas-amylase, inflammation (CRP, WBC), liver function (Bilirubin, ASAT/ALAT, GT, ALP and INR), kidney function (creatinin and urine volume), output in drains (volume, bilirubin, pancreas-amylase and hemoglobin), blood gas samples including lactate, and D-Dimer.

Daily ultrasound/Doppler of reconstructed vessels measuring flow and patency at bedside and angio-CT on POD 7.

**Antibiotic prophylaxis:** Single dose of Bactrim/Flagyl pre op. If ePTFE graft has been used continuing antibiotic treatment as long as the drains are in situ.

**Prophylaxis against DVT:** Daily single dose of 5,000 units of Fragmin (LMWH) subcutaneous with first dose the evening before surgery. During vascular reconstruction 500 mL Rheomacrodex (theoretically a rheologic effect) is given i.v. during 6-8 hours and the same dose postoperative day (POD) 1 and 2.

**Treatment of postoperative thrombosis/occlusion:**
*Vein:* Continue with Fragmin but in a thrombosis treatment dose of 100 units/kg x2 s.c. (maximum daily dose 18,000 units/day)

*Artery:* If occlusion is found POD 1 and 2 reoperation and clearance of the blood clot is mandatory often mandating a redo of the arterial anastomosis. If the occlusion is found later than POD 2, Fragmin is given in the same dose as under “vein-thrombosis”.

**Islet auto-transplantation:**
According to separate protocol.

**Histology:**
Inconsistent or incorrect distinction between pancreatic, ampullary and distal bile duct cancers leads to errors in patient management, cancer data records and analysis. Inclusion of ampullary carcinomas in pancreatic cancer series results in falsely increased survival figures, and may skew tumour size and stage. Incorrect diagnosis of cancer origin may blur pathology data regarding resection margin involvement, as highlighted below.
Although the distinction between these three cancers is often perceived as being difficult, the diagnostic criteria are well established. Assignment of cancer origin is based on the anatomical relationship of the centre of the tumour mass to the ampulla, common bile duct or pancreas, and the presence of a neoplastic precursor lesion.

Careful gross examination of the three-dimensional relationship of the cancer to key anatomical structures is of paramount importance and cannot be substituted by histomorphological or immunohistochemical investigations. Two further anatomical features that can be recognized microscopically may prove helpful in the distinction between ampullary and distal bile duct cancers. The anatomical border between both adjoining structures is characterized by the sudden transition of the sphincter of Oddi into the much thinner and lacunar muscle layer of the intrapancreatic bile duct, and the furrowed structure of the ampullary mucosa into the small irregular pleats of the mucosa lining the bile duct (Fig. 1). The shortage of reliable information precludes reaching any conclusions regarding differences in the R1 rate between pancreatic, ampullary and distal bile duct cancer. There are, however, compelling reasons to assume that R1 rates differ between the cancer groups. Numerous studies have shown that, overall, ampullary tumours are significantly smaller than pancreatic cancers and, to a lesser degree, than distal bile duct carcinomas.
Increased accuracy in detecting margin involvement in pancreatic cancer, is explained mainly by the implementation of a fully standardized approach, with extensive tissue sampling and careful examination of both tumour origin and margin status. A further factor may be the use of a novel dissection technique, based on serial specimen slicing in the axial plane (Fig. 2), instead of the traditional procedure with longitudinal opening of the main pancreatic and/or common bile duct and slicing along the plane defined by both ducts. Serial slicing along a single fixed plane (the axial plane of computed tomography) without disruption of the tumour and native structures allows careful evaluation of the cancer and its relationship to both the various specimen surfaces and key anatomical structures. The latter is paramount to correct staging and reliable identification of tumour origin. The numerous specimen slices generated by the axial dissection technique provide excellent views of the local anatomy and
pathological changes. Furthermore, the craniocaudal line-up of the slices allows accurate three-dimensional interpretation of the findings.

Serial specimen slicing in the axial plane. The various specimen surfaces are inked in different colours (red, anterior; green, superior mesenteric vein-facing surface; yellow, superior mesenteric artery-facing surface; blue, posterior surface). Figs 3–5 represent axial specimen slices taken at the indicated levels and viewed inferiorly (arrow). b Illustration of the level of axial slicing for Figs 3–5
a Margin involvement in pancreatic cancer  

b Ductal adenocarcinoma of the pancreas

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a Margin involvement in intrapancreatic CBD cancer  

b Intrapancreatic CBD adenocarcinoma
The absence of this specific pathology data item is remarkable given that the likelihood of curative resection is determined by tumour size and location. The location of a tumour is random within the confines of its tissue of origin. Therefore, the centre of ampullary cancers is found close to the position occupied by the ampulla that is at the mid-level of the craniocaudal length of the pancreatic head and in its lateral aspect, close to or within the duodenal wall. Distal bile duct cancers are de facto distributed along the course of the common bile duct, and can be found from the short stump of extrapancreatic bile duct down to the distal end of the duct at its junction with the ampulla. As the common bile duct traverses the posterior aspect of the pancreatic head, cancers developing from the duct will be located close to the posterior pancreatic surface. Although the exact cellular origin of ductal adenocarcinoma of the pancreas has yet to be identified, it is safe to assume that this cell
population is present throughout the pancreatic parenchyma and that pancreatic cancer, therefore, has no particular anatomical distribution pattern within the pancreatic head. As illustrated in Figs 3–5, these simple considerations regarding tumour origin and location are related directly to the anatomical distribution of margin involvement in the three cancer groups.

