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HIGHLIGHT ARTICLE

An Update on Surgical Staging of Patients with Pancreatic Cancer

Highlights from the "2012 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 19-21, 2012

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Summary

Accurate staging of pancreatic adenocarcinoma is a crucial step in determining the appropriate therapeutic approach to pancreatic cancer and to maximizing life expectancy. Despite the availability of high-quality abdominal imaging, the use of multi-modality imaging and of diagnostic laparoscopy, a portion of surgically explored patients fail to undergo resection secondary to metastatic disease. This review is an update from the 2012 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium of new developments in the staging of localized pancreatic adenocarcinoma. (Abstracts #168, #177, and #212).

Introduction

Pancreatic cancer is the fourth leading cause of cancer death among USA men and women, with a mortality that approaches the incidence of disease [1]. Surgical treatment of pancreatic adenocarcinoma is associated with a significant increase in overall survival; however, in a National Cancer Database study of 127,779 patients with pancreatic adenocarcinoma diagnosed between 1992 and 1998, fewer than 20% of patient received surgical treatment [2]. As pancreatic cancer carries such a poor prognosis, it is important to spare those with unresectable disease the morbidity, treatment delay, and expense of an unnecessary operation. Accurate staging is a crucial step in determining the appropriate therapeutic approach to pancreatic cancer.

What Did We Know Prior to the 2012 ASCO GI Cancers Symposium?

Prior to the widespread availability of high resolution cross-sectional abdominal imaging resection rates after surgical exploration for pancreatic cancer were dismal; in a 1978 review of 61 studies on the diagnosis and treatment of pancreatic cancer between 0% and 33% of patients explored were resected [3]. Contrast-enhanced CT was the first widely-applied non-invasive staging technique [4, 5]. While CT appears to be highly accurate (95%) in predicting unresectability on the basis of local tumor extension, several reports have published high failure rates (11-48%) of attempted resections due to occult metastatic disease undetected by modern CT (reviewed in [6]). This has led most treatment centers to use additional imaging techniques including ultrasound, magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), angiogram, and/or positron emission tomography (PET). While combined-modality imaging has sometimes resulted in higher accuracy of preoperative staging, several studies have demonstrated a persistently high rate of gross metastatic disease at surgical exploration that was undetected by CT, MRI, and FDG-PET/CT [6, 7, 8, 9, 10]. Herein we highlight a single-institution experience staging pancreatic adenocarcinoma with triple-phase CT and laparoscopy (Abstract #168 [11]).

Staging laparoscopy has been suggested to improve the detection of peritoneal and liver metastases; however, several studies have demonstrated false-negative rates remain high, even in experienced hands [6, 10, 12]. In 1991, Warshaw *et al*. studied the peritoneal washings of 40 patients with localized pancreatic adeno-carcinoma, most of which were obtained laparoscopically [13]. Between 25 and 50% of these patients demonstrated positive peritoneal cytology, which was associated with a lower frequency of tumor resectability and lower overall survival. Subsequent reports documented high specificity of peritoneal cytology, but widely varying rates of positive cytology (3-53%), likely due to differences in the populations

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studied (reviewed in [10, 14, 15, 16]). Some surgeons were of the opinion that cytologic yield was so low that routine peritoneal lavage was not indicated [16]. We will discuss Dr. Chen's findings when peritoneal cytology was examined in the setting of neoadjuvant chemotherapy (Abstract #177 [17]).

Finally, fluorescence laparoscopy has been investigated in human bladder [18], lung [19], kidney [20], ovarian [21], and gastrointestinal cancers [22, 23], and has shown promise in increasing the detection and localization of primary and metastatic tumors. We will discuss the most recent findings of a group experienced with fluorescence laparoscopy in a mouse model of metastatic pancreatic adenocarcinoma (Abstract #212 [24]).

What Did We Learn at the 2012 ASCO GI Cancers Symposium?

Is Laparoscopy Still Needed for Staging Resectable Pancreatic Cancer? (Abstract #168 [11])

Santoro *et al*. retrospectively reviewed staging practices in 107 patients receiving surgical treatment for resectable pancreatic adenocarcinoma over a six-year period (2005-2011). All patients were assessed by triple phase-CT for staging and resectability, and 80 (74.8%) individuals underwent staging laparoscopy in a non-randomized fashion. The rate of radiographically occult disease was 17.5% (14/80) in the laparoscopy group; staging laparoscopy identified metastatic disease in eight, sparing these individuals a laparotomy. Four (14.8%) of the 27 patients undergoing laparotomy without laparoscopy demonstrated metastatic disease undetected on CT scan. While laparoscopy missed some metastatic disease, it was effective in reducing surgical morbidity among those patients spared a laparotomy.

