Do arterial resections improve survival in pancreatic cancer?—a narrative review

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Objective: In this article, we outline the important features of pancreatic cancer surgery in cases with visceral artery encasement.

Background: Despite recent advances in diagnosis and treatment, pancreatic cancer continues to have a poor prognosis. Due to its limited response to chemotherapies, radiation, or targeted therapies, surgery (in combination with adjuvant chemotherapy) is the only potential way to treat pancreatic cancer in a curative manner. As only about 20% of the patients have surgically resectable disease at the time of diagnosis, the resection of encased visceral veins and arteries, along with neoadjuvant regimens, is one approach to treat otherwise palliative patients.

Methods: Based on a selective literature review, we discuss the results of several studies and meta-analyses, comparing the mortality and morbidity, as well as long-term survival in patients undergoing arterial resection vs standard treatment. We conducted a selective literature review in PubMed without restrictions regarding time of publication or study design. Only articles in English language were selected.

Conclusions: Several studies and meta-analyses comparing resection with and without arterial resection and reconstruction showed a significantly higher post-operative mortality and morbidity and shorter long-term survival in patients who required arterial resection. In patients with tumors initially considered irresectable, the approach of neoadjuvant chemotherapy followed by resection with arterial reconstruction showed a significantly increased survival compared to palliative chemotherapy alone with acceptable postoperative morbidity. Tumor resection with arterial reconstruction following intensive preoperative chemotherapy (plus radiochemotherapy in some cases) should be considered in selected patients, as it can prolong survival and potentially lead to sustained freedom from tumor recurrence.

Keywords: Arterial resection; pancreatic cancer; pancreatic surgery; vascular

Introduction

Pancreatic cancer is one of the few tumor entities with further increasing incidence. Despite all the advances in modern medicine, it continues to have a poor prognosis. In 2020, pancreatic cancer accounted for 2.6% new cancer cases and 4.7% of cancer deaths worldwide, making it the seventh leading cause of cancer-related deaths (1). Although diagnosis and treatment have improved over the past years, the overall 5-year survival still remains at around 9% (2). The main difficulty in the treatment of

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pancreatic cancer lies in the late detection of most cases, due to the unspecific symptoms caused by it, the early local spreading through perineural and venous invasion, and its rapid (metastatic) progression (3). The generally poor response to chemotherapies, radiation, or targeted therapies marks another obstacle, making surgery (in combination with adjuvant chemotherapy) the only potential way to treat pancreatic cancer in a curative manner. At the time of diagnosis, only about 20% of patients have a surgically resectable disease (4). Along with neoadjuvant regimens, the resection of encased visceral veins and arteries in patients with borderline resectable or locally unresectable disease is one approach to treat otherwise palliative patients.

This literature review will provide an overview on current evidence regarding the staging and risk assessment of pancreatic cancer with arterial invasion, possible treatment options and their technical details, and their effect on relevant outcomes. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/cco-21-39).

Methods

We conducted a selective literature review in PubMed without restrictions regarding time of publication or study design. Only fully published articles in English language were selected.

Discussion

Staging of locally advanced pancreatic cancer with suspected arterial contact or invasion

Thin-sliced (maximum slice thickness 0.3 cm) multiphase computed tomography is the first-line imaging modality in diagnosing and staging pancreatic cancer and offers the best information concerning tumor resectability especially with regard to locally advanced tumors with suspected vascular tumor contact or invasion. Magnetic resonance tomography is usually reserved for liver imaging to confirm or rule out hepatic metastases, and for cases with equivocal findings in computed tomography (5). Positron emission tomography (PET) is also highly sensitive in diagnosing pancreatic masses, but lacks the resolution to adequately stage the disease and determine resectability with regard to adjacent vascular structures (6).

Laboratory findings are mostly unspecific for local tumor extension and vascular invasion. A tumor marker connected to pancreatic cancer is CA 19-9. Though it cannot be used

alone for diagnosis, it has a prognostic value and is helpful in monitoring the disease during and after treatment (7). In case of cholestasis due to other causes, however, CA 19-9 can be high without an underlying pancreatic cancer.

