The role of laparoscopic pancreaticoduodenectomy—how take care of patient security?

Trond A. Buanes[1,2]

[1]Department of Hepato-Pancreatico-Biliary Surgery, Oslo University Hospital (OuS), Oslo, Norway; [2]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

Correspondence to: Trond A. Buanes, MD, PhD. Department of Hepato-Pancreatico-Biliary Surgery, Oslo University Hospital (OuS), Nydalen, N-0424 Oslo, Norway. Email: trond.buanes@medisin.uio.no.

A recent report from the Dutch Pancreatic Cancer Group has shown that the risk of severe complications, even postoperative death, can easily be underestimated during the introduction of laparoscopic pancreaticoduodenectomy (LPD) (1). This is hardly surprising for pancreatic surgeons. Nevertheless, data with this level of scientific evidence has never been published before and the paper is therefore incredibly important and highly relevant. The protocol of the LEOPARD 2 study (NTR5689) was published (2) as a multicenter, patient-blinded, randomized controlled phase 2/3 trial. Safety outcomes was focused during the first part (phase 2) including the initial 40 patients, when the data safety monitoring board assessed whether it would be safe to proceed to phase 3, comparing time to functional recovery as primary endpoint. The trial proceeded to phase 3, but was advised stopped early by the data safety monitoring board after inclusion of 105 patients (73% of the planned sample size) because the 90-day complication-related mortality in the LPD group, mounting to 10% compared to 2% in the open group. Thorough analysis of this trial is imperative to improve surgical society understanding, particularly on how to take care of patient safety. The trial was very well planned and conducted: strict requirements were met by the four participating hospitals. Patient volume had to be at least 20 pancreaticoduodenectomies annually and every surgeon had to complete a dedicated training program for LPD, having performed at least 20

procedures before trial participation. Based on international literature, this was expected to fill safety requirements properly. Single center randomized controlled trials (RCTs) from India (3) and Spain (4), together with registry-based studies (5) and non-comparative reports (6-8) had indicated that LPD would be feasible and safe after this learning curve. Most previous publications were based on surgical training at a similar or inferior level. A possible speculation might now be that the five patients dying within 90 days postoperatively, was simply "bad luck" as the mortality rates in the two groups are not statistically different (P=0.20). Could the real problem be that a well conducted trial was inappropriately stopped too early? The opposite conclusion seems sound, as the advice from the data safety monitoring board is entitled by high ethical obligations. The P value is probably not the key to the best answers in this case, but an overall medical consideration.

The uniqueness of the LEOPARD-2 study

Two characteristics are apparent; thoroughness and perspective/clinical setting. The protocol was engendered by a network of pancreatic surgeons, experienced in carrying out clinical trials. The data safety monitoring board became a pivotal key to good clinical practice, concurrently generating the most important new insight possible as inclusion in the trial proceeded. The intention of the trial

was spread of putative clinical benefits from laparoscopic surgery to numerous centers, making the results highly relevant in a wide surgical society. Four hospitals with sufficient patient volume and training qualified for participation, a feature which significantly increases the external validity of the study. The broadness of perspective makes the LEOPARD-2 study different from most previous reports, in which one or very few highly qualified laparoscopic surgeons performed all LPD-procedures. The internal validity of single center publications from "a single surgeon" is probably appropriate, i.e., if the investigation were repeated in the same clinical setting, outcome would be similar. But such single center results, transferred to a multicenter setting, has so far not been published, and the external validity of this exercise is supposed to be low. On the contrary, the information from the LEOPARD-2 study has probably high external validity applied on multicenter spread. The risk of 90 days postoperative mortality at a 10% level if LPD were distributed to numerous centers, seems realistic, it might even be higher. Should it never take place for this reason? The answer is not self-evident, it depends on reasons in favor of the laparoscopic technique versus rationales against it.

The beneficial potential

Surgical methods must be assessed by relevant clinical endpoints. Postoperative survival is an obvious primary endpoint for pancreatic resections as the most frequent indication is a highly lethal cancer. Laparoscopic distal pancreatic (LDP) resections spread more rapidly internationally than LPD, and the long-term oncological outcome is therefore well known from prospective, observational series (9,10), even though data from well conducted RCTs are lacking. Even without optimal adjuvant chemotherapy, median survival 32 months, 5-year survival 38.2% have been obtained after LDP in patients with pancreatic ductal adenocarcinoma (PDAC) (9). Together with other reports with similar outcome (11), these results have mostly replaced the skepticism for laparoscopic techniques in pancreatic cancer by positive expectations. This applies particularly for postoperative recovery, enabling earlier start of adjuvant chemotherapy and more frequent completeness of the treatment algorithm. After open pancreaticoduodenectomy (OPD), numerous patients are unable to initiate adjuvant chemotherapy, and additional others never finalize it (12). This has been different in some laparoscopic series. In 108 patients,

