



Distal pancreatectomy with *en bloc* celiac axis resection does not improve the R0 rate or median survival time of patients with locally advanced pancreatic cancer: a systematic review and meta-analysis

Qingbo Feng^{1#}, Zechang Xin^{2#}, Yan Du^{2#}, Feiyu Mao³, Ling Li², Huamin Zhai³, Jie Yao^{3,4}

¹Department of Liver Surgery, Center of Liver Transplantation, West China Hospital of Sichuan University, Chengdu, China; ²Dalian Medical University, Dalian, China; ³Clinic Medical College of Yangzhou University, Yangzhou, China; ⁴Department of Hepatobiliary and Pancreatic Surgery, Northern Jiangsu People's Hospital, Yangzhou, China

Contributions: (I) Conception and design: J Yao, Q Feng; (II) Administrative support: J Yao; (III) Provision of study materials or patients: L Li, H Zhai, F Mao; (IV) Collection and assembly of data: Q Feng, L Li; (V) Data analysis and interpretation: Q Feng, Z Xin, Y Du; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jie Yao. Department of Hepatobiliary and Pancreatic Surgery, Northern Jiangsu People's Hospital, Yangzhou 225001, China. Email: docyao@hotmail.com.

Background: Pancreatic cancer frequently results in celiac artery invasion, resulting in an unresectable disease that generally has a median survival period of 6–11 months. Efforts to achieve curative resection of such tumors have been made by conducting distal pancreatectomy with *en bloc* celiac axis resection (DP-CAR) in some patients, but the long-term outcome data associated with this approach or its overall value remain to be clarified.

Methods: This meta-analysis was conducted to systematically assess the clinical efficacy of the DP-CAR treatment of unresectable tumors of the pancreatic body or tail (registered with PROSPERO: CRD42019129612). The PubMed, EMBASE, the Cochrane Library, and Web of Science databases were searched to identify relevant retrospective studies pertaining to such treatment.

Results: Overall, 12 retrospective cohort analyses incorporating 213 total DP-CAR cases and 911 DP cases were incorporated into the present meta-analysis. Pooled analyses demonstrated that relative to DP, DP-CAR was related to a longer operative duration [mean difference (MD) -73.69, 95% confidence interval (CI): -112.99 to -34.38, $P=0.0002$] and higher blood transfusion rates [odds ratio (OR) 0.29, 95% CI: 0.10 to 0.87; $P=0.03$]. DP-CAR was also linked to increased rates of PV resection (OR 0.17, 95% CI: 0.07 to 0.39; $P<0.001$) and delayed gastric emptying (DGE) (OR 0.37, 95% CI: 0.15 to 0.93, $P=0.03$). In contrast, R0 resection rates were higher in the DP group (OR 2.79, 95% CI: 1.90 to 4.09, $P<0.001$), and these patients also had a significantly improved prognosis (median survival time, 27.0 *vs.* 17.7 months; $P<0.01$) relative to the DP-CAR group.

Conclusions: This analysis indicates that DP-CAR is not an effective means of improving R0 rates. However, available studies suggest that it is nonetheless a potentially valuable treatment option for pancreatic cancer patients with celiac axis involvement, and it is associated with a reasonable median survival duration of 17.7 months.

Keywords: Distal pancreatectomy (DP); modified appleby procedure; celiac axis resection (CAR); pancreatic neoplasm; meta-analysis

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Introduction

Pancreatic tumors affecting the body or tail of the pancreas are most often identified when they are at an advanced stage and are no longer eligible for resection owing to celiac axis (CA) or common hepatic artery origin involvement (1). In patients with locally advanced pancreatic cancer, chemotherapy and radiotherapy are generally the only viable treatment options, but these approaches are associated with poor efficacy. Distal pancreatectomy with *en bloc* celiac axis resection (DP-CAR) is an approach that endeavors to achieve negative CA, nerve plexus, and retroperitoneal tissue margins in such patients (2), thus potentially enabling complete tumor resection. While DP-CAR may improve tumor resection rates, it is also associated with very high rates of postoperative morbidity, making the value of this procedure unclear. Indeed, short-term studies comparing DP-CAR to DP have yielded inconsistent outcomes, and the quality of life and postoperative survival of patients following DP-CAR. Some studies have found DP-CAR to offer no survival benefits relative to DP (3,4), while other studies have found that this approach can improve the duration of disease-free survival (DFS) in some patients (5). Hirano *et al.* (2) found DP-CAR to be associated with a 5-year overall survival (OS) rate of 42%, which was significantly longer than that associated with DP. Owing to its complexity and high morbidity and mortality rates, however, DP-CAR is not commonly performed, making it challenging to conduct large sample size studies on this procedure. Most published studies of DP-CAR to date contain relatively few cases. As such, the present study sought to comprehensively compare the relative safety and feasibility of DP-CAR and DP based upon previously published data.

