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EDITORIAL – PANCREATIC TUMORS

Additional Support for Neoadjuvant Therapy in the Management of Pancreatic Cancer

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The relationship of a pancreatic head cancer to the superior mesenteric–portal vein (SMPV) confluence has intrigued and confused surgeons and oncologists for decades. The foundation for this ongoing debate began with Whipple, who described the operation of pancreaticoduodenectomy (PD) in 1935; Moore and colleagues, who first described resection and reconstruction of the superior mesenteric vein (SMV) in 1951; and Fortner, who reported his experience with regional pancreatectomy in 1973. Fortner routinely divided the distal splenic vein when performing segmental resection of the SMPV confluence, allowing for a primary end-to-end anastomosis of the SMV and portal vein (PV).[1–3] However, the failure of regional pancreatectomy to positively influence survival duration caused most to dismiss venous resection as an ineffective, high-risk, and therefore overaggressive approach to a disease that is often metastatic at diagnosis.

Adding to this controversy was the inability of preoperative imaging to predict the need for venous resection at the time of operation. In fact, despite the evolution of preoperative computed tomography (CT)-based staging in sophistication and objectivity, it remains inaccurate in predicting (preoperatively) the ability of the surgeon to separate the pancreatic head cancer from the lateral (or posterior) wall of the SMV, PV, or SMV-PV confluence at the time of surgery.[4–6] The presence of tumor–artery (hepatic or superior mesenteric) abutment (loss of a normal tissue plane between the tumor and these vessels) is reliably defined by CT imaging, but in contrast, assessment of the tumor–vein relationship (in the absence of tumor-induced compression or narrowing) is not.[7] Therefore, surgeons find themselves in the operating room with the pancreatic neck divided and the tumor adhered to the lateral or posterior wall of the SMV or SMPV confluence. In such a setting, the surgeon has three options: leave tumor behind as a grossly positive margin; perform a tangential or segmental venous resection and reconstruction as part of the PD; or persist in attempts to separate the tumor from the vein. This latter option is potentially dangerous, as it will often result in a small venotomy—which might quickly become a bigger venotomy. To facilitate venous repair, the surgeon may have to perform emergent removal of the specimen, often with a positive superior mesenteric artery (SMA) margin.

This inability to accurately preoperatively predict who may require venous resection at the time of PD has led us to develop a series of techniques to better equip surgeons to manage both suspected and unsuspected venous abutment/encasement at the time of PD.[8–13] At present, there is evolving consensus that venous resection and reconstruction at the time of PD is becoming a more widespread and accepted management strategy, and one best performed in the setting of a multimodal approach including systemic therapy and often chemoradiation.[14]

In this context, in this issue, Delpero and colleagues from the Institut of Paoli Calmettes in Marseille, France, report a retrospective review of 1399 consecutive patients treated at 37 centers from 2004 to 2009 who underwent PD or total pancreatectomy for pancreatic adenocarcinoma with ($n = 402$) and without ($n = 997$) venous resection.[15] Their definition of resectable and borderline resectable disease was based on the initial description by Varadhachary and colleagues, but the total number of patients with borderline resectable disease was not provided.[5] They concluded that a surgery-first strategy for patients who required venous resection resulted in an inferior survival (median 21 months) compared to those who did not require

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vascular resection (median 29 months), and therefore, a neoadjuvant strategy should be considered. Overall, neoadjuvant therapy was rarely provided (10 %), being utilized in only 20 % of those who required venous resection and only 7 % of those who underwent standard PD. For those patients who required venous resection and received either neoadjuvant or adjuvant therapy, there was a survival advantage compared to those who underwent surgery (venous resection) alone. As one would expect, 166 (41 %) of the 402 patients who required venous resection did not have an obvious tumor-induced abnormality of the SMV-PV on preoperative imaging. Although this was a report of a surgical registry—and therefore the authors were not able to include the total number of patients brought to surgery who did not undergo resection, as well as all patients who began neoadjuvant therapy with curative intent—the very low perioperative mortality and the impressive median survivals speak to the excellent operative and oncologic care provided at the majority of the treatment centers. Of interest, there was a volume–outcome relationship with respect to mortality (opportunity for improvement), but a remarkable 70 % of patients received adjuvant therapy—superior to what has been attained in the United States.

Delpero and colleagues suggest that all patients with suspected venous involvement at preoperative imaging be classified as having borderline resectable disease and treated with neoadjuvant therapy before consideration of surgical resection. Although the definitions of resectable and borderline resectable have been standardized by national consensus conferences and by the National Comprehensive Cancer Network,[16,17] the relationship of the tumor to the SMV or PV cannot always be accurately assessed (with respect to the need for subsequent venous resection) by preoperative imaging, as demonstrated by the authors' own data, where 41 % of the patients who required venous resection had no indication at preoperative imaging that this would be necessary. This is because the pancreas directly abuts the SMPV confluence and there often is no visible tissue plane between the pancreas and the vein. In contrast, the SMA, celiac artery, and hepatic artery are surrounded by autonomic nerve, and the lack of arterial abutment is characterized by a very visible normal soft tissue plane between the tumor and the arteries. A CT scan that demonstrates a low-density tumor abutting the SMV or PV may or may not require venous resection because the surgeon may or may not be able to successfully separate the tumor from the vein. We should not expect more from preoperative imaging than can realistically be delivered. An obvious answer to the authors' data-driven approach to asking for more neoadjuvant therapy would be to routinely (on or off a clinical trial) deliver neoadjuvant therapy to all patients with pancreatic cancer with potentially operable disease, regardless of whether they have resectable or borderline resectable disease.[18] Despite the challenges of tumor–vein imaging, anatomic definitions used in current staging systems are critically important to establish stage-specific therapies (reproducible treatment algorithms that all specialists can agree on) and to allow for objective, data-driven comparisons of similar patient populations treated on or off a clinical trial. The specific definitions used are perhaps less important than the adherence of all clinicians to definitions that are anatomically objective and reproducible.

