Resectable pancreatic cancer: The role for neoadjuvant/preoperative therapy

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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 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 superior mesenteric (SMV)-portal vein (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 if short segment venous occlusion is present (i.e. a suitable portal vein above, and a suitable SMV below the area of occlusion); tumor abutment of the SMA of \( \leq 180^\circ \); 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° 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 6th 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 (PD) specimen is evaluated pathologically, the retroperitoneal or SMA 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. 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 margin 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) SMA margin in the absence of information regarding the retroperitoneal dissection, which should be included in the operative note. The R designation should always be listed in the dictated operative report (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 report 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.

Adjuvant therapy

Postoperative adjuvant therapy for resectable pancreatic cancer

Pancreatic cancer is a systemic disease in most patients at the time of diagnosis. Following a potentially curative PD, disease recurs in 80–90% of patients, demonstrating that surgery alone is not an adequate treatment for the majority of patients with localized, resectable pancreatic cancer. While the optimal choice of adjuvant chemotherapy vs chemoradiation remains controversial, recent studies do suggest a modest survival benefit for those patients who receive adjuvant therapy. The delivery of postoperative adjuvant therapy often assumes that all patients who undergo PD receive intended postoperative therapy and that all patients also have all gross tumor removed. However, at least 25–30% of patients who undergo a curative resection do not receive postoperative therapy for reasons that are disease-related (early tumor progression), treatment-related (such as delayed recovery from surgery), or patient-related (medical co-morbidities, patient refusal). The number of patients who undergo surgery but have tumor left behind is not known due to inadequate preoperative imaging, a lack of surgical quality control, and a failure to accurately report (pathologic) margins of resection; incomplete resections are probably more common than we think. This is an important point in data analysis. For example, recent publications of single-institution experiences suggest that local failure rates are lower when either postoperative or preoperative radiation is delivered. This is in contrast to a recent report from a large multi-institutional clinical trial. However, the inability of almost all investigators to assess the completeness of resection following PD suggests that the retroperitoneal margin is undoubtedly often positive, and when negative, is usually measured in millimeters – very similar to the situation with the radial margin in rectal cancer. Clearly, as the quality of preoperative imaging and surgery improves, the value of adjuvant therapies (designed to reduce local recurrence) will decrease. Efforts to reduce local failure rates have been well studied in rectal cancer, where external beam radiation therapy has been proven to decrease the risk of local recurrence. Since it is hard to ensure or validate that a negative surgical margin has been achieved in patients who undergo PD, one may want to exercise caution in eliminating radiation therapy from the treatment of operable pancreatic cancer at this time.

Preoperative therapy for resectable pancreatic cancer

There are many practical and theoretical advantages to preoperative treatment of patients with localized pancreatic cancer. Most compelling is the ability to provide immediate systemic therapy for a disease that
is systemic at diagnosis in virtually all patients. A second more practical advantage is improved patient selection for pancreatic surgery—an operation associated with significant patient morbidity even when performed by experienced clinicians. This improved patient selection arises because patients with rapidly progressive systemic disease are identified as part of the restaging evaluation performed following neoadjuvant treatment prior to planned surgery. In prospective trials, approximately 25% of patients who begin a treatment program of preoperative treatment do not undergo successful resection of their primary tumor as a consequence of disease progression or evolution of clinically significant medical comorbidity. These patients are spared the morbidity and prolonged recovery sometimes associated with PD. In a series of trials performed at our institution, patients who demonstrated disease progression after preoperative chemoradiation had a median survival of only 7–9 months. Thus, many institutions have begun to investigate the role of chemoradiation given preoperatively.

Since 1988, four prospective preoperative trials have been completed at our institution. These trials, performed in sequence, have had identical eligibility criteria using a CT-based definition of resectable disease (as previously described), a uniform surgical technique for the performance of PD, and a standardized system for pathologic evaluation of surgical specimens including resection margins. This has maximized the number of variables held constant while varying only the chemoradiation regimens. All eligible patients were required to have biopsy-proven adenocarcinoma of the pancreatic head.

