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Systematic Review and Meta-analysis of arterial resection in pancreatic surgery

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Abstract

Background: Arterial resections in pancreatic cancer surgery have been associated with high morbidity and mortality rates. Advances in multimodality treatment of pancreatic cancer have increased the number of complex pancreatic procedures, including those with major vascular resections. The aim of this systemic review and meta-analysis was to evaluate the current outcomes of arterial resections in pancreatic surgery.

Methods: A systematic literature search for pancreatic surgery with arterial resections was carried out from January 2011 until January 2020 in the PubMed/Medline, Cochrane Library, Cinahl, ClinivalTrial.gov and WHO ICTRP databases. The MOOSE guidelines were followed for the meta-analysis, and only studies reporting on a control group without arterial resection were included. Pre-defined outcomes were analyzed using a random effects model.

Results: 30 relevant articles with a total of 7077 patients including 807 with arterial resection were identified. Morbidity and mortality in these 807 patients were 66.8% and 5.4%, respectively. Seven cohort studies with a total of 579 patients were included in the meta-analysis. Overall morbidity (48% vs 39 %, p=0.1) and mortality (3.2% vs 1.5%, p= 0.27) were not significantly different between pancreatic surgery with and without arterial resection (AR). R0 rates were lower in the AR group, both in patients without (69% vs 89%, p<0.001) and with neoadjuvant treatment (50% vs 86%, p<0.001). While there were no differences in 1-year survival rates between the AR and the no-AR groups (OR 0.92, 95% CI [0.41; 2.09], p=0.85), weighted median survival was significantly shorter in the AR group (18.6 vs 32 months, p= 0.037). In addition, AR was associated with increased blood loss and longer operating times.

Conclusions: Arterial resections increase the complexity of pancreatic resectional procedures, as demonstrated by relevant morbidity and mortality rates. Careful patient selection and multidisciplinary planning remains important.

Keywords: pancreatic resection, pancreatectomy, arterial resection, vascular resection, superior mesenteric artery, celiac artery and hepatic artery.

Contents

List of abbreviations and symbols

ACS-NSQIP	American College of Surgeons - National Surgical Quality Improvement Program
AR	Arterial resection
BL	Borderline
CA	Celiac axis
CA 19-9	Carbohydrate-Antigen 19-9
CHA	Common hepatic artery
CI	Convidence interval
CT	Computer Tomography
D	Days
DGE	Delayed gastroinstestinal emptying
DP	Distal pancreatectomy
DP-CAR	Distal pancreatectomy combined with celiac axis resection
F	Female
GDA	Gastroduodenal artery
HA	Hepatic artery
Histo. Art.	Histological arterial
HR	Hazard ratios
ICTRP	International Clinical Trials Registry Platform
ISGPS	International Study Group
IVC	Inferior vena cava
LA	Locally advanced
Lap.	Laparoscopic
LHA	Left hepatic artery
M	Male

Min.	Minutes
mL	Milliliters
Mo.	Months
N	No
NCCN	National Comprehensive Cancer Network
NS	No specification
OR	Odds Ratio
OS	Overall survival
PD	Pancreatoduodenectomy
PDAC	Pancreatic ductal adenocarcinoma
PHA	Proper hepatic artery
POPF	Postoperative pancreatic fistula
Posit.	Positive
PPPD	Pylorus Preserving Pancreatoduodectomy
PV	Portal Vein
RRHA	Replaced right hepatic artery
Retrospect.	Retrospective
RevMan	Review Manager
ROBINS-I	Risk of bias in non-randomized studies of interventions
SMA	Superior mesenteric artery
SMV	Superior mesenteric vein
SA	Splenic artery
PREVADER	Preoperative/Neoadjuvant Therapy and Vascular Debranching Followed by Resection for Locally Advanced Pancreatic Cancer
TP	Total pancreatectomy
U	Unkown
USA	United States of America
WHO	World health organization

Y	Yes

1 Introduction

1.1Overview

Each year in the USA, approximately 43,000 people die of pancreatic cancer making it the fourth most common cause of cancer-related death [1]. In Europe there were more than 78,000 new cases in 2012 [2]. Despite investigation and advances in the treatment of this disease, it is about to become the second leading cause of cancer-related death within the next decade [3]. Pancreatic surgery at early disease stages has the best chance of cure. Despite this, more than half of the patients with resectable disease do not receive surgery for various reasons [4]. In the patient group considered initially unresectable, approximately one third of the patients can potentially be resected following neoadjuvant therapy [5].

In principle, there are groups of patients with resectable, locally advanced and with metastatic disease. Because in pancreatic cancer, locally advanced is often considered unresectable, a fourth group has been defined: borderline resectable pancreatic cancer.

1.2 Definition of borderline resectable pancreatic cancer

The definition of borderline resectable PDAC has made a curative-intent surgery possible for patients to whom a curative strategy had previously not been offered. There are several different definitions. The National Comprehensive Cancer Network (NCCN) guidelines definition is based on the tumor relation with the involved major vessels (Table 1) (Figure 1) [6].

Table 1: NCCN guidelines defining resectability status of borderline pancreatic cancer [6].

	Arterial	Venous
Borderline Tumor - no distant metastasis	Pancreatic head/uncinate process: - Contact with CHA without extension to CA or CHA bifurcation - Contact with the SMA ≤180° - variant arterial anatomy Pancreatic body/tail: - Contact with the CA of ≤180° - Contact with the CA of >180° without aorta involvement and intact and uninvolved GDA	- Contact with SMV or PV with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction - Contact with the IVC.

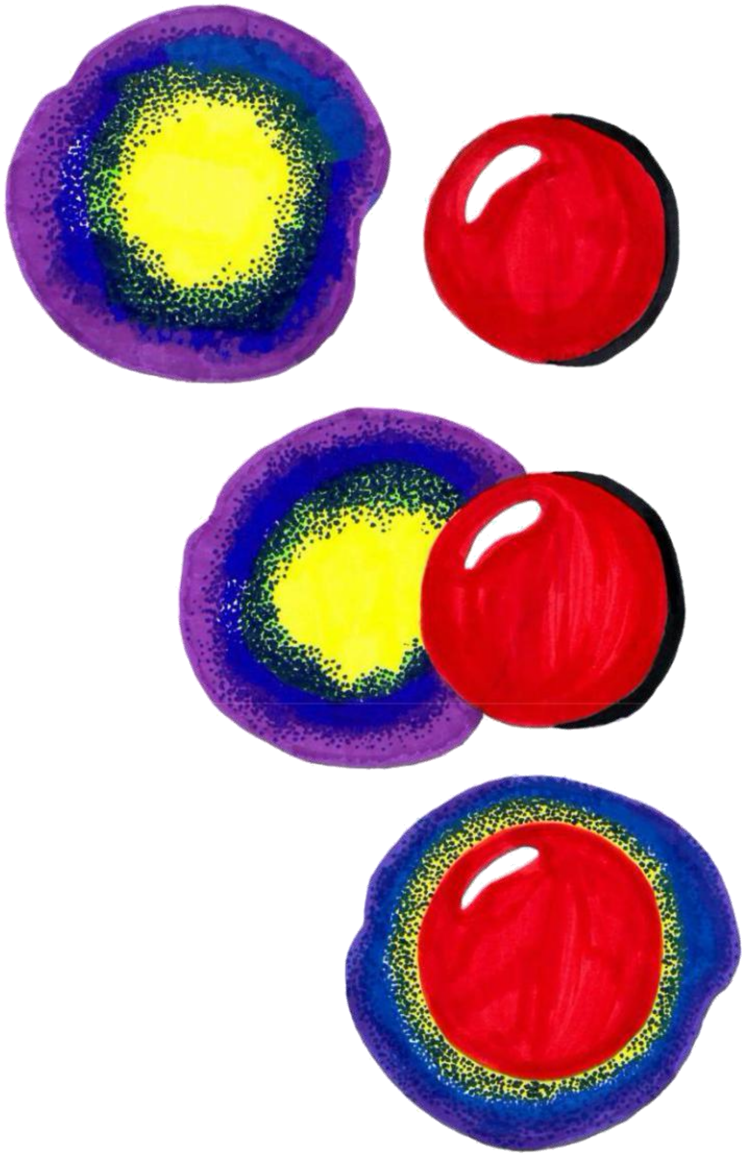


Figure 1: Definition of arterial resectability based on tumor contact (From top to bottom: Resectable, Borderline Resectable, Unresectable)

1.3 Venous Resection and Reconstruction

Depending on the extent of the invasion of the portal and superior mesenteric vein, different techniques for resection and reconstruction are used (Figure 2). In cases of minimal invasion, a partial resection and reconstruction with an autologous patch may be performed. A peritoneal patch has been described as feasible [7]. In cases of broader invasion, segmental resection and reconstruction should be performed. When an end-to-end anastomosis is not possible, autologous, homologous or prosthetic (ring) grafts are the options [8].

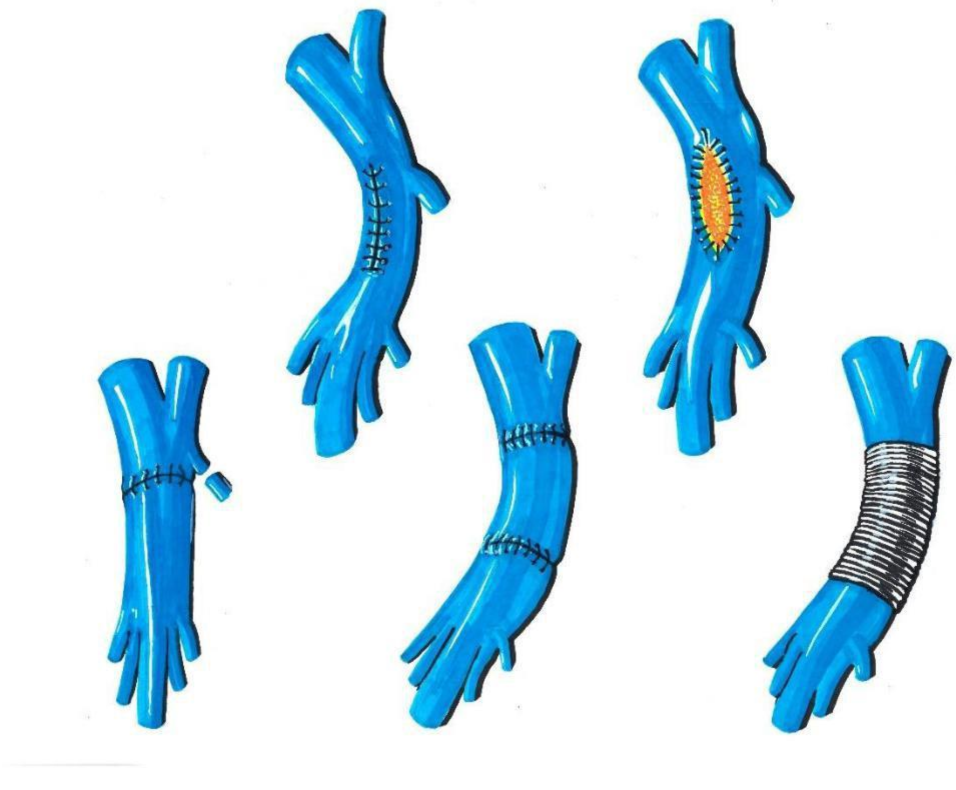


Figure 2: Various techniques of portomesenteric venous resections

The classification proposed by the International Study Group (ISGPS) divided the venous resection in 4 types depending on the performed reconstruction: venorraphy, patch, primary anastomosis and interposition conduit [9].

However, with extensive mobilization of the root of the mesentery, an end-to-end anastomosis is almost always possible. Technically, an extensive Kocher maneuver combined with a Cattell-Braasch maneuver is a safe technic to perform pancreatic and venous resection. In a retrospective analysis of 45 patients who underwent pancreatectomy with portomesenteric resection, none had a thrombosis after a median follow-up of 22 months [10].

In a retrospective analysis of a prospectively collected database of 241 patients who underwent pancreatectomy with venous resection, no differences in morbidity, mortality, and long-term survival were observed compared to patients who underwent a standard resection [11]. In a large multicenter retrospective review from the United Kingdom that included 1588 Patients with borderline resectable tumors, venous resection in pancreatic cancer surgery was also reported as safe and feasible [12]. Median survival (18 months for the standard procedure and 18.2 months for patients undergoing venous resection,) and in-hospital mortality were similar in both groups. Thus, if a resection with a tumor-negative margin seems possible, venous resection should be performed if necessary. Such an approach is now internationally well accepted.

1.4 Neoadjuvant therapy and patient selection

Neoadjuvant treatment for borderline-resectable PDAC is controversially discussed. Although there is still a lack of high-quality studies, it has become clinical practice in many countries. According to the NCCN guidelines, the clinical pathway for borderline pancreatic cancer should involve neoadjuvant chemotherapy (Figure 3) [6]. In a French multicenter review that included 1399 Patients, upfront venous resection was described as a poor prognostic factor for long-term survival [13]. Recently Mellon, et al. (2016) also supported a neoadjuvant strategy with a median overall survival of 33.5 months for the patients receiving neoadjuvant therapy compared to 23.1 months (p=0.057) for upfront resection patients who received adjuvant treatment [14].

