

Vascular Resections during Curative Surgery for Pancreatic Adenocarcinoma

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1. Abstract

The Pancreatic Adenocarcinoma (PA) is estimated to become the second leading cancer-related death cause by 2030. At the time of diagnosis, 30% of patients have a locally advanced disease especially vascular involvement. Performed firstly in 1973; the benefits of vein resection on survival have been clearly demonstrated by published reports. The vein resection and reconstruction to achieve curative resection is currently considered as standard of care for locally advanced pancreatic tumors with invaded portal/ superior mesenteric vein (PV/SMV). Regarding pancreatic surgery with arterial resection, the survival rates are encouraging compared to systemic treatment alone. Additionally, the development of more systemic therapies has increased the long-term survival after pancreatic resection with arterial resection to nearly the same level after conventional pancreatectomy. Defining better and more useful prognostic, patients-related, and biological criteria is more necessary and hopeful to select the best candidates for curative surgery. Performed in high-volume centers with specific experience in such procedure; complex vascular reconstruction does not significantly increase the operative risk. Furthermore, more designed trials are highly recommended to defining guidelines for pancreatic resection associated with vascular resection-reconstruction for clinical practice. This review focuses on the recent results of vascular resection and reconstruction to achieve curative surgery for pancreatic adenocarcinoma with consideration of new perspectives offered by more developed systemic treatments, during the last five years.

2. Keywords: Pancreatic adenocarcinoma; Neoadjuvant therapy; Resectability; Pancreatectomy; Vascular resection; Vein reconstruction.

3. Introduction

Currently, the fourth cancer-related-death cause in the western countries, the Pancreatic Adenocarcinoma (PAC) is estimated to become the second leading cancer-related death cause by 2030 [1]. At the time of diagnosis, the surgery is indicated in only 20% of patients, 50% and 30% of cases have metastases and locally advanced disease respectively [2]. First performed in 1973 [3], and despite the absence of strong evidence, pancreatectomy associated with vein resection and reconstruction have been greatly criticized and vascular resection was rarely performed during pancreatic surgery. Recently, published reports showed a similar morbidity, mortality, and survival rates after pancreatectomy with vein resection and reconstruction compared to conventional pancreatic surgery [4, 5]. Vein resection and reconstruction to achieve curative resection is currently considered as standard of care for locally advanced pancreatic tumors with invaded portal/ superior mesenteric vein (PV/SMV) [6]. Instead of vein resection, arterial resection during pancreatectomy remains a debatable matter. However, survival advantages of pancreatectomy with arterial resection over palliative procedures have been consistently demonstrated [7]. More interestingly, arterial resection alone may be associated with the better long-term outcome than

combined artery–vein resection [8]. Additionally, the development of more systemic therapies has increased long-term survival after pancreatic resection with arterial resection to nearly the same level after conventional pancreatectomy [2, 9]. This review focuses on the recent results of vascular resection and reconstruction to achieve curative surgery for pancreatic adenocarcinoma with consideration of new perspectives offered by more developed systemic treatments, during the last five years.

4. Evolution of Vascular Resection during Pancreatic Surgery

First described in 1973 by Joseph Fortner, and performed for locally advanced disease to extend surgical indications [3], vascular resection and reconstruction have gained interest resulting in starting a debate about this innovative surgical technique. Initially, this innovative approach has been criticized for the high peri-operative morbidity and mortality rates associated with vascular resection. However, for years later, Fortner reported a postoperative mortality rate of 16.6% after pancreatectomy with vascular resection [10], which was comparable to that reported in the same period of the time (15% to 20%), after conventional pancreatic surgery [11,12]. Secondly, pancreatectomy with vascular resection was criticized to be associated with a poor long-term survival (one year survival rate of 62%) [10], however, a median survival of 10 months after conventional pancreatectomy has been reported at the same time without difference in reported survival between palliative bypass and resection [13]. Despite the absence of strong evidence from literature, the future guidelines have been greatly influenced by the criticism against vascular resection and reconstruction during pancreatic resection. Till the end of 1990s, and despite the absence of strong evidence, pancreatectomy associated with vascular resection and reconstruction has rarely been performed by pancreatic surgeons. However, the more recent reports have shown an equivalent morbidity, mortality, and survival after conventional pancreatectomy versus pancreatectomy with vein resection and reconstruction [4, 5]. Vein resection and reconstruction to achieve curative resection is currently considered as standard of care for pancreatic tumors with vein invasion including the portal/superior mesenteric vein (PV/SMV) [6]. Instead of vein resection, arterial resection remains a debatable matter as the recent literature has not shown encouraging results regarding the long-term survival after pancreatectomy with combined artery-vein resection(s). On the other hand, survival advantages of pancreatectomy with arterial resection over palliative procedures have been consistently demonstrated [7]. More interestingly and as demonstrated, arterial resection alone may be associated with the better long-term outcome than combined artery–vein resection [8]. Marked progress in systemic therapies has increased the indications of surgery for borderline and

