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Progress Report

European experts consensus statement on cystic tumours of the pancreas

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ABSTRACT

Cystic lesions of the pancreas are increasingly recognized. While some lesions show benign behaviour (serous cystic neoplasm), others have an unequivocal malignant potential (mucinous cystic neoplasm, branch- and main duct intraductal papillary mucinous neoplasm and solid pseudo-papillary neoplasm). European expert pancreatologists provide updated recommendations: diagnostic computerized tomography and/or magnetic resonance imaging are indicated in all patients with cystic lesion of the pancreas. Endoscopic ultrasound with cyst fluid analysis may be used but there is no evidence to suggest this as a routine diagnostic method. The role of pancreatoscopy remains to be established. Resection should be considered in all symptomatic lesions, in mucinous cystic neoplasm, main duct intraductal papillary mucinous neoplasm and solid pseudo-papillary neoplasm as well as in branch duct intraductal papillary mucinous neoplasm with mural nodules, dilated main pancreatic duct >6 mm and possibly if rapidly increasing in size. An oncological partial resection should be performed in main duct intraductal papillary mucinous neoplasm and in lesions with a suspicion of malignancy, otherwise organ preserving procedures may be considered. Frozen section of the transection margin in intraductal papillary mucinous neoplasm is suggested. Follow up after resection is recommended for intraductal papillary mucinous neoplasm, solid pseudo-papillary neoplasm and invasive cancer.

1. Introduction

Cystic lesions of the pancreas are increasingly recognized because of the improvement of imaging techniques during the last decades. Recently, the prevalence of cystic lesions in the pancreas has been estimated up 3% using computerized tomography (CT) and up to 20% using magnetic resonance (MR) imaging technology [1–3]. The latter is coherent with post-mortem examined pancreata demonstrating cystic lesions smaller than 1 cm up to a quarter of cases [4]. Moreover, a prevalence of 45% was recently reported in a cohort study using magnetic resonance cholangiopancreatography (MRCP) for non-pancreatic indications [5]. Thus, cystic lesions of the pancreas constitute a significant clinical entity.

Pancreatic cysts form a heterogeneous group of tumours. While some show benign behaviour, others have an unequivocal malignant potential and, in addition, are precursors of pancreatic ductal adenocarcinoma [6] such that their detection allows prevention or early treatment of this disease. It is therefore of utmost importance and one of the most urgent challenges for pancreatologists today to improve the diagnosis, treatment and follow-up of cystic lesions of the pancreas, and to define criteria for the distinction of benign from malignant, or potentially malignant, lesions. Currently, guidelines dedicated only mucinous cystic neoplasms exist, while comprehensive guidance for the diagnosis and management of all cystic tumours of the pancreas are lacking [7,8]. Since there is a lack of prospective randomized trials in this field, no strong evidence are available today.

The aim of this European consensus statement is to provide guidelines for cystic tumours of the pancreas regarding their definition, classification, and diagnosis, the clinical patient management and assessment of biopsy or surgical specimens. This will not only

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Table 1
Grading of recommendations.

Grade A: at least one RCT (*Ia*, *Ib*)
Grade B: well conducted clinical studies (*IIa*, *IIb*, *III*)
Grade C: respected opinions but absence of directly applicable good quality clinical studies (*IV*)

Ia: meta-analysis of randomized controlled trials (RCT), Ib: at least one RCT, IIa: at least one well designed controlled study without randomization, IIb: at least one other type of well-designed quasi-experimental study, III: well-designed non-experimental descriptive studies (for example, comparative, correlation, case studies), IV: expert committee reports or opinions and/or clinical experiences of respected authorities.

provide up-to-date guidance for the management of pancreatic cystic neoplasms, but also allow harmonisation of diagnosis and treatment between centres, and therewith ensure comparability of data.

2. Methods

European expert pancreatologists gathered at a consensus meeting organized during the congress of the UEG (United European Gastroenterology) in Stockholm, October 2011, forming the European Study Group on Cystic Tumours of the Pancreas (Appendix A). Cystic lesions of the pancreas include more than 20 entities; however, considering the relative frequency of all, five neoplasms are by far the most common, as they account for approximately 90% of all cystic tumours of the pancreas. For this reason, the consensus meeting and ensuing guidelines focuses on this group of neoplastic cystic lesions, which consist of intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), serous cystic neoplasm (SCN) and solid pseudo papillary neoplasm (SPN) [6,9]. Eleven European experts on different topics in pancreatic disease were asked to answer open questions regarding cystic tumours of the pancreas based on an up-to-date review of the literature. During the meeting different group of expert, divided by competences, reviewed and discussed the answers proposed by the authors through a complete review of the literature. Then the proposed answers to these questions were presented at the meeting and discussed by the whole study group, before consensus was reached. Following the consensus meeting a position paper was written and the recommendations were graded as shown in Table 1. A final review was performed by all authors.

3. Results

The questions and ensuing consensus answers discussed at the consensus meeting are outlined below, and where appropriate, the grade of recommendation is stated.

3.1. Definition and classification

Q1: *What is the definition of cystic tumours of the pancreas and how can they be classified*?

A cystic tumour of the pancreas is defined as a uni- or multilocular cavity-forming neoplasm or non-neoplastic tumour-like change of the pancreas, which is composed of epithelial and/or mesenchymal tissue. Based on this definition, cystic lesions of the pancreas can be classified according to their neoplastic or non-neoplastic nature, and depending on whether the constituting tissue is of epithelial or mesenchymal derivation. The classification outlined in Table 2 is in accordance with the WHO 2010 classification of pancreatic tumours [10].

Table 2
Classification of cystic tumours of the pancreas.

Epithelial neoplastic	Epithelial non-neoplastic
Intraductal papillary-mucinous neoplasm	Lymphoepithelial cyst
Mucinous cystic neoplasm	Mucinous non-neoplastic cyst
Serous cystic adenoma (microcystic, oligocystic/macrocystic)	Enterogeneous cyst
VHL associated serous cystic adenoma	Paraampullary duodenal wall cyst
Serous cystadenocarcinoma	Retention cyst
Cystic neuroendocrine tumour G1–2	Endometrial cyst
Acinar cell cystadenoma	Congenital cyst (in malformation syndromes)
Cystic acinar cell carcinoma	
Solid pseudopapillary neoplasm	
Accessory-splenic epidermoid cyst	
Cystic hamartoma	
Cystic teratoma (dermoid cyst)	
Cystic ductal adenocarcinoma	
Cystic pancreatoblastoma	
Cystic metastatic epithelial neoplasm	
Others	
Non-epithelial neoplastic	**Non-epithelial non-neoplastic**
Benign non-epithelial neoplasm (e.g. lymphangioma)	Pancreatitis-associated pseudocyst
Malignant non-epithelial neoplasms (e.g. sarcomas)	Parasitic cyst

3.2. Diagnosis

Q2: *When are CT and MR imaging indicated for the diagnosis and assessing loco-regional infiltration of cystic tumours of the pancreas*?

CT and/or MRI imaging are indicated in all patients with cystic lesion of the pancreas for the differential diagnosis and for depicting signs suggestive of malignancy.