In cases with borderline-resectable tumors, temporal changes of CA 19-9 serum levels during neoadjuvant therapy can be important in selecting patients for surgery. In a review from Italy that included 223 patients with borderline and locally advanced pancreatic cancer who received neoadjuvant treatment, patients who underwent resection without a reduction of CA 19-9 during the treatment did not benefit from surgery. Median survival for these patients was 15.0 months compared to 31.5 months (p=0.04) in responsive patients [15].

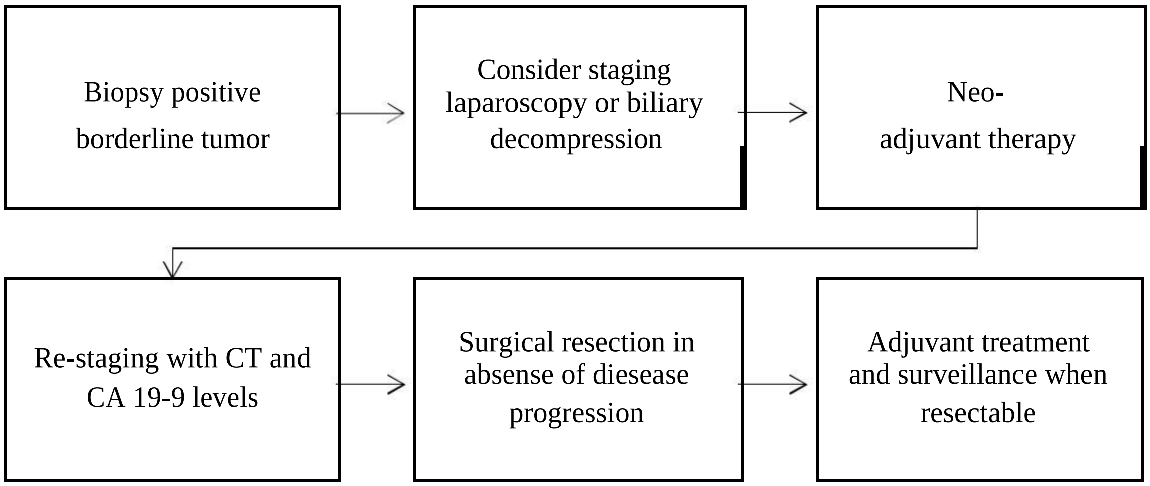


Figure 3: Treatment algorithm for borderline resectable pancreatic adenocarcinoma from workup until surgery and adjuvant treatment [6].

1. 5 Arterial resection and reconstruction

Coeliac axis resection in left-sided pancreatic resections (Figure 4) and common hepatic artery or superior mesenteric artery resections in right-sided resections are the two main procedures involving artery resection and reconstruction in pancreatic cancer. In the largest meta-analysis regarding arterial resection in pancreatic surgery, Mollberg and colleagues [22], reported a median morbidity and mortality rates of 53.6% and 11.8%, respectively. Consequently, most centers have adopted a restrictive approach for these procedures.

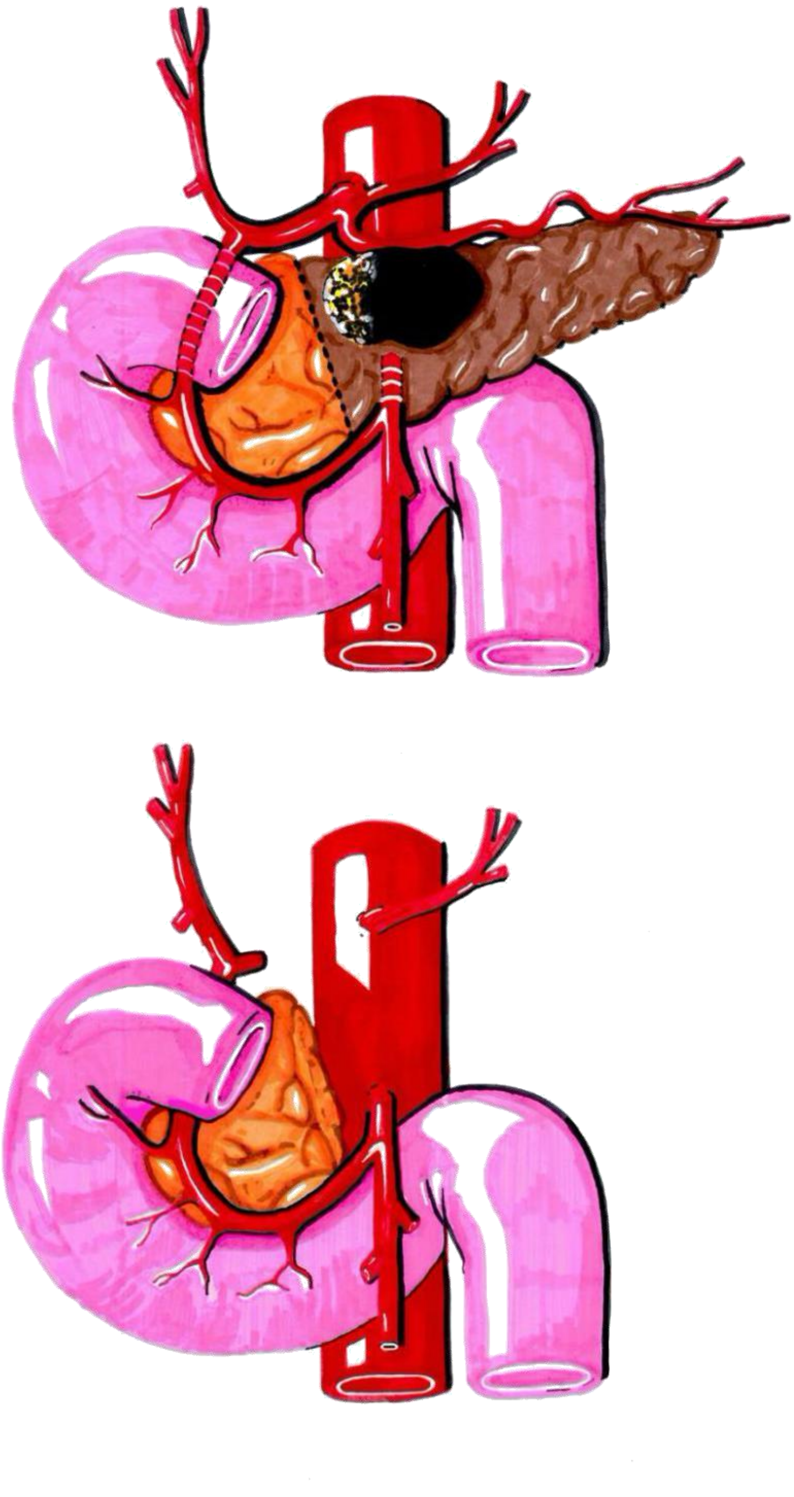


Figure 4: Pancreatic body/tail with CA resection, preservation of the left gastric artery

1.6 Outcome of distal pancreatectomy combined with celiac axis resection (DP-CAR) or modified Appleby Procedure

DP-CAR without reconstruction is based on the development of collateral vascular supply via the gastroduodenal artery. Sugiura et al. (2017) reported a poor survival time regarding patients who underwent DP-CAR having a celiac axis or common hepatic artery invasion (13.2 months, p=0.001) [17].

In a pan-European retrospective cohort study that included 68 Patients from 20 hospitals in 12 countries, the median overall survival after the Appleby procedure was 18 months. However, the 30-day (10%) and 90-day (16%) mortality were high. 82% of patients received neoadjuvant treatment [18].

In a Japanese retrospective single-center review of 80 patients who underwent DP-CAR, neoadjuvant treatment contributed to a better overall survival (30.9 months). The in-hospital mortality was 5%. Ischemic gastritis and delayed gastric emptying occurred in 28, 8% of the patients, being the second most common postoperative complication after pancreatic fistula [19].

In a 37-patient cohort that underwent DP-CAR with or without left gastric artery resection, the incidence of delayed gastric emptying was significantly lower (7%) than in patients who underwent conventional DP-CAR with left gastric artery resection (57%, p=0.048). Modified DP-CAR may be the solution for decreasing the incidence of delayed gastric emptying [20]. When the resection of the left gastric artery cannot be avoided because of its involvement in the tumor, reconstruction can be performed using the middle colic artery as proposed by Sato et al. [21].

1.7 Outcomes of pancreatectomy with common hepatic artery or superior mesenteric artery resections

In right-sided pancreatic lesions, the proximity of major vessels may explain the high unresectability rate and poor prognosis of the resectable patients. In a retrospective analysis that included 35 patients who underwent arterial resection - mostly hepatic arterial resection/reconstruction (18 patients) – there were good short-term outcomes with a high reconstruction patency. However, arterial resection was associated with worse 1-year and median survival then standard resection [22].

Miyakazi et al. analyzed 21 patients who underwent combined common hepatic arterial resection during pancreatic surgery. Overall survival was 47.6% and 6.6% at 1 and 5 years. Median survival was 11 months. Furthermore, there was a clear association between CA19-9 levels and overall survival. Comparing patients with low and high CA19-9 serum levels, median survival time was 21.5 and 8.3 months ($p<0.01$), respectively. Neither pathologically confirmed arterial invasion, R status or lymphonodal involvement was shown to be a prognostic factor. Only 9 patients from this review had preoperative therapy. This suggests that the strongest prognostic indicator for survival time in these patients is tumor biology [23].

There is scarce data on superior mesenteric artery resections. However, it has also been associated with a poor prognosis (median survival of 11 months) and an operative mortality of up to 20 % [24].

2 Objective of the work

Surgery for pancreatic cancer has become increasingly safe in the last decades. Complex venous resections are no longer a criterion of unresectability but are a standard addition to the surgical armamentarium in most centers. However, as already referred, arterial resections in pancreatic cancer surgery have been associated with high morbidity and mortality rates.

With the advent of effective chemotherapy regimens (namely FOLFIRINOX and nab-Paclitaxel/ Gemcitabine) in the last decade, an increasing number of patients with locally advanced disease at diagnosis now present with a response to neoadjuvant treatment [25, 26]. These patients – many of them considered inoperable 10 years ago – now proceed to resection, and porto-mesenteric venous resections have become routine procedures in high volume centers in this setting [27, 28]. Arterial resections – albeit to a smaller extent – are being performed in selected patients as well.

Technical improvements, including more effective means of hemorrhage control, improved perioperative care and multidisciplinary approaches comprising trained vascular surgeons have facilitated this increase. Nonetheless, arterial resections add to the intricacy and morbidity of pancreatic resections. A comprehensive analysis of the contemporary literature on arterial resections in pancreatic cancer surgery, including studies in which patients have received neoadjuvant chemotherapy, is lacking. This work aimed to systematically reviewing and meta-analyzing current perioperative and oncological outcomes of patients who underwent pancreatic cancer surgery with arterial resection.

3 Methods

The literature search and data analysis were conducted in accordance with the "meta-analysis for observational studies" (MOOSE) guidelines [29]. The study was prospectively registered in the PROSPERO database [30].

3.1 Search strategy

The PubMed/Medline, Cochrane Library, Cinahl, ClinicalTrials.gov (clinical trials registry) and WHO ICTRP (clinical trials registry,) database were searched for this study through their respective online search engines. The search was performed on studies published between January 1, 2011 (as the last meta-analysis on this topic dates back to 2011) and January 9, 2020.. The following free text terms were used with different combinations of "AND" or "OR": "Pancreatic Neoplasms", "Pancreatic Neoplasm", "Pancreatic Cancer", "Pancreatic Tumor", "Pancreatic Tumour", "Pancreas Neoplasm", "Pancreas Cancer", "Pancreas Tumor", "Pancreas Tumour", "Cancer of Pancreas", "Cancer of the Pancreas", "Resect", "Extirpation", "Excision", "ectomy", "removal", "Hepatic Artery", "Hepatic Arter", "Mesenteric Artery Superior", "Superior Mesenteric Arter", "Celiac Artery", "Celiac Arter". Furthermore, the reference lists of the available studies were manually searched to find relevant articles. Abstracts and full-text reviews were evaluated independently in an unblinded standardized manner in order to assess eligibility for inclusion or exclusion. Disagreements were resolved by consensus.