We present the following article in accordance with the PRISMA Reporting Checklist (available at <http://dx.doi.org/10.21037/tcr-19-2421>).

Methods

Literature search

The present meta-analysis was performed in a manner consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement (6), and was registered with the PROSPERO database (number CRD42019129612). Two investigators independently searched the PubMed, EMBASE, Cochrane

Library, and Web of Science databases for articles published as of June 30, 2019. Additional articles of potential relevance were identified by reviewing the references of included studies and by using the “related article” function in these databases. Only English articles were retrieved. A flow chart overview of the literature search strategy is shown in *Figure 1*. Studies were identified with the following search terms:

- (I) #1 (modified appleby) OR (appleby procedure) OR (appleby operation) OR (distal pancreatectomy with *en bloc* celiac axis resection) OR (celiac axis resection) OR (celiac resection) OR (vascular resection) OR (vessel resection) OR (dp-car) OR (distal pancreatectomy with celiac axis resection);
- (II) #2 (pancreatic carcinoma) OR (pancreatic cancer) OR (pancreatic neoplasm) OR (pancreatic body and tail carcinoma) OR (adenocarcinoma of the body and tail of the pancreas) OR (locally advanced pancreatic cancer) OR (pancreatic body and tail cancer) OR (pancreatic body cancer) OR (body-tail pancreatic cancer);
- (III) #3 (pancreatectomy) OR (distal pancreatectomy);
- (IV) #1 AND #2 AND #3.

Duplicate articles were eliminated, after which the remaining studies were assessed for potential relevance through successive title, abstract, and full-text review.

Inclusion criteria

Studies relevant for inclusion in the present study were those that were: (I) studies of patients with locally advanced pancreatic cancer involving the CA, common hepatic artery origin, or root of the splenic artery; (II) studies reporting at least one clinical outcome of interest in the form of means and standard deviations for continuous variables, or reporting sufficient data to permit the calculation of these values; (III) studies of DP-CAR and DP interventions; (IV) studies that were randomized controlled trials (RCTs), cohort studies, or case-control studies. When multiple studies from the same institution or authors were identified, only the most recent or high-quality studies were included in the final meta-analysis.

Studies were excluded from this meta-analysis if they were: (I) abstracts, reviews, letters, expert opinions, case reports, editorials, or studies lacking a control group; (II) studies with fewer than 6 DP-CAR cases; or (III) not published in English, duplicates, or non-human studies.