The purpose of CT/MR imaging is to reduce the number of differential diagnoses when a cystic pancreatic lesion is detected by ultrasonography. This may be achieved by assessment of the relationship between the cystic lesion and the pancreatic ductal system. The identification of a connection between both suggests the diagnosis of IPMNs, which by its very nature grows within the pancreatic ducts. MR cholangiopancreatography (MRCP) allows to classify these tumours according to their localization and extension within the duct system as main duct (MD), branch duct (BD) or mixed type IPMNs (Fig. 1) [11–13]. In case a connection between the cystic pancreatic lesion and the duct system is not identified, CT/MR imaging allows visualization of further features that may be helpful in the distinction between other cystic pancreatic lesions, namely (SCNs) and (MCNs) [14–16]. A multicystic pattern of pancreatic lesions is more frequently observed in SCN, whereas an oligo- and/or macrocystic pattern is more frequently observed in MCNs [17]. In the case of cystic pancreatic lesions that do not communicate with the duct system, the site of the lesion within the pancreas is an important differential diagnostic clue, as MCNs occur almost exclusively in the body-tail of the gland, whereas SCNs have no site predilection [18]. ***Grade*: *B***.

Since biopsy diagnosis is inaccurate in a high proportion of patients with cystic pancreatic lesions [17,19], imaging plays an important role in identifying or excluding malignancy. MR/MRCP enables the identification of mural nodules, which represent the most reliable sign of malignancy in IPMNs [20,21], as well as thickening of the cystic walls, which is a further sign associated with malignancy [20]. In case of malignancy, CT or MR is the preferred imaging modalities for assessment of resectability and metastatic disease [22]. ***Grade*: *B***.

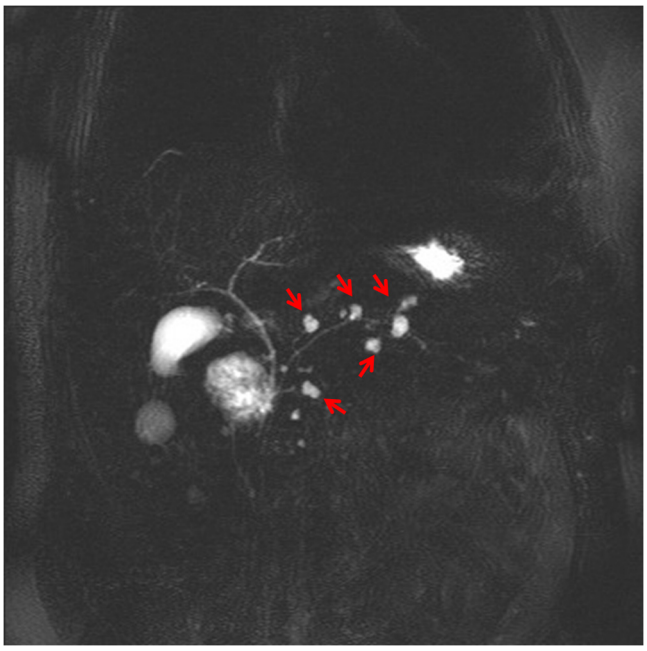

Fig. 1. Magnetic resonance cholangiopancreatography showing connections between the cystic lesions of the pancreas and the main pancreatic duct (indicated by arrows) in a patient with multifocal branch duct intraductal papillary mucinous neoplasm.

Q3: *What is the sensitivity and specificity of CT and MR for the diagnosis and assessing loco-regional infiltration of cystic tumours of the pancreas*?

The reported prevalence of pancreatic cystic lesions is 1.2–2.9%, when using CT [2,23], and 13.5–44, 7%, when MR is the imaging modality [5,24]. This difference is most likely due to the higher contrast resolution of MR compared to CT. The most frequently detected cyst is 10 mm in size. As far as staging is concerned, if using state of the art equipment, there is no significant difference between CT and MR imaging. ***Grade: B***.

Q4: *Can CT and MR be used alone or should they be used as an integrated imaging modality for the diagnosis of cystic tumours of the pancreas*?

CT and MR studies should always include assessment of the pancreatobiliary duct system and the pancreatic parenchyma, the latter by means of cross-sectional imaging. Therefore it is recommended to simultaneously perform curved multiplanar reconstructions during CT examination and MR together with MRCP imaging. ***Grade: C***.

Q5: *Is EUS a safe and useful diagnostic tool for cystic tumours of the pancreas*?

EUS is an invasive diagnostic procedure. The complication rate, even with simultaneous fine needle aspiration (FNA) is low in highly experienced centres [25,26]. EUS morphology alone has poor sensitivity and specificity in accurately classifying pancreatic cystic lesions. Cyst morphology on EUS has an overall accuracy of 50–73%. The sensitivity and specificity for EUS amount to 56–71% and 45–97% respectively [27,28]. EUS is more accurate in identifying lesions that merit resection than it is in clarifying the exact type of cystic lesion present. In addition, there is considerable inter-individual variation in diagnosis made on EUS morphology alone [27,29]. There have been no studies evaluating EUS as a staging modality in cystic tumours of the pancreas. ***Grade: B***.

Q6: *Can EUS be used alone or should it be used in a multimodality diagnostic setting*?

The absolute majority of patients will have undergone prior abdominal imaging (CT/MR) before presenting for EUS. EUS is therefore always carried out as part of a multi-modality diagnostic evaluation. ***Grade: C***.

Q7: *Is FNA and cystic fluid aspiration useful for the differential diagnosis of cystic tumours of the pancreas*?

The most important differential diagnosis is the distinction between mucinous and non-mucinous cystic lesions. A meta-analysis demonstrated that EUS with cyst fluid analysis could differentiate between mucinous and non-mucinous lesions with a sensitivity of 63% and specificity of 88% [30]. A cyst fluid CEA level >800 ng/ml was found highly specific for identification of MCNs, but did not allow distinction between invasive and non-invasive MCNs. Importantly, the study did not include IPMNs. Pseudocysts can be excluded from the differential diagnosis if the cyst amylase concentration is lower than 250 U/L [31]. Assessment of tumour markers (i.e. CEA) should be given priority if the sample size is too limited (<1 ml) to allow analysis of both cyst fluid and cytology [32]. In case of small sample size, DNA analysis may be possible and early results suggest good correlation with current diagnostic criteria [33]. Recently the presence of K-ras mutation was found helpful in the diagnosis of mucinous cysts with a sensitivity of 96%, although again sensitivity was low [34]. In summary, results of cystic fluid analysis should always be interpreted in conjunction with findings on CT/MR and EUS.EUS-FNA can provide diagnostic help in some uncertain cases, however, there is currently no evidence to suggest this as a routine method for the differential diagnosis of cystic tumours of the pancreas. ***Grade: B***.

Q8: *Is pancreatoscopy safe and useful for the diagnosis of cystic tumours of the pancreas*?

Despite 35 years of availability, pancreatoscopy has only recently gained more widely spread use through the introduction of the Spyglass® system, the largest advantage of which is a single-operator miniscope with a disposable outer sleeve. The instrument may be further combined with probe-based confocal laser endomicroscopy. It can be assumed that the rate of post-ERCP pancreatitis may be high with manipulations in the pancreatic duct. Nevertheless, only some 400 patients undergoing pancreatoscopy are reported in the literature and, thus only limited data regarding the safety of this procedure are available [35,36] ***Grade: C***.

Q9: *What is the sensitivity and specificity of pancreatoscopy*?

No trustful figures for the sensitivity and specificity of the detection of any pancreatic lesion (intraductal/IPMN or cystic) can be stated.

Q10: *Can pancreatoscopy be useful and change current management of cystic tumours of the pancreas*?

Today no evidence exists regarding the usefulness of pancreatoscopy in the management of cystic tumours. Promising areas are the distinction between benign (e.g. chronic pancreatitis) and pre-/malignant lesions (e.g. main-duct IPMN), and the assessment of the extent of disease in main duct IPMN. Regarding the latter application, pancreatoscopy could allow identification of skip lesions, which represent a problem with the frozen section analysis. ***Grade: C***.

