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Manuscript Title: Surgical complications after Pancreatic Transplantation: a CT imaging pictorial review

Running Title: Imaging of surgical complications after pancreatic transplantation

Reviewer#1

Overall comment: The present manuscript is very interesting and very specific. In my opinion, a pancreas transplant is unlike any other major surgery. Postoperative complications are also not uncommon and require adequate therapy. I always use MRI for postoperative imaging after pancreas transplantation. I find such a detailed CT diagnosis very novel and interesting. However, I would be concerned about the administration of contrast medium, since these patients usually have kidney failure.

Reply to Overall comment: Thanks for the positive feedback. We agree that pancreatic transplantation is complex and complications requiring adequate therapy not uncommon.

R1-Comment 1, For me there are a few important points to clarify: 1. I always do duodenal anastomosis to the jejunum. I never do a Y-Roux anastomosis. When I read the description in the text, this group actually doesn't either.

Reply to R1-Comment 1: Thank you for catching it. It is an oversight and indeed as indicated in the description in the text we don't do Y-Roux anastomosis either. We amended the oversight in the abstract and one portion of Figure 1.

R2-Comment 2: Why CT and not MRI?

Reply to R1-Comment 2: Thanks for the question and for the input. We are glad for the opportunity to provide an extensive reply.

There are many reasons why CT is most commonly performed at our center. First, although being a tertiary academic center, oftentimes MRI schedule is overwhelmed and it is quite difficult to find a spot within 12 hours, while in case of urgent CT it is usually not an issue to find a place. Second, CT is preferred for the assessment of arterial and venous anastomosis and the enteric anastomosis, including any vascular urgency or emergency, bowel complications (anastomotic leaks, ileus or obstruction), and the identification of any source of bleeding. This is related to the higher spatial and temporal resolutions of CT compared to MRI.

This is similar to what other centers do as well:

- França M et al. from Porto, Portugal " At our institution, MRI is rarely used for examination of pancreatic graft-related complications because of its lower spatial resolution, creating difficulties in the assessment of the enteric anastomosis, and, also, because of technical constraints involved in imaging acutely ill and intensively monitored patients." <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3259396/>].
- Tolat P et al from Wisconsin, US "Some institutions prefer not to use intravenous contrast agents in conjunction with CT scanning of suspected pancreatic graft abnormalities, based on the rationale that standard iodinated contrast agents may have deleterious effects on transplant renal function (16). We have not refrained from using

contrast-enhanced CT in patients, even in the absence of well-preserved renal function, to provide a superior angiographic and parenchymal display of the pancreas graft suitable for therapeutic planning.”

(<https://pubs.rsna.org/doi/full/10.1148/radiol.15131585>)

However, we agree with the reviewer that in these patients MRI should be preferred when kidney function is very poor or is declining. A side-by-side comparison of CT-A and MR-Angiography is lacking in these patients.

We have added the following text in response to this comment:

“MRI is rarely used for examination of pancreatic graft-related complications, and it is preferred particularly in patients with declining renal function. The main adoption of CT compared to MRI is based on different reasons, including wider availability of CT compared to MRI particularly in the emergency and urgent settings, the lower acquisition time of CT exams compared to MRI which is important in imaging acutely ill and intensively monitored patients, but also to the lower spatial and temporal resolution, creating difficulties in the assessment of the enteric anastomosis and vascular complications.”

R1-Comment 3: How does the administration of contrast medium affect kidney function. A short section discussion would be good.