The specimen is immediately transported fresh to the pathology department and analyzed in a standardized fashion according to the KVAST document (Guidelines produced by the Swedish Society of Pathology). The tumor-vascular border is specifically described and later compared with radiology.

**Follow up (see also below):**
First follow up at the out-patient clinic at 4-6 weeks after surgery with blood tests (Hb, WBC, liver function test and CRP). Angio-CT at 6 weeks. An additional pancreatic CT is done at 12 months and in case of symptoms suggestive of recurrence.

**Outcomes:**
**Primary:**
- Safety, tolerability and feasibility

**Secondary**
- Morbidity (Clavien)
- Vessel reconstruction patency
- R0 resection rate
- Concordance between radiological vascular invasion, surgical assessment and histologic vascular invasion.
- Grading of the histological tumor response
• The expression of specific antigens (e.g. NY-ESO-1) in pancreatic ductal adenocarcinoma and to detect the frequency of antigen reactive T-cells in TIL (tumor infiltrating lymphocytes) as well as in the peripheral circulation.

• Screen for and map the expression of novel potential TAAs in human pancreatic cancer.

• To test whether immune response can be elicited *ex vivo* to specific antigens (e.g. NY-ESO-1) and to test if reactivity of TAA-reactive T-cells can be improved by *ex vivo* expansion and stimulation.

• Overall survival (Kaplan-Meier)

• Disease free survival

• QoL

**Analysis plan**

The analyses will be based on the intention to treat principle.

The trial’s primary goal is to detect/achieve a conversion rate of 30 % (\(\pi = 0.3\)) with intensified pre-operative chemotherapy and to prove this with a statistically certainty (\(\beta \leq 0.05\); 1-\(\beta\) (power): 0.95) by use of the Phase II Gehan’s Method Two Stage Design.

If there are no responders among the first 9 cases (Stage I), a conversion rate of 30 % can be out-ruled, and the trial will be closed and further patients will not be recruited for the second stage. If at least three cases of the first nine cases complete and respond to the pre-operative chemotherapy and undergo R\(_{0-1}\) surgery, another 16 cases need to be included to reach a precision (\(\varepsilon\)) of 0.10.

A secondary end-point will be the rate of surviving patients at 24 months from enrollment, which is the reported median survival in the three large adjuvant trials in patients with primarily resectable disease. This end-point will also primarily be analyzed with the Phase II Gehan’s Method Two Stage Design and the sought after rate in the present cohort will be 30%. Accordingly, thereby the number of included patients needed will be similar as for the analysis of the primary end-point.
The Kaplan-Meier method will be used to evaluate progression free and overall survival and their median values. Survival will be calculated from date of enrolment until evidence of progressive disease or death.

A multivariate Cox survival analysis will be carried out to study prognostic factors. Subgroup analyses are planned for stage groups since one could expect a larger treatment difference in higher stages.

Comparisons on survival will be made with the log-rank test. The $\chi^2$ or the Fischer exact test will be used, if necessary, for comparison of qualitative variables. The Student t test will be used for quantitative variables.

**Patient information and Inform consent**

This trial should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki (Appendix VI), and that are consistent with GCP and the applicable regulatory requirement(s).

Prior to participation to the trial, the patient or the subject’s legally acceptable representative should receive a copy of the signed and dated written informed consent form, and any other information provided to the patient. During a patient’s participation in the trial, the patient or the subject’s legally acceptable representative should receive a copy of the signed and dated written consent form updates and a copy of any amendments to the written information provided to the patient.

*eCRF Handling*

Data will be entered directly in an electronic CRF available from a web site (eCRF). A personal identification code will be delivered to each investigator.
All data to be controlled or to be completed will be listed for further verification at site of investigation by the trial monitor.

After this last verification, the concerned data will be updated and locked into the database. Any further modification will be documented in an audit file before the statistical analysis is initiated. Data will be extracted from the database directly into data files for statistical analysis.

**Overall survival**

Survival will be assessed from the date of the first randomization to the date of patient death, due to any cause, or to the last date the patient was known to be alive. Patients who were not reported as having died at the time of the analysis will be censored using the date they were last known to be alive.

**Progression Free Survival**

Progression-free survival (PFS) is the time from the date of the first randomization to the date of progressive disease (RECIST criteria) or death.

Death will be regarded as a progression event in those patients who die before disease progression. Patients without documented objective progression at the time of the final analysis will be censored at the date of their last objective tumor assessment.
Postoperative follow up

- Clinical assessment: 1, 3, 6, 12 months and then twice yearly until 5 years after randomisation.

- Quality of life: 3 and 12 months

- CT-scan (3-phase): every 3rd month for two years and thereafter twice yearly until 5 years after randomisation, and in case of clinical suspicion of recurrence.

- PET-CT as above, optional
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