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SSAT DEBATE

2021 SSAT Debate: Selective Approach to Resection of the Superior Mesenteric Artery in Pancreatic Cancer vs Superior Mesenteric Artery Encasement Is Not an Absolute Contraindication for Surgery in Pancreatic Cancer

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Overview

This manuscript summarizes an excellent debate from the 2021 SSAT/Pancreas Club symposium on arterial resection in pancreas cancer. Two world-recognized experts, Professor Ugo Boggi from Pisa, IT, and Dr. Mark Truty from the Mayo Clinic in Rochester, MN, offered their views on the role of arterial resection in locally advanced pancreas ductal adenocarcinoma. Both speakers have extensive experience pushing the technical envelope with extended vascular resection in pancreatectomy. However, both highlight important concepts of resectability extending well beyond technique: namely, patient global physiology, tumor biology, and response to chemotherapy. The debate was spirited, and this subsequent review is an excellent look at the status quo. N. J. Zyromski, MD, Indianpolis, IN, November, 2021.

Introduction

Our group (Professor Boggi, Pisa IT) started performing pancreatectomy with vein resection in the mid-1980s and, after some practice, evolved to resect also arterial segments. The initial experience (1987–2004) was reported in 2009. On a total of 110 pancreatectomies for pancreatic cancer, 84 patients received an isolated vein resection, 12 patients an isolated arterial resection, and 14 patients a combined resection of an arterial and a venous segment. Resected arteries included 6 superior mesenteric arteries (SMA), 12 celiac trunks (CT), and 15 hepatic arteries (HA). We showed that combined arterial and venous resection increased post-operative complications without a survival advantage when compared to palliation. Despite most procedures were performed upfront (107/110: 97.2%), and only one-third of the patients received adjuvant treatments (39/110; 35.4%), we showed that the risk of death due to cancer recurrence was 2.2-fold higher in patients who did not receive chemotherapy [1].

With the advent of effective chemotherapy regimens [2], we revived our interest in arterial resections. In this modern experience, 90-day post-operative mortality declined from > 10 to 3.3% [3], and median overall survival doubled from 8 to 19 months [1, 3]. However, despite a rigorous selection process, some patients still had short median survival times (16.0 months) while other patients enjoyed relatively long median survival times (39.0 months) [3]. Some patients are currently disease-free more than 5 years after surgery.

General Considerations on SMA Resection

Technical complexity of pancreatectomy with SMA resection appears to be higher than that of pancreatectomy with CT/HA resection due to several reasons. First, SMA always requires arterial reconstruction [1, 4–6] and sometimes multiple arterial and venous branches of the superior mesenteric vessels need to be reconstructed (Fig. 1). Second, in nearly all patients, SMA resection is associated with superior mesenteric vein (SMV) resection. In approximately one-quarter of the patients, the SMV is occluded, thus posing additional technical problems [5]. Third, most tumors requiring SMA resection are located in the uncinated process and therefore require at least a pancreatoduodenectomy, while in many

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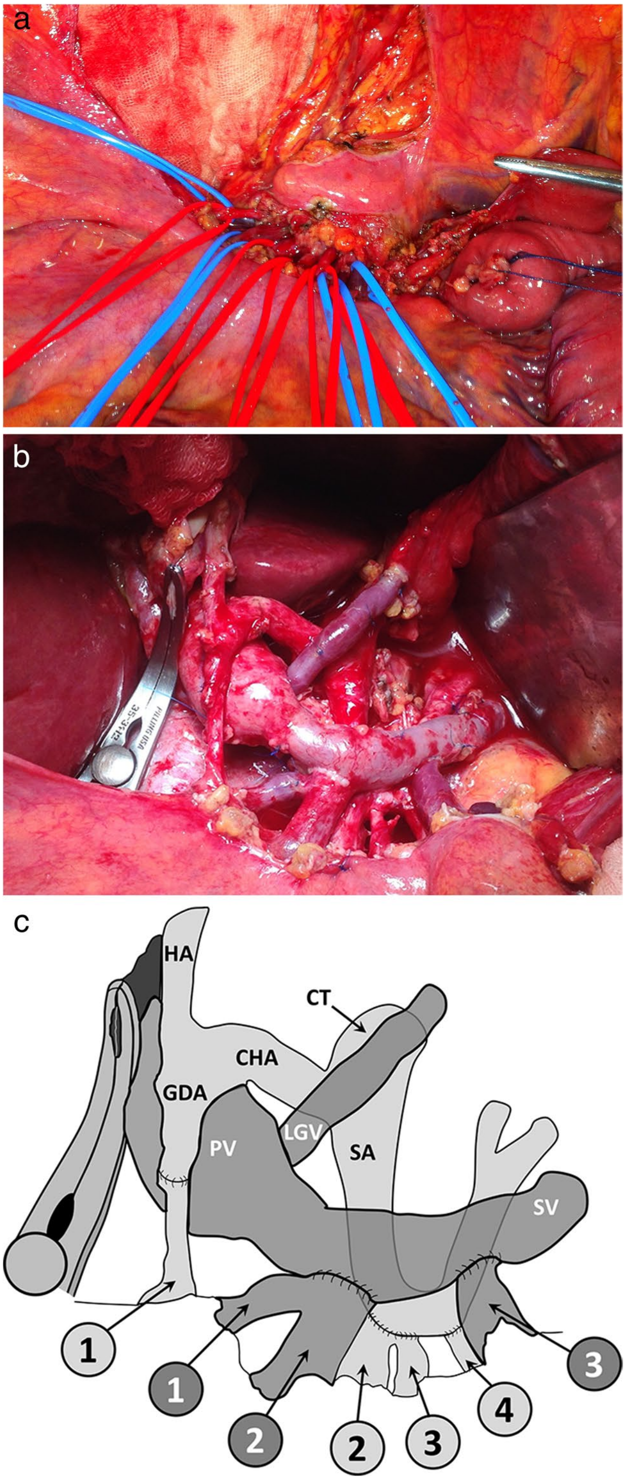


