

Pancreatic cystic neoplasms: What is the most cost-effective follow-up strategy?

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ABSTRACT

Pancreatic cystic neoplasms are one of the most frequent incidental findings in the field of pancreatic diseases, estimated to be present in up to 45% of the general population. They represent an heterogeneous group of tumors with different biological behavior and variable risk of progression to malignancy. While serous cystadenomas (SCAs) have no risk of malignant progression, mucinous cyst adenoma are malignant in 20% of cases and this risk is higher in intraductal papillary mucinous neoplasms (IPMN). Nonsurgical management could be applied in patients with a SCA and in low-risk IPMN and these patients could be managed with follow-up strategies. While follow-up could be interrupted in patients unfit for surgery due to comorbidities or age, and in SCA stable over time, recent evidences do not support surveillance discontinuation in patients with IPMNs fit for surgery.

Key words: Cost, EUS, pancreatic cystic neoplasms

THE HETEROGENEITY OF PANCREATIC CYSTIC NEOPLASMS

Pancreatic cystic neoplasms (PCNs) are pancreatic closed cavities, usually containing liquid or mucinous material, estimated to be present in 2%–45% of the general population.^[1] In most cases, they are detected as incidental findings. In a 2017 study, a population of 1077 patients was analyzed to assess the incidence and prevalence of pancreatic cysts. After 5-year follow-up, PCNs were detected in 12.9% of patients and more than half of these cysts showed an increase in size or number with age.^[2] Their identification has grown

in last decades, thanks to the widespread use of high-resolution imaging. PCNs represent a heterogeneous group of tumors with different biological behavior. They encompass benign lesions such as serous cystadenomas (SCAs) up to mutinous tumors that may progress to malignancy. Mucinous cystic neoplasms (MCNs) are malignant in less than 20% of cases,^[3] but they are usually found in the pancreatic body-tail of young or middle-aged woman. Since these lesions can be easily resected with a minimally invasive approach and they are detected in patients with a long life expectancy,

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surgery is usually recommended. A similar policy can be applied to solid pseudo papillary neoplasms. Intraductal papillary mucinous neoplasms (IPMNs) can be classified as main duct, branch duct or mixed IPMNs. Since main duct and mixed IPMNs have a risk of malignancy of 40%–90%, even without symptoms,^[4] surgery has been recommended for all surgically fit patients.^[5] Branch duct-IPMNs (BD-IPMNs) have a less clear indication for surgery, as the rate of pancreatic invasive malignancy is 2%–3.7%, comparable to the risk of mortality following pancreatectomy;^[6] a less aggressive treatment is therefore required.

In the 2017 revised version of the international guidelines,^[7] worrisome features (WF, cyst size >3 cm, main pancreatic duct (MPD) size of 5–9 mm, pancreatitis, nonenhancing nodules, thickened and enhanced cyst wall, main duct stricture with upstream dilatation, and peri-pancreatic lymphadenopathy) and high-risk stigmata (jaundice, MPD \geq 10 mm and enhancing nodules), are described. Both these categories were already introduced in the previous consensus conference of 2012.^[8] Briefly, surgery should be always considered in all patients with hepatorenal syndrome (HRS); a more careful and “patient-oriented” approach is needed when WF are present.

SURVEILLANCE IN PANCREATIC CYSTIC NEOPLASMS: WHICH PATIENTS

Based on the above-mentioned considerations, a nonoperative management with clinical-radiological surveillance can be applied to:

1. SCAs;
2. BD-IPMNs without worrisome features or high-risk stigmata.

Before starting any pancreatic cyst surveillance program, patients should be well informed about risks and benefits of either a surgical approach and of a surveillance strategy, including anxiety, quality of life, postoperative and long-term complications.^[9] A great effort should also be paid to standardize all methods and procedures of surveillance. Moreover, since mucinous tumors-including BD-IPMNs, can be associated with a risk of malignant transformation, follow-up strategies must encompass both effectiveness in detecting any cyst change and cost containment, since follow-up can be very long.

What is very clear is that, despite all patients with pancreatic cystic neoplasms require a diagnostic work-up

in order to evaluate appropriate treatment, patients who are not suitable for a possible surgical approach for comorbidities/age, should stop surveillance.^[10]

International guidelines do not define clearly a guidance for treatment in elderly and/or multi-morbid patients, and longer life expectancy often forces physicians to take decision in these kind of patients. Some scores have been used to assess patient status and comorbidities: The age-adjusted Charlson Comorbidity Index (CACI) have been widely used in cancer studies^[11] and it has been employed to classify 725 patients comorbidities in a retrospective study.^[12] Among patients with CACI \geq 7 (severe medical comorbidities), the median survival was limited to 43 months, compared with 180 months in patients with lower comorbidity scoring, so patients with high risk of death from factors other than IPMNs within a few years after diagnosis are not likely to benefit from further IPMN observation or pancreatic resection.

Adult comorbidities Evaluation (ACE) 27 is another score that has been applied to evaluate comorbidities in patients undergoing follow-up for pancreatic IPMN.^[13] In a multicenter retrospective study 281 patients with IPMN with WF or HRS, who did not undergo surgical resection mainly because of comorbidities, were evaluated. IPMN progression (increase of size, appearance of new lesions, MPD dilatation), occurred in half of patients after a median of 32 months and 12% developed an invasive pancreatic tumor. Five-year disease-specific survival (DSS) and overall survival were 81% and 89.9% but only age \geq 70 years and ACE-27 score >3 were independent predictors of DSS in patients with WF. Moreover, 5-year DSS was 96% in patients with WF, but only 60% in patients with HRS, that is still a strong indication for surgery in patients surgically fit. Considering the results of these studies, another group of patients may be also considered for surveillance: Patients with IPMNs, mainly BD-IPMNs, with worrisome features that are “borderline resectable” for comorbidities.

