Long term oncological outcome of laparoscopic techniques in pancreatic cancer

Trond Buanes, Bjørn Edwin

Abstract

The laparoscopic technique in distal pancreatic resection (LDP) has been widely accepted, and outcome data support the hypothesis that survival is improved, partly due to improved postoperative safety and recovery, thus optimizing treatment with adjuvant chemotherapy. But laparoscopic pancreaticoduodenectomy (LPD or Whipple-procedures) has spread more slowly, due to the complexity of the procedure. Surgical safety has been a problem in hospitals with low patient volume, resulting in raised postoperative mortality, requiring careful monitoring of outcome during the surgical learning curve. Robotic assistance is expected to improve surgical safety, but data on long term oncological outcome of laparoscopic Whipple procedures with or without robotic assistance is scarce. Future research should still focus surgical safety, but most importantly long term outcome, recorded as recurrence at maximal follow up or - at best - overall long term survival (OS). Available data show median survival above 2.5 years, five year OS more than 30% after LDP even in series with suboptimal adjuvant chemotherapy. Also after LPD, long term survival is reported equal to or longer than open resection. However, surgical safety during the learning curve of LPD is a problem, which hopefully can be facilitated by robotic assistance. Patient reported outcome should also be an endpoint in future trials, including patients with pancreatic ductal adenocarcinoma.

Key words: Chemotherapy; Endpoint; Imaging; Laparoscopic surgery; Long term outcome; Overall survival; Pancreatic cancer; Robotic assistance

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Core tip: Laparoscopic techniques have profoundly altered oncological gastrointestinal surgery, also resectional treatment of pancreatic ductal adenocarcinoma. Long term outcome of distal resections has been gradually improved. Median survival is more than 2.5 years, five year overall survival above 30%, whereas outcome of laparoscopic
pancreatoduodenectomy needs further evaluation before the technique can be widespread. It is an open question how wide this spread ought to be, but robotic assistance is expected to improve surgical safety.

**INTRODUCTION**

Improved survival after laparoscopic resection of gastrointestinal carcinoma was expected after elimination of the initial failures in surgical performance during the nineties. A randomized controlled trial (RCT) from Barcelona [1], comparing survival after laparoscopic and open colectomy (n = 219) supported this concept. But subsequent multicenter RCTs with comprehensive patient numbers could not verify any survival difference [2]. In patients with ductal pancreatic adenocarcinoma (PDAC), no RCT comparing long term outcome of laparoscopic and open distal resection was identified in the Cochrane review 2016 [3]. In 2017, a small series from India was published with shorter hospital stay after laparoscopic resection [4]. Nevertheless, laparoscopic distal pancreatectomy (LDP) has become a widespread technique, and selection of relevant clinical parameters for assessment of long term oncological outcome is ever more underlined [5]. Also increasing numbers of laparoscopic pancreaticoduodenectomy (LPD/Whipple procedures) have been reported with good outcome [6], and oncological advantages over an open approach have been suggested [7].

The clinical benefit of adjuvant chemotherapy after open resectional surgery in pancreatic cancer (PC) patients is well documented [8,9], whereas the question of upfront surgery vs neoadjuvant chemotherapy is unsettled. These questions have never been investigated, focusing only laparoscopically operated patients, but fair rationales indicate that evidence generated from PC patients operated openly, is transferable to laparoscopic practice. This minireview updates current evidence on long term oncological outcome of laparoscopic resection combined with applied chemotherapy in PDAC patients. The intention of the analysis is first to improve selection of endpoints in future clinical trials, second to guide the choices of surgical methodological development.

**Methods (search strategy and data management)**

Search in PubMed was performed with the key words: PC, combined with chemotherapy, laparoscopy, morbidity, outcome, safety, survival. Reports were selected, based on publication date and comprehended internal validity in each paper. Cochrane reviews, meta-analyses and review articles, relevant to the scope of this review were prioritized. Data on long term survival was particularly focused. Core information from the most relevant publications was selected for presentation in two summary tables.

