

Appleby technique: review of the state of the art

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Abstract

Introduction: Adenocarcinomas of the distal part of the pancreas frequently present as advanced stage tumours due to the presence of metastases, peritoneal carcinosis, or as locally advanced tumours invading the celiac axis. This finding leads to the non-resectability of the neoplasm, resulting in an average patient survival of about 6–11 months. To improve the prognosis, surgery has moved to advanced demolition procedures such as distal en bloc pancreatectomy with celiac axis resection (DP-CAR). However, the long-term results of disease-free survival and overall survival are still not clear and noticeable.

Aim: To carry out a retrospective review of the cases of DP-CAR present in the literature to highlight the survival benefits.

Material and methods: To identify results from retrospective research, the authors analysed studies from the PubMed, Embase, and Cochrane databases by applying various combinations of the subject-related terms. The search terms identified with the medical subject heading (MeSH) were “distal pancreatectomy (DP), distal pancreatectomy celiac axis resection (DP-CAR), median survival rates”.

Results: Eleven studies were analysed with a total of 221 DP-CARs. The analysis demonstrated that DP-CAR had a longer operative time, higher blood transfusion rates, more delayed gastric emptying, and fewer R0 resections obtained compared to classic distal pancreatectomy (DP), which demonstrated a better prognosis and a median survival of 27 months compared to 17 months with DP-CAR.

Conclusions: This study demonstrates that DP-CAR does not improve survival compared to DP, exposing the patient to even greater complications; however, in cases of distal pancreatic adenocarcinoma with celiac tripod invasion, DP-CAR appears to be a valid option to increase the average patient survival to 17 months.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) accounts for more than 90% of primary pancreatic cancers. In the US, it is estimated to account to 42,000 deaths, as the fourth most frequent cause of cancer-related death. PDAC demonstrates a poor prognosis with a 5-year survival rate of less than 5%. Surgical resection as R0 resection is the only option [1, 2]. According to the National Comprehensive Cancer Network guidelines (NCCN), PDAC is considered locally advanced and thus unresectable in most cases if it is a tumour located in the pancreatic neck or body with greater than 180° contact with the celiac artery or superior mesenteric artery (SMA) [1]. Distal pancreatic tumours are often found in an advanced stage as a finding of metastases, carcinosis, or locally advanced disease with involvement of the celiac axis or the common hepatic artery approximately

in 30% of patients at the time of diagnosis [3]. This results in the lack of eligibility criteria for resection [4]. Because chemotherapy associated with radiotherapy often fails to achieve good results, surgery appears to be the only option to improve the median survival of these patients. This is a surgery that aims to achieve R0 by resecting the distal pancreas en bloc together with the celiac axis, the retroperitoneal tissue, and the spleen – known as distal pancreatectomy-celiac axis resection (DP-CAR). This technique was initially described in 1976 [5], but it was the surgeon Appleby who described the first-ever illustrated resection of the celiac axis in 1953 during an extended resection of gastric carcinoma. Today, the technique of DP-CAR is named the Appleby procedure after the first surgeon to describe it [6]. However, the results of this technique are not yet clear in the face of a high perioperative patient morbidity. There are studies that seem to demonstrate no improvement in

survival by comparing DP-CAR with distal pancreatectomy (DP), while other studies show an improvement in disease-free survival (DFS) [7–9]. Because DP-CAR is a difficult technique and burdened with high morbidity and mortality, it is not often performed. This means that there are few cases in each published article and it is difficult to find precise clinical data. Reported indications to perform the Appleby approach were as follows: 1) tumour located in the pancreatic neck or body without macroscopic extension into the pancreatic head; 2) tumour invasion must be limited to the celiac artery, Common Hepatic Artery (CHA), or tumour < 10 mm from the origin of splenic artery with no involvement of the root of the celiac artery from the aorta; 3) no involvement of the gastroduodenal artery (GDA), proper hepatic artery, or superior mesenteric artery (SMA); and 4) absence of distant metastases. If a complete venous resection and reconstruction is deemed feasible, portal vein or superior mesenteric vein involvement does not preclude DP-CAR [10, 11].

Aim

The objective of this article is to carry out a retrospective review of the cases of DP-CAR present in the literature to highlight the survival benefits.

