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Highlights in Pancreatic Carcinoma

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Editorial

Pancreatic cancer is a malignant tumor with poor prognosis. In the Western World, during the lasting two decades, a surprising increase of incidence and cancer related mortality was observed, despite significant progress in terms of early diagnosis and treatment. In Italy the peak of incidence is registered between the sixth and the fifth decade of life and it represents the fifth leading cause of cancer death in males and fourth one in females and five years survival is less than 10% [1]. Despite medical progress, there are no mass screening procedures but closers monitoring could be performed for high-risk subjects. The risk factors associated with pancreatic cancer are still not defined although few studies show some reliable data [2,3]. Smokers have a triplicate risk of incidence than no-smoking (relative risk: 1.74) and smoking cessation results in a risk decrease because nitrates induce inactivating mutations of the K-ras. Obesity is the second most important risk factor for the development of pancreatic cancer [4]: a high body mass index (BMI> 30kg/m^2) is associated with greater risk of death from pancreatic cancer by 20% to 40% [5]. Other related conditions with pancreatic cancer are diabetes mellitus type 1 and 2 and chronic pancreatitis [6]. Regarding genetics, 10% of patients with pancreatic tumors present a genetic predisposition [7,8]. The most important mutated genes involved are FANCA [9,10], BRCA2 [11], PALB2 [12], PRSS1 [13], SPINK1 [13], STK11/LKB1 [14], CDKN2A [15], MSH2 and MLH1 [16]. Recently in USA a screening program for high-risk people, by endoscopic ultrasound, able to identify 10% of pancreatic cancer at pre-invasive stage has been described [17]. Diagnoses and resectability criteria are obtained after the evaluation of several factors. Nowadays, the multi-slice CT is the best method for both diagnosis and staging: pre-contrast study allows excluding the presence of calcifications and allowing obtaining a differential diagnosis with chronic pancreatitis [18]. CT abdomen +/- MRI offers high levels of sensitivity in the differential diagnosis of adenocarcinoma (89% to 97%) assessing the unresectable tumors (89% to 100%) in patients with pancreatic suspicious lesion [19]. Abdominal Ultrasound (US) with color Doppler is the first step in preoperative evaluation. Color Doppler has 84% accuracy for identification of porto-mesenteric axis invasion and 87% for evaluation of the arterial infiltration [20]. US are a complementary technique to CT and MRI in the pancreatic cancer study and it is useful to differentiate between benign and malignant disease [21,22]. According to several studies MRI is still the best diagnostic tool in pancreatic diseases [23]. PET-CT is indicated for study of metastatic disease to evaluate complete remission, recurrent disease and for differential diagnosis between postoperative or post radiotherapy scar tissue [24]. CA 19.9 is the most useful tumor marker for diagnosis of pancreatic cancer. The data about the predictive value in patients with advanced disease are conflicting [25,26], while it appears to have a value as a prognostic survival marker when blood levels of CA 19.9 decrease postoperatively [27-33] (Table 1). Pancreatic head carcinomas are sub classified in pancreatic carcinomas, ampullary carcinoma, and carcinoma of the lower third of the bile duct and periampullary carcinomas, the last with best prognosis [34]. In case of malignancy suspicion a correct histological diagnosis fine needle aspiration under ultrasound guidance, or true-cut biopsy, can be useful but is not mandatory. Cytology on fine needle aspiration has a sensitivity and specificity of 69% and 100% for tissue diagnosis, respectively. A histological or cytological intraoperative biopsy should be performed when an inoperable tumor is identified. Tumor grading, anatomical origin, evaluation of surgical resection margins and evaluation of lymph node involvement are the most important parameters with influence on the overall prognosis. The grading of pancreatic cancer is based on WHO histopathological criteria and it is an independent prognostic indicator. The evaluation of surgical resection margins in pancreaticoduodenectomy includes the margin of the bile duct resection, pancreatic transection with the Wirsung duct and gastroduodenal margins. For standardized evaluation of resection margins, is used R classification (residual tumor): Rx (cannot be defined the presence of residual tumor); R0 (no residual macroscopic and microscopic tumor); R1 (microscopically residual tumors are detected); R2 (macroscopic residual) [35]. Although, given the discrepancy between several international guidelines, it is very