3.2 Inclusion and Exclusion Criteria

Studies in English assessing resection of pancreatic cancer in curative intent including resection of major visceral arteries (celiac trunk and/or SMA and/or common hepatic artery), with or without a control group of patients undergoing pancreatic resection without arterial resection, were included. Studies with with less than five patients were excluded, as were reviews, case reports, comments and letters. Studies with no differentiation between venous and arterial resection were also excluded. Furthermore, all studies that involved resections of arteries other than the superior mesenteric artery, the celiac trunk/artery, or the common hepatic artery were excluded. When studies from the same authors involving the same patient population were present, the study with a control group was selected. When no control group was described, the studies with fewer patients were excluded. Only single center studies were selected. The pan-European retrospective multicenter study from Klompmaker et al [31]was not included, as its patient cohort had patients from other single center studies that were included in the analysis.

Details of the study selection process are summarized in Figure 5. Only studies with a control group of patients undergoing resection without arterial resection were selected for meta-analysis (Table 4). Studies with less than five patients with arterial resection were excluded from the meta-analysis. As our goal was to review contemporary pancreas surgery with arterial resection, studies with an inclusion period starting before 2000 were also excluded from the meta-analysis., Consequently, we excluded the studies by Takahashi et al [32], Glebova et al [22] and Yamamoto et al [33] because of their inclusion period starting in 1993, 1970 and 1991, respectively., The study by Addeo et al [34] was not included, as it reports and compares the outcomes of surgical resection of borderline resectable (BL) and locally advanced (LA) ‘unresectable’ pancreatic cancer after neoadjuvant chemotherapy and not directly an arterial resection group with a standard resection group. The study by Rehders et al [35] was also excluded because it only reported less than five patients who underwent arterial resection.

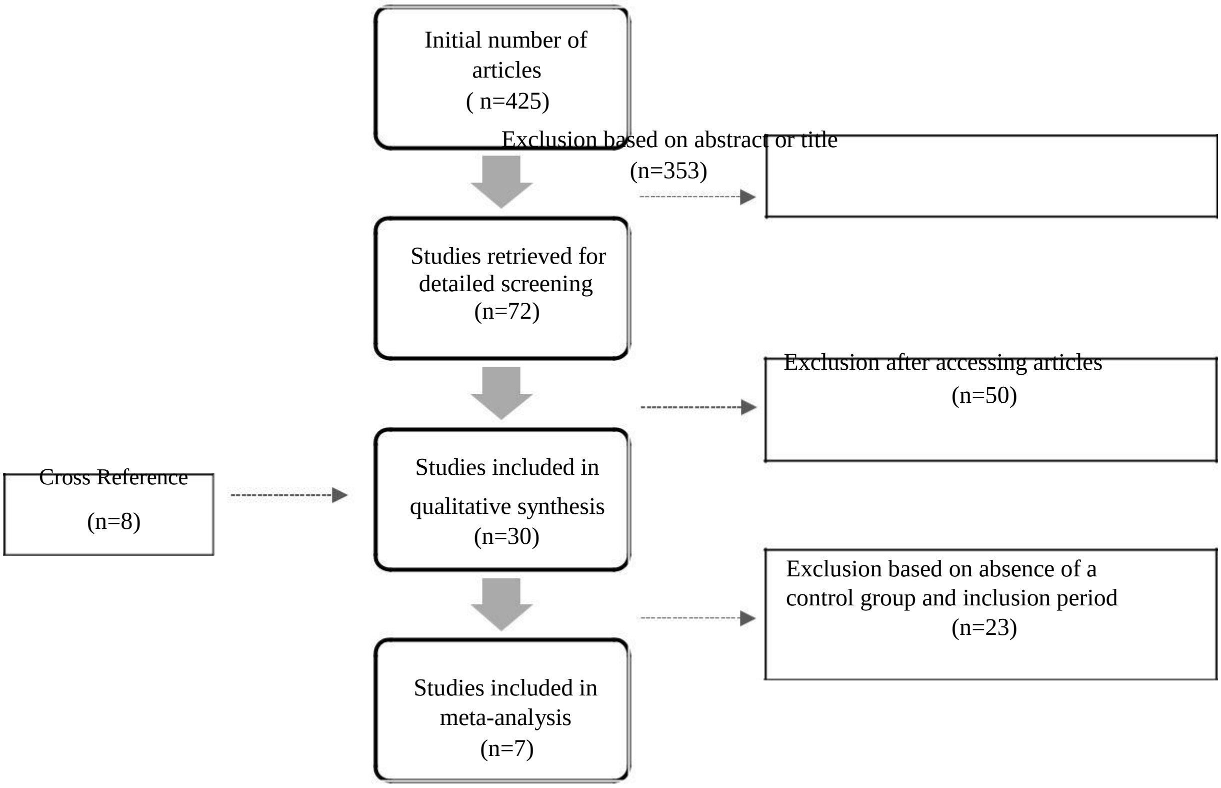


Figure 5: Flowchart with the number of studies identified, screened, assessed and finally included in the meta-analysis.

3.3 Data collection

Studies were analyzed and data was extracted and presented in a tabular fashion (Table 2-4). The following descriptive data was documented for each selected study: first author, year of publication, inclusion period, sample size, arterial resection, neoadjuvant therapy, country and median follow up (Table 2). Patient and operation characteristics were documented: age, gender, type of operation, type of artery resected, duration of surgery and blood loss (Table 3). The following clinically relevant outcomes for pancreatic surgery were extracted: morbidity, pancreatic fistula, delayed gastric emptying, postoperative bleeding, reoperation rate, mortality, length of hospital stay, median survival, actuarial survival (1, 2, 3 and 5 years), R0 resection rate, histological proof of arterial invasion and lymph node positivity (Table 4). Risk of bias was accessed using the ROBINS-I tool (risk of bias in non-randomized studies of interventions) [36].

3.4 Statistical analysis

A meta-analysis was performed with the following outcomes: morbidity using the Clavien-Dindo Classification (> Grade III) [37], perioperative mortality (30 and 90 days), 1 year survival, R0 resection, postoperative pancreatic fistula (defined according to the International Study Group on Pancreatic Fistula) [38] and delayed gastric emptying (DGE) rates (defined by the International Study Group of Pancreatic Surgery [39]) as outcome measures (random effects model) using the Review Manager (RevMan) software, version 5.3 (Cochrane Collaboration, Oxford, UK). The magnitude of the effect estimate was visualized by forest plots. An Odds Ratio (OR) was calculated for binary data. The 95% Confidence Interval (CI), heterogeneity and statistical significance were reported for each outcome. The X^2 and the Kruskal-Wallis tests were used for the evaluation of statistical significance. $P < 0.05$ was considered statistically significant. When the studies did not report mean and standard deviation, these were calculated using the methods described by the guidelines of the Cochrane Collaboration [40] and Hozo et al. [41]. As not all studies report individual patient data or hazard ratios, the survival analysis was performed with weighted rates. Furthermore, a subgroup analysis was performed based on the proportion of patients receiving neoadjuvant chemotherapy in a given study. Studies with more than 50% of patients with arterial resection receiving neoadjuvant chemotherapy were included in the neoadjuvant subgroup. No subgroup analyses on planned vs unplanned resection and on arterial reconstruction vs no reconstruction was performed because no control groups were available.

4 Results

Among the 425 articles, 30 studies from 8 countries were included in the qualitative analysis (Table 2-4). Publication years were from 2011 to 2019. The inclusion periods of the studies ranged from 1970 to 2018. Within these 30 studies, a total of 807 patients underwent pancreatic surgery with arterial resection and 6270 a procedure without arterial resection. Median age ranged from 52 to 71 years (data from 28/30 studies). Median hospital stay ranged from 6 to 62 days (data from 19/30 studies).

The median follow-up varied between 11 and 53.5 months (data from 18/30 studies). Among the AR groups from all studies, 50% of patients received neoadjuvant chemotherapy (data from 25/30 studies). The R0 resection rate was 76% in the AR group (data from 23/30 studies) vs 80% in the no AR group (data from 9/11 studies) (p= 0.112).

The weighted actuarial survival at 1, 2, 3 and 5 years was 81, 44, 29 and 21% in the AR group (data from 18, 6, 13 and 6/30 studies) vs 59, 50, 42 and 11% in the no AR group (data from 9, 5, 4 and 1/11 studies). The weighted median survival was 21.9 months (range 9.5 – 38.6 months, data from 25/30 studies) in the AR group vs 45.7 months (range 19 – 47 months, data from 10/11 studies) in the no AR group, p=0.008.

Postoperative mortality was 5.4 % (data from 18/30 studies) in the AR group vs 1.1% (data from 8/11 studies) in the no AR group (p<0.001).

The overall morbidity rate was 66.8% in the AR group (data from 29/30 studies) vs 92% in the no AR group (data from 11/11 studies, p < 0.001). The overall POPF rate (all grades combined) was 27% in the AR group (data from 25/30 studies) vs 14% in the no AR group (data from 10/11 studies, p< 0.001). Regarding DGE (all grades combined) a rate of 19% in the AR group (data from 15/30 studies) vs 13% in the no AR group (data from 7/11 studies, p<0.001) was observed. Postoperative bleeding (all grades combined) was 12.6% in the AR group (data from 11/30 studies) vs 3% in the no AR group (data from 5/11 studies, p<0.001). Re-Operation occurred in 11% of patients in the AR group (data from 13/30 studies) vs 4.6% of patients in the no AR group (data from 5/11 studies, p=0.004). No grade differentiation could be performed for POPF, DGE and postoperative bleeding because a stratification was not available in all studies.

In the AR group, 71% of patients had positive lymph nodes (data from 19/30 studies) vs 82% in the no AR group (data from 7/11 studies, p<0.001). Among 320 Patients undergoing arterial resection (data from 12/30 studies) 49% were histologically positive for arterial invasion.

Table 2: Characteristics of included studies.

Reference	**Year**	**Inclusion Period**	**Sample Size (AR/No AR)**	**AR Neoadjuvant Therapy (+/-)**	**Country**	**Median Follow up (months)**
Addeo et al [34]	2015	2007-2012	24/21	24/0	USA/France	-
Amano et al [42]	2015	2012-2013	13/0	13/0	Japan	14.5
Bachellier et al [43]	2018	1990-2017	118/0	89/29	France	15.77
Baumgartner et al [44]	2012	2007-2010	11/0	11/0	USA	-
Beane et al [45]	2015	2011-2012	20/172	3/17	USA	-
Cesaretti et al [46]	2016	1998-2015	5/0	5/0	France	-
Christians et	2014	2011-	10/0	10/0	USA	21

al [47]		2013				
Glebova et al [22]	2016	1970-2014	35/5591	6/29	USA	17
Ham et al [48]	2015	2000-2014	7/31	0/7	Korea	-
Jing et al [49]	201	2005-2010	24/0	-	China	12.67
Loveday et al [50]	2018	2009-2016	20/11	18/2	Canada	12.6
Miura et al [51]	2014	1998-2018	50/0	0/50	Japan	45.3
Miyazaki et al [23]	2017	1999-2015	21/0	9/12	Japan	11
Nakamura et al [19]	2016	1998-2015	80/0	2/78	Japan	53.5
Ocuin et al [52]	2016	2007-2015	30	27/1	USA	33
Okada et al [53]	2013	2005-2010	16/36	0/16	Japan	25
Perinel et al [54]	2016	2008-2014	14/97	4/10	France	-
Peters et al [55]	2016	2004-2016	17/51	15/2	Netherlands	8
Rehders et al [35]	2012	1998-2010	4/104	-	Germany	-
Sakuraba et al	2012	1998-	7/0	-	Japan	-

[56]		2010				
Sato et al [57]	2016	2011-2014	17/0	2/15	Japan	14.4
Sugiura et al [17]	2017	2002-2014	16/71	0/16	Japan	36
Takahashi et al [33]	2011	1993-2010	16/27	0/16	Japan	15
Tanaka et al [58]	2012	1998-2007	42/0	-	Japan	-
Tee et al [59]	2018	1990-2017	111/0	65/46	USA	19
Ueda et al [60]	2019	2004-2015	31/0	24/7	Japan	-
Wang et al [61]	2014	2003-2012	15/0	-	China	-
Yamamoto et al [33]	2012	1991-2009	13/58	-	Japan	18
Yoshitomi et al [62]	2019	2010-2016	38/0	31/7	Japan	29.6/15.6
Zhou et al [63]	2014	2006-2013	12/0	9/3	China	-
Overall	2011-2019	1970-2017	807/6270	347/346	-	-

Legend: AR: arterial resection

Table 3: Patient and operation characteristics.

