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Precancerous Lesions and Carcinoma of the Pancreas

Chair: Markus W. Büchler[a]

Participants: Irene Esposito[b] Lars Grenacher[c] Thilo Hackert[a] Julia Mayerle[d]

[a] Department for General, Visceral and Transplantation Surgery, University Hospital Heidelberg, Heidelberg, Germany,
[b] Department of Pathology, Medical University of Innsbruck, Innsbruck, Austria,
[c] Diagnostic and Interventional Radiology, University of Heidelberg, Heidelberg, Germany,
[d] Department of Medicine A, University Medicine, Ernst-Moritz-Arndt-University, Greifswald, Germany

Question 1: Will the impact of cystic pancreatic lesions in daily practice further increase in the future or have we reached a steady state already?

Esposito: The frequency of incidentally detected cystic lesions of the pancreas has substantially increased in the past years due to the increased sensitivity of detection methods. However, most of these lesions are <1 cm [1] and of unknown clinical relevance. Small, primarily cystic lesions (i.e. not resulting from degeneration of solid neoplasms, which occurs when the lesion attains a larger size) *with malignant potential* include intraductal papillary mucinous neoplasms (IPMN), mucinous cystic neoplasms (MCN), cystic neuroendocrine tumors (NET), and rare cystic mesenchymal neoplasms. There is no recent autopsy study addressing the histological characterization of incidental, small cystic lesions and incorporating the current classifications as well as the present knowledge, especially concerning their molecular physiopathology and natural history [2, 3]. Performing such a study would help in answering the question of the impact of cystic pancreatic lesions from the point of view of both their overall frequency and their clinical relevance.

Grenacher: In pancreatic cancer centers with a high level of knowledge, combined with optimized multidisciplinary imaging techniques (experienced endosonography, high spatial resolution scanners below 1 mm, and optimized protocols), we detect incidental cystic lesions of the pancreas below 1 mm in size in our daily routine, and this fact has reached a level that will only slightly increase in the near future. The impact of these lesions for our therapeutic strategies is difficult to estimate for the future because we are at the beginning of our learning curve for the estimation of malignancy of these lesions. Only when we have evidence-based data we can estimate if early therapy of early diagnosed very small cystic lesions results in longer survival for our patients or if follow-up strategies are recommended. These data is actually missing, and further studies are needed. A second point is that a wide dissemination of the knowledge of diagnostic and therapeutic algorithms will increase the overall number of identified cystic pancreatic lesions in non-pancreatic cancer centers. These two facts could overwhelm today's capacities, and a steady state will not be reached.

Hackert: Judging from the development during the last decade, it seems likely that cystic lesions will have a further increasing impact in the future. The fact that modern imaging modalities offer excellent results in terms of abdominal imaging will lead to an even higher number of accidentally diagnosed cysts than observed today. Therefore, the management of these patients will be an even more important topic. With regard to symptomatic cystic lesions, we may have reached a steady state already.

Mayerle: With an increasing sensitivity of imaging techniques such as secretin-stimulated magnetic resonance imaging (MRI) we are detecting an increasing number of cystic lesions of the pancreas in a range between 1.2% (computed tomography (CT) scan) and 27.7% (secretin-enhanced MRI) in asymptomatic patients or volunteers with a significant increase in prevalence in elderly cohorts [4]. In a cohort of 300 elderly patients (more than 80% older than 65 years), an autopsy study as gold standard reported a prevalence of 24.3% of pancreatic cysts, suggesting that modern imaging techniques are detecting 100% of pancreatic cystic lesions [5]. The median size of cysts detected is 8 mm, and 12–15% of pancreatic cystic lesions occurred at multiple sites. Our own data show that 69% of all cysts in 2,088 healthy volunteers were below 5 mm in diameter, 26% below 1 cm, and only 5.3% of all patients with cystic lesions or

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Prof. Dr. Dr. h.c. med. Markus W. Büchler
Chirurgische Universitätsklinik
Universität Heidelberg
Im Neuenheimer Feld 110, 69120 Heidelberg, Germany
markus_buechler@med.uni-heidelberg.de

1.3% of all volunteers were found to have cysts larger than 10 mm (n = 28/2,088) [6]. In autopsy studies, only 20% of cystic pancreatic lesions represent IPMNs and as such have to be regarded as premalignant lesions. The mere presence of pancreatic cysts does not answer the question of their clinical relevance.

Question 2: What is the essence for the general practitioner regarding cystic pancreatic lesions? Age-dependent screening for all, examinations only for symptomatic patients, or can risk populations be defined?

Esposito: Although the likelihood of having an incidental cystic pancreatic lesion increases with age [1, 5, 7], age-based screening is not evidence-supported so far. In fact, as stated above, the natural history and the histologic type of these incidental lesions is largely unknown. Moreover, the definition of risk populations is limited to cases of familial pancreatic cancer or other rare genetic syndromes (p16-Leiden, McCune-Albright, von Hippel-Lindau) where cystic pancreatic neoplasms with different biological behavior and malignant potential can occur [8]. The referral of patients with incidental cystic pancreatic lesions to specialized centers for further investigations seems therefore appropriate.

Grenacher: As already mentioned above, besides defining strategies based on evidence-based data I am absolutely sure that in the near future we will come to an image-based characterization of potential malignancy of cystic lesions, especially IPMNs and their subtypes.

Hackert: The essence for the general practitioner at the moment is certainly not to perform screening examinations as we do not yet have valid criteria for whom to screen. Today, it is important that all general practitioners, regardless of their subspecialization, are aware of the existence and malignant potential of pancreatic cysts. In the case of diagnosis of a cystic tumor in one of their patients, the management should be coordinated with a specialized pancreatic center – unless the general practitioner himself already has extensive experience with these lesions. The most important aim at the moment is to create awareness for cystic lesions and to encourage the presentation of the findings and/or the patient to an expert. Therefore, a sufficient number of centers and contact persons are required to facilitate this intercollegiate dialogue.

