PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Feasibility, safety, and preliminary efficacy of preoperative stereotactic radiotherapy on the future pancreatic neck transection margin to reduce the risk of pancreatic fistula after high-risk pancreatoduodenectomy (FIBROPANC): protocol for a multicenter, single-arm trial
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VERSION 1 - REVIEW

REVIEWER NAME	Ellis, Ryan J
REVIEWER AFFILIATION	Indiana University
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	16-Jul-2024

GENERAL COMMENTS	Well thought out and described study protocol. Look forward to the study results.

REVIEWER NAME	Jeune, Florence
REVIEWER AFFILIATION	AP-HP Pitié-Salpêtrière Hospital, Department of HPB Surgery and Liver transplantation
REVIEWER CONFLICT OF INTEREST	none
DATE REVIEW RETURNED	05-Aug-2024

GENERAL COMMENTS	This is a very interesting and well-designed study dealing with a major issue following pancreaticoduodenectomy (PD). Numerous strategies to prevent postoperative pancreatic fistula (POPF) have been investigated, including the type of pancreatic anastomosis (1-3), drainage techniques (4-6), and pharmacological interventions (7-11) but only limited impact and low reproducibility on POPF have been shown. To date, this study is one of the first to prospectively and specifically assess the potential benefits of radiotherapy in preventing POPF. I have a few minor questions and remarks regarding the protocol: • Could the authors explain and discuss in more detail the choice of the irradiation dose and the rationale for using a single dose? Are there any prior translational or preliminary studies in the literature supporting this choice?

	• Similarly, could they discuss the timing of radiotherapy to surgery? • Will the patients receive any pharmacological treatment, such as somatostatin or octreotide? • Will the patients receive any prophylaxis for gastric ulcer? References 1-Grobmyer SR, Kooby D, Blumgart LH, Hochwald SN. Novel pancreaticojejunostomy with a low rate of anastomotic failure-related complications. J Am Coll Surg. janv 2010;210(1):54-9. 2-Ricci C, Ingaldi C, Alberici L, Pagano N, Mosconi C, Marasco G, et al. Blumgart Anastomosis After Pancreaticoduodenectomy. A Comprehensive Systematic Review, Meta-Analysis, and Meta- Regression. World J Surg. 2021;45(6):1929-39. 3-Peng SY, Wang JW, Lau WY, Cai XJ, Mou YP, Liu YB, et al. Conventional versus binding pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. Ann Surg. Mai 2007;245(5):692-8. 4-Dai M, Liu Q, Xing C, Tian X, Cao F, Tang W, et al. Early Drain Removal is Safe in Patients With Low or Intermediate Risk of Pancreatic Fistula After Pancreaticoduodenectomy: A Multicenter, Randomized Controlled Trial. Ann Surg. 1 févr 2022;275(2):e307-14. 5- Andrianello S, Marchegiani G, Malleo G, Masini G, Balduzzi A, Paiella S, et al.Pancreaticojejunostomy With Externalized Stent vs Pancreaticogastrostomy With Externalized Stent for Patients With High-Risk Pancreatic Anastomosis: A Single-Center, Phase 3, Randomized Clinical Trial.JAMA Surg. 1 avr 2020;155(4):313-21. 6- Pessaux P, Sauvanet A, Mariette C, Paye F, Muscari F, Cunha AS, et al. External pancreatic duct stent decreases pancreatic fistula rate after pancreaticoduodenectomy: prospective multicenter randomized trial. Ann Surg. mai 2011;253(5):879-85. 7- Suc B, Msika S, Fingerhut A, Fourtanier G, Hay JM, Holmières F, et al. Temporary fibrin glue occlusion of the main pancreatic duct in the prevention of intra-abdominal complications after pancreatic resection: prospective randomized trial. Ann Surg. janv 2003;237(1):57-65. 8-Sa Cunha A, Carrere N, Meunier B, Fabre JM, Sauvanet A, Pessaux P, et al. Stump closure reinforcement with absorbable fibrin collagen sealant sponge (TachoSil) does not prevent pancreatic fistula after distal pancreatectomy: the FIABLE multicenter controlled randomized study. Am J Surg. oct 2015;210(4):739-48. 9-Allen PJ, Gönen M, Brennan MF, Bucknor AA, Robinson LM, Pappas MM, et al. Pasireotide

	for postoperative pancreatic fistula. N Engl J Med. 22 mai 2014;370(21):2014-22. 10- Laaninen M, Sand J, Nordback I, Vasama K, Laukkarinen J. Perioperative Hydrocortisone Reduces Major Complications After Pancreaticoduodenectomy: A Randomized Controlled Trial. Ann Surg. nov 2016;264(5):696-702. 11- Gaujoux S, Regimbeau JM, Piessen G, Truant S, Foissac F, Barbier L, Buc E, Adham M, Fuks D, Deguelte S, Muscari F, Sulpice L, Vaillant JC, Schwarz L, Sa Cunha A, Muzzolini M, Dousset B, Sauvanet A; Collaborators. Somatostatin Versus Octreotide for Prevention of Postoperative Pancreatic Fistula: The PREFIPS Randomized Clinical Trial: A FRENCH 007-ACHBT Study. Ann Surg. 2024 Aug 1;280(2):179-187.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (Dr. Ryan J Ellis, Indiana University)

Well thought out and described study protocol. Look forward to the study results.