locally advanced tumors, even tumors with vascular invasion. Also, these effective systemic therapies have led to increase long-term survival after resection with arterial resection to nearly the same level after conventional pancreatectomy [2, 9, 14].

5. Vein Resection and Reconstruction

Following a long debate for many years regarding the vein resection and reconstruction during pancreatectomy for adenocarcinoma, a general agreement has been adopted, considering resection and reconstruction of invaded vein (PV/SMV) to achieve radical surgery is not a contraindication when technically feasible [6]. Compared to “conventional” pancreatectomy, similar morbidity and mortality rates and long-term survival have been demonstrated after pancreatic surgery associated with vein resection and reconstruction [4, 8]. Interestingly, the published reports from the last five years showed similar survival when vein resection with reconstruction is performed to achieve curative surgery. However, the vein resections and reconstruction are commonly performed in experienced centers. Despite the limited number of available studies, the 5-year survival rate after curative pancreatic surgery with vein resection varies from 0% to 39%, which is similar to that published for “conventional” pancreatectomies [15-32]. Available data regarding the pancreatectomy with vein resection has some limitations. The studies were performed in different centers with different levels of experience in the procedure. The studies were retrospective and the indication of vein resection is not defined in many published reports. As known, a planned vascular resection to achieve radical surgery is quite different from needed resection by necessity after no reversible surgical maneuvers. Finally, tumors with vein involvement are classified as a borderline resectable disease; however, the timing of chemotherapy for this category of tumors is not reported in the available data.

6. Arterial Resection

Arterial resection includes superior mesenteric artery, celiac trunk and hepatic artery. Arterial resection can be associated with or without performing reconstruction. Also, it can be combined with vein resection and reconstruction.

6.1. Arterial Resection without Reconstruction

The tumors located in the body of pancreas are treated with distal pancreatectomy and celiac trunk resection. However, arterial reconstruction is not performed, and the blood supply to the liver and stomach is assumed by the gastroduodenal artery obviating the need for arterial reconstruction. The most advantages of this surgical procedure are the positive pancreatic margin and the postoperative insufficiency of blood supply to the liver, and more often the stomach. In fact, this procedure is rarely indicated or performed [60]. The

published data from the last five years have shown that distal pancreatectomy with celiac trunk resection was safe with encouraging median survival [34-40]. The better long-term outcome after distal pancreatectomy associated with celiac trunk resection is appeared to be more related to neoadjuvant therapies (chemo-radiation). In addition, the 5-year survival rate after resection alone and resection with neoadjuvant therapy was 78.8% and 26.7%, respectively [36]. This difference in survival (prognosis) reflects the systemic therapy improvement that helps in stratifying patients and identifying favorable biological behaviour of some tumors [41].

6.2. Artery (\pm Vein) Resections with Reconstructions

Controversy exists about arterial resection /reconstruction during pancreatic surgery. Aggressive surgical approach for pancreatic adenocarcinoma (PA) has not been clearly supported by the past data. However, recent reports on arterial resection for curative surgical from the last 5years have changed compared to the last two decades, suggesting benefit of arterial resection in high- selected cases [2, 7-8, 14]. Compared to previous results, many reports reported improvement of 5-year survival rates (around 20%) with a median survival of 53months in selected patients undergoing arterial resection after neoadjuvant therapies (NAT) [2,14,42-48]. Despite the encouraging survival rates for arterial resection compared to systemic treatment alone, data reporting morbidity and mortality remain more controversial. Operative mortality and morbidity rates after arterial resection varied from 0% to 13% and from 9.8% to 54% respectively [11, 44, 49-52]. The variability of the reported results is related to various surgical techniques and approaches, and reflecting aggressiveness in treating locally advanced disease [53]. Complex vascular reconstruction does not seem to significantly increase the perioperative risk. Indeed, at least two vascular reconstructions including vein and artery are performed during transplant surgery with very vascular complications rates [54]. Overall, improved systemic therapy has increased surgical indications to treat PA; even patients require arterial or arterial, and vein resection. However, these procedures should clearly be performed high-volume centers with specific experience in performing combined arterial–vein resection.

