

Minimally invasive versus open distal pancreatectomy for pancreatic cancer: a review of the literature

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Background and Objective: Albeit its slow implementation during the past decades, minimally invasive surgery has become the standard approach to benign and premalignant left-sided pancreatic tumors. Two randomized controlled trials reported benefits of minimally invasive distal pancreatectomy (MIDP) over open distal pancreatectomy (ODP). However, its role in the treatment of left-sided pancreatic ductal adenocarcinoma (PDAC) is yet to be established as randomized controlled trials are still lacking. In this review, we aim to provide a comprehensive overview of the currently available evidence on outcomes of MIDP compared to ODP when treating PDAC.

Methods: A literature search was performed in PubMed for studies published between January 1994 and January 2022. Besides, international guidelines were screened for eligible studies and the world health organization trial register was screened for ongoing randomized controlled trials on this subject. Only studies published in English peer-reviewed journals were considered eligible.

Key Content and Findings: The search strategy identified 30 retrospective comparative studies including over 12,000 patients undergoing either MIDP or ODP for PDAC. Most studies reported comparable radical resection rates and overall survival between the two groups, whereas contradicting results on lymph node yield have been reported. Three retrospective studies reported worse outcomes following extended MIDP compared to extended ODP for pancreatic cancer. Three currently recruiting randomized controlled trials were identified by the trial register search.

Conclusions: MIDP for benign and pre-malignant left-sided pancreatic tumors is considered as standard surgical procedure following reported benefits in two randomized controlled trials. For PDAC, available evidence suggests that MIDP is non-inferior to ODP but data from randomized trials are lacking. Currently recruiting randomized trials are expected to answer this question soon. Caution is warranted when performing extended MIDP.

Keywords: Pancreatic ductal adenocarcinoma (PDAC); minimally invasive; laparoscopic; robot; distal pancreatectomy

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Introduction

In the modern era of surgical techniques, the minimally invasive approach has gained popularity for several major abdominal surgical procedures. In recent years, several randomized controlled trials have reported benefits of minimally invasive surgery over the open approach (1-3). Suggested advantages of minimally invasive surgery include less surgical trauma, less intraoperative blood loss, less wound infections, shorter length of hospital stay and shorter time to functional recovery (4).

In contrast to the wide implementation of several minimally invasive procedures for gastrointestinal diseases, the implementation of minimally invasive pancreatic surgery has been rather slow. The first minimally invasive distal pancreatectomy (MIDP) was described in 1994 by Cuschieri *et al.* (5), but it took until 2006 before the first comparative studies were reported, which demonstrates this rather slow implementation of MIDP (6). Probable reasons for this slow implementation might have been the technical complexity owing to the retroperitoneal location of the pancreas and close proximity to major abdominal vascular structures, leading to long learning curves and uncertainty about the clinical benefits compared to open distal pancreatectomy (ODP) (7).

More recently, two randomized controlled trials comparing MIDP and ODP for patients with benign and premalignant disease have been completed. The LEOPARD-1 trial from the Netherlands and the LAPOP trial from Sweden both demonstrated a shorter time until functional recovery, shorter length of hospital stay and comparable postoperative morbidity after MIDP compared to ODP (8,9). Hence, MIDP has become widely accepted as preferred approach to benign and premalignant left-sided pancreatic tumors.

A less common indication for distal pancreatectomy is pancreatic cancer [pancreatic ductal adenocarcinoma (PDAC)]. Pancreatic cancer is a lethal disease with a fiveyear survival rate of approximately 5–10% (10,11) and only a minority of these patients has resectable disease at primary presentation (12). Traditionally, left-sided pancreatic cancer is treated with distal pancreatectomy with concomitant splenectomy using an open approach. Although favorable outcomes of MIDP have been reported in retrospective studies, uncertainty regarding oncological outcomes remains as demonstrated in a survey study among pancreatic surgeons, which reported that approximately 30% of surgeons expect non-inferior oncological outcomes after MIDP compared to ODP (13). So far, only retrospective studies have been conducted on this topic and data from randomized controlled trials are lacking (14).