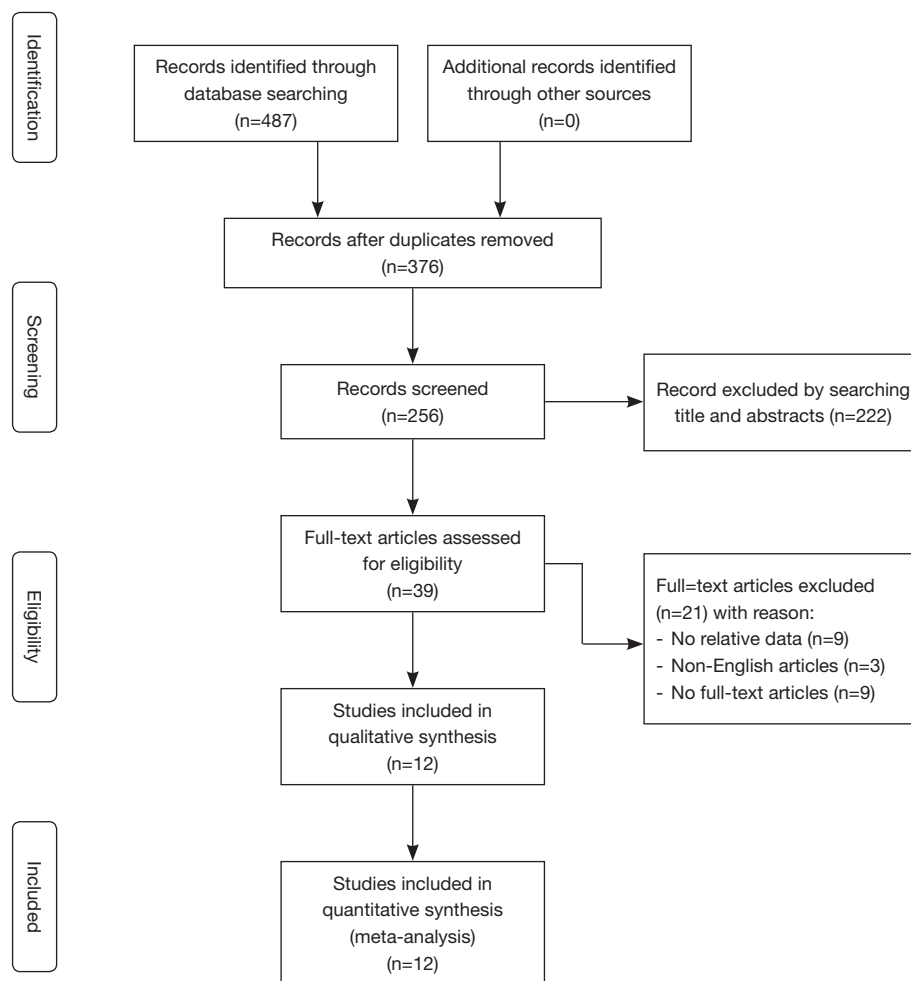


Figure 1 Study selection process.

Data extraction

Two investigators (Q Feng, L Li) independently extracted data from all included studies. These investigators first reviewed the titles and abstracts of all identified articles, after which potentially relevant studies were subjected to full-text review to confirm eligibility. Discussion with a third investigator (H Zhai) was used to resolve inconsistencies. When data were missing, efforts were made to contact the original study authors to obtain these data. Where necessary, data were estimated based upon available summary statistics or figures. Data were extracted as intention-to-treat analyses. When unavailable, per-protocol assessments were utilized. In cases where outcomes were assessed across a range of time points, outcomes measured with the longest duration were used to remove duplicate data or arbitrary variability.

Evidence quality for cohort studies was assessed based upon Newcastle-Ottawa Scale (NOS), with scores of 7 or higher being indicative of a high-quality study.

Risk of bias assessment

Two investigators (Q Feng and L Li) independently evaluated the quality and risk of bias associated with each included study using the Cochrane Handbook for Systematic Reviews of Interventions risk of bias tool (7). Briefly, such risk was assessed based upon random sequence generation, allocation concealment, participant blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other bias. Discussion with a third investigator (H Zhai) was used to resolve any discrepancies.

Table 1 The basic characteristics of included studies

Author (year)	Country	Study design	Inclusion period	No. of patients	Sex ratio (M/F)	Age (year)	MST (month)
				DP; DP-CAR	DP; DP-CAR	DP; DP-CAR	DP; DP-CAR
Toshihiko (in 1997)	Japan	RS	1975 to 1994	19; 6	n.r.; 4/2	59.5; 61.2	n.r.; n.r.
Hishinuma (in 2007)	Japan	RS	1987 to 2003	18; 7	n.r.; 4/3	n.r.; 63.8	25; 19
Wu (in 2010)	China	RS	2003 to 2008	34; 9	18/16; 4/5	62.1; 55.6	15; 14
Takahashi (in 2011)	Japan	RS	1993 to 2010	27; 16	17/10; 8/8	70; 65	30.9; 9.7
Yamamoto (in 2012)	Japan	RS	1991 to 2009	58; 13	39/19; 10/3	66; 64	21.1; 20.8
Okada (in 2013)	Japan	RS	2005 to 2010	36; 16	23/13; 11/5	68; 63	32; 25
Hyemin (in 2015)	Korea	RS	2000 to 2014	31; 7	16/15; 3/4	67.5; 58.0	25; 15
Beane (in 2015)	USA	RS	2011 to 2012	172; 20	57/115; 6/14	66; 64	n.r.; n.r.
Perinel (in 2016)	France	RS	2008 to 2014	66; 14	36/30; 9/5	67; 65	16; 17
Sugiura (in 2016)	Japan	RS	2002 to 2014	76; 16	44/32; 10/6	71; 70	43.1; 17.5
Peters (in 2016)	Netherlands	RS	2004 to 2016	51; 17	29/22; 9/8	67; 64.5	19; 20
Yamamoto (in 2017)	Japan	RS	2001 to 2012	323; 72	194/129; 40/32	69; 66	28.6; 17.5

DP, distal pancreatectomy; DP-CAR, distal pancreatectomy with celiac axis resection; M/F, male/female; MST, median survival time; RS, retrospective study; n.r., not report.