6.3. Surgical Indication Following Neoadjuvant Systemic Therapy

The development of more effective systemic therapies has increased survival in resected patients, and the significant improvement of survival reflects the effect of the more effective systemic therapies in controlling disease (NAT) [2,14]. Recently, the reported long-term survival was similar in borderline resectable or locally advanced disease treated with NAT [55]. Also, T stage alone was not showed to

be a prognostic factor for survival [56]. However, the radiological evaluation of response to neoadjuvant chemotherapy (FOLFIRINOX) for PA remains unclear. The radiological response rate after NAT is approximately 25%, and the disease remains radiologically stable in the majority of patients (69%), with 6% of progression during chemotherapy [57]. However, complete to moderate pathological response after chemotherapy can be observed in more than 77% of treated patients [58]. As clearly showed, radiology can assess only disease progression, but not response to chemotherapy [57, 58]. Therefore, determining the surgical indication for locally advanced Pancreatic Adenocarcinoma (PA) has become more complicated after improvement of systemic therapies. In fact, and as reported in a recent observational study, radical surgery (R0) could be achieved in the great majority of patients (92%) who underwent surgical exploration for unresectable tumour as determined by a post-chemotherapy staging CT scan [59]. This suggests that formal criteria used to determine respectability are inadequate or inaccurate. Additionally, the CA 19-9 and Positron Emission Tomography (PET) scan have been described to re-stage patients after NAT; however, significant number of tumors does not express this biomarker and technical issues with PET scans have limited their use in making appropriate surgical decision [60, 61]. Also, technical criteria should not be considered as a complete contraindication for surgery as radiological imaging cannot precisely differentiate tumor from post-treatment fibrosis. From 2001 to 2015, 254, 200 pancreatoduodenectomies have been performed for PA following NAT in the United States, and 30% (76,260) of them were considered unresectable without evidence of metastatic disease [62]. This may be related to applying an inaccurate re-staging after neoadjuvant therapy. Although significant or complete pathologic response after NAT was observed in 77% of patients, imaging methods were not predictive of resectability and pathological response after neoadjuvant-CRT [57, 58]. Indeed, surgical exploration for radiographically stable tumor after NAT may be considered as an appropriate option for patients with acceptable clinical conditions. However, some patients may be exposed to unnecessary exploration, but non-surgical option is an alternative for tumor progression. Therefore, defining reliable clinical and biological criteria to determine resectability after neoadjuvant systemic therapy becomes more necessary.

7. Conclusion

The resectability of non-metastatic pancreatic adenocarcinoma is currently based on local anatomical criteria. The improved systemic therapies have increased surgical indications for borderline resectable or locally advanced disease, even when arterial and vein resection were required. Unfortunately, defining radiologically candidates for

surgical exploration after NAT remains a great matter in pancreatic adenocarcinoma. The radiological criteria to determine tumor resectability after NAT remains unclear, and the radiological response rate is approximately 25%. Therefore, the surgical exploration for radiographically stable tumor after NAT may be considered as an appropriate option for patients with acceptable clinical conditions. Not limited to anatomical classification of resectability, so, defining better and more useful prognostic, patients-related, and biological criteria is more necessary and hopeful to select the best candidates for curative surgery. Vein resection and reconstruction to achieve curative surgery is currently considered as standard of care for locally advanced pancreatic tumors with invaded portal/superior mesenteric vein (PV/SMV). Regarding pancreatic resection associated with arterial resection, the survival rates are encouraging compared to systemic treatment alone. Also, performing complex vascular reconstruction does not seem to significantly increase the perioperative risk. However, these procedures should clearly be performed in high-volume centers with specific experience in performing arterial-vein resection. Furthermore, more designed trials are highly recommended to defining guidelines for pancreatic resection associated with vascular resection-reconstruction for the clinical practice.

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