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hard to standardize recommendations. Classification and staging systems reported by WHO in 2010 [36-38] and the TNM/AJCC 2009 [39] should be considered as cornerstones. Lymphnode involvement is a paramount prognostic factor and removal of 12-15 lymph nodes is considered oncologically adequate.

TNM system

Primary tumor

Tx: The primary tumor cannot be defined

T0: No evidence of primary tumor

Tis: carcinoma in situ, including PanIN-3 (Pancreatic Intraepithelial Neoplasia)

T1: tumor limited to the pancreas, 2 cm or less in diameter greater

T2: tumor limited to the pancreas, more than 2 cm in greatest diameter

T3: tumor extends beyond the pancreas without involvement of the celiac axis or superior mesenteric artery

T4: tumor involving the celiac axis or the mesenteric artery

Regional lymph nodes

Nx: regional lymph nodes cannot be assessed

N0: no metastases to regional lymph nodes

N1: metastases to regional lymph nodes

Distant metastasis

Mx: the presence of distant metastasis cannot be defined

M0: no distant metastasis

M1: presence of distant metastases

Staging

Stage 0: TisN0M0

Stage IA: T1N0M0

Stage IB: T2N0M0

Stage IIA: T3N0M0

Stage IIB: T1-3N1M0

Stage III: T4 any NM0

Stage IV: any T any N M1

Surgery is the only curative treatment for pancreatic adenocarcinoma [40,41], but unfortunately only 20% of patients with pancreatic carcinoma has a resectable disease and the overall survival does not exceed 20% [42,43]. In case of distant metastases or infiltration of adjacent viscera - with the exception of biliary tract and duodenum - surgery is contraindicated, while lymph node involvement or mesenteric arteries (celiac, superior mesenteric artery, hepatic artery) and main venous trunks infiltration might considered as relative criteria of unresecability. According to most recent scientific literature, the disease is considered borderline in case of adhesion or infiltration <180º of the spleno-porto-mesenteric venous axis with the possibility of tangential resection or full channel resection and reconstruction. The disease is locally advanced when the infiltration is >180º and/or in case of occlusion of spleno-port-

Table 1: World Health Organization (OMS) pancreatic tumorsis summarized in [28].

Entities nosographic	%
Ductal adenocarcinoma "common" ductal Adenocarcinoma variants	80 5
Serous cystadenoma	1
Mucinous cystic neoplasm	1
Intraductal papillary mucinous neoplasm	5
Acinar cell carcinoma	1
Pancreatoblastoma	1
Solid-pseudopapillary neoplasm	1
Neuroendocrine neoplasms	5

mesenteric venous axis and/or presence of portal vein thrombosis and/or infiltration of the celiac, superior mesenteric artery, hepatic artery, vein inferior vena cava, aorta [44]. A meta-analysis has shown that arterial resections were encumbered by an increased risk of post-operatory mortality and a worse survival at 1 year and 3 years [45]. The same fate has also been reported in patients who have experienced a venous resection [46]. Therefore, the debate is open and in patients with "borderline resectable" cancer or at high risk of incomplete resection according to pre-operative imaging a neoadjuvant approach is the cornerstone of a multidisciplinary treatment [47,48]. In addition, according to several authors' symptoms lasting more than 40 days, the value of CA 19.9> 200 U/mL, the presence of a poorly differentiated tumor (G3/G4) and R2 resection should be considered as independent factors associated with early mortality after surgical resection [49]. In particular, the presence of symptoms lasting >40 days, CA 19.9 >200 U/mL and a G3/G4 tumor determine a risk of mortality within 12 months after surgery equal to 60% for resections R0, to 75% for R1 resection and to 90% for resections R2. The presence of a poorly differentiated tumor is a negative factor in terms of overall survival and disease-free survival [50,51]. In a series of 169 patients undergoing surgical resection for resectable poorly differentiated pancreatic cancer, the disease-free survival was 25% at 2 years and 14% at 5 years with a median of only nine months [53]. The same study showed that adjuvant treatment conferred a benefit in terms of higher survival for G3 tumors compared to G1 and G2 forms. Radical surgery associated to lymphadenectomy is a golden standard and might have a curative value.