Statistical analysis

The Cochrane Collaboration Review Manager program (v.5.3) was used to analyze all data. Odds ratios (OR) and 95% confidence intervals (CIs) were used to assess dichotomous variables, whereas mean difference (MD) and 95% CIs were used to assess continuous variables using fixed-effects or random-effects models as appropriate. $P < 0.05$ was the significance threshold. I^2 and P values were used to assess heterogeneity among included studies, with $I^2 > 50\%$ and $P < 0.05$ being indicative of significant heterogeneity. Funnel plots were used to visually gauge the risk of publication bias.

Results

Study identification

Our initial search strategy led to the identification of 814 potentially relevant studies after the exclusion of duplicates. Of these articles, 39 were subjected to full-text review after abstract and title reviews. Of these 39 articles, 27 were excluded, leaving 12 articles for inclusion in our final meta-analysis (7-18). The overview of this study selection process is shown in *Figure 1*. Of the included studies, 7 were conducted in Japan (7,8,10-12,17,18), 1 in the United

States (14), 1 in France (15), 1 in Korea (13), 1 in the Netherlands (16), and 1 in China (9) (*Table 1*). Some articles from the same authors were included in the final analysis, as they focused on different outcomes (11,18).

Intraoperative outcomes

Operative duration

Operative duration was detailed in 11 of the included studies (8-18), with mean total operative durations of 362 and 258 minutes in the DP-CAR and DP groups, respectively. These times differed significant between groups (MD = -73.69, 95% CI: -112.99 to -34.38, P for effect = 0.0002, P for heterogeneity = 0.09, $I^2 = 55\%$) (*Figure 2*).

Intraoperative blood loss

In total, 10 studies reported intraoperative blood loss data for 907 patients (8-13,15-17), revealing mean blood loss values ranging from 428–1,777 mL. As significant heterogeneity was observed among included studies, a random-effects model was used for data analysis, revealing DP-CAR to be associated with higher intraoperative blood loss relative to DP (MD 186.70 mL, 95% CI: -0.33 to 373.73 mL, $P = 0.05$).

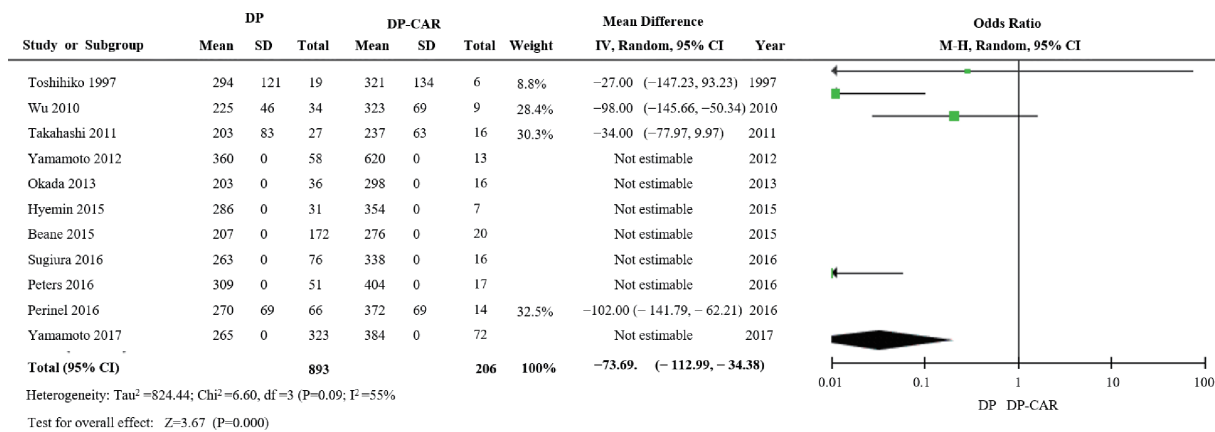


Figure 2 Forest plot for operative duration.