3.3. Clinical strategy

Q11: *Is the size of the cystic lesion an important criterion to suggest malignant transformation in BD-IPMN*?

The dimension of BD-IPMN was previously considered crucial for management decision making [7]. However, later studies showed that cyst size alone was not a predictive factor of malignancy, and that cancer was also to be found in smaller lesions [37–39]. Furthermore, it was reported that even cysts with a diameter larger than 3 cm can be followed safely, as long as there are no other specific signs of malignancy (see Q12) [40]. Thus, dimension correlates with the risk of malignancy; but there is no safe lower size limit that completely excludes malignancy. ***Grade: B***.

Table 3
Risk factors and indications for resection of branch duct intraductal papillary mucinous neoplasm.

Absolute indications
• Symptoms related to the pancreas (e.g. jaundice, diabetes, acute pancreatitis)
• Mural nodules
• Dilation of the main pancreatic duct >6 mm diameter
Relative indications
• Rapidly increasing size
• Elevated serum levels of CA 19-9

Table 4
Recommendations for further resection based on intra-operative frozen section diagnosis.

• Strongly recommended in IPMN with severe dysplasia or invasive cancer
• Recommended in IPMN with moderate dysplasia[a]
• Not recommended in IPMN with mild dysplasia
• Epithelial denudation of the duct(s) requires examination of deeper section levels or further tissue samples.

[a] In preoperatively diagnosed invasive IPMN-cancer further resection of moderate dysplasia may be omitted; IPMN: intraductal papillary mucinous neoplasia.

Q12: *Which signs can be considered important risk factors for the presence of malignancy in BD-IPMN*?

Invasive carcinoma has been reported in 11–30% of cases in larger series of resected BD-IPMNs [20,38,41–43]. The presence of mural nodules and dilatation of the pancreatic main duct (MD) are considered important factors increasing the risk for malignancy [44–48]. The growth rate of the cyst may be considered another risk factor; in particular a growth rate over 2 mm/year seems to be associated with an increased risk of malignancy [49,50]. The presence of symptoms, in particular abdominal pain, pancreatitis, new onset diabetes and jaundice are important risk factors [42,46]. Recently, an increased serum levels of CA 19-9 was demonstrated to distinguish between invasive and benign IPMNs [51]. ***Grade: B***.

Q13: *When should BD-IPMN be resected and when should it be followed up*?

Asymptomatic lesions without dimensional progression or other risk factors (Q12) can be followed until the lesion has reached a size of 4 cm in diameter. Indications for resection are listed in Table 3. In a patient fit for surgery, the presence of only one risk factor should result in consideration of a potential resection. However, due to accumulative risk of cancer [49,50] in patients with long life expectancy or with an increased risk for cancer development (see Q22), resection of cystic lesions without any risk factors may be considered in experienced centres [38,39] ***Grade: B***.

Q14: *How should BD-IPMN be resected*?

If malignancy cannot be excluded, an oncological resection should be undertaken [7,11]. Partial pancreatectomy can be performed for unifocal BD-IPMN or in case of multifocal BD-IPMN with suspicion of malignancy in one lesion. In the latter case the most suspicious lesion/s should be removed including intra-operative frozen section to evaluate the possibility of a main duct involvement from the disease at the transection margin (see Q16). ***Grade: B***. In multifocal IPMNs recent data suggests that each cyst arise independently, having its own biological behaviour, and thus, should be treated autonomously. Thus, a total pancreatectomy cannot be recommended for multifocal BD-IPMN, unless risk factors shown in Table 3 are detected in lesions located in different parts of the gland [52]. The decision regarding the extension of pancreatectomy should be made while taking into consideration the age, general condition, and the compliance (both regarding surgery and follow-up) of the patient ***Grade: B***. In BD-IPMNs without risk factors for malignancy a limited resection or an enucleation may be performed [53]. ***Grade: C***.

Q15: *When and how should BD-IPMN be followed*?

Because of the accumulative risk of cancer, patients with BD-IPMN who are fit for surgery but are managed conservatively, should be followed clinically (new onset of possibly related symptoms), through marker evaluation (CA 19-9), and preferably by non-radiating imaging (i.e. MR or EUS) [42,44–47,49]. For BD-IPMN (irrespective of the dimension), a 6-monthly follow-up should be done in the first year. If no changes occur during this time, a yearly follow up is recommended for the following 5 years. After this period, in view of the increasing risk of malignancy related to the age of the lesion, a 6-monthly follow-up interval is recommended. In asymptomatic and unchanged lesions, follow-up should be continued as long the patient is fit for surgery [52]. Different follow-up schedules may be considered in high risk individuals (see Q22). ***Grade: C***. For follow up after partial resection of BD-IPMN see Q17.

Summary of recommendations for BD-IPMN is depicted in Fig. 2 and Table 5.

Q16: *When and how should we resect main duct and mixed-type IPMN*?

Invasive carcinoma has been reported in 33–60% of cases in larger series of resected main duct IPMNs (MD-IPMNs) [20,43,54,55]. A pancreatic main duct larger than 1 cm in diameter, the presence of mural nodules and/or symptoms (especially jaundice and diabetes) are risk factors of invasive cancer [54,56,57]. However, invasive carcinoma can be found in a MD of smaller diameter, without nodules or symptoms [43,54]. A similar incidence of invasive cancer has been reported in main duct and mixed-type IPMN [58]. Hence mixed-type IPMN should be considered as a main duct disease. Based on the high prevalence of malignancy, all patients fit for surgery with MD- or mixed type-IPMN should undergo resection. ***Grade: B***.

The extent of an oncological resection should be planned based on the extent of the disease on pre-operative imaging. Prophylactic total pancreatectomy is considered unnecessarily aggressive, considering the morbidity associated with total postoperative endo- and exocrine insufficiency [59] and in view of the relatively low risk of metachronous disease [54,57,60]. Therefore, partial resection with intra-operative frozen section examination of the transaction margin is recommended. The value of frozen section consultation for intra-operative decision making in the case of MD and mixed type IPMN has been demonstrated [11,61–63]. The recommended intra-operative decisions for the various findings on frozen section are summarized in Table 4. Notably, in the case of invasive IPMN cancer, resection of dysplasia in the resection margin or total pancreatectomy confers no additional benefit regarding the recurrence rate or survival compared to standard partial resection [60]. Total pancreatectomy without frozen section may be considered in selected patients with risk factors present for malignancy in the entire gland. ***Grade: B***.

Q17: *When and how should patients be followed-up after resection of an IPMN*?

Recurrence has been reported in 5–10% of resected non-invasive IPMNs but also in 8% of patients with negative resection margins [54,56,57,60,64]. If recurrence occurs, the patient may benefit from an additional resection [63]. Therefore, a yearly follow-up with preferably non-radiating imaging (e.g. MR or EUS) is suggested for surgically fit patients, who underwent a partial pancreatectomy for IPMN. Patients resected for invasive IPMN-cancer should be followed up according to the guidelines for pancreatic cancer. ***Grade: C***.

Summary of recommendations for IPMN is depicted in Table 5.

Q18: *When and how should MCNs be resected*?