Fig. 1 Resection and reconstruction of multiple SMA and SMV branches. **1a** Four SMV branches (each tagged with a blue loop) and 5 SMA branches (each tagged with a red loop) are encircled in preparation for en bloc resection and reconstruction. **1b** After total pancreatectomy with preservation of the splenic vessels, 3 venous branches and 4 arterial branches anastomosed end-to-side to the splenic vessels. One arterial branch is anastomosed end-to-end to the stump of the gastroduodenal artery. **1c** Drawing for interpretation. Numbers in light gray circles show reconstructed arterial branches. Numbers in dark gray circles show reconstructed venous branches. CHA, common hepatic artery; CT, celiac trunk; HA, hepatic artery; LGV, left gastric vein; GDA, gastroduodenal artery; PV, portal vein; SA, splenic artery; SV, splenic vein

patients with CT/HA involvement, the pancreatic head can be spared. Fourth, temporary SMA/SMV cross-clamping is associated with intestinal ischemia/reperfusion injury [7] that may impair renal [8], pulmonary [9], and heart [10] functions, affects gut permeability [11], and reduces integrity of intestinal barrier thus facilitating bacterial translocations [7]. The systemic consequences of CT/HA resection are often less evident.

Technical Contraindications to SMA Resection

Pancreatic resection remains the backbone of all multimodality treatments of pancreatic cancer with curative intention. Although technical aspects are just one of the factors to be considered when deciding about a pancreatic resection, it is clear that feasibility is essential to include surgery among treatment options. SMA resection is a rare procedure [12]. Resection of multiple arterial segments is even more rare.

Provided that the tumor is resectable in all other respects, we consider SMA resection technically contraindicated when either SMA or SMV is not reconstructible. On the arterial side, this may result from involvement of the SMA at the aortic origin or deeply in the root of the mesentery (second-order branches). To verify these key issues, we immediately proceed with a Cattell Braasch maneuver and dissect the origin of the SMA and arterial (and venous) branches in the mesenteric root (Fig. 2). In patients with portal cavernomatosis, we also verify the presence of a patent portal segment in the hepatic hilum before proceeding with resection (Fig. 3a, b). Indeed, in most patients, impossibility to restore/preserve portal circulation, rather than inability to reconstruct the SMA, contraindicates surgical resection from a technical point of view. When the SMV/portal vein (SMV/PV) is missing, resectability revolves around the possibility to define collateral vein circulation on preoperative computed tomography scan and the ability to preserve it during surgery (Fig. 4).

SMA Resection

There is no specific article reporting on SMA resection and reconstruction during pancreatectomy. Data on SMA resection are sparse and can be found in the context of relatively few articles reporting on arterial resections [12].

