The impact of minimally invasive pancreatic surgery

Improving outcome

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Chapter 14

Discussion

DISCUSSION

This thesis provides further insights in the development of minimally invasive pancreatic resections (MIPR). Following the stages of the IDEAL recommendations[1], previous studies have shown the feasibility and early development of the minimally invasive approach, i.e. stage 1 and 2a.[2–4] Yet, standardized and randomized data, stage 2b and 3, published in recent year provided mixed signals for the widespread feasibility of minimally invasive pancreatic surgery. Several advantages of minimally invasive distal pancreatectomy (MIDP) over open distal pancreatectomy (ODP) have been reported[5,6], nevertheless safety concerns were expressed for minimally invasive pancreatoduodenectomy (MIPD) as compared to open pancreatoduodenectomy (OPD).[7] Although the use of MIPR has been established nowadays and the 2019 Miami international evidence-based guidelines on MIPR[4] provides some support for surgeons and medical societies worldwide, clear guidance regarding the indications and the usage of MIPR are still lacking. This thesis describes the importance of selecting correctly suitable patients for the minimally invasive approach.

For both distal pancreatectomy and pancreatoduodenectomy, poor selection may result in poor outcomes. For MIDP for pancreatic ductal adenocarcinoma (PDAC), tumors in proximity to vascular structures are generally speaking better off when an open approach is chosen in order to prevent emergency conversions, as these are associated with poor short- and long-term outcomes. For MIPD, although for patients with described risk factors associated with conversion, older age (≥75 year), tumor size >40 mm and pancreatobiliary tumors, the short-term surgical outcomes are comparable between those who are MIPD-converted and those who are MIPD-completed, for both groups the outcomes are generally poor with a mortality rate above 5%. The described factors should be, therefore, considered when selecting patients for the minimally invasive approach.

Regarding the advantages of MIPD, two single center randomized controlled (PADULAP and PLOT) reported shorter hospital stay and reduction in Clavien-Dindo ≥3a complications[8,9], yet the multicenter trial Dutch LEOPARD-2 reported a trend towards increased mortality in the laparoscopic arm and was hence terminated early.[7] It should be noted that the PLOT trial excluded patients older >70 years before randomization and had a larger group of patients with ampullary and duodenal tumors in the laparoscopic group (25 out of 32) as compared to the open group (18 out of 32), which may unintentional influenced the outcomes in favor of the laparoscopic group. Also in the other two randomized controlled trials these tumor characteristics were not considered during randomization and the small differences in tumor location or tumor size between both groups, may have potentially influenced the suggested outcomes. It is therefore important to consider the risk factors associated with poor outcome when developing new protocols for randomized controlled trials and stratify for these factors.

Besides the described risk factors for conversion in this thesis, several efforts have been made to develop difficulty scores to enable better selection of suitable patients for the minimally invasive approach. For MIDP the type of operation (spleen preservation or radical antegrade modular pancreatosplenectomy), level of resection line, the proximity of tumor to major vessel, the extension of tumor to peripancreatic tissue, intact fascial layer

between the distal pancreas and the left adrenal gland and kidney, and left-sided portal hypertension/splenomegaly have been proposed as factors to consider.[10,11] In addition to patient' and tumor characteristics associated with difficulty, surgeons need to be aware of their own technical skills and knowledge, but mainly their current place on the learning curve of the corresponding procedure. Although the described learning curves of MIDP and MIPD varies, respectively between 10- 30[12–14] and 20-40[15,16], these studies considered only a linear learning curve, in which for every subsequent procedure the outcomes improve bit-by-bit. In the national implementation study of laparoscopic distal pancreatectomy (LDP) in the United Kingdom, a non-linear learning curve was found. This was mainly due to expending indications for the laparoscopic approach, as with increasing experience patients selected for LDP were progressively older, more often with PDAC or more extensive tumors. Due to expanding indications, results may even get worse, before improvement sets in. It should be clear that every type of tumor, every extension of tumor, every extension of resection, every characteristic of a patient, should be considered before exposing a patient to a potentially harmful procedure, especially before sufficient proficiency is obtained by the treating clinician.[14] Specific training in the minimally invasive approach is therefore of clear importance to reduce the learning curve, learning curve associated morbidity and assure safe implementation of a minimally invasive pancreatic program in a hospital.[17,18] Unfortunately, standardized training programs are lacking and are being missed by the pancreatic community.[19]

Ohtsuka et al suggested that the indication for spleen-preservation elevates difficulty of LDP extensively.[10] Yet, their difficulty score may only be effective for laparoscopy, as the robotic approach has not been considered in the development. Robotics as minimally invasive approach for pancreatic surgery is an upcoming technique in Europe as shown by an increase in usage for MIDP from 22% in 2011-2013 to 32% in 2017-2019. Also for MIPD the use of the robotic platform is increasing.[20] This thesis showed some advantages of the robotic distal pancreatectomy (RDP) over LDP mainly in terms of spleen-preservation and conversion rates. Also for pancreatoduodenectomy reduced conversion rates for the robotic approach were found. Current difficulty scores or risk factors for severe outcomes do not consider the robotic approach and are therefore not well-suited for the assessment of procedural technical difficulty for this approach. Future studies should distinguish between the laparoscopic and robotic approach.