Reference	Group	Age(median)	Sex (M/F)	Type of Operation	Artery Resected	Duration of Surgery (min.)	Blood loss (mL)
Addeo et al [34]	AR	-	-	PD (13), TP (2), DP (9)	SMA (9), CA (12), CHA (1), SP (1), LHA (1)	-	-
	No AR	-	-	-	-	-	-
Amano et al [42]	AR	64.1	10/3	PD (3), TP (4), DP (6)	CA (10), CHA (7)	567 ± 132 (376-862)	1311±64 (860-2480)
Bachellier et al [43]	AR	62	61/57	PD (51), TP (18), DP (49)	CA (50), HA (29), SMA (35), Others (4)	600 (295-1145)	-
Baumgartner et al [44]	AR	61	5/6	DP (11)	CA (11)	494	700 (500-4500)

Beane et al [45]	AR	54	6/14	DP (20)	CA (20)	276 (164-617)	-
	No AR	66	57/115	DP (172)	-	207 (66-581)	-
Cesaretti et al [46]	AR	56.4	-	DP (5)	CA (5)	550 (450-655)	370 (300-600)
Christians et al [47]	AR	62	4/6	DP (6), CP (1), PD (2), TP (1)	CA (7), CHA (3)	417 (298-574)	800 (300-2500)
Glebova et al [22]	AR	58	21/14	PD (18), TP (1), PPPD (3), NS (3), DP (9), Laparoscopic PD (1)	CA (15), CHA (21)	319 ± 40	1285 ± 276
	No AR	63	2281/3310	PD (1365), TP (90), PPPD (2530), NS (392), DP (1213), Laparoscopic PD (1)	-	355 ± 34	828 ±220
Ham et al	AR	58	3/4	DP (7)	CA (7)	354 (307-520)	727 p=0.024

[48]	No AR	67.5	16/15	DP (31)	-	286 (157 – 502)	300 p=0.024
Jing et al [49]	AR	54.5	18/6	DP	CA (24)	200 ± 68	1779± 1934
Loveday et al [50]	AR	57	17/40	PD (16), DP (2), TP (2)	SMA (10), CA and CHA (10)	681 (448-960)	1600 (500-2500)
	No AR			PD (11)	-	563 (405-660)	575 (350-1300)
Miura et al [51]	AR	64	26/24	DP (50)	CA (50)	454 (306-1037)	940 (420-15970)
Miyazaki et al [23]	AR	66	9/12	PD (17), TP (4)	CHA (21)	2290 (740-19.895)	522 (390-774)
Nakamura et al [19]	AR	65	40/40	DP (80)	CA (80)	436 (248-1037)	880 (162-15970)
Ocuin et al [52]	AR	61.9	17/13	DP (30)	CA (30)	430.8 ± 229.9	1552.5 ± 1565.6
Okada et al [53]	AR	63	11/5	DP (16)	CA (16)	298 (212-465)	1165 (410-2240)
	No AR	68	23/13	DP (36)	-	203 (128-276)	700 (10-2850)
Perinel et al	AR	65	9/6	PD (3), TP (9), DP (2)	SMA (6), CHA (4), CA (2),	380 ± 75	826 ± 415

[54]					RRHA (2)		
	Standard	67	36/30	PD (44), TP (10), DP (12)	-	290 ±75	428 ± 428
	VR	67	20/11	PD (20), TP (10), DP (1)	-	330 ± 45	432 ±356
Peters et al [55]	AR	65	9/8	DP (17)	CA (17)	404 (342-480)	900 (400-1000)
	No AR	67	29/22	DP (51)	-	309 (220-370)	525 (300-850)
Rehders et al [35]	AR	-	-	-	SMA (4)	-	-
	Standard	-	-	-	-	-	-
	VR	-	-	-	-	-	-
Sakuraba et al [56]	AR	61	0/7	DP (1), PD (6)	CHA (7), CA (1)	-	-
Sato et al [57]	AR	68	13/4	DP (17)	CA (17)	410 (248-564)	420 (150-1650)
Sugiura et al [17]	AR	70	10/6	DP (16)	CA (16)	338 (259-507)	902 (461-1893)
	No AR	71	44/32	DP (71)	-	263 (129-557)	460 (76-2716)
Takahashi et al [33]	AR	65	8/8	DP (16)	CA (16)	237±63	782±82
	No AR	70	10/17	DP (27)	-	203±83	634±85

Tanaka et al [58]	AR	-	-	DP (42)	CA (42)	478 (311-1037)	1030 (420-15970)
Tee et al [59]	AR	62.9	62/49	PD (45), DP (46), TP (20)	CA (49), HA (60), SMA (15), Multivessel (15)	472±150	1265±1442
Ueda et al [60]	AR	62	21/10	DP (31)	CA (31)	334 (175-584)	1270 (305-10.270)
Wang et al [61]	AR	59.2	8/7	DP (15)	CA (15)	295 (225-420)	1000 (400-2000)
Yamamoto et al [33]	AR	64	10/3	DP (13)	CA (13)	620 (370-840)	1300 (570-4300)
	No AR	66	39/19	DP (58)	-	360 (220-610)	620 (27-2200)
Yoshitomie et al [62]	AR (Neoadjuvant/No Neoadjuvant)	66/62	26/12	DP (38)	CA (38)	350±104/353±87	1274±961/1347±1111
Zhou [63]	AR	52	8/4	DP (12)	CA (12)	330 (280-440)	1200 (800-2400)

Legend: AR: arterial resection; PD: pancreaticoduodenectomy ; DP: distal pancreatectomy; TP: total pancreatectomy; PPPD: pylorus-preserving pancreaticoduodenectomy; NS: Not Specified ; SMA: superior mesenteric artery; CA: celiac axis; HA: hepatic artery; CHA: common hepatic artery; SP: splenic artery; LHA: left hepatic artery; RRHA: replaced right hepatic artery; M: male ; F: female

Table 4: Surgical complications, outcomes and pathology

Reference	Group	Morbidity (%)	Pancreatic Fistula (%)	DGE (%)	Postoperative Bleeding (%)	Reoperation Rate (%)	Mortality (%)	Hospital Stay (d)	Median Survival (Mo.)	Actuarial Survival (years, %)				R0 Resection (%)	Histological arterial Invasion (%)	Lymph Node passivity (%)
										1 y	2 y	3 y	5 y			
Addeo et al [34]	AR	42	-	-	-	-	-	-	15	61	-	0	-	-	37,5	-
	No AR	24	-	-	-	-	-	-	22	81	-	24.1	-	-	-	-
Amano et al [42]	AR	61	6	46	-	-	0	49	-	92	-	-	-	92	50(CA), 0(CHA)	92

Bachellier et al [43]	AR	41.5	5.93	-	-	10.1	5.1	22	13.7	59	-	13	11.8	52.4	58	80.5
Baumgartner et al [44]	AR	45	36	-	8	0	-	9	26	-	-	-	-	-	-	91
Beane et al [45]	AR	35	10	-	35	10	10	8	-	-	-	-	-	-	-	-
	No AR	36	15	5	-	2	1	6	-	-	-	-	-	-	-	-
Cesaretti et al [46]	AR	100	80	0	-	0	0	-	24	-	-	60	-	60	-	60
Christians et al [47]	AR	30	0	0	0	10	0	9	-	-	-	-	-	-	10	-
Glebova et al [22]	AR	89	9	11	6	-	-	13	22	50	-	-	19	57	-	91
	No AR	97	13	13	3	-	-	11	47	58	-	-	11	70	-	83
Ham et al	AR	100	100	14.	0	-	0	23	15	100	44.	-	.	71	100	57

[48]				3							4					
	No AR	-	68	0	3.2	-	3.2	14.5	25	73.7	55. 3	-	-	80.6	-	-
Jing et al [49]	AR	54	42	25	-	-	0	-	9.25	46	-	4	-	-	-	-
Loveday et al [50]	AR	65	0	-	-	25	5	11.5	14.8	65	10	-	-	100	-	60
	No AR	73	0	-	-	18	0	10	24.2	82	27	-	-	100	-	55
Miura et al [51]	AR	54	-	-	-	-	-	39	24.7	80.7	-	32. 3	24. 3	92	28	72
Miyazaki et al [23]	AR	81	4.8	9.5	-	-	0	-	11	47.6	-	6.6	6.6	43	57	86
Nakamura et al [19]	AR	-	58.8	28, 8	-	7.5	1.3	38	24.9	81.1	-	56. 9	32. 7	93	-	62.5
Ocuin et al [52]	AR	73	43	-	-	7	14	10.7	35	-	-	-	-	80	62	50

Okada et al [53]	AR	-	18.8	12.5	0	0	0	-	25	81	52	-	-	31	-	-
	No AR	-	27.8	0	2.8	0	0	-	32	81	53	-	-	81	-	-
Perinel et al [54]	AR	14	0	14	-	0	0	23	-	92	55	17	-	57	-	71
	Standard	29	10	8	-	15	3	27	-	64	51	45	-	74	-	70
	VR	32	3	6	-	6	3	23	-	76	52	33	-	39	-	90
Peters et al [55]	AR	35	5.9	5.9	5.9	-	0	7	20	75	-	-	-	82	-	41.2
	No AR	24	21.6	7.8	2	-	0	6	19	85.2	-	-	-	92	-	40
Rehders et al [35]	AR	0	-	-	-	-	-	-	17	-	-	-	-	75	-	50
	Standard	67	-	-	-	-	-	-	27.9	-	-	-	-	86	-	43
	VR	49	-	-	-	-	-	-	23.4	-	-	-	-	83	-	20
Sakuraba	AR	43	-	-	15	-	-	-	-	-	-	-	-	86	-	-

et al [56]																
Sato et al [57]	AR	41	41	12	-	-	0	34	16.9	74	-	45	-	94	-	76
Sugiura et al [17]	AR	88	44	-	-	-	-	26	17.5	75	-	21.4	-	62	56	88
	No AR	63	41	-	-	-	-	21	43.1	85.2	-	52.9	-	88	-	55
Takahashi et al [33]	AR	56	31	-	-	12.5	6	38	9.7	42.6	-	25.6	-	56	75	56
	No AR	44	19	-	-	0	0	56	30.9	84.1	-	31.1	-	78	15	44
Tanaka et al [58]	AR	43	17	12	-	-	-	-	24	-	-	-	25	93	-	-
Tee et al [59]	AR	54	23	23	17	16	13	-	28.5	-	-	-	-	-	-	-
Ueda et al	AR	32.3	45.2	-	-	-	6.5	37	23.7	74.2	-	34.	-	42	45	78

[60]												4				
Wang et al [61]	AR	47	33	-	-	-	-	29.6	19	86.7	-	6.7		100	-	-
Yamamoto et al [33]	AR	92	62	31	8	-	0	62	20.8	-	25.4	-	-	31	62	-
	No AR	60	45	55	3	-	0	25	21.1	-	45.9	-	-	74	48	-
Yoshitomie et al [62]	AR (Neoadjuvant/No Neoadjuvant)	39	29	13	-	-	2.6	32/34	38.6/15.6	79	61	34	-	63	-	21
Zhou et al [63]	AR	75	25	-	0	-	-	-	10	-	-	-	-	-	-	-

Legend: AR: arterial resection; DGE: delayed gastric emptying; CA: celiac axis; CHA: common hepatic artery

From the 30 studies, seven cohort studies with a total of 579 patients were included in the meta-analysis (Table 5).

Beane et al. [46] prospectively compared the modified Appleby procedure and distal pancreatectomy, and showed longer operating time and higher post-operative mortality in the former group of patients.

Ham et al. [49] retrospectively compared DP-CAR (Distal Pancreatectomy with celiac axis resection) patients with both DP (distal pancreatectomy) and no resection. Despite longer operative time and length of hospital stay, survival in the DP-CAR group was comparable with the DP patients and better than the no resection group.

Loveday et al. [51] compared postoperative outcomes of arterial and non-arterial resection in UICC stage III pancreatic cancer patients following neoadjuvant chemotherapy in a retrospective cohort study. Except for longer operative time and more blood loss, there was no difference in pancreatic fistula rate, hospital stay, mortality and overall survival.

The prospective cohort study of Peters et al. [56] compared the Appleby procedure and classic distal pancreatectomy in locally advanced pancreatic cancer and found similar postoperative outcomes including mortality and median survival.

Okada et al. [54] retrospectively reviewed postoperative outcomes of patients undergoing standard distal pancreatectomy and the Appleby procedure concluding similar postoperative outcomes including mortality rates.

In their retrospective cohort study, Perinel et al. [55] stressed feasibility of planned arterial resection for locally advanced pancreatic cancer in highly selected patients with a tumor-free celiac trunk and superior mesenteric artery and a possible distal reconstruction. They compared pancreatectomy without vascular resection with pancreatectomy with isolated venous resection for borderline pancreatic cancer and also pancreatectomy with arterial resection for locally advanced pancreatic cancer.

Retrospectively, Sugiura et al. [17] showed decreased median survival, longer operative time and greater blood loss in the modified Appleby procedure compared to standard distal pancreatectomy.

Table 5: Data on selected studies for meta-analysis.

