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Review article

How to treat pancreatic adenocarcinoma in elderly: How far can we go in 2017?

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ABSTRACT

Pancreatic adenocarcinoma is one of the most fatal cancers that frequently affects older patients. Limited data suggest that older patients are as likely to benefit from surgery, radiation, and chemotherapy as younger patients. The only potentially curative approach for pancreatic cancer is surgery but this is only performed in less than 20% of patients considered resectable. With improvements in surgical techniques, older patients without major comorbidities show a course of disease after resection similar to that of younger patients. The use of adjuvant chemotherapy in an attempt to prolong survival is therefore reasonable for this population of patients. Historically, patients with locally-advanced disease will be offered gemcitabine as standard chemotherapy, with radiotherapy considered at a later time. In the majority, metastatic patients will preferably be offered gemcitabine chemotherapy, which can be used at a lower dose in frail or very old patients. In some cases in patients in a very good health condition, two recent intensive chemotherapies can be proposed with modified doses and a close follow-up: the 5-fluorouracil, leucovorin, irinotecan, oxaliplatin (FOLFIRINOX) regimen and the combination of gemcitabine plus *nab*-paclitaxel. For older patients with terminal disease and palliative needs, which is the majority of cases, better use of pain control and palliative measures can be beneficial. Each of these issues will be examined in detail in this review.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is very common in western countries and in Japan and remains one of the leading causes of cancer

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death in men and women worldwide; this cancer is responsible for 6% of all cancer deaths [1]. In 2010, the estimated incidence of PDAC in the Unites States was 43,140, or nearly 4% of all cancers in both sexes [2], with a high proportion of older individuals developing this disease. Despite decades of efforts and in contrast to improved survival for many cancers, PDAC life expectancy remains poor, with a 5-year survival of 5–10% [3]. Treatment of this disease is based on a multidisciplinary approach that includes surgery, radiotherapy and chemotherapy, although the impact of therapy in metastatic cases is only palliative. Until now, surgery offers the only chance of cure but, unfortunately, less than 20% of patients are candidates for surgical resection. Treatment with definitive surgery in recent decades in Phase III trials demonstrates 5-year survival rates of 8% to 11% [4]. Although surgery was a necessary component of curative therapy, adjuvant cytotoxic agents have been used to maximize survival, such as gemcitabine or fluorouracil (5-FU) in monotherapy or both combined (gemcitabine + capecitabine) [5,6], leading to a 3-year survival rate of 20 to 35%. However, the majority of patients have advanced disease at the time of diagnosis, and despite advances in understanding biological abnormalities, progress in the treatment of these advanced cases has been limited. In 1997, a randomized trial in patients with advanced symptomatic pancreatic cancer compared gemcitabine to fluoro-uracil (5FU). Gemcitabine monotherapy resulted in longer survival compared to that of the 5FU arm, and it was approved as a standard care in this setting [7]. Recently, a significant improvement in survival was achieved with two new chemotherapeutic regimens, the FOLFIRINOX trial [8], combining three major drugs: 5FU, oxaliplatin and irinotecan, and the combination of gemcitabine plus *nab*-paclitaxel [9]. Both the FOLFIRINOX strategy and the gemcitabine plus *nab*-paclitaxel regimen showed in the experimental arm a much longer overall survival (OS) compared to that of gemcitabine monotherapy arm and this occurred without a decreased quality of life. These 2 new treatment paradigms have been internationally approved as first-line treatments for metastatic PDAC. However, in both trials, those regimens were mainly offered to patients with good overall health, and the median patient age was relatively young, 61 and 63 years old, respectively. No specific age limitation was established in the *nab*-paclitaxel trial (ranging from 27 to 88 years) but patients over 75 years of age were excluded from the FOLFIRINOX trial due to possible drug toxicity.