Therefore, we aimed to provide a comprehensive overview of the currently available evidence on outcomes of MIDP compared to ODP when treating pancreatic cancer. This review will address short- and long-term oncological outcomes and technical aspects. Suggestions for future clinical practice and research are also discussed. We present the following article in accordance with the Narrative Review reporting checklist (available at https:// ls.amegroups.com/article/view/10.21037/ls-22-40/rc).

Methodology

A literature search was performed in PubMed for studies published between January 1994 and January 2022. Search terms included but were not limited to "distal pancreatectomy", "minimally invasive surgery", "laparoscopy", and "pancreatic cancer". Besides, several international guidelines were screened for eligible studies and statements regarding MIDP for cancer. Also the world health organization trial register was screened for ongoing randomized controlled trials on this subject. Titles and abstracts were screened for eligibility for all identified studies. Published studies in English peer-reviewed journals were considered eligible for the present study (*Table 1*).

Discussion

Surgical technique of distal pancreatectomy for pancreatic cancer

Standard distal pancreatectomy consists of resection of the body and/or tail of the pancreas, and should be extended to splenectomy, adequate lymphadenectomy and Gerota's fascia resection when performed for pancreatic cancer as stated in the International Study Group on Pancreatic Surgery (ISGPS) guidelines (15). Several efforts have been made to describe surgical strategies during distal pancreatectomy in order to reach safe oncological resection, thus optimizing patient survival after resection.

The technique of radical antegrade modular pancreatosplenectomy (RAMPS), described by Strasberg *et al.* (16), includes a medial to lateral approach, early vascular control and no-touch isolation with en-bloc resection, as compared to a lateral to medial approach and late vascular control in standard distal pancreatectomy

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 Table 1 Search strategy summary

| Items | Specification |
|--|--|
| Date of search | May 30, 2022 |
| Databases and other sources searched | PubMed, international guidelines, WHO trial registry |
| Search terms used | ((minimally invasive OR laparoscopic) AND (open) AND (distal pancreatectomy OR left pancreatectomy)) Laparoscopy [MeSH term] Pancreatectomy [MeSH term] |
| Timeframe | January 1994–January 2022 |
| Inclusion and exclusion criteria | Inclusion criteria: studies on MIDP <i>vs.</i> ODP, written in English, published in peer-reviewed journals Exclusion criteria: non-comparative studies, studies without availability to full-text |
| Selection process | MK and JvH conducted the title and abstract screening and article selection Conflicts during the selection process were resolved by discussion until consensus was reached |
| Any additional considerations, if applicable | None |

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(17,18). The anterior RAMPS technique is performed when the left adrenal gland is not involved, whereas the posterior RAMPS technique includes left adrenalectomy to achieve oncological safe resection (16). Routine dissection of lymph node stations 10, 11, and 18 is included in the RAMPS technique as called for in the ISGPS guideline (15,16). Included in the RAMPS technique, however, is also the routine resection of stations 8a and 9 based on lymphatic drainage as proposed by O'Morchoe *et al.* (19), which was only advised in pancreatic body tumors by the ISGPS statement (15,16). The RAMPS technique was primarily adopted in open surgery and is now widely used during oncological ODP. A laparoscopic approach to the RAMPS technique was described by Fernández-Cruz *et al.*, and was reported to be feasible during such procedures (17,20).