Reference	Inclusion Period	Sample (AR/No AR)	AR Neoadjuvant Therapy (+/-)	Operation (AR)	Artery Resected	Reconstruction (Y/N)	Planned Resection (Y/U)	Median Survival (months) (AR/No AR)	Study Type	Risk of bias
Beane 2015 et al [45]	2011-2012	20/172	5/15 -	DP (20)	CA (20)	N	U	-	Prospective	High
Ham 2015 et al [48]	2000-2014	7/31	0/7 -	DP (7)	CA (7)	N	U	15/25	Retrospective	High
Loveday 2018 et al [50]	2009-2016	20/11	18/2 +	DP (2), PD (16), TP (2)	SMA (10), CA and CHA (10)	Y	Y	14.8/24.2	Retrospetive	Low
Okada 2013 et al [53]	2005-2010	16/36	0/16 -	DP (16)	CA (16)	N	Y	25/32	Prospective	High

Perinel 2016 et al [54]	2008-2014	14/97	4/10 -	DP (2), PD (3), TP (9)	CA (2), SMA (6), CHA (4), RRHA (2)	Y	Y	-	Prospective	High
Peters 2016 et al [55]	2004-2016	17/51	15/2 +	DP (17)	CA (17)	U	U	19/20	Prospective	High
Sugiura 2017 et al [17]	2002-2014	16/71	0/16 -	DP (16)	CA (16)	N	Y	17.5/43.1	Retrospective	High
Overall	2000-2016	110/469	42/68	DP (80), PD (19), TP (11)	CA or HAB (100) SMA (10)	Y (34)	Y (66)	18.6/32 (WMS)	Retrospective (3), Prospective (4)	High (6), Low (1)

Legend: AR: arterial resection; PD: pancreaticoduodenectomy ; DP: distal pancreatectomy; TP: total pancreatectomy; SMA: superior mesenteric artery;

CA: celiac axis; HA: hepatic artery; CHA: common hepatic artery; RRHA: replaced right hepatic artery ; HAB: hepatic artery branches; Y: yes; N: no; U: unknown ; WMS: weighted median survival

Table 6: The risk of bias was classified into low (+), high (-), unclear or missing data (?) using ROBINS-I ("Risk of bias in non-randomized studies - of interventions") recommended by the Cochrane Handbook.

Reference	A	B	C	D	E	F	G	H
Beane 2015 et al [45]	-	-	-	?	-	-	-	-
Ham 2015 et al [48]	-	-	-	?	?	-	-	-
Loveday 2018 et al [50]	-	-	+	+	+	+	+	+
Okada 2013 et al [53]	-	-	-	?	+	-	?	-
Perinel 2016 et al [54]	-	-	+	-	-	-	-	-
Peters 2016 et al [55]	-	-	-	?	-	-	-	-
Sugiura 2017 et al [17]	-	-	-	?	+	-	?	-

Risk of bias legend

(A) Confounding

(B) Selection bias

(C) Classification of intervention

(D) Intended intervention

(E) Missing data

(F) Measurement of outcomes

(G) Reported result

(H) Overall

As depicted in Table 5, there were 110 Patients in the AR groups and 469 patients in the control groups of the included studies. 38% of the patients who underwent AR received neoadjuvant chemotherapy. 73% of the patients in the AR group underwent distal pancreatectomy, 17% pancreaticoduodenectomy and 10% total pancreatectomy. 91% received a CA or hepatic artery branches (HAB) resection and 9% an SMA resection. 60% of the arterial resections were planned and 34% of all patients in the AR group underwent arterial reconstruction. In almost all included studies, median survival time was reported. The weighted median survival was 18.6 months (range 14.8 – 25 months) for patients who underwent pancreatic surgery with AR compared to 32 months (range 19 - 43.1 months) for patients undergoing a standard procedure without AR, p= 0.037. In the subgroup analysis, in the neoadjuvant subgroup the weighted median survival was lower in patients undergoing AR compared to those undergoing upfront surgery (16.7 vs 21.3, range 14.8-25 months).

Six of the included studies reported data on perioperative mortality. Mortality was non-significantly higher in the AR group (OR 2.55, 95% CI [0.69; 9.42], p=0.16) (Figure 6). The weighted mortality rate was 3.2% in the AR group and 1.5% in the standard resection group (p= 0.27).

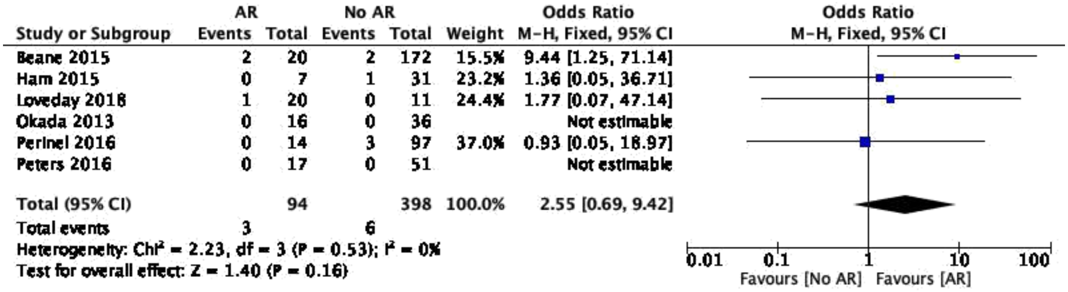


Figure 6: Forest plot of pooled odds ratio with 95% CI for comparing pancreatic surgery with and without arterial resection with regard to perioperative mortality as defined in the single studies.

Five studies provided information about overall morbidity. A total of 42 patients who underwent pancreatic surgery with AR were included in this analysis. There was no statistically significant difference between the AR and no AR groups (OR 1.15, 95% CI [0.58; 2.28], p=0.69) (Figure 7). In the subgroup analysis for neoadjuvant therapy, the results were not significantly different between the neoadjuvant group (OR 1.28, 95% CI [0.49; 3.32]) and the upfront surgery group (OR 1.12, 95% CI [0.35; 3.57], p=0.86).

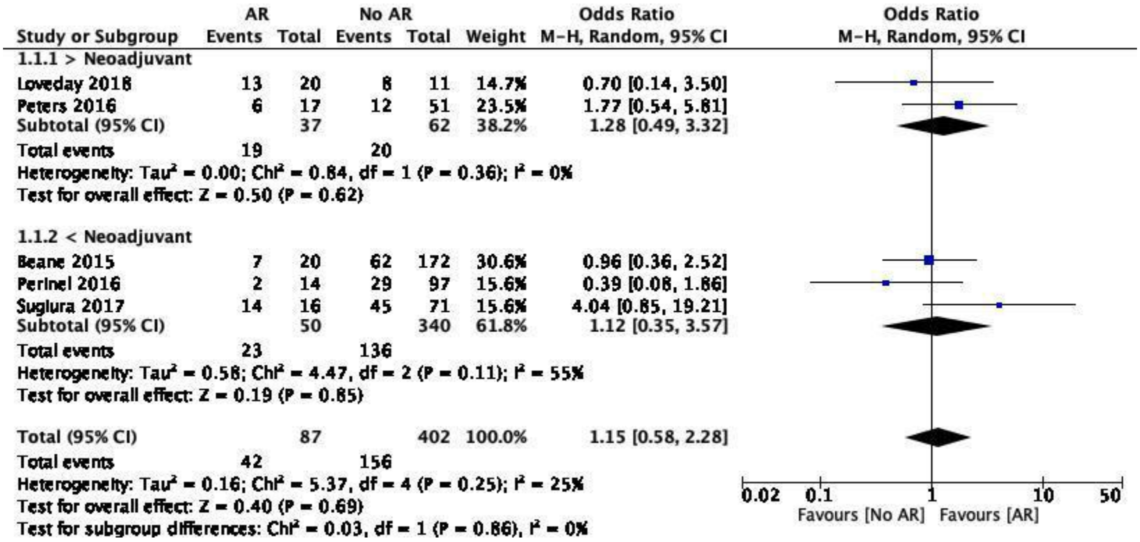
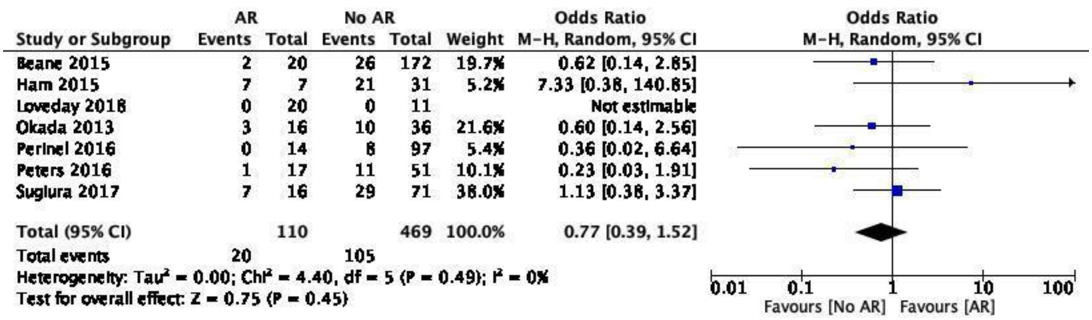


Figure 7: Forest plot of pooled odds ratio with 95% CI for pancreatic surgery with and without arterial resection regarding overall morbidity with subgroup analysis for neoadjuvant therapy.

Regarding postoperative pancreatic fistula, there was no statistically significant difference in the analysis of 110 patients undergoing pancreatic surgery with AR and 469 undergoing standard surgery (OR 0.77, 95% CI [0.39; 1.52], p=0.45) (Figure 8a). DGE was assessed in four studies. There was no significant difference in patients receiving AR versus the standard procedure (OR 2.30, 95% CI [0.36; 14.57], p=0.08) (Figure 8b). Meta-analysis for postoperative bleeding was not performed because this outcome was only reported in two of the selected studies.

a)



b)

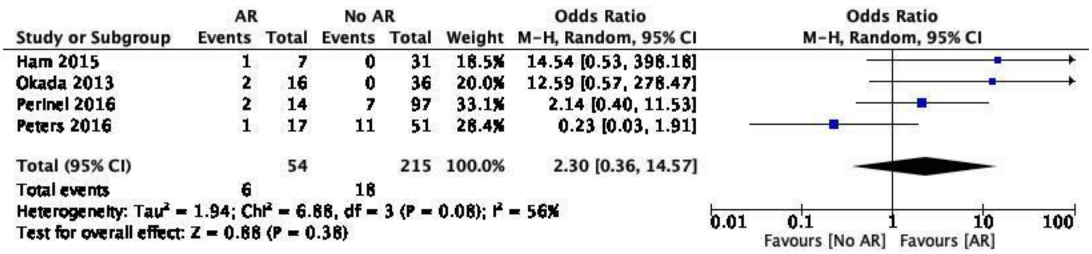
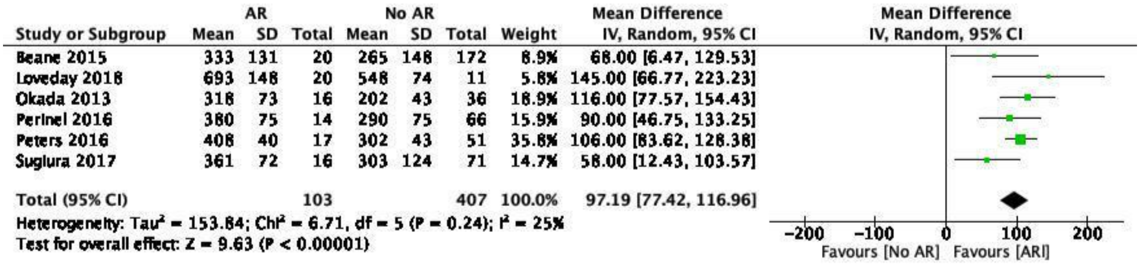


Figure 8: Forest plot of pooled odds ratio with 95% CI for pancreatic surgery with and without arterial resection with regard to postoperative pancreatic fistula (a) and delayed gastric emptying (b).

Regarding the duration of the operation, almost all studies demonstrated that pancreatic surgery with AR was longer than standard surgery. In the random-effects model, the operation time was shorter in the standard group with a mean difference of 98 minutes (95% CI [77.42; 116.96], p<0.001) (Figure 9a). In all included studies, blood loss was higher in the AR group with a mean difference of 319 mL (95% CI [150.02; 487.2], p<0.001) (Figure 9b). The study by Ham et al was excluded as no SD of the mean was provided.

a)



b)

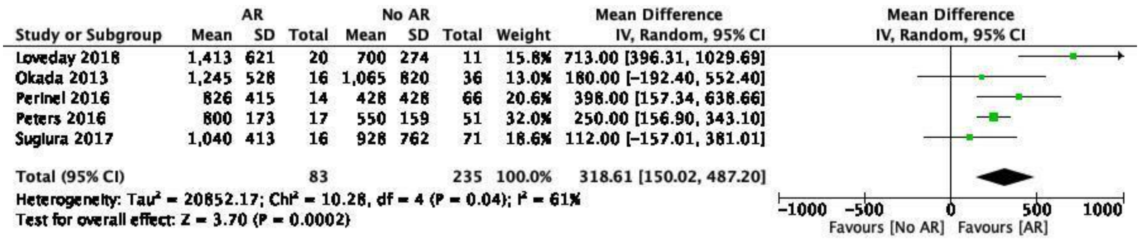


Figure 9: Forest plot of mean difference with 95% CI for pancreatic surgery with and without arterial resection with regard to operative time (a) and blood loss (b).