Pancreaticoduodenectomy is the procedure of choice in the treatment of pancreatic carcinoma of the head and uncinate process and in addition a biliary drainage should be performed selectively for patients presenting cholangitis or obstructive jaundice with secondary renal impairment. Lymphadenectomy should also include the peripancreatic stations with the hepatic and retroportal lymph nodes [53]. The procedure is associated with a lower risk of mortality in high-volume centers (5%) and with a risk of morbidity mainly related to the development of postoperative pancreatic fistula [54]. Left splenopancreasectomy with lymphadenectomy of peripancreatic stations is the treatment of choice for tumors of the body and tail of the pancreas [55,56]. In addition total pancreatectomy should be reserved to selected cases (non disease-free margins and PanIN-3). This surgical technique presents high risk of morbidity and post-operative complications such as uncontrolled diabetes which is the leading cause of death.

Nevertheless, following surgical approach alone the median overall survival (OS) range is 15-25 months. The adjuvant

chemotherapy represents the current standard of care for pancreatic adenocarcinomas in stage Ia-III which underwent R0-R1 surgery and in selected cases is possible a subsequent treatment with chemoradiation. Currently, the only evidence-based treatment is a monochemotherapy with Gemcitabine IV or 5 Fluorouracil/folinic acids IV, with an improvement of 10% at 5 years OS and a significant reduction for recurrence risk [57-60]. Nowadays, many clinical trials investigate the addition of Nab-Paclitaxel or Capecitabine to Gemcitabine to improve the OS, but results are discordant [61]. Dedicated clinical trials results are still not available and the standard of care of these patients remains controversial: in the routine practice the regimens used in metastatic setting such as FOLFIRINOX and Gemcitabine plus Nab-Paclitaxel are recommended [62]. First specific international trials are going to be designed as the phase II as "LAPACT" with the combination of Gemcitabine plus Nab-Paclitaxel [63,64]. Unresectable locally advanced disease or metastatic disease represents 70% of all patients with pancreatic cancer and require palliative treatments especially for symptoms due to biliary obstruction with jaundice [65-67]. For these patients the best palliation is represented by the placement of a biliary stent endoscopically: a plastic stent in patients with limited life expectancy and a short covered metal stent in patients with longer one. The plastic stent could be placed even in those patients with borderline and locally advanced disease in which it is expected down-staging after neoadjuvant chemotherapy/chemoradiotherapy [68,69]. Regardless of stage of disease, in patients with neoplastic duodenal stenosis with subsequent digestive obstruction and obstructive jaundice it should be considered derivative biliary-digestive surgery. Other possible approaches to locally advanced pancreatic cancer are the use of Radiofrequency Ablation (RFA) or Irreversible Electroporation (IRE). These procedures are reported in literature to be safe and feasible although there is a lack of randomized studies to corroborate these findings. RFA is an ablative procedure consisting in high frequency current applied to neoplastic tissue via one or more needle electrodes that generates a local high temperature, causing coagulative necrosis and protein denaturation. Instead, IRE is a non-thermal technique that uses short high-voltage electric pulses conducted via monopolar electrodes causing irreversible damage to cell membrane and thus activating apoptotic pathways. The main advantage of this procedure compared to RFA is the preservation of surrounding structures like nerves or blood vessels [70].

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