A recent systematic review and meta-analysis by Watanabe *et al.* including 13 studies compared oncological outcomes after RAMPS (770 patients) and standard distal pancreatectomy (871 patients) (21). Meta-analyses revealed similar radical resection rates (relative risk 1.06, P=0.14) but an increased number of retrieved lymph nodes [weighed mean difference (WMD) 4.06 nodes, P<0.001] in RAMPS procedures. Although little effect on overall survival [hazard ratio (HR) 0.92, P=0.34] and recurrence-free survival (HR 0.72, P=0.32) was observed, prolonged disease-free survival (HR 0.59, P=0.006) was observed after RAMPS procedures compared to standard distal pancreatectomies. Comparative analyses of minimally invasive versus open RAMPS procedures were reported in a recent systematic review by Takagi *et al.*, which included 7 comparative studies including 423 patients (145 minimally invasive RAMPS and 278 open RAMPS) (22). This meta-analysis demonstrated decreased tumor size (WMD –0.62 cm, P=0.002) and lymph node yield (WMD –3.14 nodes, P<0.001) but a similar radical resection rate [odds ratio (OR) 0.56, P=0.18] in the minimally invasive RAMPS group as compared to the open group. Only one included study reported a survival benefit in the minimally invasive RAMPS group, whereas the other included studies did not report a survival difference between the two groups.

Another technique, the "no-touch left pancreatectomy" technique by Abu Hilal *et al.*, was specifically described for oncological MIDP and is considered more feasible during MIDP compared to the RAMPS technique (23). This technique includes the same oncological principles as the RAMPS technique such as the "no-touch" approach to prevent possible tumor spreading by the surgical equipment, but also hanging of the pancreas at different levels to obtain optimal retropancreatic views. A single-arm analysis of this technique showed adequate oncological and survival outcomes (23). The RAMPS and "no-touch left pancreatectomy" techniques were used in the currently completed randomized DIPLOMA trial comparing MIDP with ODP specifically for pancreatic cancer (24).

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Oncological outcomes of distal pancreatectomy for pancreatic cancer

A systematic review and meta-analysis in 2019 identified 21 cohort studies including over 11,000 patients who underwent either MIDP (n=3,013) or ODP (n=8,233) for pancreatic cancer (14). This meta-analysis reported comparable radical resection rates (OR 1.24, P=0.09) and decreased lymph node yield (WMD –1.30 nodes, P<0.001), but clear selection bias as demonstrated by smaller tumors (WMD –0.46 cm, P<0.001) and less perineural (OR 0.48, P<0.001) and lymphovascular invasion (OR 0.53, P<0.001) in the minimally invasive group as compared to the open group. There were no differences in overall survival (HR 0.86, P=0.06).

The search strategy for the present review identified one additional systematic review and eight comparative cohort studies published after the meta-analysis in 2019 (25-33). The systematic review and meta-analysis by Lyu *et al.* in 2022 identified 30 studies including over 4,000 patients (25). In this study both patients with benign and malignant disease were included, but separate specific analyses for oncological outcomes were reported. Although several comparative studies focusing on pancreatic cancer specifically were missing, this meta-analysis reported similar radical resection rates (OR 1.87, P=0.12) and lymph node yield (WMD –0.48 nodes, P=0.58) for MIDP and ODP. No outcomes were reported on survival.

The identified cohort studies were published in 6 countries between 2019 and 2022 with a total of 1,091 patients (566 in the MIDP group and 525 in the ODP group) (26-33), five studies used propensity-score matching (26-28,32,33). Most studies reported comparable tumor size (26-30,32,33), radical resection rates (26-31,33), and lymph node yield (26-31,33). Overall survival was reported in six studies (27-30,32,33), which was comparable in five studies and ranged from 19-33 months after MIDP and from 17-28 months after ODP (27-30,33). A propensityscore matched analysis by Kwon et al. in 2021 assessed oncological outcomes in 312 patients (156 patients in both groups) (32). This analysis showed significantly increased radical resection rates (76.3% vs. 64.1%, P=0.019) but comparable tumor size (mean 3.4 vs. 3.5 cm, P=0.590) and lymph node yield (mean 14.1 vs. 15.6 nodes, P=0.150) after MIDP as compared to ODP. Median overall survival was also comparable between groups (35.0 vs. 26.7 months, P=0.103), but, interestingly, median disease-free survival was significantly improved after MIDP as compared to

ODP (15.1 vs. 10.6 months, P=0.001).