To complete staging postoperatively, histological work-up of the surgical specimen is necessary. It gives necessary information about the resection margins (R0–R2), grading (G1–G4) and histopathological type. Pancreatic ductal adenocarcinomas represent by far the largest group with about 90% of all pancreatic neoplasms (8).

General considerations for treatment

Curative treatment of pancreatic cancer is only possible by complete resection of the tumor and the regional lymph nodes. Complete (R0) resection margins are often difficult to achieve given the perineural growth pattern towards the retroperitoneum and surrounding major visceral arteries. While gross incomplete (R2) resection undoubtedly is associated with shorter survival, the relative benefit of R0 over microscopically incomplete (R1) resection has been a matter of debate. In earlier cohorts, a clear survival advantage for R0 over R1 resections could frequently not be shown. In hindsight, this is probably attributable to the heterogeneity of patients and resection approaches as well as differences in histopathological examination (9). Later studies on more homogenous cohorts showed that R0 resections improved survival compared with R1 resections, at least if the distance of tumor cells to the margin was >1 mm (9,10). Some analyses showed that achieving an R0 margin is particular important for pancreatic head and less so for pancreatic corpus and tail tumors (11). For carcinomas with extensive nodal metastases, an R0 resection might not be as important regarding survival compared to more limited disease (12,13).

Adjuvant chemotherapy has now become standard of care for virtually all stages of pancreatic adenocarcinoma resected in curative intent. While already less potent regimens such as 5-fluorouracil plus folinic acid or gemcitabine monotherapy have been shown to prolong survival (14), intensive combination therapy such as FOLFIRINOX is even more beneficial regarding survival. Consequently, it has become the standard of care at least for patients with an adequate postoperative performance status and no relevant co-morbidities precluding such a potentially toxic treatment (15). Yet, even for patients receiving adjuvant chemotherapy, R0 resection is important as it confers a survival benefit compared to R1 resection as demonstrated by a secondary analysis from a randomized controlled trial (16). This underlines that resection
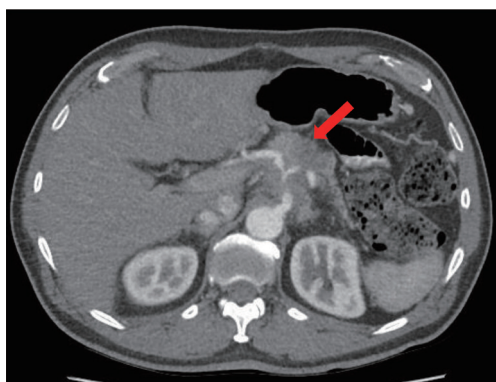
Figure 1 Irresectable pancreatic cancer, according to the international consensus classification (17). The tumor shows complete encasement of the celiac trunk (arrow).

of pancreatic cancer should only be attempted if there is a realistic chance of achieving tumor clearance.

Definition of resectability

A major obstacle to complete resection is the contact to or encasement of visceral arteries such as the celiac trunk (CT) or the superior mesenteric artery (SMA) by the tumor, which is present in up to 30% of patients at the time of diagnosis (17). An international consensus meeting developed a definition of when a tumor should be considered "borderline resectable" and when it should be considered irresectable (17). In terms of anatomy of the visceral arteries, the former is the case if there is a less than 180° tumor contact to the SMA or CT and no deformity or stenosis, or if there is isolated tumor contact to the common hepatic artery without contact to the SMA or the proper hepatic artery. More extensive arterial affection is considered irresectable according to this definition (*Figure 1*). A borderline resectable pancreatic carcinoma is still at a relevant risk that resection margins are microscopically (R1) or even grossly involved (R2) upon attempting resection. Therefore, neoadjuvant chemotherapy, ideally with an intensified regimen such as FOLFIRINOX or gemcitabine/nab-paclitaxel should be considered with the aim of increasing the probability of an R0 resection in these patients (18). Such resection will often require resection and reconstruction of visceral veins and arteries as outlined below.