Five studies reported on R0 rates. Patients undergoing arterial resection had lower R0 resection rates compared to the no AR group (69% vs 89%, OR 0.24, 95% CI [0.11; 0.54], p<0.001). In the subgroup analysis concerning neoadjuvant therapy, patients undergoing upfront surgery with AR showed lower R0 rates when compared to those undergoing standard surgery (50% vs

86%, OR 0.17, 95% CI [0.08; 0.36], p<0.001). Patients undergoing arterial resection after neoadjuvant chemotherapy had no statistically significant difference on R0 rates than the ones undergoing standard resection (92% vs 92%, OR 1.04, 95% CI [0.08; 13.31], p=0.98) (Figure 10).

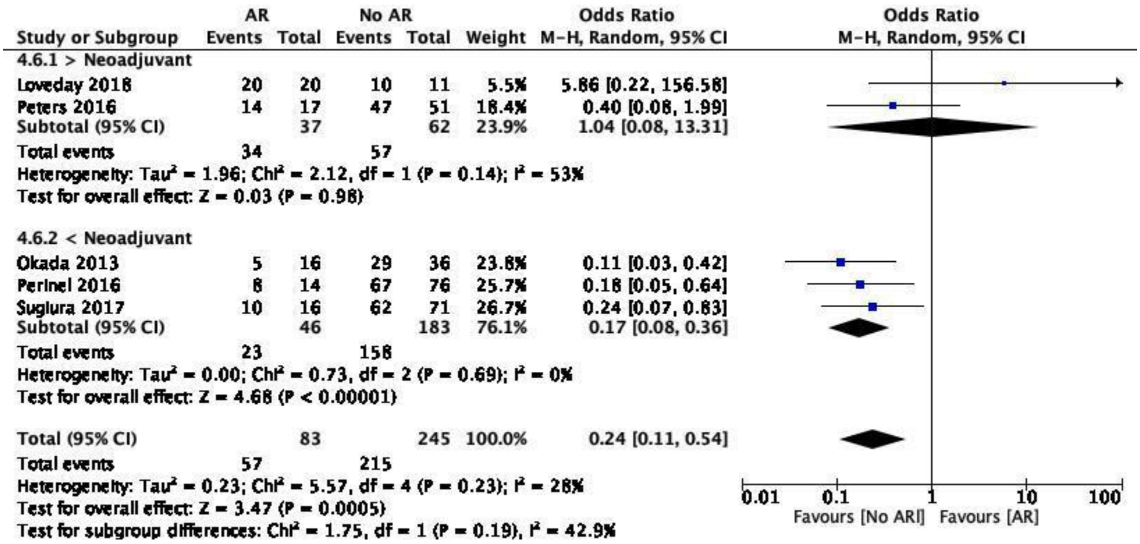


Figure 10: Forest plot of pooled odds ratio with 95% CI for pancreatic surgery with and without arterial resection regarding R0 resection with subgroup analysis of neoadjuvant therapy.

Four studies were included in the meta-analysis of lymph node positivity with 54 patients undergoing pancreatic surgery with AR and 230 patients undergoing the standard procedure. Lymph node positivity was observed in 58% of the patients with AR and 60% in the standard group (p=0.69). No significant difference was found in the meta-analysis of the four studies (OR 1.39, 95% CI [0.66; 2.92], p=0.38). In the subgroup analysis for neoadjuvant therapy, the results were not significantly different between the neoadjuvant group (OR 1.15, 95% CI [0.56; 2.36], p=0.9) and the upfront surgery group (OR 2, 95% CI [0.27; 14.61], p=0.05) (Figure 11).

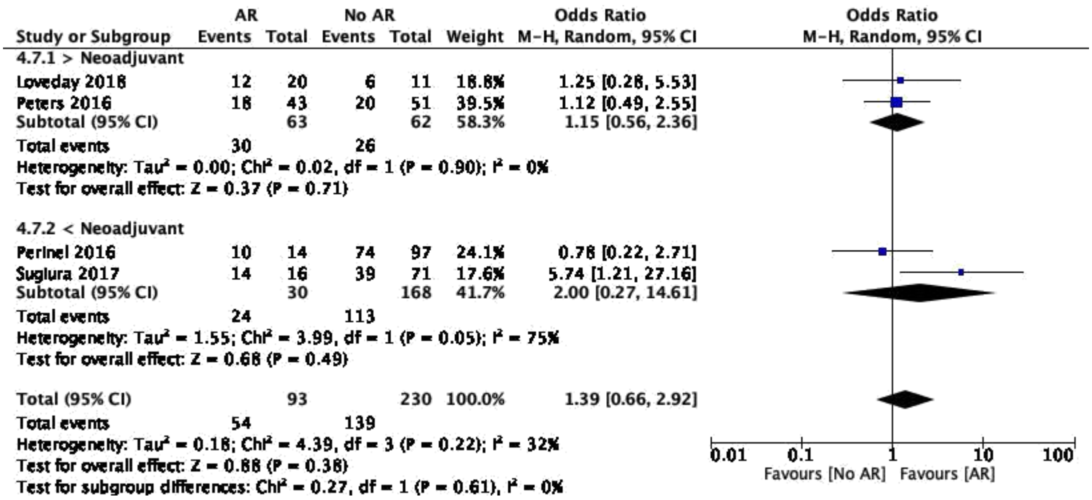


Figure 11: Forest plot of pooled odds ratio with 95% CI for pancreatic surgery with and without arterial resection with regard to lymph node positivity with subgroup analysis of neoadjuvant therapy.

Concerning 1-year survival, the meta-analysis showed no statistically significant difference between the two groups (78% vs 77%, OR 0.92, 95% CI [0.41; 2.09], p=0.85) (Figure 12). In the subgroup analysis for neoadjuvant therapy, there was no statistical significance neither in the neoadjuvant group (OR 0.47, 95% CI [0.16; 1.40] nor the upfront surgery group (OR 1.49, 95% CI [0.46; 4.88], p=0.85).

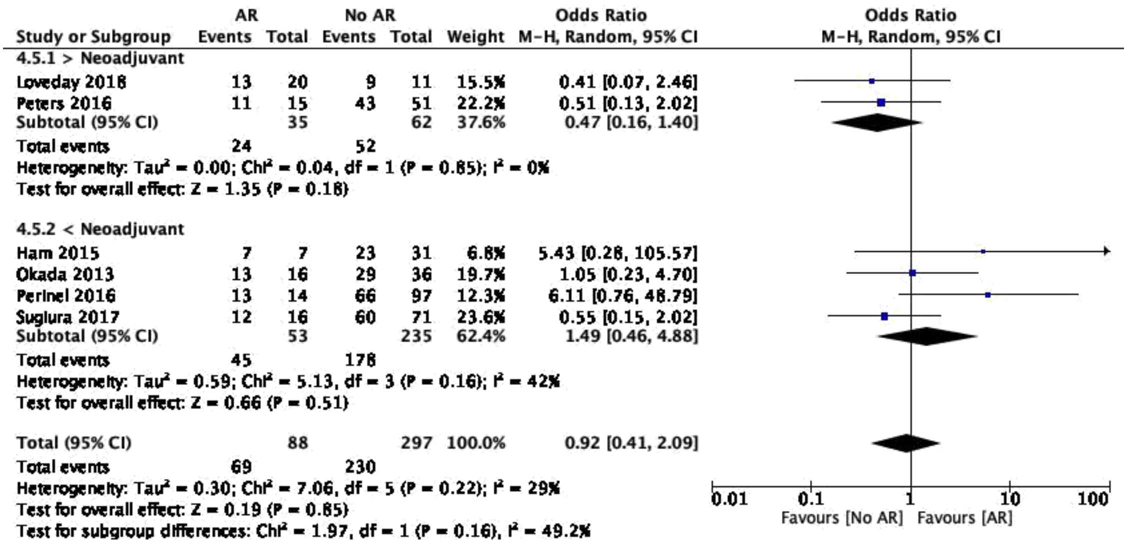


Figure 12: Forest plot of pooled odds ratio with 95% CI for pancreatic surgery with and without arterial resection regarding 1-year survival with subgroup analysis for neoadjuvant therapy.

5. Discussion

The present meta-analysis compares arterial resection for pancreatic cancer with operations without arterial resection. There are two major findings. The first concerns comparable postoperative mortality and morbidity rates and the second shorter long-term survival in the arterial resection group.

Arterial resection in pancreatic cancer is strongly related to the definition of borderline and locally advanced unresectable tumor status. In the studies included in this meta-analysis, most of the data on arterial resection refers to CA, and most resections were distal pancreatectomies, which carry a lower risk of morbidity and mortality than pancreatic head resections. 73% of the patients in the AR group underwent distal pancreatectomy, 17% underwent a pancreaticoduodenectomy and 10% a total pancreatectomy. In the included studies, there was no clear differentiation if arterial resection was performed for borderline resectable or locally advanced tumors, being this one strong limitation of our analysis.

Another important limitation of our analysis is that six of the seven included studies were classified as having a high risk of bias.

5.1 Mortality

Unlike the past meta-analysis on this topic , we observed no statistically significant difference between the arterial resection and standard surgery groups, although, the weighted mortality rate was 3.2% in the arterial resection group and 1.5% in the standard resection group. Possibly, the statistical power of our analysis was not sufficient to yield significance for such a small absolute difference. Nevertheless, our analysis reports relevantly lower absolute mortality rates compared to those reported by Mollberg et al (11.8%) [16]. Advances in surgical technique, planning and perioperative care could be the answer for this improvement. One further limitation of our study is that mortality was differently defined across the studies included in the meta-analysis, which variably used in hospital, 30-day and 90-day mortality. Also, these low mortality rates suggest that only selected patients were included in the respective analyses. The results are comparable to a recent work from Klompmaker et al. In an analysis of 240 patients, in whom DP-CAR was combined with (neo-) adjuvant chemotherapy, the 90-day mortality rate was 3.5% [64]. On the other hand, in a retrospective cohort study from the same author that included 68 patients from 20 hospitals in 12 countries, 30-day and 90-day mortality after DP-CAR was 10% and 16%, respectively [18].

There is a high risk of bias because patient selection may explain these significant differences between studies and may not reflect the reality even in high-volume centers with less stringent patient selection. Nevertheless, in the light of the presented data, pancreatic surgery with arterial resection can be performed in selected patients with reasonable mortality rates.

Morbidity could not be stratified in grades according to the Clavien-Dindo Classification owing to non-availability of pertinent data. Concerning morbidity, slightly better results could be observed in the standard resection group, but no significant difference was shown. Of note is the significant heterogeneity among the included studies.

Regarding postoperative pancreatic fistula, which is the major cause of morbidity after pancreatic resection, no significant difference was observed between the two groups. Actually, lower fistula incidence was reported among the patients with arterial resection, probably due to more advanced tumors and hence more solidified post-obstructive fibrosis [65].

A limitation of this analysis is that because of the insufficient patient data, no analysis regarding planned vs unplaned resection could be performed. Planning the arterial resection may have a positive effect on the postoperative morbidity as compared to unplanned resections because of intraoperative injuries or a preoperatively unknown arterial infiltration [54]. It is important to differentiate patients undergoing planned arterial resection from those that were resected because of intraoperative injuries or those with an unknown arterial infiltration preoperatively and postoperatively. Meticulous assessment of preoperative CT-scans for detection of possible arterial encasement is therefore essential.

According to our meta-analysis, it is safe to conclude that arterial resection in selected patients does not have a relevant effect on perioperative morbidity, especially on postoperative pancreatic fistula or delayed gastric emptying.

5.2 Long-term Survival

The second important corollary emerging from our meta-analysis is that pancreatic surgery with arterial resection is associated with a lower 1-year survival rate than surgery without arterial resection. In a large systematic review and meta-analysis involving 18 studies, DP-CAR had a better 1-year survival rate compared to palliative treatments (Pooled HR for OS 0.38 (95%CI:0.25–0.58, $P<0.01$)) [66]. These results are comparable to the weighted average of 1-year survival in our analysis, which was 78% in the AR Group. In a study from the Dutch Pancreatic Cancer Group that involved a national cohort of 36,453 patients with PDAC the 1-year survival of patients who received palliative chemotherapy improved along the last years from 13.3% to 21.2% ($p < 0.001$) [67]. This data is only partially comparable to ours, because this cohort also included patients with advanced metastatic disease (n=4,074). According to this data, arterial resection can be considered in selected patients instead of palliative chemotherapy.

Considering weighted median survival in both groups, patients undergoing arterial resection had a worse prognosis with 18.6 months compared to 32 months in patients undergoing surgery without arterial resection. In a recent systematic review that included 240 patients undergoing DP-CAR, the weighted median survival (14.4 months) was comparable to our analysis [64]. Our data are also comparable to data from a multicenter retrospective cohort study regarding patients undergoing arterial resection (18 months overall survival) [31]. Hackert et al reported in patients undergoing pancreatic surgery after neoadjuvant chemotherapy a median overall survival of 15.3 months after resection vs 8.5 months after exploration alone ($P < 0.0001$) [68].