The Heidelberg group reported on 30 SMA resections (15.4%) and 4 cases of resection of multiple arteries (2.1%) in 195 patients with arterial resections. Concurrent vein resection was required in 92 patients (42.7%) [4]. The Strasbourg group reported on 35 SMA resections (29.6%) and 17 cases of resection of multiple arteries (14.4%) in

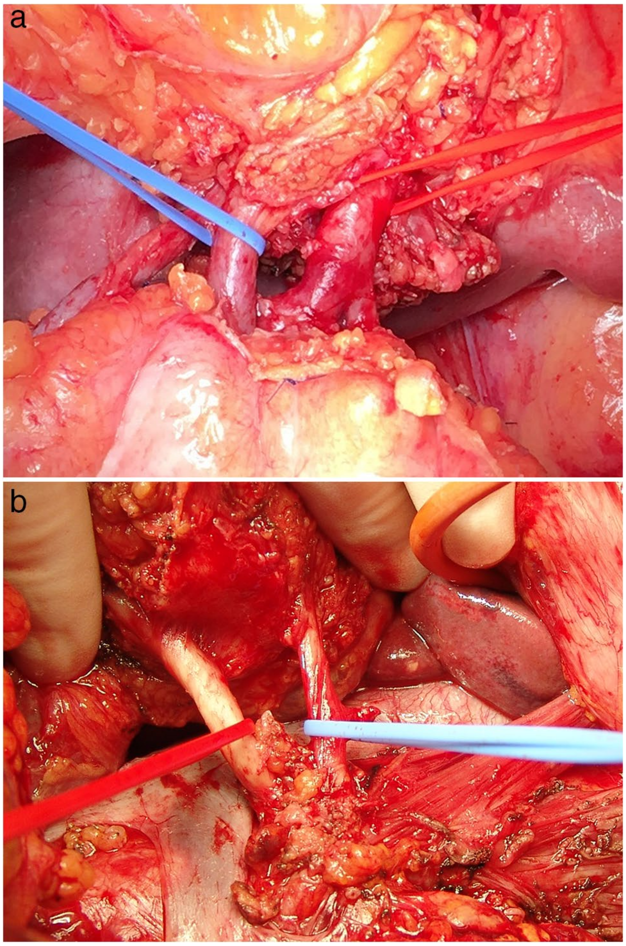


Fig. 2 Assessment of resectability. **2a** The SMA (red loop) and the SMV (blue loop) are dissected free and encircled in the mesenteric root. **2b** The SMA (red loop) and the CT (blue loop) are dissected free and encircled at the aortic origin

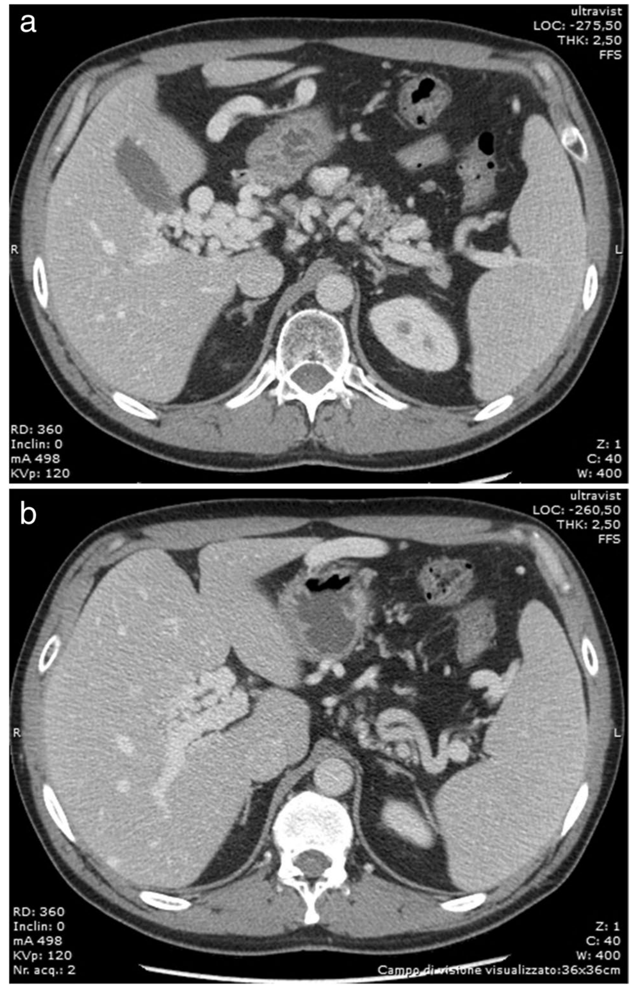


Fig. 3 Assessment of resectability. **3a** Portal cavernomatosis in a patient with a locally advanced pancreatic tumor. **3b** A patent segment of portal vein is identified at the hepatic hilum permitting vein reconstruction

118 patients. Concurrent vein resection was required in 105 patients (88.9%) [5]. The Mayo Clinic group reported on 15 SMA resections (13.5%) and 15 cases of resection of multiple arteries (13.5%) in 111 patients. Concurrent vein resection was required in 57 patients (51.4%) [13]. The Seoul group reported on 10 SMA resections (13.5%) and no case of resection of multiple arteries in 109 patients. Concurrent vein resection was required in 62 patients (56.9%) [6]. The Toronto group reported on 10 SMA resections (50.0%) and 10 cases of resection of CT/HA. Concurrent vein resection was required in 18 patients (90.0%) [14].