Indication for arterial resection

For tumors considered irresectable by the above-mentioned definition, palliative chemotherapy, combined with biliary drainage procedures or gastroenterostomy if needed, has long

been the only treatment considered appropriate. However, also with the advent of more effective regimens like the ones used for neoadjuvant treatment, chemotherapy followed by an attempt to resect the tumor, has been proposed for selected patients. In such cases, complete resection can only be achieved by resection and reconstruction of visceral arteries. One novel approach, the feasibility of which is currently evaluated in an ongoing clinical trial (PREVADER, NCT04136769), is a therapeutic splitting. This means that visceral debranching, i.e., the reconstruction of visceral arteries invaded by the tumor for example with an iliac-hepatic or iliac-mesenteric bypass, is performed as a first treatment step. Patients then proceed to intensive combination chemotherapy before they finally undergo tumor resection (19).

Types of arterial resection and reconstruction

The visceral arteries that need to be resected in advanced pancreatic cancer if invaded, i.e., the SMA (*Figure 2*), and the common or proper hepatic artery as branches of the CT (*Figure 3*), are functional end arteries. For the common hepatic artery, this holds at least true in case of pancreatic head resection or total pancreatectomy with resection of the gastroduodenal artery, which could otherwise serve as collateral to maintain sufficient liver perfusion. Therefore, arterial reconstruction to ensure appropriate perfusion of the downstream organs liver and bowel is mandatory if visceral arteries are resected during pancreatic resection.

In case of suspected arterial invasion, surgery should start with the so-called "artery first" approach (20). This means that before carrying out irreversible steps of the operation mandating pancreatic resection, such as division of the pancreas, invasion of the respective arteries and the concomitant need for resection and reconstruction are assessed. The SMA can be approached from various directions (right and left supra- and inframesocolic, or through Kocher's maneuver), the choice of which should depend on the suspected site of involvement (21). Once the exact extent of invasion has been determined, the required resection and reconstruction can be decided on.

For short-segment invasions of up to two centimeters, resection with direct reconstruction by end-to-end anastomosis is usually possible if the ends of the resected artery have been sufficiently mobilized. However, excessive tension or kinking of the vessel needs to be strictly avoided in order to ensure patency. For longer-segment invasions, direct reconstruction is not possible. In such cases, an anatomic or, more frequently, extra-anatomic reconstruction needs
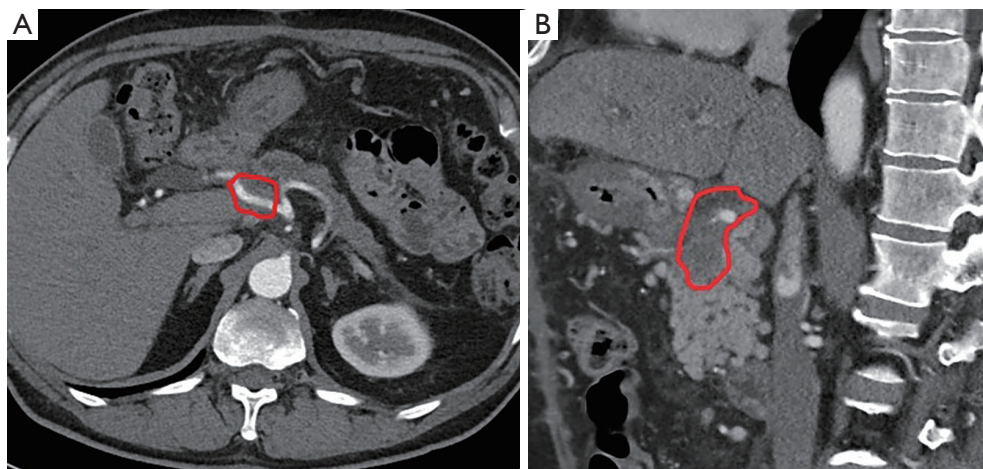
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Figure 2 Carcinoma of the pancreatic head with >180° encasement of the proper hepatic artery. Axial (A) and sagittal (B) computed tomography reconstructions, tumor encircled in red.
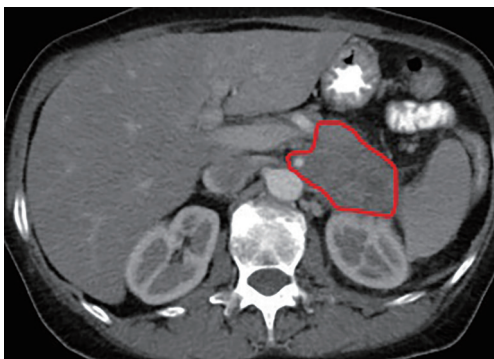

Figure 3 Large carcinoma of the pancreatic body and tail with >180° encasement of the superior mesenteric artery (axial computed tomography reconstruction, tumor encircled in red).

