BORDERLINE RESECTABLE PANCREATIC CANCER

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The Importance of Pretreatment Staging to define the extent of disease as a necessary component of the conduct of clinical trials and outcome reporting

Evaluation of the potential value of nonsurgical therapies (chemotherapy and radiation therapy) in improving local disease control and survival of patients with pancreatic cancer requires accurate pretreatment staging (to define the study population) and a standardized system for the pathologic evaluation of surgical specimens (to determine the completeness of resection). This is routinely performed in most other solid tumors yet rarely completed in an organized fashion in pancreatic cancer making the interpretation of the published literature difficult or impossible. For example, the definition of resectable pancreatic cancer used in most studies is based upon whether or not the surgeon has removed the pancreatic head, often with no system of margin analysis.

Multidetector (multislice) computed tomography (CT) is used to objectively define (anatomically) potentially resectable disease, borderline resectable disease, locally advanced disease, and metastatic disease. Although contrast-enhanced CT is widely available, accurate interpretation and reporting of the tumor-related findings remains inconsistent. For optimal pretreatment staging and assessment of operability, a CT report in a patient with suspected periampullary or pancreatic cancer should include the following information:

1. Commentary on the presence or absence of a primary tumor in the pancreas;
2. Commentary on the presence or absence of peritoneal and hepatic metastases;
3. Description of the patency of the superior mesenteric vein-portal vein confluence and the relationship of these veins to the tumor;
4. Description of the relationship of the tumor to the superior mesenteric artery (SMA), celiac axis, and hepatic artery.

Specific, objective radiographic criteria can be used to create the following definitions:
Potentially resectable disease:

1) no extrapancreatic disease, 2) a patent SMV-PV confluence (assuming the technical ability to resect and reconstruct this venous confluence), and 3) a definable tissue plane between the tumor and regional arterial structures including the celiac axis, common hepatic artery and SMA.

Borderline resectable disease:

1) no extrapancreatic disease, 2) the following possible tumor-vessel relationships: an SMV-PV confluence that can be reconstructed even is short segment venous occlusion is present (ie, a suitable portal vein above, and a suitable SMV below the area of occlusion); tumor abutment of the SMA of $< 180^{o}$; or short segment encasement of the hepatic artery amenable to resection and reconstruction (this is usually at the origin of the gastroduodenal artery and reconstruction may or may not require interposition grafting with a short segment of reversed saphenous vein).

Locally advanced disease:

1) no extrapancreatic disease, 2) tumor encasement of the SMA or celiac axis defined as tumor involvement of $> 180^{o}$ of the arterial circumference.

Metastatic disease:

Radiographic or clinical evidence of distant organ or peritoneal metastases.

Despite clear evidence that high-quality cross-sectional imaging predicts resectability accurately, many patients undergo laparotomy for pancreatic cancer without adequate preoperative assessment. Some patients are found to have unresectable tumors intraoperatively when such a conclusion might have been possible prior to surgery. Conversely, because of a lack of adequate preoperative imaging and surgical expertise, many patients who are resected with "curative intent" have been left with gross residual disease not recognized by the surgeon intraoperatively, or documented in the operative note.

Pathologic Assessment of the Surgical Specimen

The modifications to the TNM staging system in the 6^{th} edition of the AJCC Cancer Staging Manual allow the accurate staging of patients even if they do not undergo pancreatic resection. The T4 (and Stage III) designation is reserved for locally advanced unresectable primary tumors in the absence of distant metastases. In addition to TNM staging, when the pancreaticoduodenectomy