Our experience consists of 625 pancreatectomies with vascular resection, including 182 patients with arterial resection (29.1%). Concurrent vein resection was required in 143 patients (78.5%). Overall, 779 vascular segments were resected in 625 patients, including 71 SMA (9.1% of all resected vascular segments and 11.3% of all patients), 131 CT/HA (16.8% and 20.9%), and 577 SMV/portal vein (74.0% and 92.3%). Resection of multiple arteries was required in 143 patients (22.8%). Figure 5 demonstrates time distribution of these procedures.

Post-operative Complications and Mortality

Arterial resections continue to be associated with high morbidity and mortality rates [12], but results have clearly improved in the last 10–15 years [1, 3–6, 13]. Specific data on complications of pancreatectomy with SMA resection are lacking.

In the modern era, SMA resection remains associated with high complication rates [3, 13], and frequent admission to the intensive care unit [13], but does not clearly increase post-operative mortality when compared to pancreatectomy with resection of other vascular segments [3,

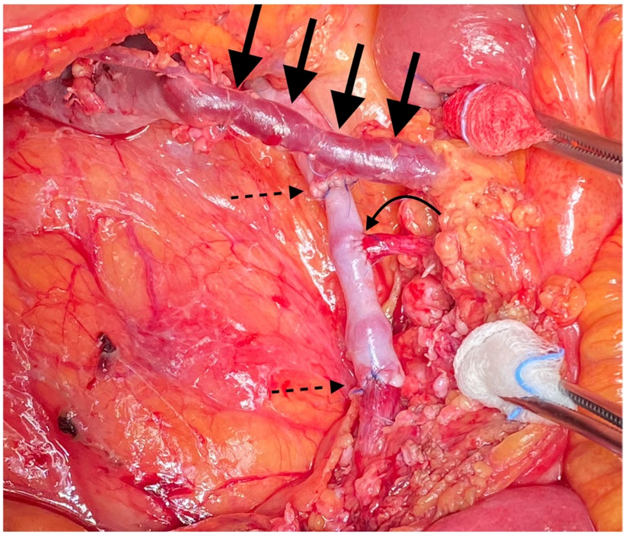


Fig. 4 Preservation of collateral venous outflow in a patient with totally thrombosed SMV and SMA encasement. Intraoperative picture taken after SMA reconstruction, using a jump graft of greater saphenous vein. Thick arrows highlight the preserved first jejunal vein. Thin dotted arrows point out proximal and distal SMA anastomoses. Curved arrow indicates a reconstructed branch of the SMA

13]. SMA resection carries the risk of ischemic complications involving the bowel, although the Heidelberg showed that this risk could be related more to SMA involvement rather than to SMA resection since ischemic complications occurred in similar proportions of patients after SMA resection (4/195; 2.0%) and SMA divestment (6/190; 3%) [4]. Techniques borrowed from transplantation of abdominal organs may be useful to deal with some of these complications (Fig. 6).

Oncologic Outcomes

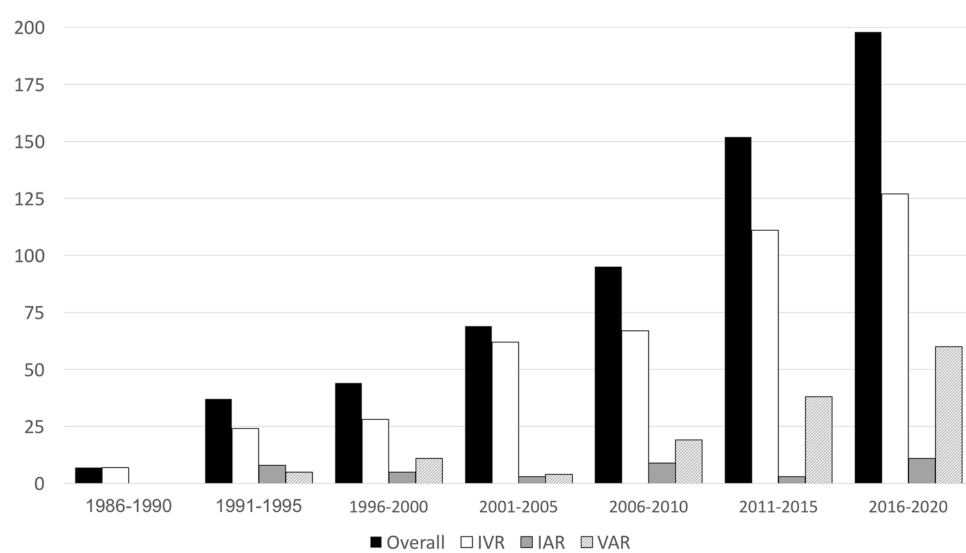
After SMA resection, R0 resection can be achieved in a proportion of patients similar to those seen in standard pancreatectomy and pancreatectomy with vein resection. In our experience, using a standardized pathology protocol assessing circumferential resection margins at 1 mm, R0 resection was achieved in 75% of the patients. A review of histology slides of 25 R0 resections showed that pursuing arterial divestment instead of arterial resection would have made 12 of these 25 resections R1, as cancer cells were present within 1 mm from the adventitia (Fig. 7). These data advised caution in pursuing arterial divestment as an alternative to arterial resection [4].