Between 12 and 20% of resected MCNs are associated with invasive cancer [65,66]. The worse survival in patients with invasive MCNs compared to non-invasive MCNs highlights the importance of resecting MCNs prior to malignant transformation. Thus, if the

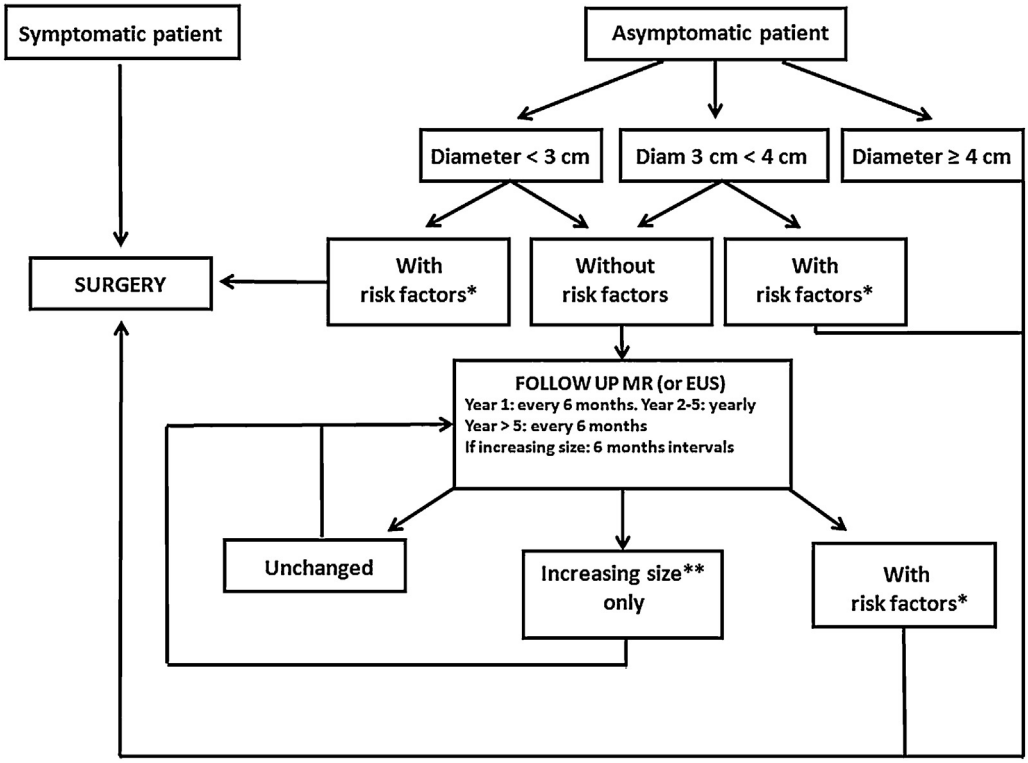

Fig. 2. Algorithm for clinical management of branch duct intraductal papillary mucinous neoplasm. *Risk factors: Mural nodules, dilatation of main pancreatic duct > 6 mm. Relative risk: Increased serum level of CA 19.9. ** In case of rapidly increasing size surgery may be considered. MR =magnetic resonance imaging; EUS = endoscopic ultrasonography.

diagnosis of MCN is clear it should be resected if the patient is fit for surgery. ***Grade*: *B***. However, preoperative distinction between MCNs and oligocystic SCNs or BD-IPMNs may be impossible, in particular in small lesions without typical radiological signs. In these situations and if smaller than 4 cm, the lesion can be managed as BD-IPMN (see Q13) [18,65]. ***Grade*: *C***.

A large size of the lesion (>4 cm), presence of mural nodules, mass forming lesions or peripheral "egg shell" calcifications are suggestive of for invasive malignancy [18,67]. In these cases an oncological resection should be performed [14,65]. ***Grade*: *B***.

Lymph node metastases are rare, thus, in MCNs lacking signs of malignancy, a pancreas- and/or spleen-preserving procedure can be considered in experienced centres [58,68,69]. ***Grade*: *C***.

Due to regressive changes within MCNs, significant part of the inner surface of the cystic lesion may be denuded of epithelial lining, which on a frozen section may lead to the erroneous diagnosis of a pseudocyst [70]. Intra-operative frozen section examination of the cyst wall has therefore a very low accuracy and should be not be used. ***Grade*: *B***.

Q19: *How should patients, who underwent resection for MCN, be followed-up*?

Patients with benign MCNs do not need to be followed-up, since several studies have shown zero recurrence after complete resection [7,65,71]. Patients with invasive MCN cancer should be followed up according to the guidelines used for pancreatic cancer. ***Grade*: *B***.

Summary of recommendations for MCN is depicted in Table 5.

Q20: *When and how should serous cystic neoplasms (SCNs) be resected*?

Malignant SCNs is exceedingly rare [72–74]. A few cases have been reported in the literature with formation of liver metastases [74], even though the diagnosis of these liver lesions may be questioned [75]. In practice SCN may be regarded as a benign entity. The presence of symptoms and/or the inability to definitely exclude a premalignant or malignant tumour (i.e. oligo- and/or macrocystic lesions) are considered indications for surgical resection [76–79]. Tumour size at presentation is not considered a factor of importance for decision making; rather oligo- and/or macrocystic pattern

Table 5
Summary of principal recommendations for cystic lesions of the pancreas.

Determined diagnosis	Resection[a]	Pancreas- and/or spleen preserving procedure[c]	Frozen section routinely?	Follow-up after resection[d]
Serous cystic neoplasm (SCN)	No	Yes	No	No
Mucinous cystic neoplasm (MCN)	Yes	Yes	No	No
BD-IPMN[e]	Maybe[b]	Yes	Yes	Yes
MD-IPMN[f]	Yes	No	Yes	Yes
Solid pseudo-papillary neoplasm (SPN)	Yes	Yes	No	Yes

[a] Symptomatic lesions should always be resected.
[b] Resection if mural nodules, dilated main pancreatic duct (MPD) >6 mm (possibly if: rapid increase in size, high CA 19-9).
[c] Always oncological resection if suspicion of malignancy.
[d] If invasive cancer, follow up as pancreatic cancer.
[e] Branch duct—intraductal papillary mucinous neoplasm (BD-IPMN).
[f] Main duct—intraductal papillary mucinous neoplasm (MD-IPMN).

than can predict the development of later symptoms [15]. In a recent series so called locally aggressive behaviour, defined as invasion of surrounding vessels or peripancreatic lymph nodes, was described in 5.1% of resected SCNs. A large tumour size (>6 cm) and location in the head of the pancreas were considered independent risk factors for this aggressive behaviour that may justify surgical resection [83]. Pancreas and/or spleen preserving resection may be considered in specialized centres [58,68,69], however if malignant tumour cannot be excluded, an oncological resection should be performed. ***Grade*: *B***.

If the patients are surgically fit, asymptomatic non-resected patients should enter a follow up program initially repeat after 3–6 months and then further interval depending on growth rate [15,80,81]. ***Grade*: *C***.

Summary of recommendations for SCN is depicted in Table 5.

*Q*21: *When and how should we resect Solid pseudo papillary neoplasm* (*SPN*)? *How do we follow up these patients*?

SPNs are of unclear cellular origin, usually involving young women in their second decade. The neoplasm has a low malignant potential with excellent overall 5-year survival rate of 95% after surgical resection [82–84]. Therefore, all SPNs should be resected. An oncological resection is generally recommended in order to prevent recurrent disease [85]. However, since lymphnode metastases are rare, pancreas- or spleen-preserving procedures may be considered in experienced centres [85–87]. Incomplete resection, large tumour size, young patient age, tumour rupture and male sex are reported risk factors for recurrent disease [88–90]. Local tumour invasion into surrounding tissues and/or vasculature may occur, necessitating extended resections. Liver or peritoneal metastases are observed in 5–15% of SPNs. [59,82,84]. However, aggressive and/or debulking resections of the primary or recurrent tumour mass, as well as both synchronous and metachronous metastatic disease is supported by the literature due to excellent long term results [82,85,91,92]. (For non-resectable SPNs, see Q24). ***Grade*: *B***.