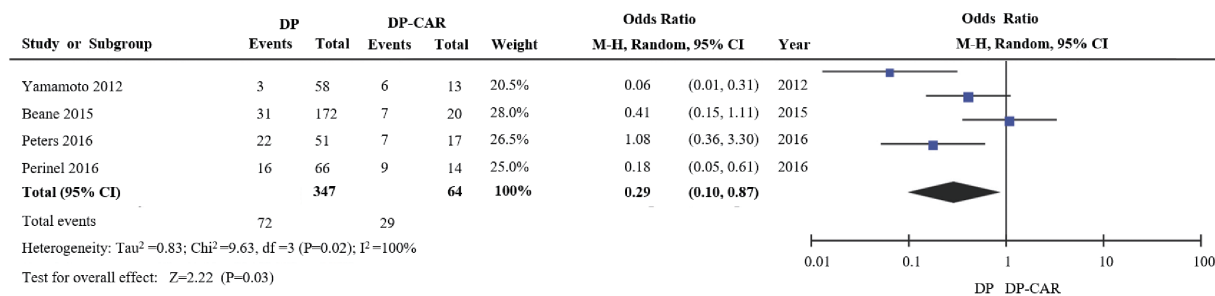


Figure 3 Forest plot for intraoperative blood transfusion.

Blood transfusion

Blood transfusion rates were only reported in four of the included studies (11,14-16), revealing higher rates of blood transfusion in the DP-CAR group relative to the DP group (OR 0.29, 95% CI: 0.10 to 0.87; P for effect =0.03, P for heterogeneity =0.02, I² =69%) (Figure 3).

Portal vein (PV) resection

Rates of PV resection were reported in just 5 of the included studies (10,11,16-18), revealing DP-CAR to be associated with significantly higher PV resection rates relative to DP (OR 6.00, 95% CI: 2.59 to 13.91; P for effect <0.0001, P for heterogeneity =0.15, I² =40%) (Figure 4).

R0 resection rate

Eight of the included studies reported on rates of R0 resection for 839 patients (10-13,15-18), demonstrating that the R0 resection rate was significantly lower for DP-CAR relative to DP (OR 2.79, 95% CI: 1.90 to 4.09; P for effect <0.00001, P for heterogeneity =0.43, I² =0%) (Figure 5).

Tumor size

Six of the included studies reported tumor size data (9,10,13,15,16,18), revealing no significant differences between the DP-CAR and DP groups with respect to such size (MD -5.04, 95% CI: -15.18 to 5.10, P for effect =0.33, P for heterogeneity =0.02, I² =76%).

Postoperative outcomes

Postoperative morbidity

Nine of the included studies reported on patient morbidity rates (7,10-12,14-18), revealing no significant differences in such morbidity between the DP-CAR and DP groups (OR 0.69, 95% CI: 0.41 to 1.14; P for effect =0.15, P for heterogeneity =0.11, I² =38%).

Postoperative mortality

Eight of the included studies reported on patient mortality rates (7,8,10-12,14,16,18), indicating no significant differences in these rates between these two groups (OR

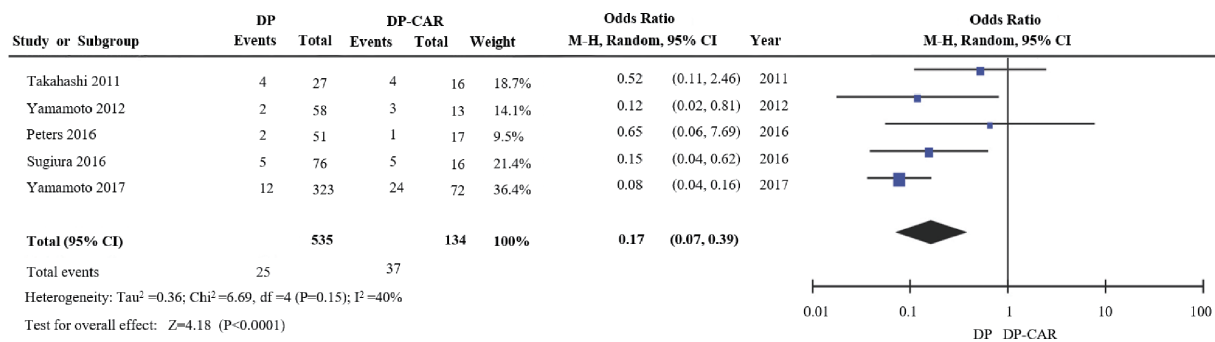


Figure 4 Forest plot for portal vein resection.