Preliminary data show that SMA resection does not worsen prognosis when compared to CT/HA resection [1, 6, 14].

Oncologic Selection Criteria

There are no specific oncologic criteria to decide when to proceed with pancreatectomy plus SMA resection. Actually, SMA involvement is still considered an absolute contraindication to resection at many institutions. Criteria generally accepted for patients with all types of arterial/venous involvement apply also to patients with SMA involvement. These criteria include delivery of either chemotherapy or chemoradiation therapy, lack of radiologic disease progression, decreasing levels of Ca 19.9 (in patients who express Ca 19.9), and good clinical conditions. Initial data suggest that fluorodeoxyglucose positron emission tomography or magnetic resonance imaging could improve our ability to assess response to neoadjuvant medical treatments [15].

Fig. 5 Increasing frequency of pancreatectomy with concurrent vascular resections over time. Black bars indicate all types of vascular resections. White bars indicate isolated venous resections. Gray bars indicate isolated arterial resections. Dotted gray bars indicate concurrent arterial and venous resections



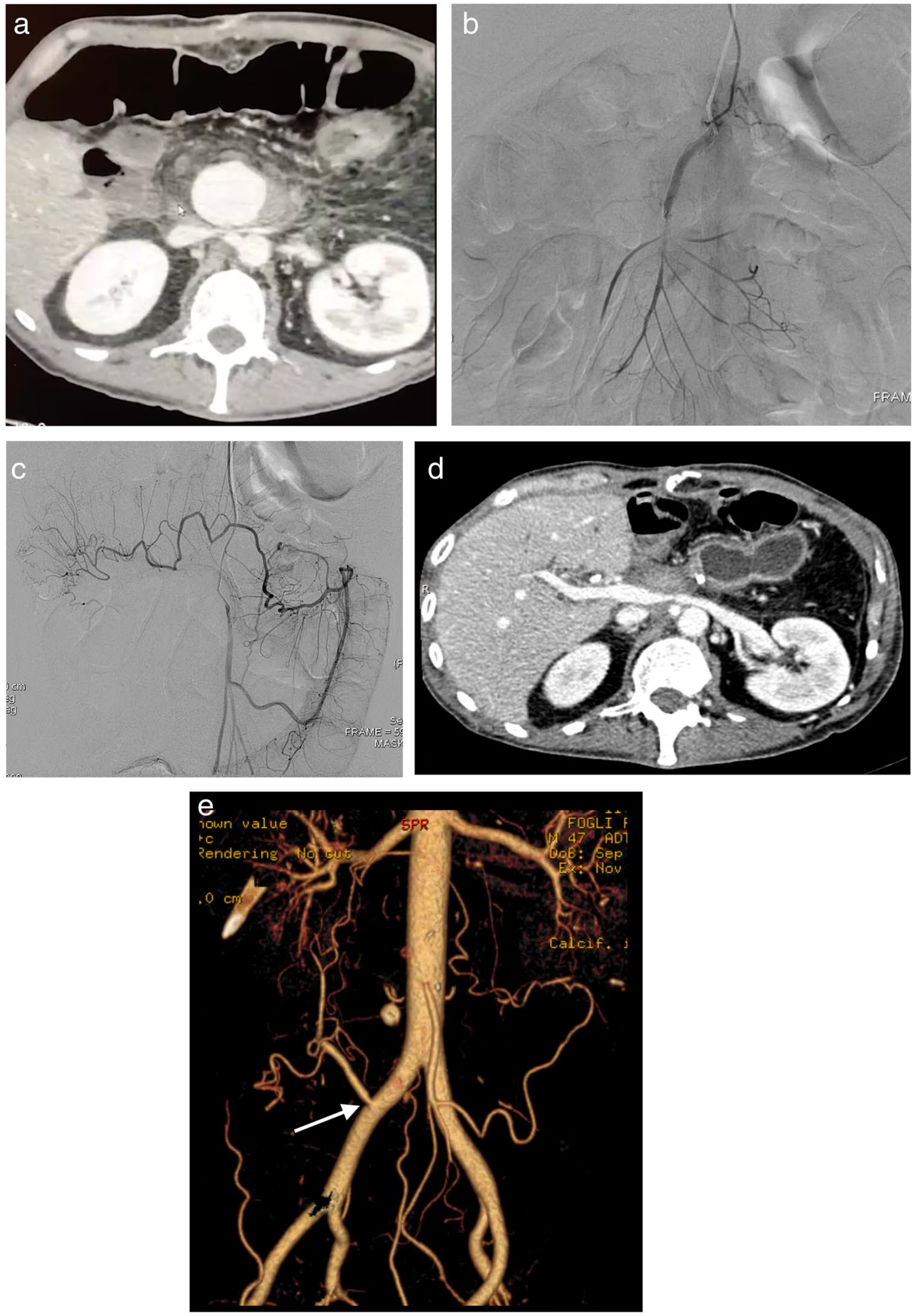


Fig. 6 Computed tomography scan and angiography images of a patient developing pseudoaneurysm at the level of primary SMA branches. After failed attempt at endovascular repair, the patient required rescue subtotal enterectomy. Restoration of portal flow was achieved by anastomosing the left renal vein to the portal vein. Preservation of distal jejunum and right colon required selective revascularization of the ileo-colic artery. **6a** Contrast-enhanced computed tomography demonstrates SMA pseudoaneurysm. **6b** Endovascular stenting of SMA pseudoaneurysm with seemingly preserved distal outflow. **6c** Selective angiography does not demonstrate collateral circulation between inferior mesenteric artery and SMA. **6d** Post-operative contrast-enhanced computed tomography demonstrates a patent reno-portal bypass. **6e** Computed tomography reconstruction shows a patent reimplantation of the ileo-colic artery on the common right iliac artery (white arrow)

There is no agreement/study indicating which chemotherapy regimen should be preferred, for how many cycles chemotherapy should be delivered, and the time window between end of preoperative treatments and surgery.

Some arterial resections however may also be unplanned [13], and may occur in patients who did not fully match the above-mentioned criteria. In these patients, the surgeon is confronted with the difficult task to decide about proceeding with resection or abort the procedure.

Conclusions

SMA resection at the time of pancreatectomy is a formidable operation associated with considerable post-operative risks and sequelae. Experience with this procedure is still limited, even at high-volume institutions. Recent data show major improvements in morbidity and mortality with increasing experience. Some patients, after neoadjuvant treatments, strongly benefit from SMA resection enjoying long-term

