Eur Surg
https://doi.org/10.1007/s10353-024-00830-5

european surgery
ACA Acta Chirurgica Austriaca

Intraoperative strategies and techniques to achieve surgical radicality in pancreatic cancer

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Received: 17 December 2023 / Accepted: 29 March 2024
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Summary The treatment of pancreatic cancer presents a challenging task in surgical oncology, demanding innovative approaches to achieve radical resection and improve patient outcomes. This article provides an overview of state-of-the-art surgical principles and techniques for achieving surgical radicality in localized pancreatic cancer, with a particular emphasis on artery-first approaches, the triangle operation, arterial and venous dissection techniques, including arterial divestment, and the significance of R0 resections with complete lymphadenectomy. By applying these techniques and principles of surgical radicality, surgeons are able to enhance resectability, minimize complications, and potentially extend patient survival in the rapidly evolving field of multimodal pancreatic cancer management.

Keywords Pancreatic cancer · Radicality · Resection margin · Lymphadenectomy · Surgical resection · Triangle · Arterial divestment · Vascular resection · Prognosis

Introduction

Pancreatic cancer (PDAC) is a highly aggressive disease and is characterized by its insidious nature, late diagnosis, and limited treatment options [1]. In the Western hemisphere, PDAC is the fourth leading cause of cancer-related death with a dismal prognosis and is predicted to become the second leading cause by 2030 [2, 3]. However, recent advances in medical research have led to the development of multimodal treatment approaches that combine several therapeutic modalities to improve patient outcomes [4].

Surgery plays a critical role in the multimodal management of PDAC, with the goal of removing the tumor and potentially curing the disease [5]. However, due to late-stage diagnosis and the aggressive nature of PDAC, surgical resection is often limited to a subset of patients who meet specific criteria. For those who undergo surgery, (neo-)adjuvant therapies are commonly employed to downsize the tumor or to target any residual cancer cells and reduce the risk of recurrence [6]. With this approach the oncological outcomes of PDAC patients with resectable or borderline-resectable disease have substantially improved over the past two decades [7–9]. The current 5-year survival in this subset of patients, which accounts for 25–30% of the entire PDAC cohort, is around 17% and increases with the use of adjuvant chemotherapy [10]. Moreover, in patients with favorable pathological determinants, the observed 5-year survival is 38% in node-negative patients and increases to over 50% in patients with a combination of favorable factors. Lastly, with the use of modern multiagent chemotherapies for initially unresectable or metastatic disease in the neoadjuvant setting, the percentage of patients with attempted surgery is increasing, with resection rates of 60% after treatment with FOLFIRINOX [11, 12]. As a result, the percentage of surgical candidates is constantly rising, and their treatment requires modern surgical techniques adapted to the challenges of resection of pancreatic cancer after neoadjuvant therapy (NAT; [13, 14]). Here, we focus mainly on intraoperative strategies to achieve surgical radicality in the era of multiagent therapies and provide a contemporaneous overview of current techniques to increase surgical outcomes for localized PDAC.

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Published online: 12 April 2024

Assessment of surgical resectability

In the past few years, several definitions of preoperative resectability have been provided with implications on treatment sequencing to either upfront surgery or NAT [6]. Most classifications are based on the anatomical extent of the primary tumor assessed by triphasic contrast-enhanced computed tomography (CT; [15]). In patients with tumors that have less than 180° contact with the portal vein or the superior mesenteric vein the tumor is classified as resectable [16, 17]. If the venous infiltration is more advanced (> 180°) or the tumor has contact with the celiac trunk (CT), common hepatic artery (CHA), or superior mesenteric artery (SMA) (< 180°) it is classified as borderline-resectable. Lastly, tumors with arterial infiltration (> 180°) or even encasement as well as unreconstructible venous infiltration are classified as locally advanced tumors. In addition, the classification of the International Association of Pancreatology (IAP) incorporates CA19-9 as a biological parameter, lymph node status, and the ECOG performance status [18]. According to the IAP, tumors are classified as borderline-resectable if CA19-9 values are greater than 500 U/mL, positive lymph nodes appear on positron emission tomography (PET) scans, or the ECOG status is ≥ 2, irrespective of the local tumor dimension.