**DISTAL RESECTIONS**

The laparoscopic technique was introduced in distal resections during the nineties, concurrent with ongoing diagnostic improvements generated from increasing use of abdominal CT, MRI and ultrasound examination. Concomitantly, awareness of the malignancy potential of mucinous cysts [10] enables surgical removal of premalignant tumors/early invasive carcinoma, thus improving postoperative survival after any surgical technique. In the first report from our department on 50 PDAC patients, undergoing LDP [11], five year survival was above 30%, which was very much better than in our previous series, obviously due to earlier diagnosis, but the early skepticism aligned with laparoscopic techniques in PDAC patients was opposed by those data. In 2012, Mitchem, Strasberg et al [12] published a modified open technique for resection of adenocarcinoma of the body/tail of the pancreas; the Radical Antegrade Modular Pancreaticosplenectomy Procedure (RAMPS), underlining new technical aspects, including the necessity of removal also of the left adrenal gland in numerous cases; “posterior RAMPS”. In 47 patients, operated by the RAMPS...
technique, median postoperative survival was 26 mo, 5 year overall actuarial survival (OS) 35.5%, mean lymph node count was 18 and rate of R0 resection (free margin) 81%. Survival in the 50 PDAC patients, operated with LDP in our department, was similar but lymph node count in our specimens was significantly lower. This observation initiated investigation of the putative impact on lymph node count of improved pathology examination, focusing specimens from patients undergoing LDP during ten years (January 2007-January 2017). The lymph node count and the number of positive glands increased significantly when specimens underwent a strictly, standardized examination\[13\]. Accordingly, comparison of lymph node count in the specimens from different centers is associated with significant uncertainty, thus also comparison of oncological outcome of surgical methods, based on lymph node count. Also the rate of R0 resections is an unsafe oncological quality indicator, first because of various R0 definitions\[14,15\], second because neoadjuvant chemotherapy is used increasingly and R0 status has not been clearly defined in this situation. Due to spot wise death of tumor tissue during chemotherapy in PDAC, the R0 concept must be redefined. Overall survival/cancer related death rate are the most appropriate clinical parameters for evaluation of long term oncological outcome of resectional surgical methods, subsidiary, recurrence rate at maximal follow up.

In a Pan-European, retrospective study (DIPLOMA), oncological outcome was compared between LDP and open distal pancreatectomy (ODP). Among 1212 patients, operated from 2007-2015 in 34 centers, distributed between 11 countries, propensity score matching was possible in 340. Postoperative survival was median 31 and 28 mo after ODP and LDP respectively\[16\]. Data registration was not standardized between the participating 34 centers, and the uncertainty of these data is substantial. In another recent report from two centers (Oslo/Norway and Seoul/South Korea) who standardized their registration, 207 patients with histologically confirmed PDAC underwent LDP from 2002-2016. Median overall and recurrence-free survival were 32 and 16 mo, five year OS and recurrence-free survival was 38, 2% and 35, 9% respectively\[17\]. Adjuvant chemotherapy was given according to national guidelines in Norway and Korea during the inclusion period, which later has been shown to be suboptimal, as the ESPAC 4 study documented improved survival of Gemcitabine plus Capecitabine\[18\]. Accordingly, even better long term oncological outcome of LDP is probably achievable, when the procedure is combined with the best adjuvant regimen. These data are in line with comparative studies from single centers in Asia. Shin et al\[19\] compared median OS and recurrence rate at maximal follow-up in 112 patients, 70 operated with LDP, 80 ODP between December 2006 and August 2013. Five year OS was 32.5% vs 27.6%, recurrence after maximal follow-up was found in 50% vs 60%, respectively; therefore there was no statistically significant difference after propensity score matching. Hu et al\[20\] reported recurrence after maximal follow-up in 18% after LDP vs 48% after ODP, but total patient number was only 34, and hence no significant difference. In a Cochrane review 2016\[21\], the authors conclude that short time outcome (hospital stay, recovery, postoperative morbidity, etc.) seems improved after LDP (medium strong evidence), whereas evidence favoring better long term oncological outcome is still weak.