Fig. 7 Histology of a resected arterial segment. Distance between tumor and artery is 226.74 mm. Dissection in the periadvential space along the artery would have made this resection R1

survival and, perhaps, even achieving cure. Other patients, however, only suffer the surgical consequences of these extended procedures. Selection is therefore key. Post-operative prognostic factors, such as those that can be acquired by specimen pathology (e.g., lymph nodes status and number of lymph nodes with metastasis), cannot be used for preoperative selection. Information provided by molecular biology studies on preoperative biopsies might provide the final solution, but are not routinely performed. A real advancement would be to have a reliable prognostic score composed by parameters commonly acquired in the diagnostic work-up of patients with pancreatic cancer. We recently proposed and published online a "survival calculator" based on this type of parameters, that was specifically designed to anticipate oncologic outcomes of arterial resections (www.survivalcalculator-lapdac-arterialresection.org) [3]. We support selective implementation of pancreatectomy with SMA resection and reconstruction in appropriately selected patients.

Superior Mesenteric Artery Encasement Is Not an Absolute Contraindication for Surgery in Pancreatic Cancer.

The surgeon's contribution to a patient with localized pancreatic adenocarcinoma (PDAC) is to provide a reasonably safe and effective operation that is curative in intent with the goal of rendering a negative margin (R0) and minimizing local recurrence. However, these principles have only been applicable for patients with traditionally anatomically resectable tumors. A significant proportion of PDAC patients present with radiologically non-metastatic but locally advanced tumors with extra-pancreatic extension and encasement of arterial structures (i.e. superior mesenteric artery). By current consensus resectability criteria, such patients are considered inoperable, and historical surgical attempts in these cases resulted in grossly positive margins, severe life-threatening complications, and excess mortality with minimal survival benefit. In contrast to en bloc venous resection, currently standard at most major centers, the general consensus for arterial resections has not been met with acceptance. In a 2011 global review [16], arterial resection was associated with significantly worse perioperative outcomes and inferior long-term oncologic survival compared to patients without arterial resection arguing against such aggressive surgical pursuits. We have however found over time through autopsy and observational studies that a non-insignificant proportion of these tumors may be more biologically favorable and harbor a less metastatic but more locoregionally aggressive phenotype. As a result, there has been a renewed interest in more advanced surgical options for such tumors in recent years since the advent of significant advances in pancreatic cancer treatment.