Reply to R1-Comment 3: The administration of contrast medium can be a serious issue in patients with AKI or CKI undergoing CT examination. As indicated by ESUR guidelines, at our center we estimate eGFR before contrast medium administration within 7 days before contrast medium administration in patients with an acute disease, an acute deterioration of a chronic diseases or who are hospital inpatients, or within 3 months in all other patients. Preventive hydration protocols are also based on ESUR at our center in at-risk patients. With regard to kidney-transplanted patients, Fananapazir et al [Fananapazir G, Troppmann C, Corwin MT, Nikpour AM, Naderi S, Lamba R. Incidences of acute kidney injury, dialysis, and graft loss following intravenous administration of low-osmolality iodinated contrast in patients with kidney transplants. *Abdom Radiol (NY)*. 2016 Nov;41(11):2182-2186. doi: 10.1007/s00261-016-0827-3. PMID: 27377897.] demonstrated that the incidence of acute kidney injury in patients with kidney transplants, who underwent CT examinations with low-osmolality iodine-based contrast material was 7% (7/104) based on a rise of ≥ 0.3 mg/dL and 3% (3/104) based on a rise of ≥ 0.5 mg/dL. All three patients with the more strict definition (≥ 0.5 mg/dL) had a pre-CT eGFR < 60 mL/min/1.73 m². The incidence of CIN after contrast-enhanced CT was similar (6.1%) in a study by Cheungpasitporn et al [Cheungpasitporn W, Thongprayoon C, Mao MA, Mao SA, D’Costa MR, Kittanamongkolchai W, Kashani KB. Contrast-induced acute kidney injury in kidney transplant recipients: a systematic review and meta-analysis. *WJT*. 2017;7:81–8.]. However, McDonald et al retrospectively examined 6175 patients who received contrast-enhanced CT in a single facility and demonstrated that there is no significant difference in the CIN onset between patients with a solitary kidney (4.1%) and bilateral kidneys (4.2%), with solitary kidney being including patients who underwent nephrectomy for malignant tumor and transplant recipients [McDonald JS, Katzberg RW, McDonald RJ, Williamson EE, Kallmes DF. Is the presence of a solitary kidney an independent risk factor for acute kidney injury after contrast-enhanced CT? *Radiology*. 2016;278:74–81.].

Anyhow, in at-risk patients according to ESUR and ACR 2023 guidelines, calculation of eGFR before administration of the contrast medium is strongly recommended to implement possible preventive premedication and use of the smallest possible amount of contrast medium is indicated in order to obtain a diagnostic test, even combining low tube voltage imaging and iterative reconstruction.

We have therefore implemented the manuscript with the following section discussing the use of contrast medium in CT in kidney transplant recipients as follows:

Contrast medium administration in CT should not be a contraindication in kidney transplant recipients. Fananapazir et al [Fananapazir G, Troppmann C, Corwin MT, Nikpour AM, Naderi S, Lamba R. Incidences of acute kidney injury, dialysis, and graft loss following intravenous administration of low-osmolality iodinated contrast in patients with kidney transplants. *Abdom Radiol (NY)*. 2016 Nov;41(11):2182-2186. doi: 10.1007/s00261-016-0827-3. PMID: 27377897.] demonstrated that the incidence of acute kidney injury in patients with kidney transplants, who underwent CT examinations with low-osmolality iodine-based contrast material was 7% (7/104) based on a rise of ≥ 0.3 mg/dL and 3% (3/104) based on a rise of ≥ 0.5 mg/dL; all three patients with the more strict definition (≥ 0.5 mg/dL) had a pre-CT eGFR < 60 mL/min/1.73 m². The incidence of CIN after contrast-enhanced CT was similar (6.1%) in a study by Cheungpasitporn et al [Cheungpasitporn W, Thongprayoon C, Mao MA, Mao SA, D'Costa MR, Kittanamongkolchai W, Kashani KB. Contrast-induced acute kidney injury in kidney transplant recipients: a systematic review and meta-analysis. *WJT*. 2017;7:81–8]. However, McDonald et al [McDonald JS, Katzberg RW, McDonald RJ, Williamson EE, Kallmes DF. Is the presence of a solitary kidney an independent risk factor for acute kidney injury after contrast-enhanced CT? *Radiology*. 2016;278:74–81] retrospectively examined 6175 patients who received contrast-enhanced CT in a single facility and demonstrated that there was no significant difference in the CIN onset between patients with a solitary kidney, including kidney transplant recipients (4.1%) and bilateral kidneys (4.2%). The assessment of estimated glomerular filtration rate calculated from the serum creatinine is recommended before contrast medium administration within 7 days before administration in patients with an acute disease, an acute deterioration of a chronic disease or in hospitalized patients, and preventive hydration protocols need to be considered in at-risk patients as indicated by guidelines [Isaka Y, Hayashi H, Aonuma K, Horio M, Terada Y, Doi K, Fujigaki Y, Yasuda H, Sato T, Fujikura T, Kuwatsuru R, Toei H, Murakami R, Saito Y, Hirayama A, Murohara T, Sato A, Ishii H, Takayama T, Watanabe M, Awai K, Oda S, Murakami T, Yagyu Y, Joki N, Komatsu Y, Miyauchi T, Ito Y, Miyazawa R, Kanno Y, Ogawa T, Hayashi H, Koshi E, Kosugi T, Yasuda Y; Japanese Society of Nephrology, Japan Radiological Society, and Japanese Circulation Society Joint Working Group. Guideline on the use of iodinated contrast media in patients with kidney disease 2018. *Clin Exp Nephrol*. 2020 Jan;24(1):1-44. doi: 10.1007/s10157-019-01750-5. ; van der Molen AJ, Reimer P, Dekkers IA, Bongartz G, Bellin MF, Bertolotto M, Clement O, Heinz-Peer G, Stacul F, Webb JAW, Thomsen HS. Post-contrast acute kidney injury. Part 2: risk stratification, role of hydration and other prophylactic measures, patients taking metformin and chronic dialysis patients : Recommendations for updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol*. 2018 Jul;28(7):2856-2869. doi: 10.1007/s00330-017-5247-4. ; ESUR Guidelines on Contrast Agents V.10.0 https://www.esur.org/wp-content/uploads/2022/03/ESUR-Guidelines-10_0-Final-Version.pdf Accessed on October 21, 2023].