**PANCREATICODUODENECTOMY (WHIPPLE PROCEDURES)**

The first international State-of-the-Art conference on Minimally Invasive Pancreatic Resection took place in Sao Paulo, Brazil on April 20\[15\], 2016, and a comprehensive summary of the proceedings have been published\[22\]. A systematic review on best-evidence of outcome after LPD identified 582 publications, 26 comparative studies\[23\]. Information from the National Cancer Data Base (NCDB) comparing short term outcome of LPD with open pancreaticoduodenectomy (OPD) describes 4421 patients, operated 2010-2011; 4037 (91%) underwent OPD, 384 (9%) LPD, and no difference was found in 30 day mortality, 5.2% vs 3.7% respectively\[16\]. This report gives no information on long term oncological outcome. Another paper based on the Nationwide Inpatient Sample Database identified 15574 Whipple procedures performed from 2000-2010; 681 of these (4.4%) laparoscopically\[24\]. The main conclusion is that even during the learning curve of laparoscopic surgeons, safety seems acceptable, short term outcome is equal or better than OPD, but no information on long term oncological outcome is given. A report from the Mayo Clinic on outcome in 108 patients after LPD, compared to 214 after OPD found no significant survival difference\[25\], but delay of recovery due to postoperative morbidity resulted of no adjuvant chemotherapy in 12% after OPD vs 4% after LPD (P = 0.04). However, at a national level, this difference could not be verified, in a report from NCDB in 7967 subjects\[26\]. Kendrick\[27\] mentions number of lymph nodes retrieved and margin status...
as relevant endpoint parameters for assessment for oncological outcome and lists five publications with this information, but only two of these reports have information on local recurrence and survival at the time of maximal follow up. A comparative study from France[25], gives only data on short term outcome, but in a recent combined report from the United States and France, favorable survival was found after LPD[26]. After propensity score matching median OS was 35.5 mo after LPD vs 29.6 after OPD; 1-, 3 and 5-year survival was 80.5% vs 49.2%, 77.7% vs 39.7%, and 46.4% vs 30% respectively. However, a recent metaanalysis shows that the immediate risk of postoperative morbidity may influence OS, as introduction of LPD in hospitals with low patient volume, resulted in more than doubling of postoperative mortality, 7.5% vs 3.4%[27]. Also a Pan European report from 14 centers having performed more than ten LPD, found increased morbidity after minimally invasive procedures[28]. All centers should obviously not introduce this procedure. Information from core papers on oncological long term outcome of distal resections is put together in Table 1, pancreaticoduodenectomy in Table 2.

ROBOTIC ASSISTANCE

Robotic surgery was first utilized for pancreatic resection in 2003[29], and is becoming increasingly utilized[30], even though the number of operated patients is still limited. Robotic assistance in distal resections has been evaluated in a metaanalysis from 2016[31], reporting nine comparative studies with all together 246 robotic vs 391 laparoscopic procedures. Short term outcome in terms of postoperative morbidity, hospital stay and recovery were similar. An updated metaanalysis 2017[32], including 813 patients, verified this but conversion rate was lower in RDP than LPD. Information about long term oncological outcome is missing in both these papers, but is reported in two small series: In ten PDAC patients median OS was 15, range 7-29 mo[33], in 72 other patients[34] mean OS was 15.6 mo ± 5.8 mo, and only 26% of the latter cases received adjuvant chemotherapy, i.e., there is a potential for further increased survival.

Safety aspects

The complexity of Whipple procedures and the resulting risk of postoperative severe morbidity and mortality are well known. Robot-assistance may possibly result in more precise dissection and safer construction of anastomoses. Institutions gaining experience with robot assisted pancreaticoduodenectomy (RPD)[31], underline that standardization of key element of the learning curve of RPD is mandatory[35]. A good model for this has been published from Pittsburgh, where quality outcomes of the first consecutive 200 RPD procedures have been monitored in subgroups of 20 cases, reviewing the learning curve during the implementation phase[36]. This program was developed also to adjust the introduction of a robotic platform to the ongoing paradigm shift in healthcare; a move from fees for service to payment for performance, thus achieving better value from available resources[37]. This is particularly relevant for RPD-procedures, as a major downside is high costs. Nevertheless, a recent comparative study found comparable surgical and oncological safety, median OS was 23 mo vs 22 mo after RDP and ODP respectively, and even costs were equal[38]. The robotic platform is expected to improve recovery significantly after major pancreatic surgery, thus obtaining better patient outcome/satisfaction for used resources.

ADJUVANT AND NEOADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy has been utilized in PC patients for more than twenty years, and selection of regimens is continuously improving, based on well accomplished RCTs. In Scandinavia, Gemcitabine plus capecitabine have been standard of care in unselected cases after the ESPAC 4 trial[9], but it has already been documented that Folfirinox is more potent[39]. Selection of patients tolerating regimens with significant toxicity leads to five year survival far above 30% after open pancreatic surgery - this probably applies also for laparoscopic techniques. So far, no prospective trials have been conducted, investigating these questions. Current knowledge stem from observational studies of patients, receiving regimens which were inferior to the present standard of care. Accordingly, a reasonable presumption is that there is room for further improvement of postoperative survival after laparoscopic pancreatic surgery, when combined with updated adjuvant treatment.

Neoadjuvant chemotherapy attracts increasing interest, and numerous RCTs are
ongoing, including resectable and borderline resectable patients undergoing open pancreatic resections. Also considerations on putative benefit and/or harm of neoadjuvant treatment algorithms in laparoscopic pancreatic surgery have to await results from these trials.