The most important advance has been the introduction of modern effective systemic chemotherapy. This past decade saw the introduction of combinatorial regimens with significant objective responses and associated survival in patients with metastatic disease, and accordingly these agents were rapidly adopted in the neoadjuvant setting for more anatomically advanced tumors. There has also been increased use of preoperative chemoradiation following neoadjuvant chemotherapy either as destination therapy or as a prelude to planned resection for locoregional control, margin enhancement, and nodal downstaging. And finally, we have become better technical surgeons, incorporating en bloc non-anatomical plane resectional techniques from other tumoral operations (liver, sarcoma, etc.) as well as have learned to better predict and potentially mitigate or treat complications associated with pancreatectomy and more extensive operations.

As a result of these recent dramatic changes in practice, several high-volume centers across the globe have taken an interest in such advanced arterial resection for pancreatic cancer. Our group in Rochester has the largest US experience in en bloc arterial resection for pancreatic cancer [13] with significant experience in the modern era (since 2010) that includes over 200 cases (hepatic artery, celiac axis, and SMA) of which 45 SMA resections have been performed since last update. Tumors can involve the SMA alone in isolation or in combination with the hepatic artery or replaced hepatic vessels, as well as the celiac axis, and in very advanced tumor can also encase all three structures. These operations are significantly more difficult than standard procedures due to the need to perform the dissection in non-anatomical planes (mesenteric root, retroperitoneum) as well as difficulty with intraoperative exposure due to multiple points of fixation (1 vessel = 2 points, 2 vessels = 4 points, etc.). The operations required are all truly "bespoke" and custom for any given patient based on the location of the tumor and the required operation necessary to remove with a negative margin while re-establishing vascular, gastrointestinal, and biliary continuity. These operations are associated with increased risks that are primarily hemorrhagic, ischemic, and infectious in etiology. With increased experience however, the operative mortality has decreased significantly over time at our center as well as other high-volume groups from a high of > 20% to currently less than 5% for our last 75 cases. As these operations increase in magnitude, the operative risks also increase, and we need to justify these risks against the predicted oncologic benefit. Given these increased risks, they are only appropriate after maximal "effective" preoperative therapy. As a result, our practice relies on three specific and distinct concepts to determine candidacy and appropriateness for such advanced procedures: responsivity, reconstructability, and recoverability.

Responsivity refers to response to modern induction neoadjuvant chemotherapy. If we believe that preoperative chemotherapy is beneficial, then we need to objectively prove it is effective. We know that traditional radiologic responses are exceedingly rare tumor in such cases, as tumors that completely encase arteries do not pull away or become "resectable" with preoperative therapy and standard anatomical radiologic responses do not predict pathologic response or survival in PDAC. These data are so strong that NCI/NCCN does not include and nor considers radiologic response in criteria for resection or as a relevant response endpoint (NCCN Version 2.2021: https://jnccn.org/view/journals/jnccn/19/4/article-p439.xml). Biochemical responses (CA19-9) are often used to determine chemotherapy efficacy however are not possible in up to 40% of patients (10% non-secretors, 30% normal at baseline) Furthermore what constitutes an adequate CA19-9 response in those with elevation is also debated (stable, partial, normalization) although there is a growing trend to consider complete normalization of CA19-9 to obtain optimal outcomes. We have previously found that arterial resection itself was not a detriment to survival in patient undergoing resection, and only identified 3 factors that predicted survival: extended chemotherapy duration, CA19-9 normalization, and major pathologic treatment response. Of these, major pathologic treatment response was most predictive, congruent with other previous reports of neoadjuvant therapy in PDAC revealing pathologic response as among the largest single independent predictors of survival [17]; however, this is a post-operative metric and not known until after surgery. Due to the poor predictive value of radiologic response and limited utility of biochemical response in many patients, at Mayo Rochester in order to determine adequacy of neoadjuvant chemotherapy for these patients and eligibility for surgery, we heavily rely on FDG-PET to assess chemotherapeutic response given its ability to assess tumor viability with greater sensitivity than the previously described radiologic or biochemical methods and its high correlation with subsequent pathologic response. [18] Although we have increased our use of PET/MR for these cases, standard PET/CT is also predictive of treatment response and in our experience either modality is superior to traditional radiologic or biochemical response in predicting pathologic response and subsequent survival and thus can be applied universally in all practices. Therefore, FDG-PET is a preoperative metric of neoadjuvant chemotherapy effectiveness and response. Why does chemotherapy responsivity matter? Because chemotherapy response is a surrogate of adequate occult distant disease control and subsequent long-term survival. In our practice, we look to maximize the responses (CA19-9 and PET) to neoadjuvant chemotherapy prior to moving onto either chemoradiation or surgery. If we cannot achieve maximal responses (normal CA19-9 or complete PET response) with extension of first-line chemotherapy, then we consider chemotherapy switch. If we cannot achieve optimal responses despite alterations in our neoadjuvant chemotherapy strategy, then we assume chemoresistant disease and high likelihood of poor long-term survival in these patients and important conversations need to take place with these patients to weigh the risks of such advanced operations compared to anticipated oncologic outcomes.