Previously, it was thought that surgical outcomes largely depend on the skills and experience of the operating surgeons only. With further understanding of patient' pathways during the pre-, intra and postoperative phases, it became clear that a multidisciplinary approach also improves surgical outcome. Multidisciplinary team meetings are currently a prerequisite for improved diagnoses, better understanding of diseases and tumor staging, providing treatment options and ultimately improving outcome for patients.[21] When dealing with pancreatic cancer, a close collaboration between surgeons, pathologists and oncologists is mandatory. For ampullary cancer this thesis showed a survival benefit when patients were treated with adjuvant treatment. Especially for patients affected by the pancreaticobiliary subtype of ampullary cancer, this survival benefit of adjuvant treatment is more profound than those with an intestinal subtype. Still, for 340 out of 887 patients the subtype of ampullary cancer was not assessed owing to a lack of general consensus regarding the

importance of assessing the subtype. Even while it is already clear that every subtype of ampullary cancer is correlated with a different life expectancy.[22] It is therefore advised to report on subtypes during grossing of ampullary cancer.

Similar to surgical procedures, worldwide standardized techniques for pathological grossing of pancreatic specimens are not yet available and different approaches to assess a specimen macro- and microscopically are used in every country, hospital or even between pathologists in the same hospital.[23,24] Accurate pathology assessment of the pancreatic specimen is essential in order to provide prognostic information and guidance in further treatment strategies, such as adjuvant therapy in pancreaticobiliary ampullary cancer. Also standardized grossing will improve international collaboration due to a common language used when reporting the pathological outcomes. Although some efforts are made to improve this, this is mainly done for the more common procedure, the pancreatoduodenectomy.[25,26] Consensus regarding the grossing of distal pancreatectomy specimens is currently lacking. The development group of the DIPLOMA trial on MIDP versus ODP for PDAC specific made a first step into standardizing the grossing, yet the impact of this standardization needs to be assessed following completion of the DIPLOMA trial. Understanding one and others procedures between surgeons and pathologists is important, however still not common. In distal pancreatectomy specimens recognizing margins may be difficult due to the absence of clear anatomical landmarks. In order to assess the right margins, surgeons should make clear which margin is where by marking margins with sutures or even painting the margins. This is definitely important when dealing with PDAC, as this thesis found that resection of Gerota's fascia, a connective layer between pancreas and kidney, is associated with improved survival. Recognizing this margin, especially tumor involvement of this margin, is essential for prognostic purposes. Resection of Gerota's fascia is therefore incorporated as standard surgical procedure in the DIPLOMA trial.

Although not associated with improved overall survival in this thesis, neoadjuvant treatment provided by the oncologist, for PDAC in the distal pancreas, decreases the rates of postoperative severe morbidity and pancreatic fistulas grade B/C. This interesting finding is not yet well understood. Several hypotheses speculate that neoadjuvant treatment, radiotherapy especially, induces lobular atrophy and fibrosis, affecting mainly the acinar cells, which are responsible for the production of exocrine enzymes.[27] Another explanation might be that patients undergoing neoadjuvant treatment have the possibility to regain strength and weight during or shortly after their treatment. Majority of patients affected with PDAC are underweight or sarcopenic due to exocrine insufficient, diabetes de novo or cancer cachexia before they undergo their major surgery.[28] Sarcopenia is an important risk factor for postoperative morbidity and even mortality. An international study found in patients during neoadjuvant treatment some improvement in lean mass by increased skeletal muscle, and decreased visceral adipose tissue.[29] The latter is an often described risk factor for postoperative pancreatic fistulae. Conversely, for patients loosing lean mass during neoadjuvant treatment, the risk to die postoperatively is elevated.[30] It might also be that only the best patients make it through neoadjuvant treatment and undergo surgery. About 20% of patients will not make surgery due to disease progression or adverse events during treatment.[31] This survival bias may have an impact on the results and should be considered when interpreting data concerning survival.

Finally the importance of further multidisciplinary collaboration between radiology, oncology and surgery became more clear. Besides for deciding whether a patient is suitable for the minimally invasive approach, this close collaboration is required to establish treatment pathways for patients. This thesis found that patients with radiological involvement of splenic vessels by PDAC in the pancreatic body or tail should undergo neoadjuvant treatment as this was associated with improved overall survival. This is an interesting finding as splenic vessel was previously not considered to be associated with survival in PDAC of pancreatic body or tail. As resection of spleen is part of the normal work-up in the treatment of these tumors. Splenic vessel resection is in general not an obstacle for surgeons. Recently, several studies have associated splenic vessel tumor involvement, both radiologically and pathologically, with reduced survival.[32] Yet the importance of involvement of the splenic vessels has been overlooked for some time and has not been considered as a prognostic marker in the TNM classification system of malignant diseases. The TNM classification was recently updated into TNM 8 which defined lymph node involvement and tumor size better.[33] Still the prognostic value of TNM 8 remains moderate due to a superseded way of looking at pancreatic cancer.[34] Pancreatic cancer is a systemic disease and classifications should consider the (possibility for) systemic dissemination and should include variables as the involvement of major vessels, such as splenic vessels or superior mesenteric vein and resection margins. Also upcoming diagnostics through liquid biopsies and analyzing circulating tumor cells may be useful in the future for better understanding of disease dynamics during treatment.[35,36]

This thesis underlines the importance of understanding when and how to select patients suitable for the minimally invasive approach in order to prevent patients from potential learning curve or implementation associated harm. Also the multidisciplinary collaboration is highlighted; as working together will improve the surgical and ultimately patient' outcome.

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