CLINICAL PRACTICE UPDATE: COMMENTARY

Tumor Seeding Associated With Selected Gastrointestinal Endoscopic Interventions

Q6 Ferga C. Gleeson, Jeffrey H. Lee, and John M. Dewitt

Department of Gastroenterology, MD Anderson Cancer Center, Houston, Texas

Q4 Metastasis is a complex biologic process by which cancer cells spread from a primary tumor site to 1 or more secondary locations. These cells follow the seed and soil hypothesis, and disseminate via a hematogenous or lymphatic route to predisposed compatible microenvironments. The biologic principles that govern cancer metastasis are poorly understood. The stromal or extracellular matrix interaction with metastatic cells is vital to the proliferation of cells and determines their behavior.

Device seeding or implantation of tumor occurs because of iatrogenic metastasis that may lead to modification of tumor stage. This may occur when diagnostic or therapeutic needles are used to sample or ablate a malignant lesion. The inducement of this form of metastasis should not be disregarded. For example, the incidence from radiology literature is approximately 0.005%–0.009% for percutaneous abdominal biopsies.[1] A systematic review and meta-analysis of observational studies noted that the incidence of needle tract seeding following biopsy of hepatocellular carcinoma was 2.7%.[2] A retrospective study of percutaneous radiofrequency ablation–associated tract seeding in a hepatocellular carcinoma population was 1.6%.

In this commentary, we highlight what is currently known with respect to the tumor seeding risk and occurrence in procedures performed by gastroenterologists. Specific procedures at risk include:

1. Percutaneous endoscopic gastrostomy (PEG) tube placement in patients with oropharyngeal or esophageal cancer.
2. Endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) in the setting of cholangiocarcinoma (CCA) and pancreas neoplasia.
3. Endoscopic resection of early cancer and subepithelial tumors (SETs).
4. Inadvertent perforation in the presence of gastrointestinal cancer.

Optimal Percutaneous Endoscopic Gastrostomy Technique for Patients With Oropharyngeal and Esophageal Cancer

Placement of PEG tubes initially described by Gauderer in 1980 is a commonly performed procedure with technique variations to include the pull (Ponsky), push (Sachs-Vine), introducer (Russell), and Versa (T-fastener) methods. The pull technique is the most commonly performed, but special consideration is needed regarding placement to minimize stomal metastatic deposits in patients with oropharyngeal and esophageal cancer. Our surgical colleagues have identified that the incidence of laparoscopic port-site metastasis in incidental gallbladder cancer has decreased from 18.6% to 10.3% because of heightened awareness and surgeon education in relation to the problem, vigilant preoperative investigation, and referral to hepatopancreatobiliary specialists when there is any suspicion of gallbladder cancer.[3]

A prospective evaluation of pull-style PEGs placed in patients with oropharyngeal and esophageal tumors revealed malignant cells in 22.5% of stoma site or PEG tube brush cytology specimens obtained immediately following tube placement. Sixteen weeks later, malignant cells were again evident by cytology in 9.4% at the local PEG site and only in locations with initial documentation of malignant brush cytology samples. Furthermore, all cases with implantation metastases were from esophageal squamous cell carcinomas in an older age population with higher tumor stages.[4] A subsequent retrospective assessment of the incidence of abdominal wall metastases following PEG placement in patients with oropharyngeal cancer was 0.64%.[5] Therefore, the pull-through PEG placement method should be avoided in all patients with oropharyngeal or esophageal cancer and the introducer PEG method is favored instead.[6]

Endoscopic Ultrasound Pearls in the Setting of Cholangiocarcinoma

Tissue confirmation is highly desirable for management of patients with suspected CCA. The growing utility

Abbreviations used in this paper: **CCA, cholangiocarcinoma; EFTR, endoscopic full-thickness resection; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; PEG, percutaneous endoscopic gastrostomy; SET, subepithelial tumors.**

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of EUS for CCA verification and staging is driven by the technical limitations and insensitivity of endoscopic bile duct cytopathology sampling. Many hepatobiliary centers now offer liver transplantation for unresectable hilar CCA with a 5-year survival approaching 75%. Endoscopic biliary drainage is recommended as the optimal method for preoperative biliary drainage because percutaneous transhepatic biliary drainage increases the incidence of seeding metastasis and shortens postoperative survival.[7]