operated with LPD at the Mayo clinic, delayed recovery resulting in loss of adjuvant chemotherapy was found in only 4% compared to 12% in 214 open procedures (13). This difference could not be verified at a national level (14), but this is probably caused by high complications rates after LPD in hospitals with low patient volume (15). The hypothesis of improved postoperative recovery after LPD was a main reason also for the LEOPARD-2 study, and if such a benefit could be spread among numerous hospitals, the advantage might be substantial. This perspective is further underlined by the continuously improving adjuvant regimens. The ESPAC-4 trial documented median overall survival (OS) 28.0 months after gemcitabine/capecitabine (16), and with adjuvant FOLFIRINOX median OS 54.4 months/3 years OS 63.4% has been obtained (17). If secure laparoscopic resection of adenocarcinoma in any part of the pancreas results in more patients enabled to receive the most effective adjuvant regimen, significant increased survival can be anticipated.

In addition, the postoperative immunological responses might favor laparoscopic above open resections. In the OSLO-COMET trial, eight inflammatory markers were analyzed postoperatively in an RCT, comparing 23 patients undergoing laparoscopic local resection of colorectal liver metastases with 22 patients operated openly. Five markers increased significantly more in the open than in the laparoscopic group, and interleukin 6 (IL-6) was one of those (18). This observation is oncologically interesting as IL-6 seems to play a role during the development of liver metastasis in PDAC patients. Lee *et al.* has recently described that hepatocytes can direct the formation of pro-metastatic niches in the liver (19) and IL-6 plays a role for this hepatocyte function.

Patient security—the burden of the learning curve

During a State-of the-Art conference, Brazil 2016, a systematic review on best evidence of outcome after LPD was presented, identifying 26 comparative studies, most with low level evidence (20). The conference highlighted the complexity of the procedure, the long learning curve and emphasized that achieving proficiency would require significant investments of time and determination. The outcome of the LEOPARD-2 study further underlines these facts, and yields information about necessary learning curve requirements. van Hilst *et al.* underline that further proficiency could have been achieved by a longer learning

curve (1). Introduction of minimally invasive esophagectomy required more than 100 procedures to reach a learning plateau level (21), and the complexity of LPD is probably even higher (22). Among 41 videos of procedures in the LEOPARD-2 trial, 22% received technical summary score below average. These details illustrate the depth and comprehensiveness of the research work, explaining why this new information holds high scientific quality. Concurrently, the necessity of comprehensive surgical training becomes evident. The practical consequences are that "uncritical", wide spread of LPD to numerous hospitals should not take place. Oppositely, focused efforts in dedicated centers is mandatory. The development of robotic assistance during minimally invasive robotic pancreaticoduodenectomy (RPD) is a possible way to go. In Pittsburgh, quality outcomes have been analyzed in subgroups of 20 cases during the first 200 RPD procedures (23), and this center has at the same time trained several surgical teams in a simulator. The advantages of robotic assistance may become an important key to secure introduction of the laparoscopic technique in this setting.

Conclusions

The level of evidence in clinical decision making is crucial, as lack of valid data may become a threat for patient security, particularly in surgery. The differences between information, generated in well conducted RCTs and even comprehensive registry-based reports is clearly illustrated by records from 22,013 OPD procedures, compared with 3,754 patients undergoing LPD. Equivalent short-term outcome is described (24) and reduced 90-day mortality in high volume centers was found for both surgical approaches. The new insight from the LEOPRD-2 trial more than suggests a high risk during a long learning curve for LPD, strongly underlining the patient security aspect of surgical development. As emphasized above, these facts do not at all suggest that LPD should not be done, as great clinical advantages may be achieved, but efforts must continue, guided by replenished knowledge.