Revisiting the Prognostic Significance of Positive Peritoneal Cytology in Pancreatic Cancer (Abstract #177 [17])

Chen *et al*. sought to re-evaluate the role of peritoneal cytology in the setting of neoadjuvant therapy, which is becoming an increasingly common treatment to improve surgical resection of locally advanced pancreatic adenocarcinoma, and may soon be evaluated as a standard treatment for resectable adenocarcinoma. Chen *et al*. retrospectively reviewed 185 patients surgically treated for pancreatic adenocarcinoma over an 11-year period (from 2000 to present), 86 (46.5%) of whom had neoadjuvant therapy. All patients had peritoneal washings at the time of resection. No patient had visible metastatic disease, and pancreatic resection was completed in all cases. Twenty (10.8%) individuals had positive peritoneal cytology, 11 of whom had received neoadjuvant therapy. In univariable analysis, positive peritoneal cytology was significantly associated with worse disease-free and overall survival ($P<0.05$), and 42% of patients with negative peritoneal cytology were alive two years after resection *versus* only 20% of those with positive peritoneal cytology. This relationship persisted in individuals with stage II disease or greater who did not receive neoadjuvant therapy, but peritoneal cytology was no longer significantly associated with disease-free or overall survival among individuals with stage II disease or greater receiving neoadjuvant chemotherapy.

Use of High-Resolution Fluorescence Laparoscopy with Fluorophore-Conjugated Tumor-Specific Antibodies for the Detection of Pancreatic Cancer Metastasis Invisible with Standard Laparoscopy (Abstract #212 [24])

Over the last several years investigators at the University of California, San Diego, CA, USA have used fluorescent proteins to image tumors and to guide surgery in mouse models of human cancer [25, 26]. This group has recently applied this technology to laparoscopy in an orthotopic mouse model of pancreatic cancer [27], utilizing green fluorescent protein (GFP)-expressing human pancreatic cancer cells. Metildi *et al*. present the group's most recent experience with fluorescence laparoscopy in a carcinomatosis mouse model of human pancreatic cancer, this time utilizing fluorescent-conjugated antibody labeling of tumor cells. Two to four weeks after implantation of non-fluorescent BxPC-3 human pancreatic cancer cells, mice were administered fluorophore-conjugated (Alexa Fluor® 488/555, Life Technologies, Carlsbad, CA, USA) anti-CEA antibodies by tail-vein injection. Twenty-four hours later the mice underwent diagnostic laparoscopy with both LED (L9000, Stryker, Kalamazoo, MI, USA) and xenon (X8000, Stryker, Kalamazoo, MI, USA) light sources. Pancreatic tumors were localized using each light mode; post-laparoscopy intravital images served as positive controls. Fluorescent-conjugated antibody labeling increased the sensitivity of staging laparoscopy from 40% using bright light to 96% with fluorescence laparoscopy, which was able to detect sub-millimeter tumor deposits missed by bright light.

Discussion

Diagnostic laparoscopy is feasible, with high success rates between 94 and 100%, and reported morbidity and mortality is low [6]. The best evidence for the oncologic effect of laparoscopy can be found in the colorectal literature: randomized trials have demonstrated wound recurrence, disease-free and overall survival equivalent between laparoscopic and open operations [28, 29]. Moreover, in a population-based Surveillance, Epidemiology and End Results (SEER)-Medicare study of 112 patients who had a laparoscopic procedure *vs*. 791 who had an open procedure, exposure to laparoscopic surgery did not adversely affect survival in the cohort of patients who had a diagnostic laparoscopy but no pancreatic resection [30]. One question that still needs to be answered is the extent of laparoscopic exploration required for adequate staging.

The value of laparoscopy in the detection of superficial liver and peritoneal disease invisible on cross-sectional abdominal imaging must be continually re-evaluated as the quality of both cross-sectional and laparoscopic imaging improves. The added value of laparoscopy in facilitating laparoscopic ultrasound and peritoneal washings should not be overlooked. It has also been suggested that laparoscopy may be superior to laparotomy in the detection of very small (less than 3 mm) metastatic deposits, as it presents a magnified view and allows visualization of the anterior abdominal wall [31]. Recently reviewed literature suggests that with use of routine diagnostic laparoscopy, between 10 and 36% of patients can be spared an unnecessary laparotomy [6]. Based on such findings, several analyses have found diagnostic laparoscopy to generally result in a cost-savings, although modeling methods and assumptions varied [32, 33, 34, 35]. The limitations of the current literature should not be minimized. There is no level I evidence on the efficacy of diagnostic laparoscopy. Series published to date have largely been single-institution, retrospective reviews, and lack clear descriptions of the quality of preoperative imaging, the criteria used to define resectability, the number of R0 resections, and the nature of recurrent disease. Patient samples are often a heterogeneous mix, with localized and locally advanced cancers. Multi-institutional studies addressing these issues can contribute to a standard of care for staging patients with adenocarcinoma.

While fluorescence-laparoscopy has shown great promise in the laparoscopic detection and staging of human cancers, many methods rely on 5-aminolevulinic acid (ALA)-induced protoporphyrin IX (PpIX) fluorescence [20, 21, 22, 23], which can at times label benign lesions [20, 21]. Moreover, the fluorescent signal can be weak; darkening the field to increase fluorescence detection can limit laparoscopic applications. Dr. Metildi *et al.* have developed a method of fluorescence-enhanced laparoscopy that is both cancer-specific, relying on expression of CEA, and that allows identification and localization of tumor while maintaining adequate visualization of the surgical field. Application of this method in human pancreatic adenocarcinoma may help to reduce under staging of patients and increase the utility and power of diagnostic laparoscopy.

Conflicts of interest The authors have no conflicts to disclose

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