Material and methods

We retrospectively evaluated the PubMed, Embase, and Cochrane Library databases by applying various combinations of subject-related terms. The search terms identified with the medical subject heading (MeSH) were “distal pancreatectomy (DP), distal pancreatectomy celiac axis resection (DP-CAR), median survival rates”. The databases were used to collect literature published up to 2010. Inclusion criteria were reports that contained the following: “distal pancreatectomy (DP), distal pancreatectomy celiac axis resection (DP-CAR), median survival rates”. Exclusion criteria were as follows: case reports, letters, comments, and abstracts. Duplicate reports and studies that contained non-cancer patients were also excluded. No language restriction was applied in the search strategy. Two independent researchers performed the review. The PRISMA guidelines were followed during all stages of this systematic review. Recommendations were protocol, research question, search strategy, study eligibility, data extraction, study designs, risk of bias, publication bias, heterogeneity, and statistical analysis. Risk was assessed on the basis of a random sequence, blinded evaluation of results, and selective reporting. Results: The systematic literature search retrieved 1254 articles, 565 of which were duplicates and were excluded from analysis. The titles and abstracts from the remaining

700 articles were assessed. After careful evaluation, 317 articles were determined to be unrelated to our study and were subsequently excluded. The full text of the remaining 394 articles was thoroughly assessed. Case reports, editorials, letters to the editor, and general reviews were then excluded (in total 358). A total of 36 articles were ultimately included for this review, and after exclusion of repetitive reports, 25 manuscripts comprised the relevant literature for this review article. All procedures were in accordance with ethical standards of the relevant committee on human experimentation and the Helsinki Declaration. Informed consent was waived because the study was retrospective. After excluding repetitive reports, 11 manuscripts comprised the relevant literature for this review article. We evaluated the following: operative time (OT), intraoperative blood loss (BL), blood transfusion (BT), portal vein resection (PVR), R0 rates (R0), morbidity, mortality (M), post-operative pancreatic fistula (POPF), and delayed gastric emptying (DGE). Eleven studies were analysed with a total of 221 DP-CARs. Analyses demonstrated that DP-CAR had a longer operative time, higher blood transfusion rates, more delayed gastric emptying, and fewer R0 resections obtained compared to classic distal pancreatectomy (DP), which demonstrated a better prognosis and a median survival of 27 months compared to 17 months of DP-CAR.

Operative technique

In 1953 a Canadian surgeon called Lyon H. Appleby [6] first described resection of the celiac axis for locally advanced gastric cancer. He described preliminary clamping of the common hepatic artery (CHA) to confirm sufficient palpable pulsatility of the proper hepatic artery perfused through the gastro-duodenal-artery (GDA), followed by an en bloc resection the celiac artery, stomach, tail of the pancreas, and spleen. The procedure usually does not require arterial reconstruction unless surgeons find inadequate liver blood supply. In this case, arterial reconstruction of the celiac artery or CHA is needed. The technique can be performed with resection and reconstruction of the porto-mesenteric vein or multiorgan resection such as left adrenal gland, kidney, stomach, or colon [12–15].

Results

Beane *et al.* [16], in their study on 192 distal pancreatectomies, treated 20 patients with DP-CAR and performed 172 classic DPs. They stated an operative time (OT) between 207 and 276 min, but did not give the rate of R0 resection or survival time of patients with DP-CAR. Malinka *et al.* [17] performed a matched-pair-analysis between 20 patients with DP-CAR versus 20 with DP.

They noted comparable postoperative histopathology examination tumour T stage as T3 (69.2%), and similar nodal positivity – 55% vs. 0%. DP-CARs were treated with neoadjuvant treatment with either FOLFIRINOX or Gemcitabine/nabPaclitaxel in 25% of cases vs. 20% in DP. Overall, the complications were comparable in both groups (60% vs. 65%). However, the overall of postoperative pancreatic haemorrhage (PPH) was similar but with higher severity in the DP group, while in the DP-CAR group 2 patients developed gastric complications such as a gastric perforation and gastric ischaemia. Thirty-day mortality was similar (0/2). The in-hospital stay was comparable in both groups, with a mean of 29.45 days (7–162) in the DP-CAR group and 31.65 days (11–93) in the control group ($p = 0.409$). The survival rates for both groups did not reveal any significant differences. In their retrospective study, Okada *et al.* [18] revised 16 DP-CARs and 36 DPs. They demonstrated the estimated 81% vs. 81% and 52% vs. 53% of overall 1- and 2-year survival rates, respectively, between DP and DP-CAR, and median survival times of 32 and 25 months. There were no differences in the mortality and morbidity. The authors concluded that DP-CAR was a feasible and safe procedure, similar to standard DP. Peters *et al.* [19] matched 17 DP-CARs with 51 DPs for resection of PDAC. 15/17 (88.2%) patients with DP-CAR received neoadjuvant therapy using FOLFIRINOX (80.0 %) prior to DP-CAR. DP-CAR was associated with longer operative time (404 vs. 309 min; $p = 0.003$), but the authors noted no difference in estimated blood loss and length of hospitalization. R0 resection was similar: it was achieved in 82.4% of DP-CAR patients versus 92.2% of DP patients ($p = 0.355$). Regarding postoperative outcomes, including overall complications, pancreatic fistula, readmission, and mortality, no difference was observed. Median survival was similar, amounting to 20 months for DP-CAR versus 19 months in the DP group ($p = 0.757$). Storkholm *et al.* [20] noted similar median survival of 24.0 and 23.5 months, respectively, in patients who underwent DP and DP-CAR procedures, and R0 resection was achieved in 75% of DP-CARs, similar to DP. Sugiura *et al.* [10] noted that median survival time was only 17.5 months for DP-CAR while it was of 43.1 months in the DP group. DP-CAR had longer operative time and greater amount of blood loss than DP. They highlighted that the median survival was 35.1 months in the DP-CAR without common hepatic artery invasion (CA/CHA-) and 13.2 months in the CA/CHA+ group ($p = 0.001$). They concluded that it is recommended to perform DP-CAR in patients with a CA/CHA- status. Takahashi *et al.* [21] demonstrated that mean operative time, mean blood loss, and postoperative mortality and morbidity between DP-CAR and