Figure 4 Multiplanar computed tomography reconstruction of a patient with an iliac-hepatic interposition graft (6 mm PTFE ring enforced, arrow) used to maintain liver perfusion following pancreatoduodenectomy.

to be performed. Usually, this requires using a graft, which can either consist of an autologous vein such as the greater saphenous or the internal jugular vein (22), or an allogeneic prosthesis usually made of polytetrafluoroethylene (PTFE) or polyethylene terephthalate (PET, Dacron). Alternatively, the patient's splenic artery could be used for reconstruction either by transposition if the root of the CA is not affected, or by harvesting and interposition. However, both approaches require total pancreatectomy and splenectomy in order to allow dissection and mobilization of the splenic artery (23). The use of autologous graft material bears the risk of graft infection and a higher risk of erosion bleeding compared to autologous grafts, particularly so in case of postoperative pancreatic fistula. Therefore, some authors recommend
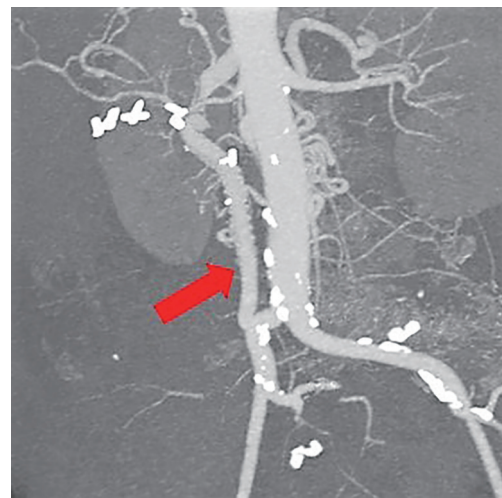
avoiding autologous material altogether or always performing total pancreatectomy if allogeneic grafts are used (21).

Anatomic reconstruction is carried out through an aorto-mesenteric or aorto-hepatic interposition or an interposition from the root of the resected visceral artery if this can be preserved with a sufficient length. This requires cross-clamping of the aorta in the renovisceral segment and can be technically demanding particularly in obese patients. Extra-anatomic reconstruction is most often done by allogeneous
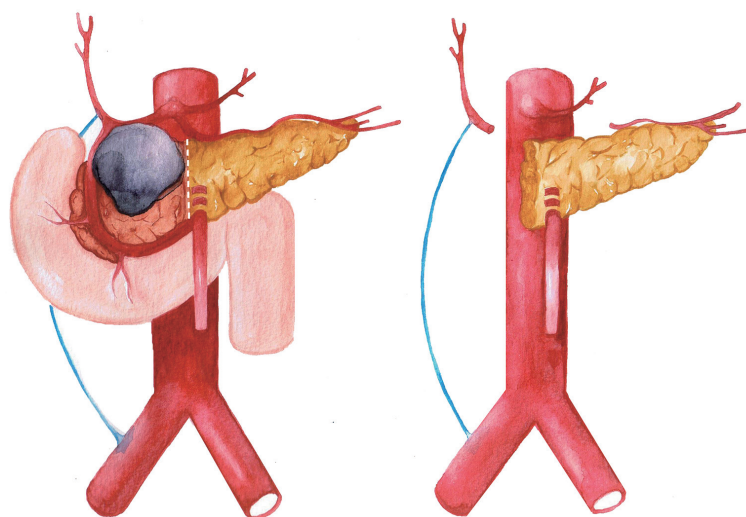
Figure 5 Illustration of a typical visceral debranching procedure: iliac-hepatic autologous vein bypass before (left) and after neoadjuvant chemotherapy and pancreatoduodenectomy (right) in a patient with a locally advanced carcinoma of the pancreatic head.
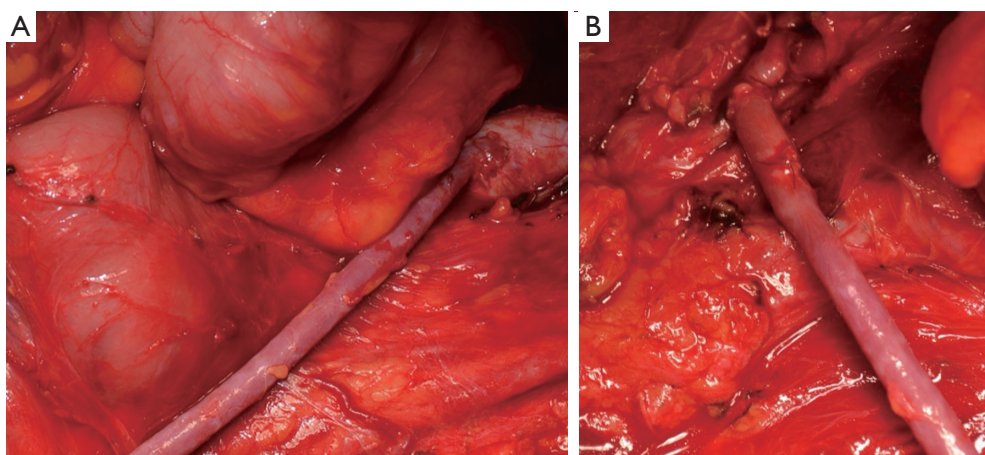

