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Review

Metastases of pancreatic adenocarcinoma: A systematic review of literature and a new functional concept

Marco Cannistrà [a, *], Michele Ruggiero [a], Alessandra Zullo [b], Simone Serafini [a], Raffaele Grande [b], Bruno Nardo [a, c]

[a] Department of Surgery, Annunziata Hospital of Cosenza, Cosenza, Italy
[b] Department of Medical and Surgical Sciences, University of Catanzaro, Italy
[c] Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna, Italy

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ABSTRACT

Introduction: Pancreatic cancer, especially Pancreatic Adenocarcinoma, is still associated with a high mortality and morbidity for affected patients notwithstanding considerable progresses in diagnosis and both surgical pharmacological therapy. Despite metastases from colorectal, gastric and neuroendocrine primary tumor and their treatment are widely reported, the literature has been rarely investigated the impact of localization and numbers of pancreatic metastases. This study performed a systematic analysis of the most recent scientific literature on the natural history of Pancreatic Adenocarcinoma focusing attention on the role that the "M" parameter has on a possible prognostic stratification of these patients.
Material and Methods: PubMed and Science Direct databases were searched for relevant articles on these issue.
Results: Initial database searches yielded 7231 studies from PubMed and 29101 from Science Direct. We evaluated 1031 eligible full text articles.
Conclusions: An updated insight into the world of Pancreatic Tumors might help physicians in better evaluating mechanisms of metastases, patients selection and survival and in programming appropriate interventions to modify the worst outcomes of advanced disease.

1. Introduction

Pancreatic cancer is the fifth commonest cause of cancer death in the world [1,2] and several risk factors such us tobacco smoking, diabetes mellitus, obesity, heavy alcohol drinking, family history, certain genetic polymorphisms, and chronic pancreatitis have been detected [3–5]. Median survival for locally advanced disease is just 6–10 months, however in patients with metastatic disease this falls to 3–6 months. Overall 5 year survival is less than 4% [6]. Pancreatic Adenocarcinoma (PA) constitutes more than two thirds of all pancreatic cancers and pancreatectomy offers the only chance for long-term survival [7,8]. The recurrence rate of PA is very high and high-volume centers report 5-year survival rates of only 10–20% [9]. Many cases are in well-advanced stages of metastases and dissemination with peripheral invasion of the retroperitoneum, vascular system, or nerves [10–12] and frequently, the types of recurrences from pancreatic cancer are liver metastases (LM) and peritoneum dissemination [13–15]. Synchronous or metachronous disease is categorized mainly by LM, peripancreatic or retroperitoneal recurrence, peritoneal seeding, and other distant metastasis [16]. Patients with PA are generally unsuitable for curative surgical resection. Despite this, there are some reports discussing hepatectomy for LM from pancreatic cancer [17–22] but the indications for resection of other PA metastases are not as clearly defined.

The purpose of this systematic review is to examine the epidemiology and natural history of PA, the prognostic stratification options and the consequent approaches in the light of recent scientific evidences.

2. Methods

PubMed and ScienceDirect databases were searched for articles using the terms: Pancreatic Cancer, Hereditary, Risk factors and

* Corresponding author.
E-mail addresses: anubis_m@libero.it (M. Cannistrà), ruggant@alice.it (M. Ruggiero), alessandra.zullo@gmail.com (A. Zullo), seraf87@gmail.com (S. Serafini), raffaele.eia@alice.it (R. Grande), bruno.nardo@unibo.it (B. Nardo).

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Stratification, Management of Pancreatic Tumors, Survival, Chronic Inflammation.

Only publications in English were included. Titles and abstracts were screened by 2 authors (R. M., C. M.) to identify potentially relevant studies. Reference lists of retrieved articles were also searched for relevant publications.

Clinical Trial, Meta-Analysis, Systematic Reviews and Case Reports were included. Studies were excluded if performed in no English languages, if the cohort was defined by the presence of Pancreatic Tumors and an additional confounding disease process (eg, chronic renal failure or other hepatobiliary diseases) or if Pancreatic Tumors specific results could not be distinguished from those of a larger population consisting of individuals without disease. Studies were excluded when the primary focus was vascular diseases and inflammatory diseases.

3. Results

3.1. Study selection

Initial database searches yielded 7231 studies from PubMed and 29101 from Science Direct. We evaluated 1031 eligible full text articles (Fig. 1).

The epidemiology of PA and its natural history, the risk factors, the clinical and instrumental diagnosis, the prognostic systems for tumors stadiation and the possible new the role of M component of TNM classification in management of PA is given below.