In our initial preoperative study, 28 patients received a course of continuous infusional 5-fluorouracil (5-FU; 300 mg/m²/day) in combination with standard fractionation external beam radiation therapy (EBRT; 50.4 Gy; 180 cGy/fraction for 28 fractions over 5.5 weeks). The gastrointestinal toxic effects (nausea, vomiting, and dehydration) were severe enough to require hospital admission in a third of patients. Preoperative (post-chemoradiation) restaging radiographic evaluation 4–5 weeks after completing preoperative therapy disclosed evidence of metastatic disease in 25% of patients. Another 15% had intraoperative evidence of metastatic disease at laparotomy for an overall resectability rate of 60%. Median survival for the patients who underwent PD with curative intent was 18 months. The degree of tumor cell kill was graded using a standardized scoring system, and 40% of the resected specimens had a pathologic partial response to therapy (>50% of the tumor cells were nonviable). While the results from this initial trial of preoperative therapy for pancreatic cancer appeared equivalent to those seen with postoperative therapy, the toxicity and hospitalization rate was discouraging. These findings led to a change in the delivery of EBRT in all subsequent preoperative trials performed at our institution.

A chemoradiation program delivered over 2 weeks was designed to avoid the gastrointestinal toxicity associated with standard fractionation chemoradiation delivered over 5.5 weeks, while maintaining the excellent local tumor control achieved with multimodality therapy. Chemoradiation was delivered with 18-MeV photons using a four-field technique to a total dose of 30 Gy (3 Gy/fraction, 10 fractions over 2 weeks). Sequentially performed preoperative chemoradiation trials have evaluated continuous infusion 5-FU, paclitaxel, and gemcitabine, all given as single agents. In our study of short-course EBRT with infusional 5-FU, 35 patients were enrolled, 27 were taken to surgery, and 20 (57%) underwent successful PD. Local tumor control and patient survival were equal to the results with standard fractionation (5.5 weeks) chemoradiation. Of note, only 2 (10%) of the 20 patients who underwent resection developed local-regional recurrence, and the median survival for all 20 resected patients was 25 months. Paclitaxel did not provide an advantage over 5-FU-based chemoradiation programs in terms of resection rate, local treatment effect, or overall survival.

We then moved to gemcitabine-based chemoradiation and performed a phase I study of gemcitabine in combination with EBRT in patients with locally advanced disease. This regimen combined 2 weeks of EBRT with 7 weekly infusions of gemcitabine. The maximum tolerated dose of gemcitabine using this treatment schedule was 350 mg/m²/week, roughly one-third the standard weekly dose. The results of this phase I study were sufficiently encouraging to proceed with gemcitabine-based preoperative chemoradiation in a group of patients with potentially resectable disease. A total of 86 patients were enrolled in this phase II clinical trial from July 1998 to October 2001 (unpublished data). Despite a longer elapsed time from enrollment to surgery (PD) compared with previous trials (11–12 weeks rather than 7–9 weeks), 74% of patients underwent successful PD (compared with 60% with 5-FU-based chemoradiation). A pathologic partial response (>50% of tumor cells nonviable) was seen in just over 50% of the surgical specimens. We have just completed a trial involving a similar number of patients using a combination of gemcitabine and cisplatin, followed by gemcitabine-based chemoradiation prior to planned PD. Current/future trials are combining targeted therapy (bevacizumab, cetuximab) with gemcitabine-based chemoradiation.

Unfortunately, many reports of neoadjuvant therapy for pancreatic cancer have included heterogeneous patient populations, enrolling patients with locally advanced or marginally resectable pancreatic cancer. 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 are subjective and not reproducible. In general, patients with locally advanced pancreatic cancer should not be included in studies of preoperative therapy because their inclusion confounds reports of resection rates, and complicates comparisons to other studies. Therein lies the importance of using accurate, reproducible, anatomic definitions for resectability based on high-quality CT imaging.

Further Reading