Figure 6 Iliac-hepatic autologous vein bypass using the greater saphenous vein: (A) iliac anastomosis, (B) hepatic anastomosis.

or autologous graft interposition from the infrarenal aorta or common iliac artery to the target visceral artery (*Figures 4-6*).

In the specific situation of distal pancreatectomy with CT resection, arterial resection without reconstruction can be done without compromising organ perfusion. This operation is sometimes referred to as "modified Appleby procedure" (24). The CT is resected at its origin eliminating antegrade flow to the common hepatic artery. Liver perfusion is maintained via gastroduodenal artery collateralisation. Intraoperatively, sufficient hepatic inflow should be ensured by Doppler sonographic flow measurement after test clamping of the common hepatic

artery. As a means to enhance gastroduodenal collateral flow, preoperative embolization of the CT or common hepatic artery is suggested by some authors, although there is no conclusive evidence that this approach indeed improves subsequent liver perfusion (25,26).

Short- and long-term outcomes

Arterial resections *vs.* standard surgery
Surgery for locally advanced pancreatic cancer with venous reconstruction can be performed with acceptable morbidity and mortality and is now widely established (27). In contrast,

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Table 1 Outcomes from studies on DP-CAR and SMA resection

Reference	Year	Study type	Type of surgery	Sample size	Mortality rate (%)	Morbidity rate (%)	Median survival (months)	1-year survival (%)	R0 rate (%)
Yamamoto et al. (31)	2018	Retrospective	DP-CAR	72	1.2	63	17.5	17	67
			DP	323	4.2	47	28.6	40	80
Peters et al. (32)	2016	Prospective	DP-CAR	17	0	5.9	20	75	82.4
			DP	51	0	21.6	19	85.2	92.2
Perinel et al. (33)	2016	Prospective	AR	14	0	14	92	55	57
			No AR	97	3	29	67	51	74
Klompmaker et al. (34)	2016	Retrospective	DP-CAR	240	3.5	27	14.4	–	74.5
Klompmaker et al. (35)	2018	Retrospective	DP-CAR	68	16	25	18	60	53

DP, distal pancreatectomy; CAR, celiac axis resection; AR, arterial resection; SMA, superior mesenteric artery.

