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Progress Report

Italian consensus guidelines for the diagnostic work-up and follow-up of cystic pancreatic neoplasms

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ABSTRACT

This report contains clinically oriented guidelines for the diagnostic work-up and follow-up of cystic pancreatic neoplasms in patients fit for treatment. The statements were elaborated by working groups of experts by searching and analysing the literature, and then underwent a consensus process using a modified Delphi procedure. The statements report recommendations regarding the most appropriate use and timing of various imaging techniques and of endoscopic ultrasound, the role of circulating and intracystic markers and the pathologic evaluation for the diagnosis and follow-up of cystic pancreatic neoplasms.

1. Introduction

Cystic pancreatic neoplasms (CPNs) have been increasingly identified over the past two decades due to the widespread use of high-resolution non-invasive abdominal imaging.

The characterisation and management of these cysts are a dilemma since there is a significant overlap in the morphology of benign and premalignant lesions; the 2010 WHO classification of CPNs is reported in Table 1 [1]. Of these entities, five types of neoplasms account for approximately 90% of all cystic tumours of the pancreas: intraductal papillary mucinous neoplasms (IPMNs) (either main duct, branch duct or mixed), mucinous cystic neoplasms (MCNs), serous cystic neoplasms (SCNs) and pseudopapillary neoplasms.

CPNs are mostly detected incidentally when non-invasive abdominal imaging is performed for unrelated indications. The prevalence of incidental pancreatic cystic lesions in the adult population is high, and ranges from 2.6 to 19.6% [2–4]. Autopsy series report an increase in CPN prevalence with age: 8% below 70 yrs of age and 18%, 30% and 35% in the age ranges of 70–79, 80–89 and >90 yrs of age, respectively [5]. The size and number of CPNs (per patient) also increase with age [2–4]. Of note, a non-negligible proportion of CPNs, especially those with small diameters, are usually not described in imaging reports in patients without a past history of pancreatic disease (69% of cystic lesions with a mean diameter of 6 mm were not reported) [3].

While there is now an increased awareness of these lesions, their natural history is still partially unclear, and optimal management is still under debate.

Therefore, clinicians are faced with a high, and ever increasing, prevalence of CPNs due to population ageing, and management difficulties of these lesions, with the inherent risks of over- or misuse of diagnostic tests, entailing unnecessary risk and discomfort for patients and resources wasted for the health care system.

Evidence-based practice guidelines exist for pancreatic mucinous neoplasms [6]; European consensus statements regarding all CPNs have also been drafted [7].

Comprehensive guidelines regarding all CPNs, oriented by clinical patient presentation rather than the pathologic diagnosis, and based on a sound consensus methodology, are however lacking. Additionally, in Europe, the national welfare systems are significantly different, and the availability of high-end diagnostic techniques is not uniform in different countries. Thus, guidelines need to be tailored to the specific country [8].

Of note, consensus regarding clinical practice is particularly valuable in this context where limited data are available and health providers are faced with difficult clinical decisions; controversial issues still exist in the evaluation and management of CPNs, particularly regarding lesion size, the presence of high-risk lesion features,

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Table 1
WHO classification of cystic pancreatic tumours, 2010.

Epithelial tumours
Benign
Acinar cell cystadenoma
Serous cystadenoma
Premalignant lesions
Intraductal papillary mucinous neoplasm (IPMN)
Mucinous cystic neoplasm (MCN)
Malignant lesions
Acinar cell cystadenocarcinoma
Intraductal papillary mucinous carcinoma (IPMN) with an associated invasive carcinoma
Mucinous cystic neoplasm (MCN) with an associated invasive carcinoma
Serous cystadenocarcinoma
Solid-pseudopapillary neoplasm
Neuroendocrine neoplasms with cystic degeneration
Mesenchymal tumours
Lymphangioma, NOS
Secondary tumours with cystic degeneration

the role of different diagnostic techniques, and the accuracy of markers and cytology for CPN definition.