REPLY: We thank the reviewer for this comment.

Reviewer 2 (Dr. Florence Jeune, AP-HP Pitié-Salpêtrière Hospital)

This is a very interesting and well-designed study dealing with a major issue following pancreaticoduodenectomy (PD). Numerous strategies to prevent postoperative pancreatic fistula (POPF) have been investigated, including the type of pancreatic anastomosis (1-3), drainage techniques (4-6), and pharmacological interventions (7-11) but only limited impact and low reproducibility on POPF have been shown. To date, this study is one of the first to prospectively and specifically assess the potential benefits of radiotherapy in preventing POPF. I have a few minor questions and remarks regarding the protocol:

REPLY: We thank the reviewer for the comment and valuable remarks.

1. Could the authors explain and discuss in more detail the choice of the irradiation dose and the rationale for using a single dose? Are there any prior translational or preliminary studies in the literature supporting this choice?

REPLY: Thank you for this question. No human studies on the dose-effect relationship between radiotherapy and pancreatic fibrosis have been performed to date. Therefore, our SBRT dose was based on the results of the multicenter randomized controlled PREOPANC trial since this trial found a pancreatic fistula rate of 0% after neoadjuvant chemoradiotherapy (1). The main reason for converting the PREOPANC dose, including 15 fractions of 2.4 Gy over 3 weeks, to a single high dose was to reduce the number of visits and the duration of the intervention. Additionally, hypofractionation (higher doses delivered in fewer fractions) is described to correlate with the degree of radiation-induced fibrosis in other tissue types (2). We may consider escalating the dose in future studies based on the clinical and histopathological outcomes observed after the current dose. We now elaborate on this topic on page 9, lines 174-179:

The radiotherapy dose was calculated based on the dose given in the PREOPANC randomized trial (15 fractions of 2.4 Gy, delivered in 3 weeks) since a POPF rate of 0% was observed in the chemoradiotherapy group of that trial. To lower patient burden and the number of visits for study participants, the dose was converted to a single fraction of 12 Gy. Hypofractionation (increased dose per fraction) correlates directly with the degree of radiation-induced fibrosis in other tissue types.

2. Similarly, could they discuss the timing of radiotherapy to surgery?

REPLY: Similar to the previous question, the optimal dose and timing of radiotherapy required to induce fibrosis is yet to be determined. In general, radiation-induced injury is divided into an early inflammatory phase, which typically occurs directly after radiation exposure and a late fibroproliferative phase after months (3). The FIBROPANC trial requires a minimum of four weeks after SBRT to surgery. Although maintaining a longer period after SBRT might benefit fibrosis, postponing surgery in patients with (pre-)malignant disease is not desirable, given the risk of disease progression. Therefore, we decided to maintain a 4-week wait for patients with malignant disease and 6 weeks in case of patients with pre-malignant disease. We explain this better on page 13, lines 271-275:

Radiation-induced injury is divided into an early inflammatory phase, which typically occurs directly after radiation exposure and a late fibroproliferative phase, occuring after months. Although maintaining a longer period after radiotherapy might benefit fibrosis, postponing surgery for several months in patients with (pre-)malignant disease is not desirable.

3. Will the patients receive any pharmacological treatment, such as somatostatin or octreotide?

REPLY: Thank you for bringing up this important point. Since we will include only patients at high risk for developing POPF, somatostatin analogs, e.g., Pasireotide, will be administered perioperatively according to the institutional protocols for each center. Data on perioperative use will be collected.

We added this on page 13, lines 258-259:

Somatostatin analogs, e.g., Pasireotide, will be administered perioperatively according to the institutional protocols for each center.

4. Will the patients receive any prophylaxis for gastric ulcer?

REPLY: Thank you for this question. Patients will receive prophylaxis for gastric ulcers, such as proton pump inhibitors, during or after radiotherapy according to institutional protocols. However, we anticipate limited toxicity to neighbouring organs, as MRI or fiducial marker-guided stereotactic radiotherapy provides precise targeting. After pancreaticoduodenectomy, proton pump inhibitors are prescribed as the standard of care in all participating centres.

References

1. van Dongen JC, Suker M, Versteijne E, Bonsing BA, Mieog JSD, de Vos-Geelen J, et al. Surgical Complications in a Multicenter Randomized Trial Comparing Preoperative Chemoradiotherapy and Immediate Surgery in Patients With Resectable and Borderline Resectable Pancreatic Cancer (PREOPANC Trial). Ann Surg. 2022;275(5):979-84.

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3. Fijardo M, Kwan JYY, Bissey PA, Citrin DE, Yip KW, Liu FF. The clinical manifestations and molecular pathogenesis of radiation fibrosis. EBioMedicine. 2024;103:105089.