Survival after distal pancreatectomy for pancreatic cancer

As reported in the aforementioned studies, overall survival after distal pancreatectomy for pancreatic cancer ranges from 17-33 months postoperatively (14,22,27-30,32,33). To identify the survival contribution of different treatment options, several studies have reported on the prognostic value of surgical and non-surgical parameters (34-41). Routine resection of the spleen and adequate lymphadenectomy are considered mandatory in the described surgical techniques to obtain optimal oncological resection and therefore survival after surgery. Also Gerota's fascia resection is advised during such procedures. A recent post-hoc analysis of the DIPLOMA cohort study in over 1,200 patients analyzed the survival contribution of several surgical parameters including surgical approach, radical resection, splenectomy, Gerota's fascia resection, extended resection, and lymph node yield (35). Multivariable analysis in this study showed that resection of Gerota' fascia was an independent predictor for improved survival (HR 0.74, P=0.019), as were radical resection (HR 0.70, P=0.006), decreased lymph node ratio (HR 0.28, P<0.001), and adjuvant chemotherapy (HR 0.67, P=0.003). Extended resection was associated with impaired survival (HR 1.75, P<0.001) due to advanced tumor stage, whereas splenectomy was however not identified as predictor for overall survival. This was considered to be caused by the small number of patients that did not receive splenectomy in that cohort (n=57). A recent study by Sahakyan et al. in 2022 (41), evaluating predictors for survival in 124 patients, also identified extended resection (HR 2.03, P=0.003), lymph node ratio (HR 1.03, P=0.001), perineural invasion (HR 3.9, P=0.003), and adjuvant chemotherapy (HR 0.41, P=0.001) as independent predictors for survival. Interestingly, the multivariable analysis in this study did however not include the parameter of radical resection (R0 vs. R1), but only included the positive anterior surface as parameter which was identified as independent predictor for survival (HR 2.03, P=0.004). These results suggest that not only surgical margins, i.e., the transection and posterior margin, but also the anterior surface is crucial for patient prognostication after distal pancreatectomy.

Similar survival after MIDP and ODP was reported in several studies (14,22,27-30,32,33), and surgical approach was not identified as independent predictor for overall and disease-free survival (34-39).

In contrast, the aforementioned study by Kwon et al. observed a disease-free survival benefit after MIDP as compared to ODP. Despite no overall survival difference was found, the authors concluded that this disease-free survival benefit was most probably explained by the earlier initiation of adjuvant systemic treatment in the minimally invasive group compared to the open group (mean 37.6 vs. 46.0 days, P=0.002) (32). Supporting these findings is a recent report by Salehi et al. including 3,411 patients (996 minimally invasive and 2,415 open procedures) from the United States, which reported increased adjuvant treatment use (OR 2.14, P=0.045) and fewer delays until initiation of adjuvant treatment (OR 0.79, P=0.045) in the minimally invasive group compared to the open group when performed in high-volume centers (42). Conformingly, the meta-analysis by van Hilst et al. also reported a slightly earlier initiation of adjuvant treatment after MIDP (14).

Extended distal pancreatectomy for pancreatic cancer

Extended distal pancreatectomies are defined as either multivisceral resections beyond the pancreas and spleen or vascular resections beyond the splenic vessels (15).

The role of minimally invasive surgery in the surgical treatment of borderline resectable and locally advanced pancreatic cancer remains controversial. Only three studies have evaluated outcomes after extended laparoscopic distal pancreatectomy and reported worse oncological outcomes compared to standard distal pancreatectomies (43-45).