Based on the anatomical/radiological resectability criteria, patients should undergo upfront surgery for resectable tumors or receive NAT for borderline-resectable and locally advanced tumors [19]. This treatment allocation assumes that NAT leads to (a) downstaging of the primary tumor; (b) biological selection of patients with response or at least without systemic progression during NAT, pointing to less aggressive tumor biology; and (c) an increased chance of achieving a R0 resection, which is associated with improved postresection survival [6]. While this approach has been widely accepted for locally advanced tumors, the ESPAC-5 trial suggested that NAT is also beneficial in patients with borderline-resectable disease [20]. Conversely, studies that investigated a NAT approach in resectable tumors failed to demonstrate a superiority of preoperative chemotherapy over immediate surgery [21, 22]. This was also shown in the recently published NORPACT-1 trial [23].

Once patients are scheduled for pancreatic resection, several surgical techniques must be considered depending on the anatomical tumor dimension, the relationship to the peripancreatic vessels, the tumor biology, and the patient's condition.

Dissection techniques to achieve surgical radicality

Several dissection techniques have been further improved from the classic medial-to-lateral approach after dissection of the pancreas at the level of the portal vein to increase resectability rates and surgical outcomes with tumor clearance of soft tissue along the CHA and the SMA [24]. This includes the artery-first approach to immediately determine arterial involvement before committing irreversible steps of the operation and to dissect the tumor along the SMA, as this margin is frequently infiltrated by tumor on final pathology studies [25, 26]. The artery-first approach can be carried out after a wide Kocher maneuver via an anterior, superior, right posterior, left posterior, medial uncinate, or mesenteric approach. Based on the tumor localization and the suspected vascular involvement, these approaches should be combined. In a meta-analysis published in 2018, it was shown that patients with artery-first versus standard pancreatic head resection experienced less blood loss, lower need for blood transfusion, and fewer postoperative complications, while the R0 rate and the overall survival were significantly higher [27]. After the artery-first maneuver, the pancreatic head is dissected from the SMA beginning at the uncinate process in a lateral-to-medial and posterior-to-anterior approach with the pancreatic tissue dissected at the end [28]. In addition, the term "mesopancreas" has gained wide acceptance although this is not a "true" meso but an anatomical space between the posterior surface of the pancreatic head to the mesenteric vessels with soft tissue, lymphatic, and neural structures, and which should be entirely dissected as it adds to the prognosis of PDAC patients (total mesopancreas excision; [29, 30]). The dissection of the mesopancreas can be carried out in different levels:

- Level I: Dividing the mesopancreas and leaving lymphatic and nerve tissue surrounding the SMA intact
- Level II: Removing systematically all lymph nodes along the SMA with dissection of inferior pancreaticoduodenal vessels
- Level III: Entire clearance of periarterial neurolymphatic tissues of the arterial wall from the right and posterior circumference of the SMA

We propose level III as the standard dissection plane for state-of-the-art pancreatic surgery.

In addition to artery-first approaches and level III dissection, the triangle operation has been recognized over the past 5 years [31]. As local recurrence frequently occurs in the preaortic region, clearance of the space between the CT (superior), the origin of the SMA (inferior) and the portal vein (anterior) has become standard for pancreatic resection. A recent study with more than 160 patients undergoing triangle dissection revealed no significant increase in postoperative morbidity and mortality compared to standard resections, while the number of harvested lymph nodes and the R0 rate were higher [32]. However, so far, no oncological follow-up exists. The results from the ongoing randomized controlled TRIANGLE trial will add to the evidence on this topic (German Clinical Trials Register DRKS00030576).

In patients with tumors of the pancreatic body and tail, the dissection should be carried out en bloc with a layer of retroperitoneal tissue, as tumors frequently infiltrate toward the renal fascia. This dissection method is known as radical antegrade modular pancreatosplenectomy (RAMPS; [33]). After ligation of the splenic vessels at their origin, the left circumference of the SMA is cleared and followed posteriorly. The pancreatic body and tail are dissected following a layer behind the anterior renal fascia (anterior RAMPS) or behind the adrenal gland (posterior RAMPS; [34]). Tumors infiltrating the celiac trunk represent a special subgroup of locally advanced tumors that can be addressed by a modified Appleby procedure after primary chemotherapy with distal pancreatectomy and celiac-axis resection (DP-CAR) without arterial reconstruction to achieve surgical radicality [35, 36].