No pathological factors can predict the outcome in an individual case and recurrence of liver metastases has been reported more than 15 years after complete resection of a SPN [93]. Due to this relatively indolent behaviour of these tumours, even in locally advanced or metastatic disease, or after re-resection of recurrent disease, a yearly life-long follow-up is mandatory as long as the patient is fit for surgery [81]. ***Grade*: *B***.

Summary of recommendations for SPN is depicted in Table 5.

*Q*22: *Are cystic tumours in "high risk individuals" to be managed differently*?

Cystic tumours of the pancreas (mainly BD-IPMNs) are frequently found in individuals with a history of familial pancreatic cancer (FPC) [94–96]. However, information regarding the natural history of the detected BD-IPMNs in these individuals is lacking. Some studies showed that a family history of pancreatic cancer is associated with a worse prognosis in patients with invasive IPMN [97], with faster progression of IPMNs [94], and with a major risk for the development of other pre-neoplastic lesions in the remainder of the pancreas [98]. To date, however, there is not sufficient data to suggest a different clinical strategy for the management of patients with cystic pancreatic tumours in the setting of FPC, though a more aggressive approach has been proposed [99]. On the other hand, in individuals with a familial risk for pancreatic cancer particular attention should be paid to the development of cystic lesions [100,101]. ***Grade*: *C***.

*Q*23: *Can adjuvant treatment of a patient with an invasive cystic cancer be recommended*? *Which kind of therapy should be given*?

Published data regarding the role of adjuvant treatment after resection of malignant cystic tumours of the pancreas is scarce. However, in a recent series, a survival advantage in patient resected for IPMN cancer was demonstrated after adjuvant treatment, in particular for individuals with lymph node metastasis or positive resections margins [102]. However, other studies were not able to confirm these results [103]. Nevertheless, considering the data in the literature and the similarities between malignant IPMN and pancreatic cancer, adjuvant treatment may be recommended. Since no studies are available regarding specific chemotherapeutic agents for IPMN cancer, standard pancreatic cancer protocols (i.e. gemcitabine or 5-FU) can be used. ***Grade*: *C***.

*Q*24: *Can neo-adjuvant therapy be considered in locally advanced cystic tumours of the pancreas*?

No consistent data are available in the current literature regarding the role of neo-adjuvant treatment in cystic tumours of the pancreas. Some studies observed tumour regression of SPNs after different chemotherapy or radiotherapy regimens [104–106], whereas others found no response [107]. In conclusion, no standard downstaging treatment can be recommended today. ***Grade*: *C***.

3.4. Standards in histological classification, specimen assessment and margin definition

*Q*25: *How should the specimen be examined*?

While there is currently no international consensus regarding the optimal dissection technique for pancreatic resection specimens, the axial slicing technique has become the standard in several European countries and pancreatic centres [108–110]. In brief, as described previously [111], the specimen is left intact, without previous probing or opening of the pancreatic or bile duct, and serially sliced in the axial plane, i.e. perpendicular to the longitudinal duodenal axis. Photographic documentation is recommended, as close-up images of the individual specimen slices allow exact correlation with the histological findings as well as retrospective review of the gross findings. Depending on local expertise, horizontal slicing of the specimen along the plane of a probe inserted in the main pancreatic duct may also be performed [10].

Careful and extensive sampling of cystic lesions, in particular IPMN and MCNs is of paramount importance, as high-grade dysplasia may be present only focally, and invasive carcinoma may be small and/or multifocal and difficult to identify macroscopically. In particular for specimens with IPMN, microscopic examination may reveal that the neoplastic lesion is more extensive than appreciated by naked-eye inspection, involves both the main and branch ducts, or shows so-called skip lesions. To date there has been no systematic study of the minimum number of tissue samples that should be taken to ascertain an accurate diagnosis. However, the following recommendations can be made for both IPMN and MCN. All solid and gelatinous areas should be sampled, as these are suspicious for malignancy. All other areas require extensive sampling. In the absence of grossly obvious invasive carcinoma, embedding the entire gross lesion may be considered, in particular if microscopic examination reveals high-grade dysplasia but no invasion [112]. Careful inspection and sampling of the background pancreas is also important to identify skip lesions and/or invasive adenocarcinoma. The latter has been found in 6.7–8.5% of specimens with non-invasive IPMN [112–114]. In some cases of MCN, extensive sampling will be necessary for the identification of ovarian-type stroma, which is a diagnostic requirement for this tumour entity, or to visualize the neoplastic epithelial lining, which due to regressive change is not uncommonly largely absent [10]. Sampling of the resection margins can be performed according to the recommendations for margin assessment in pancreatic specimens resected for ductal adenocarcinoma of the pancreas [115]. ***Grade*: *B***.

*Q*26: *Which histological prognostic factors should be analyzed in the specimen*?

The size of the lesion, based on gross examination, and - if needed - corrected based on microscopic assessment, should be recorded for all lesions. For IPMN and MCN the degree of dysplasia

is to be reported, based on the most severe dysplasia observed. For IPMN it is important to record whether the main pancreatic duct, side branch duct(s), or both are involved. Extensive sampling from the grossly uninvolved pancreas adjacent to the macroscopic lesion is important, as involvement of the pancreatic duct system may be more extensive microscopically than appreciated by naked-eye inspection. The epithelial type of IPMN – gastric, intestinal, pancreatobiliary or oncocytic – is of prognostic significance and maybe of value in determining the follow-up of the patient. Morphological features of the four types along with differences in immunohistochemical staining for mucins and CDX-2, have been characterized in detail [10,116,117]. The presence of invasive carcinoma in association with IPMN or MCN is the main determinant of outcome, and the usual descriptors of invasive carcinoma should be recorded, that is histological tumour type (tubular, colloid, oncocytic, or other variants [10]), grade of differentiation, tumour size and tumour extension. The latter should include locoregional and, if appropriate, distant tumour spread, allowing accurate staging according to the TNM UICC/AJCC system [118]. If multiple invasive cancer foci are present, it is recommended to record the size of the largest focus. Completeness of resection for both invasive and non-invasive lesions is to be reported according to the recommendations for ductal adenocarcinoma of the pancreas, or as outlined in Table 4. Recently, the concept of 'minimally invasive' carcinoma measuring $\leq$5 mm in maximum diameter has been introduced to describe a group of early cancers associated with IPMN that have a better outcome [119]. Early stromal invasion may be difficult to distinguish from extension into a small branch duct or spillage of mucin into the stroma following duct rupture. If in doubt, immunostaining for Ki67 and p53 or elastin stains may prove helpful [112]. ***Grade: B***.

Conflict of interest statement

The author of the manuscript declares that there is no conflict of interest.