A multicenter retrospective study by Sahakyan et al. among 184 patients reported a higher recurrence rate (63% vs. 37%, P=0.009) and decreased median overall survival (20.2 vs. 33.3 months, P=0.032) after extended laparoscopic procedures (30 patients) compared to standard laparoscopic procedures (154 patients) (44). Another study including 81 patients reported shorter recurrence-free survival (median 6.2 vs. 9.6 months, P=0.047) and overall survival (median 12.9 vs. 27 months, P<0.01) after extended laparoscopic procedures (22 patients) compared to standard laparoscopic procedures (59 patients) (45). A multicenter propensityscore matched study by Balduzzi et al. (43) compared outcomes after laparoscopic versus open extended distal pancreatectomy (in total 320 patients included; 44 laparoscopic procedures matched to 44 open procedures). Matched outcomes showed a conversion rate of 35%, comparable R0 resection rate (67% vs. 48%, P=0.063) and median overall survival (19 vs. 20 months, P=0.571), but a lower lymph node yield in the laparoscopic group

(median 11 vs. 19, P=0.023). Only a minority of patients in the aforementioned studies received vascular resection demonstrating that the role of minimally invasive surgery when performing such resections is yet to be defined.

More specifically, several efforts have been made to evaluate outcomes of distal pancreatectomy with celiac axis resections (DP-CAR). A systematic review by Klompmaker et al. in 2016 evaluated outcomes of 240 DP-CAR procedures and reported acceptable morbidity and mortality, and a median overall survival of 18 months when combined with systemic therapies (46). A recent systematic review by Nigri et al. identified 24 studies reporting outcomes after DP-CAR, eventually including 11 studies with 1,077 patients (221 DP-CAR and 856 standard distal pancreatectomy) in the comparative metaanalyses (47). This study reported a comparable 1-year survival rate between the two groups (OR 0.67, P=0.240). DP-CAR procedures were associated with T4 tumors (OR 28.45, P<0.001) and positive resection margins (OR 2.28, P=0.008) as compared to standard distal pancreatectomy. Long-term results could not be reported on because studies were not suitable for meta-analysis. Considering this, DP-CAR has shown to provide acceptable oncological outcomes and authors conclude that such procedure should no longer be considered a contra-indication when treating locally advanced pancreatic cancer. To our knowledge, the feasibility of a minimally invasive approach to DP-CAR procedures has been studied in only three studies with contradicting results (48-50).

Randomized controlled trials on distal pancreatectomy for pancreatic cancer

A search of the World Health Organization trial registry, which incorporates all international trial registries, currently (search: May 30, 2022) includes three trials comparing MIDP (or laparoscopy only) with ODP. The first trial is the multicenter, patient and pathologist blinded, non-inferiority randomized DIPLOMA trial (ISRCTN44897265) was initiated in 2018 and completed recruitment of all 258 patients in 2021. Primary outcomes of this trial are radical (R0) resection and outcomes are expected in 2022. The second trial is a multicenter trial from China (NCT03792932), which is expected to recruit 306 patients. Primary outcome is recurrence free survival (during a time frame of 2 years postoperatively). The third trial is a multicenter trial from South-Korea (NCT03957135) which is expected to recruit 244 patients. Primary outcome is the

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2-year survival rate.

Conclusions and future perspectives

Minimally invasive pancreatic surgery is on the rise worldwide and its use when performing distal pancreatectomy has increased significantly. For benign and pre-malignant left-sided pancreatic tumors, the minimally invasive approach is considered as standard following the reported benefits in two recent randomized controlled trials. For malignant left-sided pancreatic tumors, however, its use is still under debate. Although numerous studies have been published that focused on the oncological safety and feasibility of MIDP, data from randomized controlled trials are lacking. Nevertheless, currently available evidence suggests that a safe oncological resection can be achieved in MIDP which is at least non-inferior to the open approach. Whether the minimally invasive approach provides equivalent oncological outcomes as compared to the open approach is expected to be answered soon by currently recruiting randomized controlled trials.

With respect to the further implementation of MIDP for pancreatic cancer, future research should focus on outcomes after vascular or multivisceral resection during MIDP. Although some evidence exists, most is based on small sample sizes with heterogeneous data. Hence, the role of a minimally invasive approach to extended resections or DP-CAR procedures remains controversial. In these procedures, the focus should not be on the superiority of one approach over the other, but on adequate patient selection and safe surgical technique that follows oncological principles and enables safe oncological outcome.

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