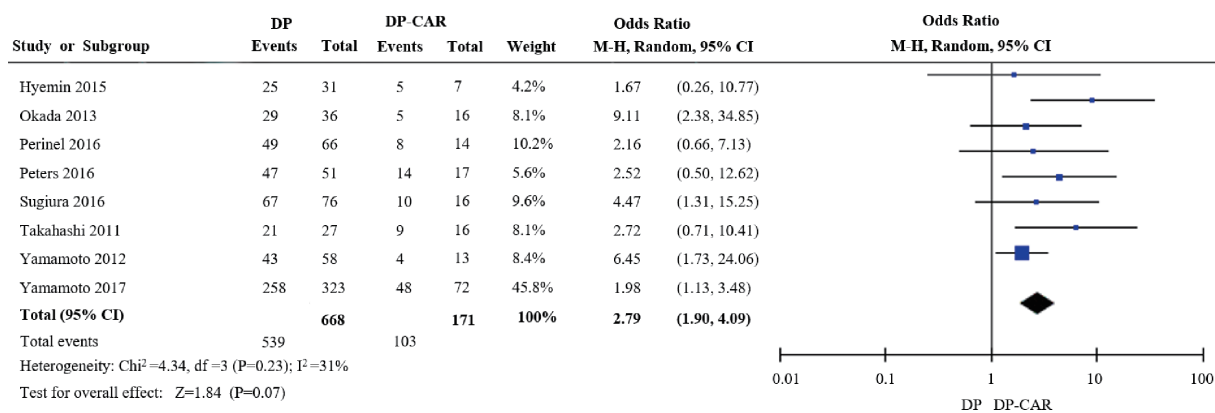


Figure 5 Forest plot for R0 rates.

0.40, 95% CI: 0.15 to 1.06; P for effect =0.07, P for heterogeneity =0.23, I²=31%).

Postoperative pancreatic fistula (POPF)

POPF incidence rates were described for 340 patients in 10 of the studies included in this meta-analysis (9-18). Of these studies, 8 defined POPF as per the criteria of the International Study Group on Pancreatic Fistula. No significant differences in POPF rates were observed between these two groups (OR 1.15, 95% CI: 0.79 to 1.66; P for effect =0.36, P for heterogeneity =0.61, I²=0%), and no evidence of publication bias was observed.

Delayed gastric emptying (DGE)

In total, six of the studies in this meta-analysis reported on DGE (11-16), and indicated that DGE rates differed significantly between the DP-CAR and DP patient cohorts (OR 0.37, 95% CI: 0.15 to 0.93, P for effect =0.03, P for heterogeneity =0.38, I²=6%) (Figure 6).

Discussion

Advanced pancreatic cancer is often not eligible for resection owing to CA involvement at the time of initial diagnosis. DP-CAR approaches can dramatically increase the resectability of tumors by completely resecting both the tumor and involved vessels. Hirano *et al.* (2) initially reported a series of DP-CAR cases associated with lower R1 resection rates and an acceptable 21-month median OS among treated patients. However, more recent studies have yielded outcomes inconsistent with this initial report, with median OS durations ranging from 9.3 to 26 months (9-11). To date, only small sporadic retrospective analyses of DP-CAR have been published, and these studies lack clear comparisons of postoperative outcomes between DP-CAR and standard DP patient cohorts. As such, it remains uncertain as to whether DP-CAR is an effective approach to improving survival outcomes in individuals suffering from locally advanced pancreatic body/tail cancer.

