Progress Report

European experts consensus statement on cystic tumours of the pancreas

Marco Del Chiaro a,∗, Caroline Verbeke b, Roberto Salvia c, Gunter Klöppel d, Jens Werner e, Colin McKay f, Helmut Friess g, Riccardo Manfredi h, Eric Van Cutsem i, Matthias Löhr a, Ralf Segersvård a, the European Study Group on Cystic Tumours of the Pancreas

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A B S T R A C T

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.

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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 4% 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...
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 1
Grading of recommendations.

| Grade A | at least one RCT (Ia, Ib) |
| Grade B | well conducted clinical studies (Ila, 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, Ila: 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.

Table 2
Classification of cystic tumours of the pancreas.

<table>
<thead>
<tr>
<th>Epithelial neoplastic</th>
<th>Epithelial non-neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraductal papillary-mucinous neoplasm</td>
<td>Lymphoepithelial cyst</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm</td>
<td>Mucinous non-neoplastic cyst</td>
</tr>
<tr>
<td>Serous cystic adenoma (microcystic, oligocystic/macroscopic)</td>
<td>Enterogeneous cyst</td>
</tr>
<tr>
<td>VHL associated serous cystic adenoma</td>
<td>Paraa pylar duodenal wall cyst</td>
</tr>
<tr>
<td>Serous cystadenocarcinoma</td>
<td>Retention cyst</td>
</tr>
<tr>
<td>Cystic neuroendocrine tumour G1-2</td>
<td>Endometrial cyst</td>
</tr>
<tr>
<td>Acinar cell cystadenoma</td>
<td>Congenital cyst (in malformation syndromes)</td>
</tr>
<tr>
<td>Cystic acinar cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Solid pseudopapillary neoplasm</td>
<td></td>
</tr>
<tr>
<td>Accessory-splenic epidermoid cyst</td>
<td></td>
</tr>
<tr>
<td>Cystic hamartoma</td>
<td></td>
</tr>
<tr>
<td>Cystic teratoma (dermoid cyst)</td>
<td></td>
</tr>
<tr>
<td>Cystic ductal adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Cystic pancreatoblastoma</td>
<td></td>
</tr>
<tr>
<td>Cystic metastatic epithelial neoplasm</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
</tbody>
</table>

Non-epithelial neoplastic  |
Non-epithelial non-neoplastic

| Benign non-epithelial neoplasm (e.g. lymphangioma) | Parasitic cyst |
| Malignant non-epithelial neoplasms (e.g. sarcomas) | |

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.
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 pancreaticobiliary 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 minoscope with a disposable outer sheave. 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.

<table>
<thead>
<tr>
<th>Absolute indications</th>
<th>Relative indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Symptoms related to the pancreas (e.g., jaundice, diabetes, acute pancreatitis)</td>
<td>• Rapidly increasing size</td>
</tr>
<tr>
<td>• Mural nodules</td>
<td>• Elevated serum levels of CA 19-9</td>
</tr>
<tr>
<td>• Dilation of the main pancreatic duct &gt;6 mm diameter</td>
<td></td>
</tr>
</tbody>
</table>

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 intraoperative 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.**

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
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: B.**

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 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

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**Table 5**

Summary of principal recommendations for cystic lesions of the pancreas.

<table>
<thead>
<tr>
<th>Determined diagnosis</th>
<th>Resection*</th>
<th>Pancreas- and/or spleen-preserving procedure*</th>
<th>Frozen section routinely?</th>
<th>Follow-up after resection*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous cystic neoplasm (SCN)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm (MCN)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>BD-IPMN*</td>
<td>Maybe</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>MD-IPMN†</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Solid pseudo-papillary neoplasm (SPN)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Symptomatic lesions should always be resected.
† Resection if mural nodules, dilated main pancreatic duct (MPD) >6 mm (possibly if: rapid increase in size, high CA 19-9).
‡ Always oncological resection if suspicion of malignancy.
§ If invasive cancer, follow up as pancreatic cancer.
* Branch duct—intraductal papillary mucinous neoplasm (BD-IPMN).
† 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.

Q21: When and how should we resect solid pseudopapillary 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.

Q22: 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.

Q23: 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.

Q24: 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

Q25: 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 regresive 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.

Q26: 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 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, as outlined in Table 4. Recently, the concept of ‘minimally invasive’ carcinoma measuring ≤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
Abakken I, Oslo University, Norway; Adham M, Centre Hospitalier Universitaire de Lyon, France; Albin N, Karolinska Institutet, Stockholm, Sweden; Andren-Sandberg Å, Karolinska Institutet, Stockholm, Sweden; Arneol U, Karolinska Institutet, Stockholm, Sweden; Bruno M, University Medical Centre Rotterdam, The Netherlands; Cahen D, University Medical Centre Rotterdam, The Netherlands; Cappelli C, Pisa University Hospital, Italy; Costamagna G, Università Cattolica del Sacro Cuore, Italy; Del Chiaro M, Karolinska Institutet, Stockholm, Sweden; Delle Fave G, Università La Sapienza, Roma, Italy; Esposito I, Technical University of Munich, Germany; Falconi M, Università Politecnica delle Marche, Ancona, Italy; Friess H, Technical University of Munich, Germany; Ghanee F, University of Liverpool, Liverpool, UK; Gladhaug IP, Oslo University, Norway; Haas S, Karolinska Institutet, Stockholm, Sweden; Hauge T, Oslo University, Norway; Izbicki JR, University of Hamburg, Germany; Klöppel G, University of Kiel, Germany; Lerch M, University of Greifswald, Germany; Lundell L, Karolinska Institutet, Stockholm, Sweden; Lüttges J, Saarbrücken Hospital, Germany; Löhr M, Karolinska Institutet, Stockholm, Sweden; Manfredi R, University of Verona, Italy; Mayerle J, University of Greifswald, Germany; McKay C, Glasgow Royal Infirmary, Glasgow, United Kingdom; Oppong K, Freeman Hospital, Newcastle, UK; Puikitis A, P, Stradin Clinical University Hospital, Latvia; Rangelova E, Karolinska Institutet, Stockholm, Sweden; Rosch T, Hamburg University, Germany; Salvia R, University of Verona, Italy; Schulinck R, University of Colorado, USA; Segerstård R, Karolinska Institutet, Stockholm, Sweden; Sufferlein T, University of Ulm, Germany; Van Cutsem E, University Hospital Gasthuisberg, Leuven, Belgium; Van der Merwe SW, University Hospital Gasthuisberg, Leuven, Belgium; Verbeke C, Karolinska Institutet, Stockholm, Sweden; Werner J, University of Heidelberg, Germany; Zamboni G, University of Verona, Italy.

References