In the United States, the average age at diagnosis for PDAC is 72 years, and one-third of the patients were older than 75 years in the Surveillance, Epidemiology and End Results (SEER) series [10]. In Japan, 46% of the 24,400 patients with PDAC were older than 75 years [11]. These patients are commonly excluded or under-represented in clinical trials, and the rare data available come from retrospective series without precise guidelines to aid in the treatment of pancreatic cancer in this particular subgroup. Thus, the goal of medical collaboration between oncologists and oncogeriatrician is twofold: to control the cancer in the most effective way possible and to maximally preserve autonomy of the older patient. To assess patients, the geriatrician can use the Standardized Geriatric Evaluation (SGE), which is a multidisciplinary evaluation based on the evaluation of medical problems (comorbidities) and the functional status (measurement of the individual's disability) of the patient. The cognitive state and the psychosocial, nutritional and environmental status of the individual are inconsistently evaluated in routine practice. The role of the geriatrician in the management of PDAC differs, depending on the disease stage, and starts from the diagnosis (managing the necessity, for the majority of cases, to obtain histological proof of PDAC by endoscopic ultrasound-guided biopsy of the pancreatic mass or percutaneous biopsy of a metastasis) to the best supportive care at the end of life. The geriatrician can improve the overall care by helping oncologists to better determine which patients can receive aggressive treatment (surgical resection and/or systemic chemotherapy) or by offering less difficult treatment for frail patients, assisting in postoperative recovery, managing side effects and improving the return to 'normal life'. It is important to mention that most centers will not have access to a geriatrician, and the oncologist must take on this role by conducting a thorough assessment and providing the best possible care for the older patients. Finally, treatment choices should also incorporate an assessment of life expectancy to provide guidance on whether the offered therapy is appropriate for each patient. The goal of this review is to present current PDAC management strategies, focusing on the specific issues of older patients and geriatric management.

2. Diagnosis, Staging, Pathological Evidence of Adenocarcinoma

2.1. Diagnosis

Several studies have shown that older patients are less likely to be staged than younger patients and with advanced age, more women are diagnosed proportionally without any differences in tumor grade, location (head/body/tail) or in the incidence of local spread [12]. Although this subgroup appears to present with earlier-stage disease, they seem to have a worse overall 5-year survival compared to younger patients [13,14] mainly due to less aggressive treatment strategies. It is known that numerous molecular events have been found in the pathogenesis of pancreatic cancer, such as the K-ras mutation and the p53 tumor-suppressor gene mutation. *Sato* et al. showed that overexpression of p53 mutations in tumors was significantly associated with a worse prognosis and was more frequent with aging, regardless of stage [15]. Further research is still needed to determine how aging is involved in the pathogenesis of PDAC. Of note, blood tests cannot help out screen for PDAC.

2.2. Staging

The first line investigation for PDAC screening/staging should use imaging such as a transabdominal ultrasound and/or contrast-enhanced ultrasonography, especially in older patients with abdominal pain or jaundice [16,17]. However, abdo-pelvic computed tomography (CT) scan with iodine injection, which is limited to patients without renal dysfunction, or abdominal magnetic resonance imaging (MRI) than can probably be safely performed, are more accurate in determining the tumor stage and its proximity to surroundings structures [18,19].

The good quality of preoperative imaging is challenging to determine the resectability of the tumor, particularly in some cases that are considered 'borderline resectable'. Thus, older patients who cannot benefit from high quality CT scan due to the limitations of the imaging related to major organ dysfunctions, may have underestimated PDAC extension.

2.3. Cytological Diagnosis

Endoscopic retrograde cholangiopancreatography (ECRP) can be used first to image the pancreatic duct and biliary tree but then to perform a cytological diagnosis by sampling or brushing the pancreatic duct. However, sometimes more than 2 or 3 procedures are needed to prove the histological diagnosis of adenocarcinoma and leads to repeat invasive procedures with general anesthesia that may be at risk for older patients. Considering the challenges in older patients to obtain tissue diagnosis, each repeat invasive procedure has to be discussed in a case-by-case basis.

Thus, depending on the radiological and endoscopic findings, older patients with PDAC should be divided into three subgroups: resectable, locally-advanced and metastatic PDAC patients with different treatment goals that shoult take into account the general medical condition of each patient.

3. Surgery for Resectable Disease

The main contraindications for surgery in PDAC patients are peritoneal carcinomatosis, metastases, distant lymph node involvement and involvement of the celiac axis or the superior mesenteric artery as assessed by imaging (CT scan or endoscopic ultrasound).