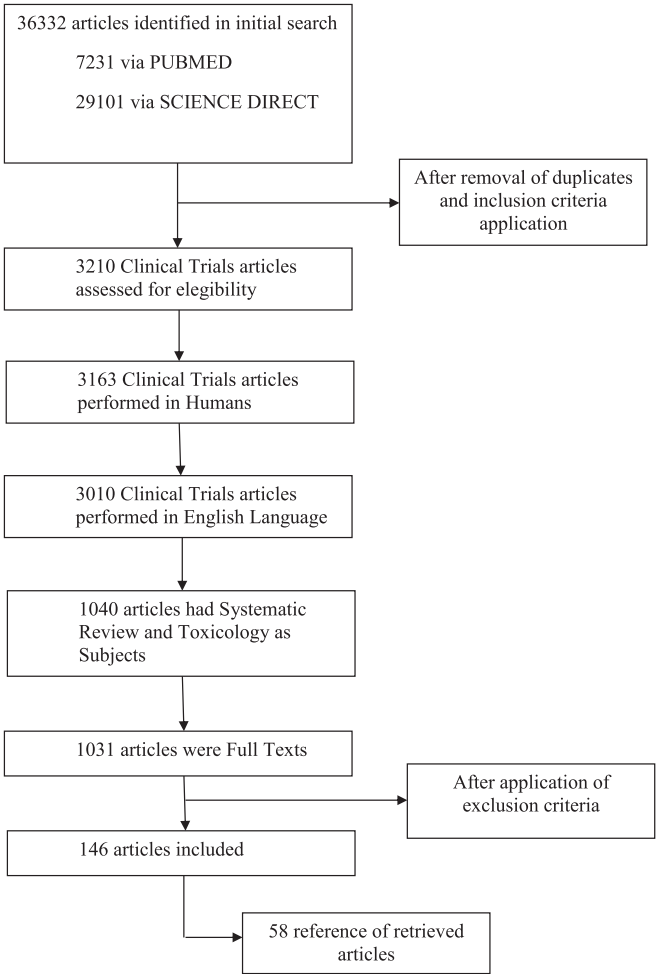

Fig. 1. Flow of papers identified from search strategy.

3.1.1. Epidemiology of pancreatic tumors and natural history

Pancreatic cancer is the fourth leading cause of death from cancer in the industrialized countries and annually affects at least 250,000 individuals worldwide [23]. It is the tenth most common cancer in men and the fourth leading cause of cancer-related deaths in both men and women [24,25]. The incidence of PA is higher in men than women and the mean age at diagnosis was 69.9 years, and was slightly lower in men than in women [25]. Poor prognosis is related to four factors: subtle presentation, tumor aggressiveness, technically difficult surgical resection, and few effective systemic therapies [26,27]. The head-neck localization predominated (77%) among the registered cases of pancreatic cancer and ductal adenocarcinoma is preferentially localized to the head of the organ (47–65%), followed by the body and tail (15–18%) [28,29].

3.1.2. The genes and the modifiable factors

Despite BRCA1 mutations show approximately 2-fold increased risk of PA, in families without a solid history of breast cancer, the mutation is hardly shown [30–34]. It is clear the association between the germline mutations of BRCA2 and PA: deleterious mutations in the BRCA2 has been found in 7.3% of apparently sporadic pancreatic cancers and in 17–19% of familial pancreatic cancer families [35–37].

Lynch syndrome resulted in mutations in the MSH2, MSH6, MLH1, PMS2, and EPCAM genes [38]. In relation with the general population, patients with Lynch syndrome have shown to have an 8.6-fold increased risk of developing PA, with frequency about 1:660 to 1:2000 [45–47].

*Familial Adenomatous Polyposis (*FAP) is characterized by APC gene mutation, which codes for a protein involved in the destruction of targeting β-catenin and acts as regulator on microtubule stabilizer and cell cycle's progression [39,40]. It has been shown that the relative risk of PA is 4.5–6-fold [41,42].

*Peutz-Jeghers syndrome (*PJS) is characterized by a mutation of tumor suppressor gene which encodes for a serine/threonine kinase, the STK11/LKB1 gene [43]. A 93% overall rate of cancer by age 64 and a relative risk of 15.2 has been shown to be associated with PJS [44,45].

Smoking is a risk factor for PA and contributing to 20–35% of PA cases [46–48]. Carcinogens including nitrosamines and polycyclic aromatic hydrocarbons cause mutations in both protoncogenes (K-RAS) and tumor suppressors (p53) and result to pancreatic inflammation [49–51].

Diagnosis of *Diabetes Mellitus* (DM) for a longer time is associated with a decreased PA risk compared to newly-diagnosed [52–55]. Type 3c DM (pancreatogenic), represent 8% of all diabetes, occurs in up to 30% of patients with PA [56]. The insulin resistance, in this case, is an hepatic resistance, with relatively normal peripheral insulin sensitivity [57,58]. In addition, associated new-onset DM has been shown to resolve after tumor resection [59,60].

Chronic pancreatitis is caused by alcohol abuse, which is responsible for 60–90% of cases [61]. A relative risk of 13.3 for developing PA in patients with chronic pancreatitis was shown [62].

3.2. Clinical and instrumental evaluation

Magnetic resonance cholangiopancreatography (MRCP) allows the best visualization of possible communication with the main pancreatic duct, while magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) have demonstrated the most accuracy as screening modalities for PA in terms of detecting small, cystic lesions [63,64]. Compared to EUS and MRI, CT subjects patients to radiation and has a suboptimal detection rate. Abdominal