The next concept is reconstructability. Although seemingly complicated, the principle is quite simple: "does the patient have the appropriate anatomy to create a custom operation to resect the tumor and all at risk tissues with a negative margin operation and prevent local recurrence?" We utilize the same doctrine that we apply to consensus criteria for technical hepatic resectability for liver tumors: an operation that removes the tumor, leaving adequate functional status, and re-establishes critical arterial/venous inflow and outflow and restoration of gastrointestinal and biliary continuity. Reconstructability is completely dependent on patient and tumor anatomy as well as surgical expertise, experience, and comfort in performing such atypical en bloc operations. The current "resectability" criteria for pancreatic cancer are not applicable in these patients as they were specifically developed to determine margin risk in "upfront" surgery (i.e., no neoadjuvant therapy) using standard anatomical plane-based techniques (i.e., no en bloc vascular resection). In our practice, patients are either reconstructable or they are not based on high-quality cross-sectional imaging. It is uncommon to have SMA-only involvement without associated SMV encasement (complete or partial) thus an unreconstructable SMV (long segment occlusion with no adequate target) is the primary limitation to SMA resection in our practice. SMA involvement can be partial or complete. For partial involvement, divestment techniques can be considered to avoid formal segmental resection; however, such techniques may weaken the arterial wall and potentially lead to post-operative vascular complications (i.e., pseudoaneurysm). For those with more extensive encasement, segmental resection is indicated, and eligibility depends on the extent of the tumor on the SMA. Our relative distal limit on the SMA is the origin of the middle colic artery as resection below this vessel typically requires resection of numerous proximal jejunal arcades and more extensive bowel resection with significant diarrhea, malabsorption, and risk of colonic ischemia. In SMA-only encasement, typical segmental resections with interposition grafts are performed using either autologous (superficial femoral artery) or cryopreserved cadaveric arterial conduits in our practice. We have abandoned venous grafts as well as synthetic grafts due to poor long-term patency rates and infection risks. Tumors can encase replaced hepatic arteries arising from the SMA requiring dual arterial resection and hepatic and visceral revascularization. Cancers encasing the celiac axis may extend inferiorly onto the SMA requiring dual combined celiac/SMA resection and revascularization. And the most advanced cases require combined SMA/Celiac/and HA resection with multivisceral resection and complex revascularization procedures. Our cumulative SMA resection experience reveals an equal proportion of both SMA-only versus combined artery resections. We also only consider SMA resection for those patients with a patent IMA, as this allows retrograde mesenteric perfusion in case of graft occlusion. In our SMA series of 45 patients, we have had two 90-day mortalities, one of which was specifically related to bowel ischemia after graft occlusion with a non-patent inferior mesenteric artery. We also consider total pancreatectomy in many cases to eliminate POPF risk and its effect on graft infection, hemorrhage, thrombosis, and ischemia.

Finally, the concept of recoverability needs to be discussed. We need to balance the higher risk of these operations, both short and long term, with overall patient health, performance status, and future expectations. We have incorporated many adjuncts for these specific operations to improve perioperative outcomes and have involved a multidisciplinary post-operative team to manage these patients long term. Furthermore, the outcomes for non-operative therapy (i.e., induction chemotherapy and consolidative chemoradiation only) in patients with locally advanced pancreatic cancer have markedly increased over time with a median of 15–24 months survival without surgery. Therefore, comparative outcomes need to be assessed over time to justify such resections moving forward and assuring that adding a complicated operation will add significant survival benefit (years rather than months) above and beyond that provided by initial non-operative treatment modalities alone.

In conclusion, the arbitrary location of a patient's pancreatic cancer should not by itself preclude the potential for a curative-intent operation in the modern era. As these operations carry with them greater risks, they should only be performed at experienced centers and only after maximal preoperative chemotherapy with objective response. Finally, the current resectability classification system is meaningless in the modern era, as it was never intended to determine resectability for patients undergoing modern neoadjuvant therapy with subsequent custom en bloc resections and we need new concepts in 2021 and beyond, namely responsivity, reconstructability, and recoverability.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11605-021-05237-1.

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