Venous resections

Venous infiltration of the portomesenteric axis is a common feature in patients with PDAC, and portal vein (PV) resection can be carried out safely compared to standard resections [37, 38]. In general, preoperative CT scans have to be evaluated regarding the extent of infiltration, PV thrombosis, portal venous congestion, and cavernous transformation, as these features may determine surgical resectability as well as intraoperative blood loss. In patients with cavernous transformation, a venous bypass graft first between the superior mesenteric vein or its tributaries and the PV might be beneficial to ensure radical pancreatic surgery [39]. The majority of patients with portomesenteric vein involvement receive vascular resections without any bypass procedures and its extent depends on the venous infiltration (Figs. 1 and 2). The International Study Group of Pancreatic Surgery (ISGPS) classifies the reconstruction of the portomesenteric vein into four categories [15]: (1) partial venous resection with direct closure, (2) partial portal venous resection using a patch, (3) segmental resection with primary venous anastomosis (Figs. 1 and 2), (4) segmental resection with interposition graft. In a recent study with 694 PV resections, the authors showed that pancreas-specific complications and risk of thrombosis increasingly correlated with the type of reconstruction. However, if radical resection was achieved with negative resection margins, postresection survival was beneficial with a median of 23.3 months [40].

Besides the aforementioned resection techniques, gastric venous congestion may occur during resection of the portomesenteric confluence with dissection of the splenic vein to achieve surgical radicality. Usually, the venous blood drains through collaterals; however, several complications have been reported such as left-sided portal hypertension and gastric/splenic venous congestion, which is even more dangerous after total pancreatectomy [41, 42]. To avoid these complications, a splenorenal shunt for reconstruction may be performed to ensure venous drainage (Fig. 2). In a recent study, the authors demonstrated encouraging data on short- and long-term shunt patency in ten patients, while there were no signs of left-sided portal hypertension or gastrointestinal bleeding [43].

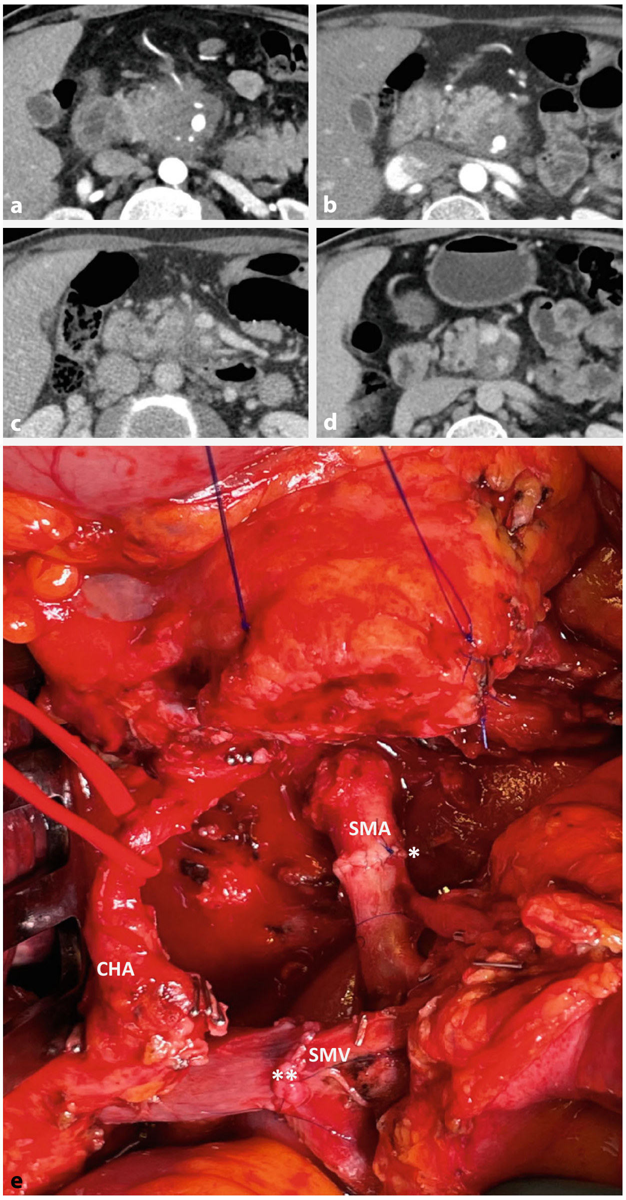

Fig. 1 Contrast-enhanced computed tomography scan of a 47-year-old patient with locally advanced pancreatic cancer with 360° encasement of the superior mesenteric artery (*SMA*) and occlusion of the portovenous axis before neoadjuvant chemotherapy (**a**, **b**) and with partial response according to the RECIST criteria after 6 cycles of FOLFIRINOX (**c**, **d**). Operative site (**e**) after extended tumor resection with artery-first approach, pancreatic head resection with resection of the SMA with end-to-end anastomosis (*), and resection of the portal venous confluence and superior mesenteric vein (*SMV*) with end-to-end anastomosis (**). Final pathology revealed ypT4, ypN2, R1 (<1 mm). *CHA* common hepatic artery