DP were similar with DP-CAR, but DP-CAR had greater morbidity and in-hospital mortality: 56% and 6%, respectively. In 15 DP-CARs no hepatic infarctions were clinically encountered despite the fact that the hepatic artery did not require reconstruction. The authors estimated that the overall 1- and 3-year survival rates for DP-CAR were 42.6 and 25.6%, respectively, and they noted that the survival time was significantly less than that of patients who underwent DP (median survival time: 9.7 vs. 30.9 months, $p = 0.033$). DP-CAR had R1 resection rates of 44% while DP had 22%. DP-CAR presented a high rate of R1 resection and for this reason did not improve the long-term survival. Wu *et al.* [22] presented a single-centre experience including 11 patients who underwent DP combined with celiac axis resection and 54 patients who received conventional DP. DP-CAR had longer mean operative time (323 vs. 225 min, $p < 0.001$); there was no difference in mean estimated blood loss, percentage of pancreatic fistula, or median survival time (14 vs. 15 months, $p = 0.197$). When comparing DP-CAR with not-fit-for-surgery DP, DP-CAR has better survival. Yamamoto *et al.* [23] performed a retrospective study on 395 patients to determine the efficacy of DP-CAR: 72 patients underwent (DP-CAR) and 323 patients underwent conventional DP. The overall morbidity was 63% in the DP-CAR group vs. 47% in the DP group. The median survival time of the DP-CAR group was 17.5 months, which was significantly shorter than that of the DP group (28.6 months). DP-CAR followed by adjuvant chemotherapy provided an acceptable overall survival rate. We have summarized the principal results of the Appleby procedure (Tables I, II).

Discussion

Current definitions of resectability, defining pancreatic cancer of the distal part of the pancreas, can be subdivided into subgroups such as potentially resectable (RPC), borderline resectable (BRPC), and locally advanced types (LAPC) focusing on vessel involvement. Nevertheless, vessel involvement cannot always be considered the limiting factor in decision-making. About 80% of PDACs are in an unresectable state at the time of diagnosis due to a lack of specific symptoms. These present as distant metastases in about two-thirds and advanced disease involving CA and SMA without distant metastasis in one-third. Unlike T4 tumours with SMA

Table I. Summary

Uninvolved margins (R0) rate (%): 55–92%
Mortality rate (%): 1–16% [10, 16–23]
Morbidity rate (%): 10–42% [10, 16–23]
Median survival: 16–35 months [10, 16–23]