specimen is evaluated pathologically, the retroperitoneal margin (the soft tissue margin directly adjacent to the proximal 3–4 cm of the SMA) must be evaluated on permanent sections by inking the margin and sectioning the tumor perpendicular to the margin. It is critical that the surgeon identify this margin at the time of resection because it cannot be assessed retrospectively and many pathologists cannot accurately identify the retroperitoneal margin on a pancreaticoduodenectomy specimen. The surgeon and pathologist should classify the retroperitoneal margin after integrating the operative findings and the histologic assessment of this margin. All pancreatic resections should be classified according to residual disease status (termed "R" factor): R0, no gross or microscopic residual disease; R1, microscopic residual disease (microscopically positive surgical margins with no gross residual disease); and R2, grossly evident residual disease. The pathologist cannot usually differentiate an R1 (microscopically positive) from an R2 (grossly positive) retroperitoneal margin in the absence of information regarding the retroperitoneal dissection, which should be included in the operative note. The R designation should appear in the final pathology report if possible and should always be listed in the dictated operative note (we do not sign off on the operative note until the pathology report is available for review). For example, if the surgeon states that gross tumor was encountered when completing the retroperitoneal dissection, a positive histologic margin should result in the R2 designation in the operative note and the medical record. In the absence of this information being included in the operative report, the proper R designation cannot be determined. The difficulty in differentiating R1 from R2 resections has significant implications for the conduct of clinical trials examining the potential advantage of nonsurgical therapies, especially in patients with borderline resectable tumors.

Preoperative Therapy for Borderline Resectable Pancreatic Cancer

There are many obvious advantages to preoperative treatment of patients with borderline resectable pancreatic cancer.

1) The ability to provide immediate systemic therapy for a disease that is systemic at diagnosis in most patients.
2) Improved patient selection for surgery; pancreaticoduodenectomy is associated with significant patient morbidity even when performed in experienced hands. This improved patient selection arises because patients with progressive systemic or local disease are

identified as part of the restaging evaluation performed periodically during neoadjuvant treatment prior to planned surgery.

3) Chemoradiation may lessen the risk of a positive margin resection, analogous to the data on the value of preoperative therapy for patients with rectal cancer. In fact, the mesorectum and the radial margin of resection following a low anterior resection is quite similar to the retroperitoneal margin following pancreaticoduodenectomy.

Unfortunately, many reports of neoadjuvant therapy for pancreatic cancer have included heterogeneous patient populations, enrolling patients with locally advanced and borderline resectable (also termed marginally resectable) pancreatic cancer often with unclear anatomic definitions of the local extent of disease. Few investigators report clear anatomic definitions of locally advanced disease and many studies incorporate intraoperative assessment of the extent of local tumor growth, data which is subjective and not reproducible. In general, patients with locally advanced pancreatic cancer (as defined above) should not be included in studies of preoperative therapy because their inclusion confounds reports of resection rates, and complicates comparisons to other studies.

Our current approach to the patient with borderline resectable pancreatic cancer involves either protocol or off-protocol therapy. Off protocol therapy involves initial treatment with systemic therapy (gemcitabine alone or in combination for 2 to 6 months) followed by standard-fractionation (50.4 Gy) chemoradiation (gemcitabine or capecitabine as a radiation sensitizer).

SELECTED REFERENCES

1. Breslin TM, Hess KR, Harbison DB, et al. Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration. Ann Surg Oncol, 2001;8:123-132.

2. Crane CH, Wolff RA, Abbruzzese JL, et al. Combining gemcitabine with radiation in pancreatic cancer: understanding important variables influencing the therapeutic index. Semin Oncol, 2001;28(suppl 10)1025-1033.

3. Raut CP, Evans DB, Crane CH, Pisters PWT, Wolff RA. Neoadjuvant therapy for resectable pancreatic cancer. Surg Oncol Clin N Am. 2004;4:639-61.

4. Wolff RA, Abbruzzese JL, Evans DB. Neoplasms of the exocrine pancreas. In Holland JF, Frei E, Bast RC, Kufe DW, Pollock RE, Weichelbaum RR, eds. Cancer Medicine, Sixth Edition. Ontario: B.C. Decker, Inc. 2003, 1585-1614.

5. Wolff RA, Evans DB, Gravel DM, et al. Phase I trial of gemcitabine combined with radiation for the treatment of locally advanced pancreatic adenocarcinoma. Clin Cancer Res, 2001;7:2246-2253.