In an effort to overcome this uncertainty, we conducted a

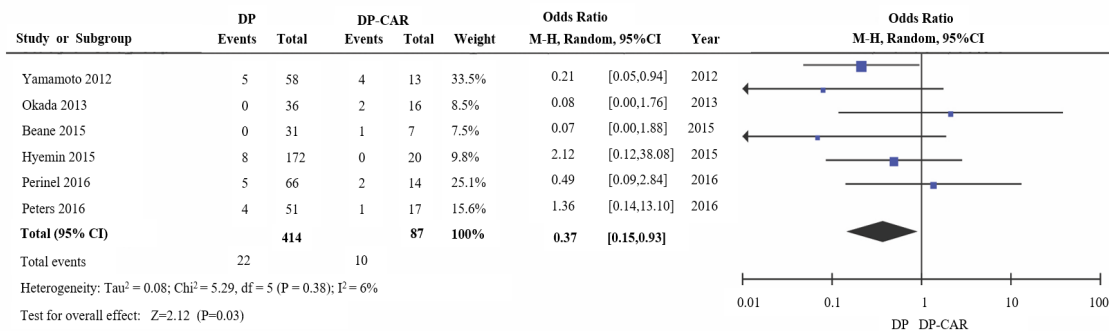


Figure 6 Forest plot for delayed gastric emptying.

meta-analysis comparing the DP-CAR and DP approaches, revealing that DP-CAR is a complex procedure that is associated with high postoperative morbidity but also with acceptable postoperative survival and quality of life in treated patients. Rates of microscopically curative (R0) resection were found to be significantly decreased in the DP-CAR group relative to the DP group (55.55% vs. 80.68%, P<0.0001). DP-CAR was also associated with prolonged operative duration and greater intraoperative blood loss and the need for transfusion relative to DP. Rates of postoperative mortality and morbidity were high in DP-CAR-treated patients, but did not differ significantly from those in patients that underwent DP. The most common complications of DP-CAR were DGE and POPF, with a postoperative POPF incidence rate of 31.31% (95% CI: 23.69% to 40.12%) following DP-CAR that was comparable to that following DP. Rates of DGE were significantly higher among patients that underwent DP-CAR relative to patients that underwent DP. While most studies have found DP-CAR to be associated with significant improvements in patient quality of life, the association between this treatment and patient OS remains uncertain. Rates of 5-year OS varied from 0–42% in published studies following DP-CAR (2,19), with a median OS of 9–26 months in patients with advanced pancreatic cancer. When institutional data regarding patient outcomes were reviewed, an apparent trend towards increased OS was evident when specifically assessing patients with borderline resectable or locally advanced pancreatic body or tail tumors that underwent DP-CAR relative to patients not given the opportunity to undergo resection. Just 10 of the 12 studies included in this analysis reported on survival outcomes, with median survival durations of 14–30.9 months. Overall,

our analysis found that DP-CAR exhibited a median 17.7 month survival.

DP-CAR was linked with reduced OS relative to DP. This finding was not surprising, given that patients that underwent DP-CAR generally had more advanced disease. No RCTs analyzing DP-CAR have been published to date, and as such all data included herein was derived from retrospective studies with limited clinical evidence and small sample sizes. Many years or decades may be required to obtain a series of >10 DP-CAR cases in a clinical setting, and the mean interval for studies in the present meta-analysis ranged from 4–19 years. As such, these study outcomes may be affected by variations in treatment protocols and perioperative management over these prolonged intervals. Some evidence of heterogeneity and possible publication bias was detected when analyzing certain outcomes.

In those that have advanced or borderline resectable pancreatic cancer, preoperative neoadjuvant chemoradiotherapy has been used in an effort to improve patient outcomes. Baumgartner *et al.* (5). found that DP-CAR following neoadjuvant chemoradiotherapy in those that have locally advanced pancreatic cancer was associated with higher local control rates, with a 91% R0 resection rate and a 26-month median OS. Cesaretti *et al.* (20) found that 5/7 cases of borderline resectable/locally advanced pancreatic cancer were able to undergo DP-CR following neoadjuvant chemotherapy, with a median OS of 24 months. This approach offers multiple advantages, including preoperative disease downstaging that can aid in achieving R0 resection, early micrometastasis treatment, and the identification of patients most likely to benefit from DP-CAR treatment.

Conclusions

In summary, in the present meta-analysis we determined that DP-CAR represents a reasonable approach to treating those that have locally advanced pancreatic body/tail cancer, as this approach is associated with a median OS of 17.7 months. This approach is also associated with an acceptable resectability rate and benefits to postoperative patient survival. Even so, this is a high-risk and complex procedure that can only be conducted by skilled surgeons. In addition, this study has a number of limitations, and as such, the relative value of DP-CAR as a treatment approach remains to be established, and our results must be interpreted with caution. Future large-scale prospective comparative studies and randomized clinical trials will be essential in order to firmly establish the safety and long-term efficacy of DP-CAR.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-19-2421>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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