Therefore, the Italian Association of Hospital Gastroenterologists and Endoscopists (Associazione Italiana Gastroenterologi ed Endoscopisti Ospedalieri, AIGO) and the Italian Association for the Study of the Pancreas (Associazione Italiana per lo Studio del Pancreas, AISP) have produced the present consensus guidelines which: (1) are limited to the diagnostic work-up and follow-up of all CPNs according to WHO classification (and excluding cystic inflammatory lesions of the pancreas due to acute or chronic pancreatitis with a compatible patient history), (2) are based on a sound consensus methodology (see Appendix D) to allow evaluation of published data and their quality, and to synthesise them with expert opinions wherever data in the literature are either missing or of low quality, (3) are clinically oriented in order to address the clinical scenarios encountered when caring for patients with CPNs, and (4) consider also the characteristics of the Italian Health Care System, with its inherent availability of different diagnostic techniques. The consensus was reached for each statement according to the Delphi procedure [9] and both the level of evidence (EL) and the grade of recommendation (RG) were reported according to the Oxford criteria [10]. The following recommendations are applicable only to those patients for whom a therapeutic opportunity is suitable at the time of diagnosis or during the follow-up. No additional examinations are required when the patient, after diagnosis, is found to be unfit for any treatment and asymptomatic.

2. Consensus statements

2.1. Indications for work-up

1) Which patients with pancreatic cystic lesions need an additional diagnostic work-up, after exclusion of those unsuitable for treatment or unwilling to undergo diagnostic work-up?

Statement

All patients with pancreatic cystic neoplasms require a diagnostic work-up [11–18].

Evidence level 2a, Recommendation grade B, Agreement 96%

Comment

All patients with pancreatic cystic neoplasms, symptomatic or asymptomatic, require a diagnostic work-up in order to evaluate appropriate treatment or surveillance.

Patients with asymptomatic, small (<1 cm) pancreatic cystic neoplasms also require a diagnostic work-up since malignancy can occur (2%). If the cystic lesion was discovered by a high resolution technique (such as MRI or MDCT), no further investigation is usually needed.

2) Define clinical presentation on the basis of the presence/absence of sign/symptoms.

In *symptomatic* patients, what are the signs/symptoms of a pancreatic cystic lesion?

Statement

Signs/symptoms of a pancreatic cystic lesion include: abdominal pain, acute pancreatitis, nausea, vomiting, weight loss also due to exocrine pancreatic insufficiency with steatorrhea, anorexia, recent onset or worsening diabetes, obstructive jaundice and a palpable mass [14,19–33].

Evidence level 4, Recommendation grade D, Agreement 94%

Comment

Symptoms can differ according to the type of cystic lesion: IPMNs are often discovered after pancreatitis; large MCNs and SCNs may be discovered as a result of the presence of a palpable abdominal mass. Jaundice, severe abdominal pain, weight loss, anorexia and diabetes are more likely associated with malignant behaviour.

3) In the setting of *symptomatic* patients, which diagnostic technique/s is/are necessary before treatment?

Statement

In the setting of symptomatic patients, high resolution imaging techniques, including MRI with MRCP and/or MDCT with a pancreatic protocol, represent the first diagnostic step [12,34–47].

Evidence level 1a, Recommendation grade A, Agreement 98%

Comment

MRI with MRCP and/or MDCT characterise the cyst and stage the neoplasm (i.e. local infiltration, distant metastases). Since surgery is required for all symptomatic resectable cystic lesions no additional procedures are usually necessary. If distant metastases are suspected, but not clearly demonstrated, PET/CT with ^{18}FDG can be performed.

If local infiltration is suspected, MDCT is usually enough to assess the infiltration; in doubtful cases, EUS with or without FNA can also be carried out.

4) Which data regarding personal or familial history, and which laboratory findings should be considered in asymptomatic patients?

Statement

A family history for pancreatic cancer and/or other malignancies, and a personal and familial history consistent with Von Hippel–Lindau (VHL) disease should be considered.

Serum carbohydrate antigen (CA) 19-9 and glucose levels should be evaluated as well [48–59].

Evidence level 2a, Recommendation grade B, Agreement 94%

Comment

Von Hippel–Lindau disease is associated with pancreatic involvement in approximately 75% of cases (more frequently true cysts (90%), serous cystic tumours (12%), and neuroendocrine cystic tumours (12%) or combined lesions (11%)).

The development of extra-pancreatic neoplasms is reported in 10–40% of patients with IPMNs, and they most frequently include benign colonic polyps, and colorectal, breast and gastric cancer.

Family history of pancreatic cancer is reported as a risk factor for malignant degeneration in IPMNs, although this observation has not been confirmed in large cohorts of resected patients.