Appendix A. European Study Group on Cystic Tumours of the Pancreas

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References

[1] Ip IK, Mortele KJ, Prevedello LM, et al. Focal cystic pancreatic lesions: assessing variation in radiologists management recommendations. Radiology 2011;259:136–41.
[2] Laffan TA, Horton KM, Klein AP, et al. Prevalence of unsuspected pancreatic cysts on MDCT. American Journal of Roentgenology 2008;191:802–7.
[3] Zhang XM, Mitchell DG, Dohke M, et al. Pancreatic cysts: depiction on single-shot fast spin-echo MR images. Radiology 2002;223:547–53.
[4] Kimura W, Nagai H, Kuroda A, et al. Analysis of small cystic lesions of the pancreas. International Journal of Pancreatology 1995;18:197–206.
[5] Girometti R, Intini S, Brondani G, et al. Incidental pancreatic cysts on 3D turbo spin echo magnetic resonance cholangiopancreatography: prevalence and relation with clinical and imaging features. Abdominal Imaging 2011;36:196–205.
[6] Kosmahl M, Pauser U, Peters K, et al. Cystic neoplasms of the pancreas and tumor-like lesions with cystic features: a review of 418 cases and a classification proposal. Virchows Archiv—An International Journal of Pathology 2004;445:168–78.
[7] Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 2006;6:17–32.
[8] Tanaka M, Fernandez-Del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 2012;12:183–97.
[9] Fernandez-del Castillo C, Warshaw AL. Cystic neoplasms of the pancreas. Pancreatology 2001;1:641–7.
[10] Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. 4th ed. Lyon: International Agency for Research on Cancer; 2010.
[11] Falconi M, Salvia R, Bassi C, et al. Clinicopathological features and treatment of intraductal papillary mucinous tumour of the pancreas. British Journal of Surgery 2001;88:376–81.
[12] Salvia R, Crippa S, Falconi M, et al. Branch-duct intraductal papillary mucinous neoplasms of the pancreas: to operate or not to operate? Gut 2007;56:1086–90.
[13] Salvia R, Festa L, Butturini G, et al. Pancreatic cystic tumors. Minerva Chirurgica 2004;59:185–207.
[14] Fernandez-del Castillo C. Mucinous cystic neoplasms. Journal of Gastrointestinal Surgery 2008;12:411–3.
[15] Malleo G, Bassi C, Rossini R, et al. Growth pattern of serous cystic neoplasms of the pancreas: observational study with long-term magnetic resonance surveillance and recommendations for treatment. Gut 2011;2011:22.
[16] Tseng JF. Management of serous cystadenoma of the pancreas. Journal of Gastrointestinal Surgery 2008;12:408–10.
[17] Bassi C, Salvia R, Molinari E, et al. Management of 100 consecutive cases of pancreatic serous cystadenoma: wait for symptoms and see at imaging or vice versa? World Journal of Surgery 2003;27:319–23.
[18] Zamboni G, Scarpa A, Bogina G, et al. Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and relationship to other mucinous cystic tumors. American Journal of Surgical Pathology 1999;23:410–22.
[19] Gaujoux S, Brennan MF, Gonen M, et al. Cystic lesions of the pancreas: changes in the presentation and management of 1,424 patients at a single institution over a 15-year time period. Journal of the American College of Surgeons 2011;212:590–600 [discussion-3].
[20] Crippa S, Fernandez-Del Castillo C, Salvia R, et al. Mucin-producing neoplasms of the pancreas: an analysis of distinguishing clinical and epidemiologic characteristics. Clinical Gastroenterology and Hepatology 2010;8:213–9.
[21] Manfredi R, Graziani R, Motton M, et al. Main pancreatic duct intraductal papillary mucinous neoplasms: accuracy of MR imaging in differentiation between benign and malignant tumors compared with histopathologic analysis. Radiology 2009;253:106–15.
[22] Bipat S, Phoa SS, van Delden OM, et al. Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis and determining resectability of pancreatic adenocarcinoma: a meta-analysis. Journal of Computer Assisted Tomography 2005;29:438–45.
[23] Berland LL. The American College of Radiology strategy for managing incidental findings on abdominal computed tomography. Radiologic Clinics of North America 2011;49:237–43.
[24] Lee KS, Sekhar A, Rofsky NM, et al. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. American Journal of Gastroenterology 2010;105:2079–84.
[25] Adler DG, Jacobson BC, Davila RE, et al. ASGE guideline: complications of EUS. Gastrointestinal Endoscopy 2005;61:8–12.
[26] Al-Haddad M, Wallace MB, Woodward TA, et al. The safety of fine-needle aspiration guided by endoscopic ultrasound: a prospective study. Endoscopy 2008;40:204–8.