Table 2 Outcomes from meta-analyses on arterial resection *vs.* standard resection

Reference	Year	Mortality	Morbidity	1-year survival
Mollberg et al. (36)	2011	OR 5.04; 95% CI, 2.69–9.45; P<0.0001	OR 2.17; 95% CI, 1.26–3.75; P=0.006	OR 3.02; 95% CI, 1.13–8.11; P=0.03
Jegatheeswaran et al. (37)	2017	20%	39% to 91%	–
Rebelo et al. (38)	2020	OR 2.55; 95% CI, 0.69, 9.42; P=0.16	OR 1.15; 95% CI, 0.58–2.28; P=0.69	OR 0.92; 95% CI, 0.41–2.09; P=0.85
Małczak et al. (39)	2020	RR 4.09; P<0.001	RR 1.4; P=0.01	–
Haines et al. (40)	2020	5%	52%	59%

the role of arterial resections in pancreatic surgery is still a matter of debate (28,29). They were associated with high mortality rates in the past (30). *Table 1* summarizes the outcomes of studies on arterial resections. In a retrospective study, 395 patients with pancreatic adenocarcinoma from seven high-volume centers in Japan who underwent distal pancreatectomy (DP) were investigated. Seventy-two patients underwent distal pancreatectomy with *en bloc* celiac axis resection (DP-CAR). The overall morbidity was significantly higher in the arterial resection group than in the standard group (63% *vs.* 47%, P=0.02). The median survival time of the standard group was significantly longer than that of the arterial group (28.6 *vs.* 17.5 months, P<0.01) (31). In a matched analysis of 17 patients who underwent DP-CAR were compared to 51 patients who underwent DP for pancreatic adenocarcinoma. Fifteen (88.2 %) patients who underwent DP-CAR had received neoadjuvant chemotherapy. The R0 resection rate was 82.4 % after DP-CAR versus 92.2 % after DP (P=0.36). Mortality, morbidity and median

survival were not different between both groups (32). Another single center study from a high-volume center in France involved 14 patients who underwent pancreatic oncologic surgery with arterial resection and 97 patients with standard resection. Morbidity and mortality were not significantly different between the arterial resection and standard group (14% *vs.* 29% and 0% *vs.* 3%), while R0 resection rate and 1-year survival were (57% *vs.* 74%, P<0.01 and 92% *vs.* 64%, not significant) (33). A systematic review by Klompmaker et al. analysed 240 patients who underwent DP-CAR combined with (neo-) adjuvant chemotherapy and found a 90-day mortality rate of 3.5%. The overall median survival for the whole patient collective was 14.4 months (34). A retrospective cohort study from the same group included 68 patients from 20 hospitals in 12 countries and reported 30- and 90-day mortality rates after DP-CAR of 10% and 16%, respectively (35).

The available evidence has been synthesized by several meta-analyses (*Table 2*). In 2011, Mollberg et al. described a

Table 3 Outcomes from studies comparing surgery to palliative treatments

Reference	Year	Study type	Study type	Mortality	Morbidity	1-year survival (%)	3-year survival (%)	5-year survival (%)	Overall survival
Satoi et al. (42)	2013	Retrospective	AR	–	–	95	53	34	–
			Palliative	–	–	88	18	10	–
Gong et al. (43)	2016	Systematic review and meta-analysis	AR vs. palliative	OR 1.80 (95% CI, 0.36–8.99)	OR 2.11 (95% CI, 0.83–5.35)	–	–	–	OR 0.38 (95% CI: 0.25–0.58, P<0.01)
Del Chiaro et al. (44)	2019	Retrospective	AR	2.9%	38.2%	63.7	41.7	3.2	–
			Palliative	2.6%	25.6%	23.4	23.4	0	–

AR, arterial resection.

high postoperative mortality after arterial resection (11.8%). Arterial resections were also related to increased morbidity (53.6%, OR: 2.17) and lower 1- and 3-year survival rates compared to patients without arterial resections (36). In 2017, Jegatheeswaran et al. performed a meta-analysis of the outcome of resection and reconstruction of the superior mesenteric artery (SMA) during surgery for pancreatic cancer. It included a total of 70 patients undergoing pancreatectomy with SMA resection and 10,726 undergoing the standard procedure. Peri-operative morbidity ranged from 39% to 91% and postoperative mortality was 20 % (data from 25 patients) with a median survival of 11 months (37).