As demonstrated by the authors, venous resection and reconstruction can be done safely in high-volume centers where the entire team obtains adequate experience; practice does matter. Our work has emphasized standard principles of surgical technique; proximal and distal control of the PV and SMV, respectively; systemic heparinization with arterial inflow occlusion on the SMA; a perfect contour of the reconstructed venous segment (if not, it will occlude in the postoperative period because it is a low-pressure system); and lack of tension on the venous anastomosis. These latter two points are perhaps in disagreement with Delpero and colleagues, who found that the extent of venous resection did affect outcome (the more extensive the resection, the worse the outcome), and they rarely used interposition grafts. After venous reconstruction, it is critically important that the SMPV confluence be as close to normal as possible with regard to size, shape, and contour. Whether one performs a tangential repair with saphenous vein or an interposition graft with internal jugular vein—either can look perfect or unacceptable—can stay patent for the life of the patient or can eventually occlude, resulting in extrahepatic portal hypertension and ascites. The surgeon should not leave the operating room unless the reconstructed venous segment looks as close to perfect as possible, as narrowing of the SMV-PV will be a problem in the postoperative period.

Regarding segmental resection of the SMV at the time of PD, we agree that interposition grafting is often not necessary when the distal splenic vein is divided. If the splenic vein confluence is preserved, segmental resection and reconstruction of the SMV will usually require an interposition graft (the internal jugular vein is our preferred conduit); unnecessary tension on the anastomosis may encourage thrombosis. We extend a word of caution to those who attempt to routinely complete primary end-to-end anastomoses for segmental resections of the SMV by releasing the retroperitoneal attachments of the right colon and small bowel through performance of a Cattell-Braasch maneuver. Although this may appear to gain length for both ends to come together, it may result in a rotational twist of the distal SMV (if one is not careful) and will not properly close large gaps (>2–3 cm) resulting from a more lengthy segmental resection of the SMV.

Finally, let us briefly comment on resection margins and lymph node positivity. The challenges of standardizing the pathologic evaluation of the PD specimen as well as the high rate of lymph node positivity were once again confirmed by Delpero and colleagues. They found that only 50 % of surgical specimens underwent a standardized pathologic evaluation, and positive lymph nodes were found in 70 % of patients. The obvious concern in patients who are reported to have undergone venous resection is that the venous resection may not have been elective; an inadvertent venotomy may have led to the need for venous resection. In such situations, the PD specimen may need to be removed in a more expeditious fashion, thereby compromising the SMA margin. The high rate of lymph node positivity in this multi-institution report also reflects the bias of the investigators for a surgery-first strategy rather than neoadjuvant therapy. The ability of neoadjuvant therapy to downstage regional lymph node metastases is well described (the incidence of positive nodes is approximately 30 % when surgery is performed after induction therapy), and to the extent that occult liver or lung metastases (which may have a similar stromal component to regional lymph node metastases) behave in a similar biologic way, treatment sequencing may matter.[13]

Although we have not yet achieved consensus for the neoadjuvant treatment of resectable pancreas cancer, all patients with borderline resectable disease should receive induction therapy before considering surgery. Our approach to borderline resectable cases has evolved with greater experience, and our working definitions are similar to published guidelines.[6] Outside of a clinical trial, for patients with borderline resectable pancreatic cancer, we initiate systemic therapy (FOLFIRINOX or nab-paclitaxel/gemcitabine are the most frequently used regimens) and restage the disease after 2 months of treatment. In the setting of stable or responding disease, we then transition the patient to chemoradiotherapy (gemcitabine-based, standard fractionation, intensity-modulated radiotherapy is the current standard) and restage again; then, in the absence of disease progression, we proceed to surgery.[19] With regard to neoadjuvant therapy for resectable pancreatic cancer, the median survival for patients who undergo PD after successfully completing neoadjuvant therapy is now approaching 3 years, which consistently compares favorably to the approximately 2 years for those who complete adjuvant therapy after a surgery-first approach, and less than 2 years (closer to 12 months) for those who do not receive adjuvant therapy after pancreatectomy alone.[20] This survival advantage is more than simply patient selection; among a host of possible biologic factors, treatment sequencing may influence the host–tumor relationship and response to a given anticancer therapy. For example, neoadjuvant therapy provides early treatment of low-volume, radiographically occult micrometastases (such as those in liver or lung) in the setting of an immune-competent host before the stress of a large operation. Importantly, those who experience disease progression during or after neoadjuvant therapy will not be exposed to the morbidity and risk for mortality associated with pancreatic surgery.

In summary, the authors have achieved truly excellent results in a consecutive series of complicated cases in patients treated at multiple centers for a biologically aggressive disease. We agree with their conclusion in support of neoadjuvant therapy (rather than up-front surgery); such a change in treatment philosophy becomes even more compelling as systemic therapies increase in complexity and toxicity, making their delivery after a large operation difficult, especially in patients of advanced age. Importantly, the inability of the surgeon to separate a pancreatic cancer from the SMV-PV cannot be reliably predicted in all patients at preoperative imaging. Therefore, to achieve the authors' goal that neoadjuvant therapy and a complete R0 resection be performed in all patients who require venous resection and reconstruction, such patients will need a treatment team experienced in both preoperative/neoadjuvant therapy and vascular resection at the time of PD. Such expertise is not available at all centers, which makes another strong case for the regionalization of complex cancer care that involves multiple treatments in series including a large, often multivisceral operation.

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