[27] Ahmad NA, Kochman ML, Brensinger C, et al. Interobserver agreement among endosonographers for the diagnosis of neoplastic versus non-neoplastic pancreatic cystic lesions. Gastrointestinal Endoscopy 2003;58:59–64.
[28] Brugge WR, Lewandrowski K, Lee-Lewandrowski E, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology 2004;126:1330–6.
[29] Zhong N, Zhang L, Takahashi N, et al. Histologic and imaging features of mural nodules in mucinous pancreatic cysts. Clinical Gastroenterology and Hepatology 2012;10:192–8.
[30] Thosani N, Thosani S, Qiao W, et al. Role of EUS-FNA-based cytology in the diagnosis of mucinous pancreatic cystic lesions: a systematic review and meta-analysis. Digestive Diseases and Sciences 2010;55:2756–66.
[31] van der Waaij LA, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointestinal Endoscopy 2005;62:383–9.
[32] Pitman MB, Lewandrowski K, Shen J, et al. Pancreatic cysts: preoperative diagnosis and clinical management. Cancer Cytopathology 2010;118:1–13.
[33] Shen J, Brugge WR, Dimaio CJ, et al. Molecular analysis of pancreatic cyst fluid: a comparative analysis with current practice of diagnosis. Cancer 2009;117:217–27.
[34] Khalid A, Zahid M, Finkelstein SD, et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. Gastrointestinal Endoscopy 2009;69:1095–102.
[35] Kawakubo K, Isayama H, Sasahira N, et al. Clinical utility of single operator cholangiopancreatoscopy using a SpyGlass probe through an endoscopic retrograde cholangiopancreatography catheter. Journal of Gastroenterology and Hepatology 2012.
[36] Meining A, Shah RJ, Slivka A, et al. Classification of probe-based confocal laser endomicroscopy findings in pancreaticobiliary strictures. Endoscopy 2012;44:251–7.
[37] Walsh RM, Vogt DP, Henderson JM, et al. Management of suspected pancreatic cystic neoplasms based on cyst size. Surgery 2008;144:677–84 [discussion 84–5. Epub 2008 August 29].
[38] Jang JY, Kim SW, Lee SE, et al. Treatment guidelines for branch duct type intraductal papillary mucinous neoplasms of the pancreas: when can we operate or observe? Annals of Surgical Oncology 2008;15:199–205.
[39] Weinberg BM, Spiegel BM, Tomlinson JS, et al. Asymptomatic pancreatic cystic neoplasms: maximizing survival and quality of life using Markov-based clinical nomograms. Gastroenterology 2010;138:531–40.
[40] Tanno S, Nakano Y, Nishikawa T, et al. Natural history of branch duct intraductal papillary-mucinous neoplasms of the pancreas without mural nodules: long-term follow-up results. Gut 2008;57:339–43.
[41] Kanno A, Satoh K, Hirota M, et al. Prediction of invasive carcinoma in branch type intraductal papillary mucinous neoplasms of the pancreas. Journal of Gastroenterology 2010;45:952–9.
[42] Rodriguez JR, Salvia R, Crippa S, et al. Branch-duct intraductal papillary mucinous neoplasms: observations in 145 patients who underwent resection. Gastroenterology 2007;133:72–9 [quiz 309–310].
[43] Schmidt CM, White PB, Waters JA, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. Annals of Surgery 2007;246:644–51 [discussion 51–4].
[44] Akita H, Takeda Y, Hoshino H, et al. Mural nodule in branch duct-type intraductal papillary mucinous neoplasms of the pancreas is a marker of malignant transformation and indication for surgery. American Journal of Surgery 2011;202:214–9.
[45] Maguchi H, Tanno S, Mizuno N, et al. Natural history of branch duct intraductal papillary mucinous neoplasms of the pancreas: a multicenter study in Japan. Pancreas 2011;40:364–70.
[46] Pelaez-Luna M, Chari ST, Smyrk TC, et al. Do consensus indications for resection in branch duct intraductal papillary mucinous neoplasm predict malignancy? A study of 147 patients. American Journal of Gastroenterology 2007;102:1759–64.
[47] Shin SH, Han DJ, Park KT, et al. Validating a simple scoring system to predict malignancy and invasiveness of intraductal papillary mucinous neoplasms of the pancreas. World Journal of Surgery 2010;34:776–83.
[48] Sadakari Y, Ienaga J, Kobayashi K, et al. Cyst size indicates malignant transformation in branch duct intraductal papillary mucinous neoplasm of the pancreas without mural nodules. Pancreas 2010;39:232–6.
[49] Kang MJ, Jang JY, Kim SJ, et al. Cyst growth rate predicts malignancy in patients with branch duct intraductal papillary mucinous neoplasms. Clinical Gastroenterology and Hepatology 2011;9:87–93.
[50] Rautou PE, Levy P, Vullierme MP, et al. Morphologic changes in branch duct intraductal papillary mucinous neoplasms of the pancreas: a midterm follow-up study. Clinical Gastroenterology and Hepatology 2008;6:807–14.
[51] Fritz S, Hackert T, Hinz U, et al. Role of serum carbohydrate antigen 19-9 and carcinoembryonic antigen in distinguishing between benign and invasive intraductal papillary mucinous neoplasm of the pancreas. British Journal of Surgery 2011;98:104–10.
[52] Matthaei H, Norris AL, Tsiatis AC, et al. Clinicopathological characteristics and molecular analyses of multifocal intraductal papillary mucinous neoplasms of the pancreas. Annals of Surgery 2012;255:326–33.
[53] Hackert T, Hinz U, Fritz S, et al. Enucleation in pancreatic surgery: indications, technique, and outcome compared to standard pancreatic resections. Langenbeck's Archives of Surgery 2011;396:1197–203.
[54] Salvia R, Fernandez-del Castillo C, Bassi C, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. Annals of Surgery 2004;239:678–85 [discussion 85–7].
[55] Kim SC, Park KT, Lee YJ, et al. Intraductal papillary mucinous neoplasm of the pancreas: clinical characteristics and treatment outcomes of 118 consecutive patients from a single center. Journal of Hepato-Biliary-Pancreatic Surgery 2008;15:183–8.
[56] Schnelldorfer T, Sarr MG, Nagorney DM, et al. Experience with 208 resections for intraductal papillary mucinous neoplasm of the pancreas. Archives of Surgery 2008;143:639–46 [discussion 46].
[57] Sohn TA, Yeo CJ, Cameron JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. Annals of Surgery 2004;239:788–97 [discussion 97–9].
[58] Crippa S, Partelli S, Falconi M. Extent of surgical resections for intraductal papillary mucinous neoplasms. World Journal of Gastrointestinal Surgery 2010;2:347–51.
[59] Garcea G, Ong SL, Rajesh A, et al. Cystic lesions of the pancreas. A diagnostic and management dilemma. Pancreatology 2008;8:236–51.
[60] Chari ST, Yadav D, Smyrk TC, et al. Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. Gastroenterology 2002;123:1500–7.
[61] Couvelard A, Sauvanet A, Kianmanesh R, et al. Frozen sectioning of the pancreatic cut surface during resection of intraductal papillary mucinous neoplasms of the pancreas is useful and reliable: a prospective evaluation. Annals of Surgery 2005;242:774–8 [discussion 8–80].
[62] Gigot JF, Deprez P, Sempoux C, et al. Surgical management of intraductal papillary mucinous tumors of the pancreas: the role of routine frozen section of the surgical margin, intraoperative endoscopic staged biopsies of the Wirsung duct, and pancreaticogastric anastomosis. Archives of Surgery 2001;136:1256–62.
[63] White R, D'Angelica M, Katabi N, et al. Fate of the remnant pancreas after resection of noninvasive intraductal papillary mucinous neoplasm. Journal of the American College of Surgeons 2007;204:987–93 [discussion 93–5].
[64] Fujii T, Kato K, Kodera Y, et al. Prognostic impact of pancreatic margin status in the intraductal papillary mucinous neoplasms of the pancreas. Surgery 2010;148:285–90.
[65] Crippa S, Salvia R, Warshaw AL, et al. Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients. Annals of Surgery 2008;247:571–9.
[66] Goh BK, Tan YM, Chung YF, et al. A review of mucinous cystic neoplasms of the pancreas defined by ovarian-type stroma: clinicopathological features of 344 patients. World Journal of Surgery 2006;30:2236–45.
[67] Maitra A, Fukushima N, Takaori K, et al. Precursors to invasive pancreatic cancer. Advances in Anatomic Pathology 2005;12:81–91.
[68] Sperti C, Beltrame V, Milanetto AC, et al. Parenchyma-sparing pancreatectomies for benign or border-line tumors of the pancreas. World Journal of Gastrointestinal Oncology 2010;2:272–81.
[69] Yamao K, Yanagisawa A, Takahashi K, et al. Clinicopathological features and prognosis of mucinous cystic neoplasm with ovarian-type stroma: a multi-institutional study of the Japan pancreas society. Pancreas 2011;40:67–71.
[70] Sarr MG, Murr M, Smyrk TC, et al. Primary cystic neoplasms of the pancreas. Neoplastic disorders of emerging importance-current state-of-the-art and unanswered questions. Journal of Gastrointestinal Surgery 2003;7:417–28.
[71] Reddy RP, Smyrk TC, Zapiach M, et al. Pancreatic mucinous cystic neoplasm defined by ovarian stroma: demographics, clinical features, and prevalence of cancer. Clinical Gastroenterology and Hepatology 2004;2:1026–31.
[72] Galanis C, Zamani A, Cameron JL, et al. Resected serous cystic neoplasms of the pancreas: a review of 158 patients with recommendations for treatment. Journal of Gastrointestinal Surgery 2007;11:820–6.
[73] Khashab MA, Shin EJ, Amateau S, et al. Tumor size and location correlate with behavior of pancreatic serous cystic neoplasms. American Journal of Gastroenterology 2011;106:1521–6.
[74] Strobel O, Z'Graggen K, Schmitz-Winnenthal FH, et al. Risk of malignancy in serous cystic neoplasms of the pancreas. Digestion 2003;68:24–33.
[75] Compton CC. Serous cystic tumors of the pancreas. Seminars in Diagnostic pathology 2000;17:43–55.
[76] Correa-Gallego C, Ferrone CR, Thayer SP, et al. Incidental pancreatic cysts: do we really know what we are watching? Pancreatology 2010;10:144–50.
[77] Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. American Journal of Gastroenterology 2007;102:2339–49.
[78] Tseng JF, Warshaw AL, Sahani DV, et al. Serous cystadenoma of the pancreas: tumor growth rates and recommendations for treatment. Annals of Surgery 2005;242:413–9 [discussion 9–21].
[79] Zanini N, Fantini L, Casadei R, et al. Serous cystic tumors of the pancreas: when to observe and when to operate: a single-center experience. Digestive Surgery 2008;25:233–9 [discussion 40].
[80] Das A, Wells CD, Nguyen CC. Incidental cystic neoplasms of pancreas: what is the optimal interval of imaging surveillance? American Journal of Gastroenterology 2008;103:1657–62.
[81] Katz MH, Mortenson MM, Wang H, et al. Diagnosis and management of cystic neoplasms of the pancreas: an evidence-based approach. Journal of the American College of Surgeons 2008;207:106–20.
[82] Papavramidis T, Papavramidis S. Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in English literature. Journal of the American College of Surgeons 2005;200:965–72.