**DISCUSSION**

Five year OS above 30%-35% after LDP has recently been reported from numerous centers, illustrating that increasing evidence show good long term oncological outcome. Comparison with outcome of ODP favors the laparoscopic technique, even though data from RCTs are still lacking. In recent reports, five year OS is 25% after the RAMPS procedure\(^{40,41}\). Patients with PDAC in the pancreatic body or tail should therefore be offered laparoscopic resection if the HepatoPancreaticoBiliary (HPB) center possesses the required expertize. But pancreatic head tumors are still resected openly in most HPB-centers, as the role of LPD is not at all clear and long term oncological outcome is mostly unknown. The international State-of-the-Art conference on Minimally Invasive Pancreatic Resection in 2016 concluded that the small number of comparative studies of LPD vs ODP is also of low quality, Newcastle-Ottawa score (NOS) < 6\(^{21}\). This score is a risk of bias assessment tool for observational studies\(^{42}\). During the State-of-the-Art conference 2016, a specific session evaluated what would be the future most essential scientific contributions in this field, underlining that numerous important questions need valid answers\(^{43}\). Even though RCT is the reference standard for clinical comparative research according to the traditional pyramid of evidence level, the applicability of this study design is limited and numerous clinical questions cannot be solved by any randomized trial. A critical question in any trial is selection of primary and secondary outcome variables (clinical endpoints). The importance of adequate choice of endpoint is clearly illustrated by finalized or ongoing RCTs comparing outcome of open and laparoscopic techniques in pancreatic surgery. The PLOT trial\(^{4}\) randomized 60 Whipple operated patients, focusing hospital stay, and found median 13 d after ODP vs 7 d after LPD, \(P = 0.001\), which is relevant and interesting, but marginally important. In the Netherlands, the LEOPARD 1 study\(^{44}\) includes patients in need of distal resection, randomizing between open and laparoscopic technique with time to functional recovery as primary endpoint. Similarly, the LEOPARD 2 studies\(^{45}\) randomize upfront resectable patients between ODP and LPD with the same endpoint. These studies represent relevant clinical research, and valid answers might be generated, but it is already well known from numerous prospective observational studies that LPD is associated with rapid recovery in most centers, and it would be more interesting to investigate whether or not robotic assistance could further improve recovery, safety and particularly long term OS.

In trials focusing outcome of any Whipple procedures focus on safety aspects, especially postoperative mortality, is critically important. This is emphasized in comprehensive registry studies\(^{22,46}\) and single center reports\(^{47}\). In the State-of-the-Art conference 2016\(^{21}\), an important “take home messages” to HPB-centers on their way to introduce LPD was; “Surgeons should assess their level of commitment with a clear understanding of the procedure complex, any expected learning curve, and requirements to achieve proficiency”. This message is further underlined by recent information from the Leopard 2 study. The data monitoring board has recommended early termination of the trial because of too high 90-d complication-related mortality.
in the laparoscopic arm, i.e., 10% vs 2% in the open arm\(^4\).

The implementation of laparoscopic techniques in oncological surgery has put focus on the traditional pyramid of evidence level, raising the question: how should surgical methods be developed, evaluated and broadened? Both internal and external validity of published investigations are highly relevant, as prospective data, documenting increased survival will probably be reproducible in the publishing center. However, the same outcome data cannot be presupposed transferable to other centers if core conditions differ. Methodological considerations should also be developed across surgical subspecialties, illustrated by a recent report on 10 597 patients with lung cancer stage 1, included in a propensity match study, comparing long term oncological outcome of minimally invasive (MI) and open lung resection\(^6\). For five year survival was 68.6% after MI procedures vs 64.8% after open lung resection \((P = 0.003)\). For patients with lung cancer, these data is a significant contribution to evidence based guidance of surgical methodological development.

Finally, the lack of patient reported outcome (PRO) in the literature is a major problem, raising the uncertainty concerning short- and long term outcome in patients with PDAC. There are numerous explanations for the scarcity of data on health related quality of life (HQoL) in this group of patients. One important problem is that disease specific QoL measures are comprehensive, including irrelevant questions which result in low response rates from patients included in prospective trials\(^49\). This problem has recently been solved by development of the PC Disease Impact (PACADI) score\(^50\). This is a brief, disease specific measure, and item selection was based on the patients’ priorities of which dimensions of PRO had greatest impact on their everyday QoL. In our opinion, every trial evaluating laparoscopic techniques in PC patients should also include PRO as an endpoint. Prospective comparative studies with long follow-up of OS as primary outcome parameter, longitudinally recorded PRO as secondary endpoint, are strongly warranted.

### CONCLUSION

The potential for clinical benefit from laparoscopic techniques in pancreatic surgery is great, but available evidence is still limited. Outcome of LPD and RPD is associated with great uncertainty. For all Whipple procedures, surgical safety is a particular concern, which probably can be improved by robotic assistance.

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P- Reviewer: Fogli L, Noshiro H, Peng B, Ramia JM, Rungsakulkij N
S- Editor: Ma YJ  L- Editor: A  E- Editor: Tan WW
