ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2018 December 16; 10(12): 378-441

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 10 Number 12 December 16, 2018

EDITORIAL

MINIREVIEWS

META-ANALYSIS

World Journal of Gastrointestinal Endoscopy
Volume 10 Number 12 December 16, 2018

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

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PUBLICATION DATE
December 16, 2018

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World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2018 December 16; 10(12): 383-391

DOI: 10.4253/wjge.v10.i12.383

ISSN 1948-5190 (online)

MINIREVIEWS

Long term oncological outcome of laparoscopic techniques in pancreatic cancer

Trond Buanes, Bjørn Edwin

ORCID number: Trond Buanes (0000-0002-4652-2782); Bjørn Edwin (0000-0002-3137-6225).

Conflict-of-interest statement: All authors have no conflicts of interest to report.

Manuscript source: Invited manuscript

Corresponding author to: Trond Buanes, PhD, Full Professor, Department of Gastroenterological Surgery, Division of Cancer, Surgery and Transplantation, Institute of Clinical Medicine, Faculty of Medicine, Oslo University Hospital, Pb 4956, Oslo N-0424, Norway.
trond.buanes@medisin.uio.no
Telephone: +47-23-070958
Fax: +47-23-072526

Received: August 28, 2018
Peer-review started: August 28, 2018
First decision: October 4, 2018

Trond Buanes, Department of Gastroenterological Surgery, Division of Cancer, Surgery and Transplantation, Institute of Clinical Medicine, Faculty of Medicine, Oslo University Hospital, Oslo N-0424, Norway

Bjørn Edwin, the Intervention Centre and Department of Hepato-Pancreatico-Biliary Surgery, Institute of Clinical Medicine, Faculty of Medicine, Oslo University Hospital, Oslo N-0424, Norway

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

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

Revised: November 5, 2018
Accepted: December 5, 2018
Article in press: December 5, 2018
Published online: December 16, 2018

pancreaticoduodenectomy 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.

Buanes T, Edwin B. Long term oncological outcome of laparoscopic techniques in pancreatic cancer. *World J Gastrointest Endosc* 2018; 10(12): 383-391
URL: https://www.wjgnet.com/1948-5190/full/v10/i12/383.htm
DOI: https://dx.doi.org/10.4253/wjge.v10.i12.383

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[9]. 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*[18] compared median OS and recurrence rate at maximal follow-up in PDAC 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, but there was no statistically significant difference after propensity score matching. Hu *et al*[19] 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[3], 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 20th, 2016, and a comprehensive summary of the proceedings have been published[20]. A systematic review on best-evidence of outcome after LPD identified 582 publications, 26 comparative studies[21]. 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[22]. 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[23]. 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[7], 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[24]. Kendrick[21] 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 LDP. 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

Table 1 Core information on distal pancreatic resection in pancreatic cancer patients

Ref.	No. of patients reported	Study	Median survival (mo)	
			Open	Laparoscopic
Van Hilst *et al*[16], 2017	680	Comparative, 34 centers (propensity score matching) retrospective	28	31
Mitchem *et al*[12], 2012	47	Non comparative, single center retrospective	26	NA
Sahakyan *et al*[17], 2017	207	Non comparative, two centers retrospective	NA	32
Shin *et al*[18], 2015	150	Comparative, single center (propensity score matching) retrospective	29	33
Grossman *et al*[40], 2016	78	Non comparative, single center retrospective	25	NA

NA: Not applicable.

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* OPD 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 OPD *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 OPD 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] and single center reports[46]. 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 complexity, 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

Table 2 Core information on pancreaticoduodenectomy/Whipple-procedures in pancreatic cancer patients

Ref.	No. of patients reported	Study	Overall survival		
			Open	Laparoscopic	*P* value
Croome *et al*[7], 2014	322 LPD 108 OPD214	Comparative, retrospective single center	Median 21.8 mo	Median 25.3 mo	0.22
Nussbaum *et al*[24], 2016	7967 LPD 1191 OPD 6776	Comparative Registry (NCDB) Retrospective	Two year 47%	Two year 43%	NS
Conrad *et al*[26], 2017	65 LPD 40 OPD 25	Comparative, retrospective two centers	Median 29.6 mo	Median 35.5 mo	NS

LPD: Laparoscopic pancreaticoduodenectomy; OPD: Open pancreaticoduodenectomy; NCDB: National Cancer Data Base; NS: Not significant.

in the laparoscopic arm, *i.e*., 10% *vs* 2% in the open arm[47] .

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 10597 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[48]. Four 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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