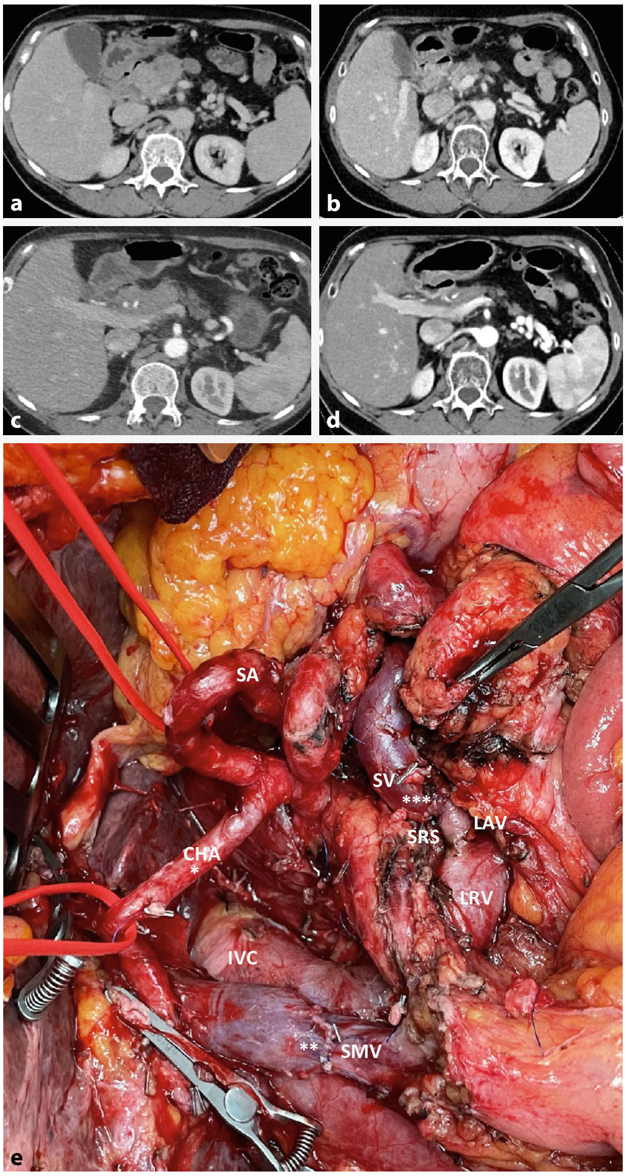

Fig. 2 Contrast-enhanced computed tomography scan of a 72-year-old patient with locally advanced pancreatic cancer with infiltration of the common hepatic artery (*CHA*) and portovenous axis before neoadjuvant chemotherapy (**a**, **b**) and with partial response according to the RECIST criteria after 6 cycles of FOLFIRINOX + intensity modulated radiotherapy (**c**, **d**). Operative site (**e**) after extended tumor resection with artery-first approach, pancreatic head resection, divestment of the common hepatic artery (*CHA**), portal venous confluence and superior mesenteric vein (*SMV*) resection with end-to-end anastomosis (**) and splenorenal shunt (here: anastomosis of splenic vein with left adrenal vein; ***). Final pathology revealed ypT1, ypN0, R0. *SA* splenic artery, *SRS* splenorenal shunt, *SV* splenic vein, *LAV* left adrenal vein, *LRV* left renal vein, *IVC* inferior vena cava

Arterial divestment or arterial resections

Arterial resections in patients with advanced pancreatic tumors have been associated with high morbidity and mortality and impaired oncological outcomes in the era of upfront resection for pancreatic cancer [44]. With the increase of NAT for some of these patients, the periarterial neurolymphatic tissue along the arterial wall can be removed by arterial divestment without the need for arterial resection to achieve complete tumor removal (Fig. 2; [45]). This is due to the fact that the tumor dissemination follows the periarterial sheet without actually infiltrating the arterial wall, and the effect of NAT results in a fibrotic devitalized periarterial sheet [46]. The cold dissection technique is carried out by entering a plane between the arterial wall and the residual tumor tissue to clear the cuff of the vessel [47]. Usually, this plane is situated between the periarterial nerve plexus and the tunica adventitia. It is recommended to take frozen sections of these specimens, and if positive, reevaluate the effectiveness of arterial divestment or pursue with arterial resection. Initial results demonstrated encouraging data on the feasibility and patient safety [46, 48].

