Pancreatic cancer: current standards, research updates and future directions

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J Gastrointest Oncol 2011; 2: 123-125. DOI: 10.3978/j.issn.2078-6891.2011.037

Adenocarcinoma of pancreas is the fourth most common cause of cancer-related death among U.S. men and women. Due to lack of specific symptoms and effective screening modality, about 80% of pancreatic cancer cases are diagnosed at advanced stage with locally advanced or metastatic disease. Surgical resection remains the only curative therapy for pancreatic cancer patients, and 5-year survival for surgically resected patients is only 30%. Therefore, more research and novel strategies are urgently needed to understand biology better, detect the disease sooner, and develop better treatment to improve survival and quality of life. In this focused issue, we have covered important topics related to biology, detection and treatment of pancreatic cancer.

Imaging modality is important to identify patients at risk for pancreatic cancer. With the advance of imaging modality and technique, there has been significant improvement in identifying smaller tumor in pancreas. At present time, only about 15-20% of patients have resectable disease at the time of diagnosis. Preoperative staging to assess the extent of disease is critical to select patients for complete (R0) resection. Besides distant metastasis, lesions involving superior mesenteric artery and/or celiac axis are generally considered unresectable. Pre-operative evaluation with computed tomography and other modality such as endoscopic ultrasound can better select patients for R0 resection. Tummala et al. have reviewed different imaging modalities and their utility in assessing patients with suspicious pancreatic lesion, and identifying unresectable disease in patients with pancreatic cancer (1).

The improvement in perioperative care and surgical techniques has led to decrease in mortality and morbidity for patients receiving resection of pancreatic cancer. Kim and colleagues have reviewed the surgical management including preoperative evaluation, different surgical techniques including minimally invasive surgery and advances in perioperative care (2). Furthermore, they have discussed the recent consensus definition of borderline resectable disease, which has emerged as a unique entity with active clinical investigation.

Chemotherapy and chemoradiation (CRT) are treatment options for resected pancreatic cancer as adjuvant treatment, and as primary treatment for locally advanced disease not amenable for resection. There is no standard neoadjuvant treatment for patients with resectable or borderline resectable disease. Clinical studies using chemotherapy followed by CRT as neoadjuvant treatment in locally advanced disease have demonstrated benefits in converting borderline resectable to resectable disease. Varadhachary has provided a thorough review of the staging systems for borderline resectable lesions, rationale and clinical investigation of preoperative therapies, and the utility of predictive biomarkers (3).

Less than half of pancreatic cancer patients in U.S.A. are being referred to high-volume centers for surgery (4). Many reports have shown pancreatic cancer patients undergoing surgery have better outcomes at high-volume hospitals, and National Comprehensive Cancer Network (NCCN) recommends resection to be done in a center with more than 15-20 resection experience annually (5-7). Moreover, regardless the volume of the hospital, the surgeon experience seems to contribute most to the outcome of patients receiving pancreatic surgery (8). Cheng and colleagues of a multidisciplinary team in a community hospital have reported a similar outcome of pancreatic surgery compared to published results from high-volume centers (9). This echoes the importance of multidisciplinary approach and experienced surgeon in managing pancreatic cancer.

Adjuvant chemotherapy with gemcitabine or 5-fluorouracil has been shown in several large randomized

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Submitted Aug 14, 2011. Accepted for publication Aug 15, 2011.
Available at www.thejgo.org

ISSN: 2078-6891

studies to significantly increase the 5-year survival (from approximately 10 to 20%), and should be offered if the patient is fit after surgery (10-12). Adjuvant CRT is a heavily debated topic, with practices in U.S.A. often favoring the use of this adjuvant approach, but not recommended in Europe to lack of any randomized study to show survival benefit of this strategy (7, 13). For locally advanced pancreatic cancer not amenable for resection, the treatment options could either be chemotherapy alone or chemotherapy in conjunction with CRT. By using advanced radiotherapy modalities such as intensity modulation and stereotactic body radiation therapy, the toxicity of radiotherapy could be reduced and dose escalation of radiation becomes possible to improve locoregional control. Wang and Kumar have presented an excellent review on the historic evolution of CRT, and the application of modern radiotherapy modalities in the treatment of pancreatic cancer (14).

Gemcitabine has become the standard therapy for advanced pancreatic cancer since its approval more than a decade ago. Subsequent investigational strategies have included the addition of targeted or other cytotoxic agents to gemcitabine, and all yielded disappointing results except 2-week gain of survival by adding erlotinib to gemcitabine (15). The addition of other targeted agent such as cetuximab or bevacizumab to gemcitabine, on the other hand did not result in any survival improvement (16). The combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) has shown improved overall survival by 4 to 5 months vs. gemcitabine in a phase III study involving more than 340 patients with metastatic pancreatic cancer (17). FOLFIRINOX has become a new standard for patients with advanced pancreatic cancer, as recommended by NCCN; this regimen should be used with caution due to significant toxicities and lack of safety data in patients with suboptimal performance status. Nevertheless, identification of novel pathways and incorporating novel targeted agents to standard regimen are the continuing efforts of research to advance the treatment (18).

Emerging data have indicated epithelial-mesenchymal transition (EMT) plays important role in the development and progression of pancreatic adenocarcinoma. During EMT, cancer cells shed off epithelial characteristics and pick up properties of mesenchymal cells with increased motility and invasiveness. Therefore EMT of pancreatic cancer may provide a promising novel target for therapeutic development. Pan and Yang have reviewed EMT of pancreatic cancer with involved signal transduction pathways and its therapeutic implications (19).

Nanomedicines are pharmaceuticals prepared by manipulating matter at the nanoscale (< 1000 nm); i.e. manipulations at less than 1000th of a millimeter. The vast majority of nanomedicines are the result of the packaging of pharmacologically active compounds within nanovectors (5 ~ 800 nm). Nanovector formulations have several advantages over conventional chemotherapy: protecting drugs from being degraded in the body before they reach their target, enhancing uptake of drugs into tumor, allowing for better control over the timing and distribution of drugs to tumor tissue, and preventing drugs from interacting with normal cells thus decreasing the toxicities. In this issue, Tsai et al. present a comprehensive review of nanovector-based therapies in patients with advanced pancreatic cancer (20).

Palliative care is an important part of treatment for patients with advanced pancreatic cancer. Pain is frequently reported by patients with advanced disease, and about 10 to 15% of patients have inadequate pain control with routine management (21). Pain syndromes are mainly due to the proximity of pancreas to a number of other critical structures: the duodenum, liver, stomach, jejunum, and transverse colon. In this issue, Khokhlova and Hwang present the rationale and data of high intensity focused ultrasound (HIFU), a novel non-invasive ablation modality, for palliative treatment of pancreatic cancer (22). HIFU delivers ultrasound energy from an extracorporeal source to tumor, and causes thermal damages of tumor tissue at the focus without affecting surrounding organs.

Although the treatment of pancreatic cancer remains a daunting task, it is entering a new avenue with the development of novel strategies, innovative trials and multidisciplinary approach. Additionally, identification of prognostic and predictive markers can personalize treatment and select patients for target-driven therapy. Collaborative efforts have been put into action to facilitate the translation of bench research to bedside study (23, 24). We should anticipate progress beyond baby steps in the not-too-distant future.

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