Acknowledgments

Footnote

References

1. van Hilst J, de Rooij T, Bosscha K, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial. Lancet Gastroenterol Hepatol 2019;4:199-207.
2. de Rooij T, van Hilst J, Bosscha K, et al. Minimally invasive versus open pancreatoduodenectomy (LEOPARD-2): study protocol for a randomized controlled trial. Trials 2018;19:1.
3. Palanivelu C, Senthilnathan P, Sabnis SC, et al. Randomized clinical trial of laparoscopic versus open pancreatoduodenectomy for periampullary tumours. Br J Surg 2017;104:1443-50.
4. Poves I, Burdío F, Morató O, et al. Comparison of Perioperative Outcomes Between Laparoscopic and Open Approach for Pancreatoduodenectomy: The PADULAP Randomized Controlled Trial. Ann Surg 2018;268:731-9.
5. Nassour I, Wang SC, Christie A, et al. Minimally Invasive Versus Open Pancreaticoduodenectomy: A Propensity-matched Study From a National Cohort of Patients. Ann Surg 2018;268:151-7.
6. Lu C, Jin W, Mou YP, et al. Analysis of learning curve for laparoscopic pancreaticoduodenectomy. J Vis Surg 2016;2:145.
7. Wang M, Meng L, Cai Y, et al. Learning Curve for Laparoscopic Pancreaticoduodenectomy: a CUSUM Analysis. J Gastrointest Surg 2016;20:924-35.
8. Kim SC, Song KB, Jung YS, et al. Short-term clinical outcomes for 100 consecutive cases of laparoscopic pylorus-preserving pancreatoduodenectomy: improvement with surgical experience. Surg Endosc 2013;27:95-103.
9. Sahakyan MA, Kim SC, Kleive D, et al. Laparoscopic distal pancreatectomy for pancreatic ductal adenocarcinoma: Long-term oncologic outcomes after standard resection. Surgery 2017;162:802-11.
10. Buanes T, Edwin B. Long term oncological outcome of laparoscopic techniques in pancreatic cancer. World J Gastrointest Endosc 2018;10:383-91.
11. van Hilst J, de Rooij T, Klompmaker S, et al. Minimally Invasive versus Open Distal Pancreatectomy for Ductal Adenocarcinoma (DIPLOMA): A Pan-European Propensity Score Matched Study. Ann Surg 2019;269:10-7.
12. Labori KJ, Katz MH, Tzeng CW, et al. Impact of early disease progression and surgical complications on adjuvant chemotherapy completion rates and survival in patients

undergoing the surgery first approach for resectable pancreatic ductal adenocarcinoma - A population-based cohort study. Acta Oncol 2016;55:265-77.

13. Croome KP, Farnell MB, Que FG, et al. Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? Ann Surg 2014;260:633-8; discussion 638-40.

14. Nussbaum DP, Adam MA, Youngwirth LM, et al. Minimally Invasive Pancreaticoduodenectomy Does Not Improve Use or Time to Initiation of Adjuvant Chemotherapy for Patients With Pancreatic Adenocarcinoma. Ann Surg Oncol 2016;23:1026-33.

15. de Rooij T, Lu MZ, Steen MW, et al. Minimally Invasive Versus Open Pancreatoduodenectomy: Systematic Review and Meta-analysis of Comparative Cohort and Registry Studies. Ann Surg 2016;264:257-67.

16. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet 2017;389:1011-24.

17. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med 2018;379:2395-406.

18. Fretland AA, Sokolov A, Postriganova N, et al. Inflammatory Response After Laparoscopic Versus Open

Resection of Colorectal Liver Metastases: Data From the Oslo-CoMet Trial. Medicine (Baltimore) 2015;94:e1786.

19. Lee JW, Stone ML, Porrett PM, et al. Hepatocytes direct the formation of a pro-metastatic niche in the liver. Nature 2019;567:249-52.

20. Kendrick ML, van Hilst J, Boggi U, et al. Minimally invasive pancreatoduodenectomy. HPB (Oxford) 2017;19:215-24.

21. van Workum F, Stenstra MHBC, Berkelmans GHK, et al. Learning Curve and Associated Morbidity of Minimally Invasive Esophagectomy: A Retrospective Multicenter Study. Ann Surg 2019;269:88-94.

22. Barkun J, Fisher W, Davidson G, et al. Research considerations in the evaluation of minimally invasive pancreatic resection (MIPR). HPB (Oxford) 2017;19:246-53.

23. Boone BA, Zenati M, Hogg ME, et al. Assessment of quality outcomes for robotic pancreaticoduodenectomy: identification of the learning curve. JAMA Surg 2015;150:416-22.

24. Torphy RJ, Friedman C, Halpern A, et al. Comparing Short-term and Oncologic Outcomes of Minimally Invasive Versus Open Pancreaticoduodenectomy Across Low and High Volume Centers. Ann Surg 2018. [Epub ahead of print].