SURVEILLANCE IN PANCREATIC CYSTIC NEOPLASMS: TIMING OF FOLLOW-UP AND DISCONTINUATION OF SURVEILLANCE

Different guidelines are nowadays available for management of PCNs: Italian Guidelines published in 2014,^[10] American Guidelines in 2015,^[9] International Association of Pancreatology Guidelines in 2017,^[7]

European Guidelines in 2018^[1] have provided recommendations, during years, about timing and modality of surveillance, according to cyst size and growth rate/stability. The best imaging is magnetic resonance (MR) cholangiopancreatography (MRCP), since MR is more sensitive than computed tomography (CT) to identify communication between a PCN and the pancreatic duct system, and the presence of a mural nodule or internal septations, avoiding any radiation exposure.

The American Guidelines, proposed in 2015, introduced another suggestion: Patients with pancreatic cyst ≤ 3 cm undergo MR imaging (MRI) for surveillance in 1 year and then every 2 years for a total of 5 years, without any changes, could stop surveillance. Indeed, a recently published work^[6] has followed 144 patients with BD-IPMNs without WF for a minimum of 5 years for every single patient. Mean size of the largest cyst was 15.5 mm and new onset of WF/HRS during follow-up was analyzed. WF and HRS were found in 26 patients after a median of 71 and 77.5 months from initial diagnosis, and they were not preceded by any changes in 73% of these patients. The authors concluded that long-term non-operative management for BD-IPMNs is safe, but discontinuation of surveillance after 5 years, even if no changes occur in this period and cyst size is ≤ 30 mm, should not be recommended.

According to another recent study,^[14] in which 577 patients with BD-IPMNs were followed-up for a median of 6.8 years, malignancies (high-grade dysplasia or invasive neoplasm) developed after 5 years in 5.5% of cases and after 10 years in 4.1% of cases, even in absence of WF. In this study, authors found that development of malignancy not only persists, but it may be greater after 5 years from diagnosis. Only patients with cyst size ≤ 15 mm for more than 5 years might be considered low-risk for progression to malignancy, since the very low rate of progression in this study (0.9%), and only in these cases suspension of follow-up could be cautiously considered. In conclusions, according to more recent guidelines:

- Discontinuation of surveillance is always indicated in those patients who are not fit for surgery at diagnosis or those who become unfit for surgery during follow-up, because of age or new comorbidities
- Discontinuation of surveillance can be strongly considered in patients with SCAs if stable in size and features after 3–5 years, especially for elderly

- Discontinuation of surveillance might be considered in patients with BD-IPMNs with cyst size ≤ 15 mm stable for more than 5 years although there are few data from the literature to strongly support this statement.

SURVEILLANCE AFTER SURGICAL RESECTION

Last indication is that all patients with IPMNs, even those with noninvasive IPMNs and negative surgical margin, should undergo surveillance after resection, to detect a new possible IPMN requiring surgery or a concomitant ductal carcinoma. This indication derives from the observation that IPMN recurrence after resection is 7%–10% and development of skip or metachronous lesions it's possible. Surveillance should therefore continue as long as the patient remains fit for surgery.^[1,7] In patients with invasive IPMNs, surveillance after surgery should be carried out with the same timing and modalities of patients with ductal adenocarcinoma.

Finally, in last European guidelines,^[1] a conservative approach is recommended for asymptomatic MCN and IPMN measuring < 40 mm, without an enhancing nodule. Relative indications for surgery in IPMN include a MPD diameter between 5 and 9.9 mm or a cyst diameter ≥ 40 mm. Absolute indications for surgery in IPMN, due to the high-risk of malignant transformation, include jaundice, an enhancing mural nodule > 5 mm, and MPD diameter > 10 mm. Lifelong follow-up of IPMN is recommended in patients who are fit for surgery.^[1]

COST-EFFECTIVENESS OF SURVEILLANCE STRATEGIES

Despite the interests in PCNs, few studies are available regarding the economic cost analysis of different surveillance strategies. This is somehow strange since surveillance strategies are based on high-resolution imaging techniques and/or EUS that are costly, and involve a large number of patients that should be followed for years.

Huang *et al.*^[15] has compared, in his study, three different management strategies for a cohort of 60-year-old patients with branch duct IPMN: Surveillance strategy, using consensus guidelines,

surgical resection based on symptoms onset but without surveillance, and immediate surgery after initial diagnosis. The primary outcome was quality-adjusted life years (QALYs) cost and the no surveillance strategy was the least costly, but also the least effective, while the surgery strategy was the most costly and effective. The surveillance strategy cost an additional \$20,096 per QALY compared with the no surveillance strategy, but it's more effective, so the surveillance strategy seems to be a cost-effective option compared to no surveillance.^[15] The other aspect that we can consider is patients quality of life, especially in those patients with slow-growing cystic neoplasms, such as BD-IPMNs and a work by Pezzilli and Calculli^[16] has shown that a 6 or 12 months follow-up with MRI does not affect patients quality of life.

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Conflicts of interest

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