Reviewer#2

Overall comment: In the manuscript "Surgical complications after Pancreatic Transplantation: a CT imaging pictorial review", the authors illustrate CT findings of surgical-related complications after pancreatic transplantation. provide a short summary of the main techniques of pancreas transplantation. They provide a practical imaging approach to pancreatic transplantation and its complications and provide tips and tricks for the prompt imaging diagnosis on CT. Pancreatic Transplantation is a complex surgical procedure that may lead to complications needing diagnosis by CT. In fact, CT is important especially post surgery. This topic is interesting.

Reply to Overall comment: Thanks for the positive feedback. We agree that pancreatic transplantation is complex and CT may prove very helpful in the postoperative setting.

R2-Comment 1, graft thrombosis is serious after transplantation. The authors provide graft thrombosis graded on contrast-enhanced CT based on the system proposed by Hakeem. However, the information is not detailed enough. I suggest the authors would show the changes of pancreas volume and CT HU before and after venous thrombosis and arterial thrombosis comparing with no thrombosis. And give systemic typical CT images if possible.

Reply to R2-Comment 1:

Imaging findings of inflammatory and ischemic pancreatitis unfortunately overlap on CT with regard to the pancreatic parenchyma, and include enlargement of the, ill-defined parenchymal contours, decreased density and inhomogeneity of the pancreatic parenchyma in the acute setting. The inflammatory reaction can produce increased attenuation of the peripancreatic fat tissue commonly described as "stranding". Normal pancreatic parenchyma has CT attenuation values of 40–50 Hounsfield units (HU) on the unenhanced CT. A normal pancreas should demonstrate a homogeneous increase in attenuation with intravenous contrast agent to 100–150 HU [25]. In case of both ischemic and inflammatory pancreatitis there will be a decrease in the HU value of the pancreas which is due to the oedema in the inflammatory form, or to reduced vascularization in the ischemic form. In our own experience, we did not find unambiguous parenchymal patterns, but we cannot provide solid data to indicate this. However, the study by Hakeem et al showed that peripancreatic edema and/or peripancreatic inflammatory changes at baseline CT scan were present in the majority of patients and their presence reduced over time at 1- and 3 months. Based on the reviewer's input we have implemented the Figures with an additional figure showing pancreatic parenchymal changes

from different causes, including inflammatory pancreatitis, arterial and venous thrombosis