If the arterial tumor infiltration is beyond the adventitial layer, arterial resection may be performed [45]. In cases of short segment infiltration of the artery, an end-to-end anastomosis is recommended after segmental resection (Fig. 1). Larger infiltration of the celiac axis or the SMA require graft interposition (venous graft; vascular allografts or PTFE prothesis) or transposition of the splenic artery.

The importance of R0 resections and radical lymphadenectomy

The resection margin status (R status) serves as a crucial indicator of surgical radicality and a significant prognostic factor influenced by surgical quality [4]. Recent studies and guidelines have emphasized an R status with the prerequisite of a 1-mm tumor-free margin for a true R0 resection [49]. In 2014, the ISGPS published consensus definitions, supporting the report of seven distinct margins with a 1-mm free margin; however, there is a large heterogeneity of reported R0 rates between centers, which make the comparability of studies challenging [15]. A systematic review and meta-analysis of 19 studies revealed substantial variation in reported R0 and R1 rates, emphasizing the need for consistent definitions to assess the prognostic significance of the R status [50]. In two large studies the benefit of achieving a true R0 resection in the upfront setting with adjuvant therapy was demonstrated: First, for pancreatic head tumors with 561 patients [51]. In this study, 112 patients had a true R0 resection, 123 had an R1 resection of < 1 mm, and 326 had R1 resections with direct margin involvement. The corresponding 5-year survival rates were 37%, 30%, and 20%, respectively. Furthermore, in patients with a pN0, R0 resection, the 5-year survival was 62%. The second study for tumors located in the pancreatic body or tail showed an even higher survival advantage with an R0 resection (23%; [52]). These patients had a 5-year survival rate of 62% in comparison with patients with R1 < 1 mm and R1 direct resections who had survival rates of 16% and 13%, respectively.

More recently, the importance of achieving an R0 resection was also demonstrated for the emerging cohort of patients with previous NAT. A bicentric study from Vienna and Boston highlighted the importance of an R0 resection based on a 1-mm rule in 357 patients [53]. More than 272 patients (76%) achieved an R0 resection while 24% had an R1 resection. The median overall survival was 41 months after R0 resection in comparison with 20 months after R1 resection. Moreover, the R0 status was confirmed as an independent predictor of overall survival, which was recently also confirmed in a meta-analysis on this topic [54]. Therefore, achieving an R0 resection is the foremost goal of surgical strategies to achieve surgical radicality in PDAC patients with or without NAT.

Regarding the extent of lymphadenectomy in PDAC, the current evidence endorses a thorough locoregional lymphadenectomy as recommended by the ISGPS [55]. In line with these recommendations, a study of the prognostic relevance of lymph node dissection in 811 patients undergoing pancreatic head resection demonstrated the importance of several prognostic categories dependent on the number of harvested lymph nodes [56]. In this study, patients with one lymph node metastasis had an improved survival in comparison with patients who had a higher number of positive lymph nodes, ranging from 31 months to 18 months. Strikingly, the updated 8th edition of the American Joint Committee on Cancer incorporated a refined staging of lymph node metastasis with different categories for an improved TNM staging in pancreatic cancer [57].

However, it is important to note that performing an extended retroperitoneal lymphadenectomy, such as paracaval, interaortocaval, or para-aortic lymphadenectomy, as a routine procedure is not advisable, as it fails to enhance overall survival and could potentially lead to increased complications in unselected patients [58]. Instead, the consideration for extended lymphadenectomy should be reserved for specific cases where lymph node metastases in these regions are suspected during upfront resections or following NAT. Furthermore, in instances of isolated lymph node recurrences detected during surveillance, surgical re-resection may be a viable option [59].

Conclusion

The management of pancreatic cancer has undergone significant advancements over the past few years, particularly in the era of multimodal therapies. Surgery remains a critical component of multimodal therapy, and the cornerstone of potentially curative therapy aiming at radical resection. This review article highlights key considerations, including accurate assessment of resectability, innovative dissection techniques, management of venous and arterial involvement, and the importance of achieving R0 resections. These evolving surgical strategies are crucial in improving resectability, reducing complications, and extending survival in patients with pancreatic cancer.

Funding Open access funding provided by Medical University of Vienna.

Conflict of interest T. Hank, C. Leonhardt, U. Klaiber and O. Strobel declare that they have no competing interests.

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