This finding may be attributed to unfavorable tumor biology with more advanced tumor stages and more aggressive growth in tumors affecting visceral arteries and requiring arterial resection. Longer operative time, lower R0 resection rates and fewer patients with neoadjuvant treatment in the arterial resection group are all factors playing a role in this.

In our analyses, the R0 resection rate was significantly lower in the patients undergoing pancreatic surgery with arterial resection. This can be explained by the local extent of tumor growth and hence the surgical complexity of the resection. Moreover, neoadjuvant treatment was associated with higher R0 resection rates. Kluger et al. showed in their study that a tumor-free resection margin could be achieved in 80% of the cases after neoadjuvant treatment in locally advanced pancreatic cancer with arterial encasement [69]. Hackert et al reported in a 575 patients collective that received neoadjuvant treatment and were scheduled for resection after re-staging a successful resection in 292 patients (50.8%) [68]. In the present series, the weighted average of R0 resection in arterial resection patients within the neoadjuvant subgroup was 92% compared to 50%, in the patients undergoing arterial resection without neoadjuvant chemotherapy ($p<0.001$).

Although neoadjuvant chemotherapy was not associated with prolonged long-term survival, this analysis suggests that it is crucial for achieving negative resection margins in pancreatic surgery. Also, regarding morbidity there was also no statistically significant between the neoadjuvant chemotherapy group and the standard resection group. This suggests that neoadjuvant chemotherapy doesn’t influence the postoperative patient outcome, and safety of the operation procedure. Neoadjuvant chemotherapy was also not associated with higher lymph node positivity rates. This may reveal the positive impact of preoperative chemotherapy on decreasing tumor burden and on downstage tumors. Ferrone et al reported in a retrospective study including 188 patients with locally advanced and borderline PDAC that progression occurred in 38% of patients receiving neoadjuvant FOLFIRINOX, compared with 49% of patients receiving no neoadjuvant therapy. 35% of patients had positive lymph nodes on neoadjuvant group, compared to 79% of patients who underwent upfront surgery (p<0.001). Also, morbidity, especially POPF was reduced in the neoadjuvant therapy group [73]. A main limitation of this analysis is the fact that subgroup division is not based on individual patient data. Controversy still exists if arterial invasion is a risk factor for clinically indolent (micro) metastases in pancreatic cancer patients. Neoadjuvant therapy is now an important therapy option for these patients. Understanding of tumor biology and micrometastases are key to developing better neoadjuvant therapies [71].

Also, the role of alternative therapies like chemoradiotherapy or staged resection needs further investigation. In a Phase 3 randomized trial involving 449 patients that underwent weather chemotherapy alone or radiochemotherapy, no significant difference between overall survivals of both groups was observed [72]. In a multicenter phase II trial in four hospitals in Neatherlands that enrolled 50 patients, Stereotactic body radiotherapy was reported as feasible and 12 % of the patients a potentially curative resection could be performed [73]. In another retrospective cohort study involving neoadjuvant radiotherapy was associated with increased pathologic down staging and R0 resection rates [74].

Regarding alternative stage resection, in a currently ongoing clinical trial (PREVADER) on the University Hospital Haale (Saale), the role of neoadjuvant therapy and vascular debranching followed by resection for locally advanced pancreatic cancer is being evaluated. In this study patients with borderline or locally advanced pancreatic cancer with arterial infiltration undergo in a first operation an arterial reconstruction and tumor biopsy without arterial or tumor resection. After a neoadjuvant therapy, Re-Staging with CT is performed in order to evaluate tumor progress and arterial reconstruction patency. If the tumor responded to neoadjuvant chemotherapy and the arterial bypass is patent, tumor resection will be performed in a second surgery. The objective is to reduce perioperative mortality and morbidity of the arterial resection procedures [75]. Also, evaluating the tumor biology and aggressiveness and potentially resistance or response to chemotherapy is important. Histology analysis of the tumor biopsy may play a central role on selecting patients in the future because of the known limitations of CT-Scan.

Maybe, combing different and new neoadjuvant approaches like neo-radiochemotherapy, staged arterial reconstruction and tumor resection could be the better locally treatment for treating borderline and locally advanced pancreatic cancer.

Also, further investigation on individualized therapy targeting the metabolic reprogramming in cancer cells plays an important role [76, 77].

The main weakness of this meta-analysis is that it is based exclusively on non-randomized, and partially retrospective, studies. The MOOSE guidelines were followed to ensure transparency and standardized reporting, but the risk of bias is still considerable because of the nature of studies included in the meta-analysis. Furthermore, as most of the studies did not report individual patient data or hazard ratios, the survival analysis was performed with weighted rates or weighted median survival witch are rather inaccurate surrogate measures for meta-analyses of survival outcomes [78].

6. Conclusion

In this meta-analysis, all relevant studies published within the last ten years, after the last comprehensive meta-analysis on the topic had been published, providing comparative information on the outcome of patients undergoing pancreatic surgery with arterial resection were included. Arterial resections were not associated with significantly higher mortality and morbidity. However, probably owing to more aggressive tumor biology, patients undergoing arterial resection had a shorter survival than patients who did not require arterial resection. Arterial infiltration should not be a strict contraindication against resection in patients with locally advanced disease anymore. Neoadjuvant treatment could play a role on achieving negative margins. Careful patient selection and multidisciplinary planning will play an important role in the new era of pancreatic cancer treatment. In conclusion, in the hands of experienced pancreatic and vascular surgeons in high volume centers, arterial resections can be performed safely.

7. References

[1]. Siegel R, Miller KD, Ahmedin J. Cancer statistics. CA Cancer J Clin 2017; 67:7–30.

[2]. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2015; 51:1201–1202.

[3]. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014; 74:2913–2921.

[4]. Bilimoria KY, Bentrem DJ, Ko CY, et al. National failure to operate on early stage pancreatic cancer. Ann Surg 2007;246:173–180.

[5]. Gillen S, Schuster T, Büschenfelde CM, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med 2010; 7:1–15.

[6]. Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, Asbun HJ, Bassi C, Büchler M, Charnley RM, Conlon K, Cruz LF, Dervenis C, Fingerhutt A, Friess H, Gouma DJ, Hartwig W, Lillemoe KD, Montorsi M, Neoptolemos JP, Shrikhande SV, Takaori K, Traverso W, Vashist YK, Vollmer C, Yeo CJ, Izbicki JR, International Study Group of Pancreatic Surgery. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2014;155(6): 977–88

[7]. Dokmak S, Aussilhou B, Sauvanet A, et al. Parietal peritoneum as an autologous substitute for venous reconstruction in hepatopancreatobiliary surgery. Ann Surg 2015; 262:366–371.

[8]. Yoshioka M, Uchinami H,Watanabe G, et al. Domino reconstruction of the portal vein using the external iliac vein and an ePTFE graft in pancreatic surgery. J Gastrointest Surg 2017; 21:1278–1286.

[9]. Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA et al.; International Study Group of Pancreatic Surgery. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2014; 155: 977–988.

[10]. Del Chiaro M, Segersvärd R, Rangelova E, et al. Cattell–Braasch maneuver combined with artery-first approach for superior mesenteric portal vein resection during pancreatectomy. J Gastrointest Surg 2015; 19:2264–2268.

[11]. Beltrame V, Gruppo M, Pedrazzoli S, et al. Mesenteric-portal vein Resection during pancreatectomy for pancreatic cancer. Gastroenterol Res Pract 2015; 2015:1–5.

[12]. Ravikumar R, Sabin C, Hilal MA, et al. Portal vein resection in borderline resectable pancreatic cancer: a United Kingdom multicenter study. J Am Coll Surg 2014; 218:401–411.

[13]. Delpero JR, Boher JM, Sauvanet A, et al. Pancreatic adenocarcinoma with venous involvement: is up-front synchronous portal-superior mesenteric vein resection still justified? A survey of the Association Française de Chirurgie. Ann Surg Oncol 2015; 22:1874–1883.

[14]. Mellon EA, Strom TJ, Hoffe SE, et al. Favorable perioperative outcomes after resection of borderline resectable pancreatic cancer treated with neoadjuvant stereotactic radiation and chemotherapy compared with upfront pancreatectomy for resectable cancer. J Gastrointest Oncol2016; 7:547–555.

[15]. Reni M, Zanon S, Balzano G, et al. Selecting patients for resection after primary chemotherapy for non-metastatic pancreatic adenocarcinoma. Ann Oncol 2017; 28:2786–2792.

[16]. Mollberg N, Rahbari NN, Koch M, et al. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and metaanalysis. Ann Surg 2011;254:882–893.

[17]. Sugiura T, Okamura Y, Ito T, et al. Surgical indications of distal pancreatectomy with celiac axis resection for pancreatic body/tail cancer. World J Surg 2017; 41:258–266.

[18]. Klompmaker S, van Hilst J, Gerritsen SL, et al. Outcomes after distal pancreatectomy with celiac axis resection for pancreatic cancer: a pan-European retrospective cohort study. Ann Surg Oncol 2018; 25:1440–1447.

[19]. Nakamura T, Hirano S, Noji T, et al. Distal pancreatectomy with en bloc celiac axis resection (modified Appleby procedure) for locally advanced pancreatic body cancer: a single-center review of 80 consecutive patients. Ann Surg Oncol 2016; 23 (S5):969–975.

[20]. Okada K-I, KawaiM, Tani M, et al. Preservation of the left gastric artery on the basis of anatomical features in patients undergoing distal pancreatectomy with celiac axis en-bloc resection (DP-CAR). World J Surg 2014; 38:2980–2985.

[21]. Sato T, Inoue Y, Takahashi Y, et al. Distal pancreatectomy with celiac axis resection combined with reconstruction of the left gastric artery. J Gastrointest Surg 2017; 21:910–917.

[22]. Glebova NO, Hicks CW, Tosoian JJ, et al. Outcomes of arterial resection during pancreatectomy for tumor. J Vasc Surg 2016; 63:722–729.e1.

[23]. Miyazaki M, Yoshitomi H, Takano S, et al. Combined hepatic arterial resection in pancreatic resections for locally advanced pancreatic cancer. Langenbecks Arch Surg 2017; 402:447–456.

[24]. Jegatheeswaran S, Baltatzis M, Jamdar S, et al. Superior mesenteric artery (SMA) resection during pancreatectomy for malignant disease of the pancreas: a systematic review. HPB 2017; 19:483–490.

[25]. LimKH, Chung E, Khan A, Cao D, Linehan D, Ben-JosefE, et al. Neoadjuvant therapy of pancreatic cancer: the emerging paradigm? Oncologist. (2012) 17:192–200.

[26]. van Tienhoven G, Versteijne E, Suker M, Groothuis KBC, Busch OR, Bonsing BA, et al. Preoperative chemoradiotherapy potentially improves outcome for (borderline) resectable pancreatic cancer: preliminary results of the Dutch randomized phase III PREOPANC trial. Int J Rad Oncol Biol Phys. (2018) 102:1606–1167.

[27]. Carrere N, Sauvanet A, Goere D et al. Pancreaticoduodenectomy with mesentericoportal vein resection for adenocarcinoma of the pancreatic head. World J. Surg. 2006; 30: 1526–1535.

[28]. Riediger H, Makowiec F, Fischer E, Adam U, Hopt UT. Postoperative morbidity and long-term survival after pancreaticoduodenectomy with superior mesenterico-portal vein resection. J. Gastrointest. Surg. 2006; 10.

[29]. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-2012.

[30]. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019140206.

[31]. Klompmaker S, van Hilst J, Gerritsen SL, Adham M, Quer MTA, Bassi C, et al. Outcomes after distal pancreatectomy with celiac axis resection for pancreatic cancer: a pan-European retrospective cohort study. Ann Surg Oncol. 2018;25(5):1440-1447.

[32]. Takahashi, Y., Kaneoka, Y., Maeda, A., & Isogai, M. (2011). Distal Pancreatectomy with Celiac Axis Resection for Carcinoma of the Body and Tail of the Pancreas. World Journal of Surgery, 35(11), 2535–2542.

[33]. Yamamoto Y, Sakamoto Y, Ban D, Shimada K, Esaki M, Nara S, et al. Is celiac axis resection justified for T4 pancreatic body cancer? Surgery. 2012;151(1):61-69.

[34]. Addeo P, Rosso E, Fuchshuber P, Oussoultzoglou E, De Blasi V, Simone G, et al. Resection of Borderline Resectable and Locally Advanced Pancreatic Adenocarcinomas after Neoadjuvant Chemotherapy. Oncology. 2015;89(1):37-46.17.