[83] Sakorafas GH, Smyrniotis V, Reid-Lombardo KM, et al. Primary pancreatic cystic neoplasms of the pancreas revisited. Part IV: Rare cystic neoplasms. Surgical Oncology 2011;2011:2.
[84] Tipton SG, Smyrk TC, Sarr MG, et al. Malignant potential of solid pseudopapillary neoplasm of the pancreas. British Journal of Surgery 2006;93:733–7.
[85] Alexandrescu DT, O'Boyle K, Feliz A, et al. Metastatic solid-pseudopapillary tumour of the pancreas: clinico-biological correlates and management. Clinical Oncology (Royal College of Radiologists) 2005;17:358–63.
[86] Butte JM, Brennan MF, Gonen M, et al. Solid pseudopapillary tumors of the pancreas. Clinical features, surgical outcomes, and long-term survival in 45 consecutive patients from a single center. Journal of Gastrointestinal Surgery 2011;15:350–7.
[87] Goh BK, Tan YM, Cheow PC, et al. Solid pseudopapillary neoplasms of the pancreas: an updated experience. Journal of Surgical Oncology 2007;95:640–4.
[88] Campanile M, Nicolas A, LeBel S, et al. Frantz's tumor: is mutilating surgery always justified in young patients? Surgical Oncology 2011;20:121–5.
[89] Kim HH, Yun SK, Kim JC, et al. Clinical features and surgical outcome of solid pseudopapillary tumor of the pancreas: 30 consecutive clinical cases. Hepatogastroenterology 2011;58:1002–8.
[90] Lin MY, Stabile BE. Solid pseudopapillary neoplasm of the pancreas: a rare and atypically aggressive disease among male patients. American Surgeon 2010;76:1075–8.
[91] Fasanella KE, McGrath K. Cystic lesions and intraductal neoplasms of the pancreas. Best Practice and Research Clinical Gastroenterology 2009;23:35–48.
[92] Lee JS, Han HJ, Choi SB, et al. Surgical outcomes of solid pseudopapillary neoplasm of the pancreas: a single institution's experience for the last ten years. American Surgeon 2012;78:216–9.
[93] Gomez P, Yorke R, Ayala AG, et al. Solid-pseudopapillary neoplasm of pancreas with long delayed liver metastasis. Annals of Diagnostic Pathology 2011;2011:3.
[94] Canto MI, Goggins M, Hruban RH, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. Clinical Gastroenterology and Hepatology 2006;4:766–81 [quiz 665].
[95] Poley JW, Kluijt I, Gouma DJ, et al. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. American Journal of Gastroenterology 2009;104:2175–81.
[96] Schneider R, Slater EP, Sina M, et al. German national case collection for familial pancreatic cancer (FaPaCa): ten years experience. Familial Cancer 2011;10:323–30.
[97] Partelli S, Fernandez-Del Castillo C, Bassi C, et al. Invasive intraductal papillary mucinous carcinomas of the pancreas: predictors of survival and the role of lymph node ratio. Annals of Surgery 2010;251:477–82.
[98] Shi C, Klein AP, Goggins M, et al. Increased Prevalence of Precursor Lesions in Familial Pancreatic Cancer Patients. Clinical Cancer Research 2009;15:7737–43.
[99] Steinberg WM, Barkin JS, Bradley 3rd EL, et al. Should patients with a strong family history of pancreatic cancer be screened on a periodic basis for cancer of the pancreas? Pancreas 2009;38:e137–50.
[100] Brand RE, Lerch MM, Rubinstein WS, et al. Advances in counselling and surveillance of patients at risk for pancreatic cancer. Gut 2007;56:1460–9.
[101] Del Chiaro M, Zerbi A, Capurso G, et al. Familial pancreatic cancer in Italy. Risk assessment, screening programs and clinical approach: a position paper from the Italian Registry. Digestive and Liver Disease 2010;42:597–605.
[102] Schwarz M, Pauls S, Sokiranski R, et al. Is a preoperative multidiagnostic approach to predict surgical resectability of periampullary tumors still effective? American Journal of Surgery 2001;182:243–9.
[103] Turrini O, Waters JA, Schnelldorfer T, et al. Invasive intraductal papillary mucinous neoplasm: predictors of survival and role of adjuvant therapy. HPB (Oxford) 2010;12:447–55.
[104] Maffuz A, Bustamante Fde T, Silva JA, et al. Preoperative gemcitabine for unresectable, solid pseudopapillary tumour of the pancreas. Lancet Oncology 2005;6:185–6.
[105] Romics Jr L, Olah A, Belagyi T, et al. Solid pseudopapillary neoplasm of the pancreas—proposed algorithms for diagnosis and surgical treatment. Langenbeck's Archives of Surgery 2010;395:747–55.
[106] Strauss JF, Hirsch VJ, Rubey CN, et al. Resection of a solid and papillary epithelial neoplasm of the pancreas following treatment with cis-platinum and 5-fluorouracil: a case report. Medical and Pediatric Oncology 1993;21:365–7.
[107] Martin RC, Klimstra DS, Brennan MF, et al. Solid-pseudopapillary tumor of the pancreas: a surgical enigma? Annals of Surgical Oncology 2002;9:35–40.
[108] Campbell F, Smith RA, Whelan P, et al. Classification of R1 resections for pancreatic cancer: the prognostic relevance of tumour involvement within 1 mm of a resection margin. Histopathology 2009;55:277–83.
[109] Esposito I, Kleeff J, Bergmann F, et al. Most pancreatic cancer resections are R1 resections. Annals of Surgical Oncology 2008;15:1651–60.
[110] Jamieson NB, Foulis AK, Oien KA, et al. Positive mobilization margins alone do not influence survival following pancreatico-duodenectomy for pancreatic ductal adenocarcinoma. Annals of Surgery 2010;251:1003–10.
[111] Verbeke CS. Resection margins and R1 rates in pancreatic cancer—are we there yet? Histopathology 2008;52:787–96.
[112] Katabi N, Klimstra DS. Intraductal papillary mucinous neoplasms of the pancreas: clinical and pathological features and diagnostic approach. Journal of Clinical Pathology 2008;61:1303–13.
[113] Ingkakul T, Sadakari Y, Ienaga J, et al. Predictors of the presence of concomitant invasive ductal carcinoma in intraductal papillary mucinous neoplasm of the pancreas. Annals of Surgery 2010;251:70–5.
[114] Yamaguchi K, Ohuchida J, Ohtsuka T, et al. Intraductal papillary-mucinous tumor of the pancreas concomitant with ductal carcinoma of the pancreas. Pancreatology 2002;2:484–90.
[115] Campbell F, Foulis AK, Verbeke CS. Standards and datasets for reporting cancers. Dataset for the histopathological reporting of carcinomas of the pancreas, ampulla of Vater and common bile duct. 2nd ed. London: The Royal College of Pathologists; 2010.
[116] Furukawa T, Hatori T, Fujita I, et al. Prognostic relevance of morphological types of intraductal papillary mucinous neoplasms of the pancreas. Gut 2011;60:509–16.
[117] Furukawa T, Kloppel G, Volkan Adsay N, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. Virchows Archiv—An International Journal of Pathology 2005;447:794–9.
[118] Sobin LHGM, Wittekind C. UICC 7th edition: TNM classification of malignant tumours. 7th ed. Oxford: Wiley-Blackwell; 2009.
[119] Nara S, Shimada K, Kosuge T, et al. Minimally invasive intraductal papillary-mucinous carcinoma of the pancreas: clinicopathologic study of 104 intraductal papillary-mucinous neoplasms. American Journal of Surgical Pathology 2008;32:243–55.