Table II. Appleby procedure review

Author	Year	DP-CAR	DP	TNM	Neo-CHT/ RT	Outcomes – survival [months]	Operative time [min]	Blood loss [ml]	R+
Beane <i>et al.</i>	2015	20	172	NR	NR	NR	206–272	NR	NR
Ham <i>et al.</i>	2015	7	31	T3: 4/25 T4: 4/2	NR	15/25	354	300–700	2
Hishinuma <i>et al.</i>	2007	7	18	T3: 6 T4: 1	NR	19/25	NR	NR	3
Malinka <i>et al.</i>	2020	20	20	T1: 1 T2: 3 T3: 12 T4: 2	5	NR	NR	NR	12
Okada <i>et al.</i>	2012	16	36	NR	NR	25	298	1165	11
Peters <i>et al.</i>	2016	17	51	T1: 6 T2: 3 T3: 1 T4: 7	15	20	400	900	3
Storkholm <i>et al.</i>	2020	21	68	T1: 0 T2: 3/17 T3: 6/46 T4: 2	3	24	245.7	600	5
Sugiura <i>et al.</i>	2017	16	76	NR	NR	17	338	900	NR
Takahashi <i>et al.</i>	2011	16	27	T1: 0 T2: 0 T3: 8/19 T4: 8/0	0	9.7	237	700	7
Wu <i>et al.</i>	2010	9	34	NR	NR	14	323	900	NR
Yamamoto <i>et al.</i>	2017	72	323	T1: 3/27 T2: 0/28 T3: 57/267 T4: 12/1	40	17.5	384	1033	24

TNM of AJCC. NR – not revealed, DP – distal pancreatectomy, DP-CAR – distal pancreatectomy with celiac axis resection, PDAC – pancreatic ductal adenocarcinoma.

invasion, T4 tumours that invade the CA can be resected by resection of the CA without arterial reconstruction if hepatic blood flows through the arterial system that connects the axis of the hepatic artery with the axis of the SMA, such as the gastroduodenal artery [24, 25]. PDAC of the pancreatic body is often associated with the involvement of the celiac axis (CA) as well unspecific symptoms such as back pain, weight loss, and unspecific abdominal pain and, usually, a reduced resection rate and a mean overall survival of 3–4 months [26–28]. DP-CAR is a technically challenging but feasible procedure for patients with locally advanced pancreatic cancer (LAPC). LAPC of the pancreatic body showed a poor prognosis and is associated with a resectability rate of 10% and a mean survival of 3–4 months. DP-CAR resections obtained a higher median survival of 24.1 months following resection [29]. Studies demonstrated that DP-CAR presented mortality and morbidity of 0% and 47.1%, 2.1% and 40.6%, 0% and 62%, and

0% and 60%, respectively [17, 30–32]. Based on the fact that blood supply to the common hepatic artery (CHA) is maintained through the gastroduodenal artery (GDA), and that the stomach perfusion is maintained through the right gastric artery, the right gastroepiploic artery, left phrenic artery, and intramural capillary network from the oesophagogastric junction, this allows the stomach to be preserved because DP-CAR can be performed preserving the stomach and liver blood supply. Preservation of the stomach during DP-CAR is controversial. Some authors stated favourable median survival times of 21 and 26 months [30, 33], but they noted that rates of postoperative mortality were similar in the 2 groups whereas overall complications were more frequent in the DP-CAR group. Rates of pancreatic fistula, delayed gastric emptying, postoperative bleeding, and reoperations were similar [34]. Malinka *et al.* [17] in their cohort study demonstrated that patients both with DP-CAR or not undergoing CA resection had

comparable survival rates. Gastric ischaemia has been described to occur in 12% to 14% of cases. It is considered a typical complication related to CA resection with hepatic ischaemia [29]. Hirano *et al.* [33] performed pre-operative embolization of the CHA. This method seems to activate the neoangiogenesis and collateralization to the hepatobiliary system (via the pancreaticoduodenal arcade) and the stomach (via the right gastric and gastropiploic arteries), to reduce the ischaemic complications. Meta-analysis and cohort-studies demonstrated an R0 resection rate between 40% and 70% [17, 29]. 91% of R0 resection if DP-CAR was performed following neoadjuvant chemotherapy [9, 35–37].

The limitations of this study are that it was a retrospective study, the operable cases with DP-CAR were few, and patients with DP-CAR and control patients of the DP group and non-resection group were not matched well. It is difficult to determine the prognostic effect of DP-CAR exactly, so further studies with a large number of patients at the multicentre level is required.

Conclusions

DP-CAR is a technically challenging but feasible procedure for patients with locally advanced pancreatic cancer (LAPC). LAPC of the pancreatic body has a poor prognosis and is associated with a resectability rate of 10% and a mean survival of 3–4 months. DP-CAR resections obtain a higher median survival of 24.1 months following resection. It is associated with a high morbidity and mortality rate and a survival rate similar to that of DP. For the surgeon it is important to have knowledge of the surgical technique, the normal anatomy, vascular anatomic variants, post-operative anatomy, and potential complications. However, its benefits need to be verified with further studies in the future.

Conflict of interest

All Authors declare no commercial associations that might represent conflicts of interest with this article and have nothing to disclose. All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-19-2421>).

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