[35]. Rehders A, Stoecklein NH, Guray A, Riediger R, Alexander A, Knoefel WT. Vascular invasion in pancreatic cancer: tumor biology or tumor topography? Surgery. 2012;152(3 Suppl 1):S143-151.

[36]. Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016.

[37]. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-213.

[38]. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138(1):8-13.

[39]. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142(5):761-768.

[40]. Green S, Higgins J, Alderson P, Clarke M, Mulrow C, Oxman A. Cochrane handbook for systematic reviews of interventions. West Sussex, England: John Wiley & Sons Ltd. 2008.

[41]. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13.

[42]. Amano R, Kimura K, Nakata B, Yamazoe S, Motomura H, Yamamoto A, et al. Pancreatectomy with major arterial resection after neoadjuvant chemoradiotherapy gemcitabine and S-1 and concurrent radiotherapy for locally advanced unresectable pancreatic cancer. Surgery. 2015;158(1):191-200.

[43]. Bachellier P, Addeo P, Faitot F, Nappo G, Dufour P. Pancreatectomy With Arterial Resection for Pancreatic Adenocarcinoma: How Can It Be Done Safely and With Which Outcomes?: A Single Institution's Experience With 118 Patients. Ann Surg. 2018.

[44]. Baumgartner JM, Krasinskas A, Daouadi M, Zureikat A, Marsh W, Lee K, et al. Distal pancreatectomy with en bloc celiac axis resection for locally advanced pancreatic adenocarcinoma following neoadjuvant therapy. J Gastrointest Surg. 2012;16(6):1152-1159.

[45]. Beane JD, House MG, Pitt SC, Kilbane EM, Hall BL, Parmar AD, et al. Distal pancreatectomy with celiac axis resection: what are the added risks? HPB (Oxford). 2015;17(9):777-7784.

[46]. Cesaretti M, Abdel-Rehim M, Barbier L, Dokmak S, Hammel P, Sauvanet A. Modified Appleby procedure for borderline resectable/locally advanced distal pancreatic adenocarcinoma: A major procedure for selected patients. J Visc Surg. 2016;153(3):173-181.

[47]. Christians KK, Pilgrim CH, Tsai S, Ritch P, George B, Erickson B, et al. Arterial resection at the time of pancreatectomy for cancer. Surgery. 2014;155(5):919-926.

[48]. Ham, H., Kim, S. G., Kwon, H. J., Ha, H., & Choi, Y. Y. (2015). Distal pancreatectomy with celiac axis resection for pancreatic body and tail cancer invading celiac axis. Annals of Surgical Treatment and Research, 89(4), 167–175.

[49]. Jing W, Zhu G, Hu X, Jing G, Shao C, Zhou Y, et al. Distal pancreatectomy with en bloc celiac axis resection for the treatment of locally advanced pancreatic body and tail cancer. Hepatogastroenterology. 2013;60(121):187-190.

[50]. Loveday BPT, Zilbert N, Serrano PE, Tomiyama K, Tremblay A, Fox AM, et al. Neoadjuvant therapy and major arterial resection for potentially reconstructable arterial involvement by stage 3 adenocarcinoma of the pancreas. HPB (Oxford). 2019;21(6):643-652.

[51]. Miura T, Hirano S, Nakamura T, Tanaka E, Shichinohe T, Tsuchikawa T, et al. A new preoperative prognostic scoring system to predict prognosis in patients with locally advanced pancreatic body cancer who undergo distal pancreatectomy with en bloc celiac axis resection: a retrospective cohort study. Surgery. 2014;155(3):457-467.

[52]. Ocuin LM, Miller-Ocuin JL, Novak SM, Bartlett DL, Marsh JW, Tsung A, et al. Robotic and open distal pancreatectomy with celiac axis resection for locally advanced pancreatic body tumors: a single institutional assessment of perioperative outcomes and survival. HPB (Oxford). 2016;18(10):835-842.

[53]. Okada K, Kawai M, Tani M, Hirono S, Miyazawa M, Shimizu A, et al. Surgical strategy for patients with pancreatic body/tail carcinoma: who should undergo distal pancreatectomy with en-bloc celiac axis resection? Surgery. 2013;153(3):365-372.

[54]. Perinel J, Nappo G, El Bechwaty M, Walter T, Hervieu V, Valette PJ, et al. Locally advanced pancreatic duct adenocarcinoma: pancreatectomy with planned arterial resection based on axial arterial encasement. Langenbecks Arch Surg. 2016;401(8):1131-1142.

[55]. Peters NA, Javed AA, Cameron JL, Makary MA, Hirose K, Pawlik TM, et al. Modified Appleby Procedure for Pancreatic Adenocarcinoma: Does Improved Neoadjuvant Therapy Warrant Such an Aggressive Approach? Ann Surg Oncol. 2016;23(11):3757-3764.

[56]. Sakuraba M, Miyamoto S, Nagamatsu S, Kayano S, Taji M, Kinoshita T, et al. Hepatic artery reconstruction following ablative surgery for hepatobiliary and pancreatic malignancies. Eur J Surg Oncol. 2012;38(7):580-585.

[57]. Sato, T., Saiura, A., Inoue, Y., Takahashi, Y., Arita, J., & Takemura, N. (2016). Distal Pancreatectomy with En Bloc Resection of the Celiac Axis with Preservation or Reconstruction of the Left Gastric Artery in Patients with Pancreatic Body Cancer. World Journal of Surgery, 40(9), 2245–2253.

[58]. Tanaka E, Hirano S, Tsuchikawa T, Kato K, Matsumoto J, Shichinohe T. Important technical remarks on distal pancreatectomy with en-bloc celiac axis resection for locally advanced pancreatic body cancer (with video). J Hepatobiliary Pancreat Sci. 2012;19(2):141-

[59]. Tee MC, Krajewski AC, Groeschl RT, Farnell MB, Nagorney DM, Kendrick ML, et al. Indications and Perioperative Outcomes for Pancreatectomy with Arterial Resection. J Am Coll Surg. 2018;227(2):255-269.

[60]. Ueda, A., Sakai, N., Yoshitomi, H., Furukawa, K., Takayashiki, T., Kuboki, S., … Ohtsuka, M. (2019). Is hepatic artery coil embolization useful in distal pancreatectomy with en bloc celiac axis resection for locally advanced pancreatic cancer? World Journal of Surgical Oncology, 17(1), 124.

[61]. Wang X, Dong Y, Jin J, Liu Q, Zhan Q, Chen H, et al. Efficacy of modified Appleby surgery: a benefit for elderly patients? J Surg Res. 2015;194(1):83-90.

[62]. Yoshitomi, H., Sakai, N., Kagawa, S., Takano, S., Ueda, A., Kato, A., … Ohtsuka, M. (2019). Feasibility and safety of distal pancreatectomy with en bloc celiac axis resection (DP-CAR) combined with neoadjuvant therapy for borderline resectable and unresectable pancreatic body/tail cancer. Langenbeck's Archives of Surgery, 404(4), 451–458.

[63]. Zhou YM, Zhang XF, Li XD, Liu XB, Wu LP, Li B. Distal pancreatectomy with en bloc celiac axis resection for pancreatic body-tail cancer: Is it justified? Med Sci Monit. 2014;20:1-5.

[64]. Klompmaker S, de Rooij T, Korteweg JJ, van Dieren S, van Lienden KP, van Gulik TM, et al. Systematic review of outcomes after distal pancreatectomy with coeliac axis resection for locally advanced pancreatic cancer. BJS. 2016;103(8):941-949.

[65]. Kurtoglu M, Schlitter AM, Goklemez S, Budeyri I, Tesfay T, Gurses B, et al. Obstructive pancreatitis is a stronger fibrogenic stimulus than cancer-specific stellate cell activation in pancreatic ductal adenocarcinoma. Pancreatology. 2016;3(16):S36-S7.

[66]. Gong H, Ma R, Gong J, Cai C, Song Z, Xu B. Distal pancreatectomy with en bloc celiac axis resection for locally advanced pancreatic cancer: a systematic review and meta-analysis. Medicine. 2016;95(10).

[67]. Latenstein, A. E. J., van der Geest, L. G. M., Bonsing, B. A., Groot Koerkamp, B., Haj Mohammad, N., de Hingh, I. H. J. T., … Wilmink, J. W. (2020). Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma. European Journal of Cancer, 125, 83–93.

[68]. T. Hackert, M. Sachsenmaier, U. Hinz, L. Schneider, C.W. Michalski, C. Springfeld, et al. Locally advanced pancreatic cancer: neoadjuvant therapy with folfirinox results in resectability in 60% of the patients Ann. Surg., 264 (3) (2016), pp. 457-463

[69]. Kluger MD, Rashid MF, Rosario VL, Schrope BA, Steinman JA, Hecht EM, et al. Resection of locally advanced pancreatic cancer without regression of arterial encasement after modern-era neoadjuvant therapy. J Gastrointest Surg. 2018;22(2):235-241.

[70]. C.R. Ferrone, G. Marchegiani, Hong T.S., D.P. Ryan, V. Deshpande, EI McDonnell, et al. Radiological and surgical implications of neoadjuvant treatment with folfirinox for locally advanced and borderline resectable pancreatic cancer. Ann Surg, 261 (1) (2015), pp. 12-17

[71]. Sunami Y, Rebelo A, Kleeff J. Lipid metabolism and lipid droplets in pancreatic cancer and stellate cells. Cancers (Basel). 2017;10(1):3.

[72]. P. Hammel, F. Huguet, J.L. van Laethem, D. Goldstein, B. Glimelius, P. Artru, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 Randomized Clinical Trial. Jama, 315 (17) (2016), pp. 1844-1853

[73]. M. Suker, Nuyttens J.J., FALM. Eskens, BCM. Haberkorn, PPLO. Coene, E. van der Harst, et al. Efficacy and feasibility of stereotactic radiotherapy after folfirinox in patients with locally advanced pancreatic cancer (LAPC-1 trial). EClin Med, 17 (C) (2019), Article 100200

[74]. R.J. Vidri, A.O. Vogt, D.C. Macgillivray, I.J. Bristol, T.L Fitzgerald. Better defining the role of total neoadjuvant radiation: changing paradigms in locally advanced pancreatic cancer. Ann Surg Oncol, 26 (11) (2019), pp. 3701-3708.

[75]. https://clinicaltrials.gov/ct2/history/NCT04136769?A=1&B=3&C=merged.

[76]. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, et al. Pancreatic cancer. Nature reviews Disease primers. 2016;2:16022.

[77]. Halbrook CJ, Lyssiotis CA. Employing metabolism to improve the diagnosis and treatment of pancreatic cancer. Cancer Cell. 2017;31(1):5-19.

[78]. Michiels, S., Piedbois, P., Burdett, S., Syz, N., Stewart, L., & Pignon, J. (2005). Meta-analysis when only the median survival times are known: A comparison with individual patient data results. International Journal of Technology Assessment in Health Care, 21(1), 119-125.

Illustrations by Paula Vieira

8. Thesis

1. Pancreatic cancer is a devastating disease. Selecting patients with borderline pancreatic cancer that benefit from a surgical resection is still a challenge. The aggressive biology makes it difficult to diagnose pancreatic cancer at an early stage without metastatic or not detected microscopic metastatic disease. Neoadjuvant therapy has proven to play an important role regarding the outcome of these patients.

2. Arterial resections were not associated with significantly higher mortality and morbidity. However, probably owing to more aggressive tumor biology, patients undergoing arterial resection had a shorter survival than patients who did not require arterial resection.

3. Arterial resections/reconstructions may be helpful in select cases—particularly after neoadjuvant treatment. Further studies will be needed to better define the value of such extensive operations in the era of aggressive multimodal treatment.

Publications

This Thesis was partially published on following articles:

1- Rebelo A, Michalski CW, Ukkat J, Kleeff J. Pancreatic cancer surgery with vascular resection: current concepts and perspectives. J Pancreatol 2019;2:1–5. doi: 10.1097/JP9.0000000000000013

2- Rebelo A, Büdeyri I., Heckler M., Partsakashvili J., Ronellenfitsch U., Ukkat J., Kleeff J., Michalski C., Systematic Review and Meta-Analysis of Contemporary Pancreas Surgery with Arterial Resection – *submitted to publication*

Declaration - Selbständigkeitserklärung

Ich erkläre hiermit, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe der Quelle gekennzeichnet. Die Regeln zur Sicherung guter wissenschaftlicher Praxis wurden beachtet.

Ich versichere, dass ich für die inhaltliche Erstellung der vorliegenden Arbeit nicht die entgeltliche Hilfe von Vermittlungs- und Beratungsdiensten (Promotionsberater oder andere Personen) in Anspruch genommen habe. Niemand hat von mir unmittelbar oder mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen.

Halle (Saale), den

Artur Rebelo

Erklärung über frühere Promotionsversuche

Die Arbeit wurde bisher weder im In- noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Weiterhin erkläre ich, dass frühere Promotionsversuche mit der gleichen oder einer anderen Dissertation nicht erfolgt sind.

Halle (Saale), den

Artur Rebelo

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