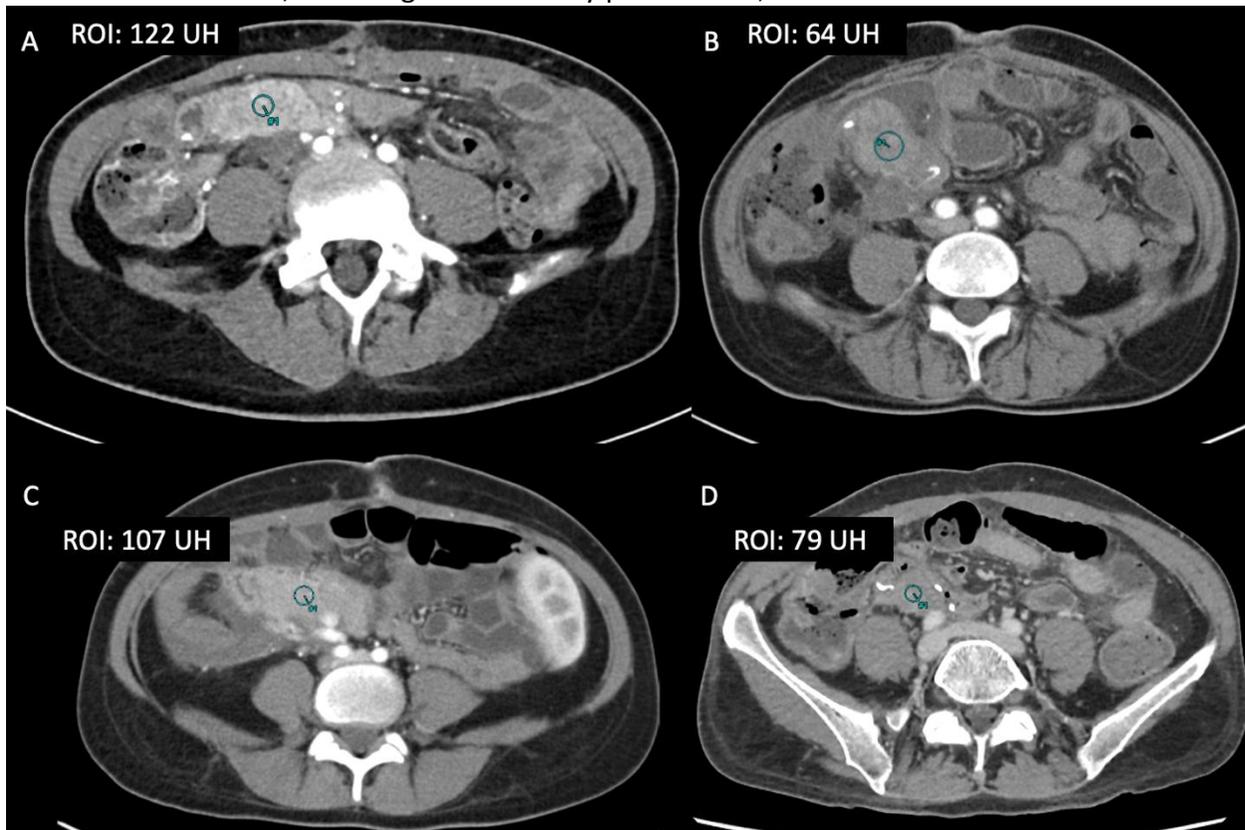


Figure 7 – Contrast enhanced CT in four different patients after pancreatic transplantation. A region of interest (ROI) is drawn in the pancreas in the four patients. A. normal pancreatic parenchyma; B. Inflammatory pancreatitis; C. decreased parenchymal enhancement from venous thrombosis; D. decreased parenchymal enhancement from arterial thrombosis.

R2-Comment 2: Is there any detailed parameters to differentiate graft pancreatitis and thrombosis by CT?

Reply to R2-Comment 2: We have now implemented this part. We have added the following content in the Section on “Graft thrombosis” “In case of vascular thrombosis, a decreased enhancement of the transplanted pancreas usually occurs due to the organ ischemia, and the main differential diagnosis between arterial and venous thrombosis is made by direct visualization of the thrombus in the vessel.” and we have added four different cases in the new figure 7, with normal transplanted pancreas, inflammatory pancreatitis, pancreatitis from venous thrombosis and pancreatic ischemia from arterial thrombosis. The postcontrast phases are diriment in the diagnosis of thrombosis by depicting the vascular filling defect.

R2-Comment 3, Regarding exocrine pancreas drainage, the authors mentioned donor duodenum- recipient ileum and duodenojejunostomy in the main text. In Fig 1, Roux loop was mentioned. I suggest the authors summarize and compare the three kinds of surgical procedure when they describe the surgical techniques.