In a meta-analysis from 2020, Rebelo et al. included all contemporary relevant studies regarding arterial resection and reconstruction. A qualitative analysis with 841 patients with arterial resection was performed. Morbidity and mortality were 66.8% and 5.4%, respectively, in patients undergoing arterial resection for pancreatic cancer. In the meta-analysis, 7 studies with a control group including patients undergoing standard resection were included. Overall morbidity and mortality were 48% vs. 39% and 3.2% vs. 1.5% in patients undergoing arterial resection vs.. patients without arterial resection. Weighted median survival was longer in patients who underwent a standard resection (32 vs. 18.6 months). Neoadjuvant treatment was associated with higher R0 resection rates and R0 rates were higher in the standard compared with the arterial resection group, both in patients without (69% vs. 89%) and with neoadjuvant treatment (50% vs. 86%) (38). In another meta-analysis from 2020, 19 studies were included in an analysis involving 2,710 patients. Arterial resection was associated with a higher risk of death (RR: 4.09; P<0.001) and morbidity (RR: 1.4; P=0.01) and a shorter long-term

survival (39). Also in 2020, Haines et al. performed a meta-analysis of 13 studies with 467 patients who underwent pancreatic surgery with arterial resection for pancreatic cancer. The median overall morbidity and 90-day mortality were 52% and 5%, respectively. The R0 rate was 66% and the median survival was 17 months with a 1- and 3-year survival of 59% and 17%, respectively (40).

Arterial resections vs. palliative treatments

According to a national cohort study from the Dutch Pancreatic Cancer Group involving 36,453 patients with pancreatic ductal carcinoma, the 1-year survival of patients who received palliative chemotherapy improved along the last years from 13.3% to 21.2% (P<0.001) (41). Therefore, it needs to be critically evaluated if arterial resection for locally advanced pancreatic cancer can in fact achieve longer overall survival. Table 3 shows outcomes from studies comparing surgery with arterial resection to palliative treatments. The Japanese Society of Hepato-Biliary-Pancreatic Surgery analysed 58 patients with initially unresectable PDAC who underwent 8 months of neoadjuvant treatment followed by surgery. The approach resulted in clearly improved survival times compared to a palliative approach. The overall survival rates at 1, 3, and 5 years were 95%, 53%, and 34% in the patients that underwent surgery and 88, 18, and 10% in the group with chemotherapy only. The survival time in the surgery group was significantly longer than in the chemotherapy group (P<0.001) (42). In a meta-analysis involving 18 studies, Gong et al. reported a higher 1-year survival rate for DP-CAR compared to palliative treatments (pooled HR for OS 0.38, 95% CI 0.25–0.58, P<0.01) (43). In 2019, Del Chiaro et al. analyzed 73 patients with borderline or locally

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advanced pancreatic cancer with arterial involvement. Thirty-four patients underwent an arterial resection and 39 underwent palliative surgery only. Post-operative mortality (2.9% *vs.* 2.6%) and morbidity (38.2% *vs.* 25.6%) were not significantly different. The 1-, 3- and 5-year survival in the palliative group was inferior to the patients who underwent arterial resection (63.7%, 23.4% and 23.4% *vs.* 41.7%, 3.2% and 0) (44).

Summary

Pancreatic cancer is despite all recent successes in diagnosis and treatment still a disease with high morbidity and short long-term survival. Potentially curative treatment is only possible with complete resection of the tumor and lymphonodal metastases, in combination with neoadjuvant and adjuvant chemotherapy. Studies have shown a significantly longer survival when R0 resection is achieved. One of the main obstacles to R0 resection is the partial or full encasement of visceral arteries by the tumor mass.

Several studies and meta-analyses comparing resection with and without arterial reconstruction showed a significantly higher post-operative mortality and morbidity and shorter long-term survival in patients who required arterial resection.

In patients whose tumors were initially considered irresectable, on the other hand, the approach of neoadjuvant chemotherapy followed by resection with arterial reconstruction showed a significantly increased survival compared to palliative chemotherapy. Single series comparing palliative surgery and resection with arterial reconstruction showed similar post-operative mortality and morbidity with higher 1-, 3- and 5-year survival rates after arterial resection.

In conclusion, resection with arterial reconstruction following intensive preoperative chemotherapy (in some cases plus radiochemotherapy) should be considered in selected patients because it can prolong survival and potentially lead to sustained freedom from tumor recurrence.

Acknowledgments

Footnote

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