There is much controversy concerning primary tumor FNA because it may permit an otherwise unattainable diagnosis but it is also deemed to facilitate tumor cell dissemination albeit in a limited number of studies.[8] In general, risk factors for FNA cytology related needle tract seeding include larger tumor size, large-caliber needles, multiple needle passes, a high-grade tumor, and scanty normal parenchyma along the needle tract.[9] A study of 191 patients with locally unresectable hilar CCA who underwent a liver transplant evaluation included 16 patients who underwent primary tumor transperitoneal FNA at various referral centers before assessment. Peritoneal metastasis was discovered at surgery in 83% of patients who underwent preoperative transperitoneal FNA, compared with only 8% of patients who did not ($P = .0097$).[10] The study groups had similar CA 19-9 levels, frequency of mass detection, tumor size, and histology. Therefore, performance of a primary hilar tumor FNA may render a patient with CCA ineligible for entry into a liver transplantation protocol and is best to avoid or at least discuss management in advance of an EUS with a transplant hepatologist.

However, EUS should be performed to evaluate suspicious lymphadenopathy in patients with CCA who are considered for liver transplantation because detection of malignant lymphadenopathy precludes unnecessary neoadjuvant chemoradiation or staging laparotomy. Furthermore, EUS is indicated regardless of computed tomography and/or magnetic resonance imaging lymph node morphology findings because these studies lack sufficient sensitivity for lymph node detection and poorly discriminate benign from malignant lymph node infiltration. Thorough sampling is necessary irrespective of node morphology because of the poor predictive value of EUS features alone.[11] Patients with a negative FNA must undergo a subsequent staging laparotomy before liver transplantation to verify absence of nodal disease before proceeding in the next steps in management.

Endoscopic-Guided Biopsy of Pancreatic Neoplasms

When available, EUS has become the primary technique used to biopsy accessible abdominal lymph nodes or masses. The most common abdominal lesions sampled by EUS include solid pancreatic neoplasms, such as ductal adenocarcinoma, or cystic pancreatic neoplasms, such as intraductal papillary mucinous neoplasms. Pancreatic cystic neoplasms have a very low malignant potential and fluid sampled from these cysts is relatively insensitive (60%) for malignancy. Therefore, current American Gastroenterological Association guidelines recommend EUS-FNA of incidentally discovered, asymptomatic pancreatic cysts only when 2 of 3 high risk features (size >3 cm, dilated pancreatic duct, or solid component) are present.[12] Compared with cystic tumors, sampling of solid pancreatic lesions has a higher sensitivity for the correct pathologic diagnosis and detection of malignancy. Therefore, all solid pancreatic lesions are generally sampled by EUS if a tissue diagnosis will guide clinical management.

The clinical information gained from pathologic specimens or fluid analysis of these lesions must be balanced against the risk of the procedure. EUS-guided FNA or EUS-guided fine-needle biopsy is relatively safe with an overall adverse rate of 1%–2%.[13] One rare adverse event of sampling the pancreas or other abdominal sites includes needle implantation of neoplastic cells into the punctured bowel wall or peritoneal cavity. The overall incidence of needle tract seeding following EUS-FNA is unknown and there are no prospective data evaluating this question. A recent review[14] documented 15 case reports published since 2003 describing needle tract seeding following EUS-FNA. Twelve of these 15 were caused by biopsy of a pancreatic cancer or cyst and all biopsies involved transgastric sampling of a lesion in the body and tail. These lesions presented a median 20 months (range, 3–48) after biopsy and typically were identified initially on cross-sectional imaging or as a subepithelial lesion on endoscopy. The exact mechanism of abdominal or mural tumor implantation is unknown; however, it may be presumed that implantation is caused by direct placement of tumor cells directly into the gastrointestinal wall or peritoneal cavity during needle withdrawal or the to-and-fro motion of biopsy. This hypothesis is supported by evidence of malignant cells within the fluid of the gastrointestinal tract during EUS-FNA of pancreatic cancer.[15]

Because of this potential complication, the safety or necessity of EUS-guided biopsy, particularly in the pancreas, has been raised in 2 principle situations: biopsy of potentially surgically resectable tumors; or transgastric sampling of malignant tumors in the pancreatic body and tail where surgical resection of the needle tract may not be performed. Several retrospective, single-center studies have documented that EUS-FNA of the pancreas does not increase the incidence of needle tract seeding, implantation of tumor cells in the peritoneal cavity, or decrease overall survival.[16–20] In a study of patients with nonmetastatic pancreatic cancer who underwent percutaneous (n = 43) or EUS-guided (n = 46) biopsy followed by preoperative chemoradiation, Micames et al[16] found that intraoperative detection of peritoneal carcinomatosis was lower in the EUS-FNA group (2.2%) compared with the percutaneous group (16.3%; $P < .025$). Similarly, Ngamruengphong et al[17] reported that among patients undergoing surgery