Mayerle: Until today, there are no data indicating a benefit for the patients' survival if asymptomatic individuals are screened for a cystic pancreatic lesion. Furthermore, we have no data supporting that earlier diagnosis or aggressive treatment results in increased survival or is cost-effective. Examination and follow-up of symptomatic patients or incidental cysts is justified on the background that 2.9% of the cases with a non-inflammatory cystic lesion are diagnosed with a pancreatic malignancy. However, the majority (74%) of malignant cystic pancreatic lesions is detected at the time of cyst diagnosis, and those are only asymptomatic in a minority of cases. The incidence of malignant transformation of a non-inflammatory cystic pancreatic neoplasm is 0.4% per year. The prevalence rate of mucin-producing adenocarcinoma arising in patients with pancreatic cysts is 32.8/100,000 population. The overall age- and gender-adjusted standardized incidence ratio of pancreatic malignancy in this cohort is 35 times greater than that of the general (non-cyst) population. This increased risk for pancreatic cancer justifies surveillance of patients with a cystic pancreatic lesion [9]. An obvious, but rare risk cohort for IPMN is patients suffering from McCune-Albright syndrome with germline GNAS mutations. Recently, IPMNs have been described as a McCune-Albright syndrome-associated tumor, present in about 15% of the patients [10]. In familial pancreatic cancer families, cystic lesions of the pancreas are more common (42%). IPMNs can be found in 33% of the patients with familial polyposis coli (FPC) in the surroundings of pancreatic cancer resection specimens while they are present in only 6% of resection specimens from sporadic pancreatic cancer patients. Thus, in FPC patients IPMNs need to be considered as indicator lesion for pancreatic cancer [8]. In case of diagnosis of a pancreatic cystic lesion, the recommendation for the general practitioners is to refer the patient to a specialized center.

Question 3: Which high-risk features of precancerous pancreas lesions are the most valid and important ones?

Grenacher: Beside the statements of my interdisciplinary colleagues I want to add that we have already started with functional imaging (so-called diffusion-weighted MRI (DW-MRI)) to analyze the viscosity of the intraductal mucin of the different types of IPMN as a potentially relevant cofactor for the prediction of malignancy. The future will then show us if the difficult search for identifying intraductal nodules could be abandoned.

Hackert: Currently, probably symptoms, elevated serum carbohydrate antigen (CA) 19-9, and solid components in the imaging seem to be the most reliable features, as well as a growth tendency in the follow-up. The size of a lesion itself does not seem to be a sufficient parameter, especially in branch-duct IPMN. The discussion about a cut-off of 2 or 3 cm in these lesions as a criterion for surgery and the controversy about the malignancy risk correlated with these thresholds underline the insufficiency of size alone. Therefore, more precise parameters are urgently needed to improve this grey area of management recommendations to achieve more evidence-based consensus statements and guidelines in the future.

Mayerle: The risk of malignancy in main-duct IPMN is up to 95.8%, justifying resection at all costs. For side-branch IPMN, in addition to the Sendai criteria, the Fukuoka criteria suggest that high-risk stigmata or worrisome features such as obstructive jaundice in a patient with cystic lesion of the head of the pancreas, en-

hancing solid component within cysts, main pancreatic duct >10 mm in size or pancreatitis, a cyst >3 cm, thickened/enhancing cyst walls, main duct size of 5–9 mm, non-enhancing mural nodule, and abrupt change in caliber of pancreatic duct with distal pancreatic atrophy are associated with an increased risk of malignancy, and this has been confirmed in independent studies [11]. The rate of pancreatic cancer in patients with a Sendai-negative side-branch IPMN is given with 1 in 500 (0.26%). Nodules >5 mm (or >10 mm [12]) are regarded as the best predictor of malignancy. However, even in the presence of nodules the rate of malignancy in resected branch-duct IPMN is below 30% [13]. As size is a less accurate predictor of malignancy, cysts with a diameter above 2 cm should be surveyed with care to be on the safe side [13].

Question 4: In case of surveillance – which tests, which imaging modalities, which intervals should be chosen?

Esposito: Both questions 3 and 4 are better answered by colleagues from clinical disciplines. However, as a pathologist, I would like to add a few considerations which may prove useful to refine the recommendations for surveillance and/or treatment of cystic pancreatic lesions *in the future* [2]. According to some recent large surgical series, which include resected cystic lesions from both asymptomatic (i.e. incidentally discovered) and symptomatic patients [14, 15], the following entities largely predominate: IPMN, MCN, serous cystic neoplasms (SCN), and cystic neuroendocrine neoplasms (cNEN). Of these, only SCN are almost entirely benign and without risk of progression. IPMN, MCN, and cNEN are all potentially malignant, but with different biological risks of progression. IPMN and MCN are precursors of invasive carcinoma. However, among main-duct IPMN, only the pancreatobiliary subtype is usually a high-grade (in situ or already invasive) lesion at diagnosis, therefore warranting resection. The more common intestinal subtype displays low-grade features at diagnosis in about 50% of the cases; moreover, due to its association with the colloid type of invasive cancer and not with classical pancreatic ductal adenocarcinoma, it can be considered a lesion with a low biological risk of progression. Gastric-type IPMN largely predominates in the branch-duct IPMN category and is in most cases a low-grade lesion at diagnosis. MCN can be also considered as lesions with low biological risk, since they are slowly growing tumors with usually low incidence of invasive cancer. NEN are all potentially malignant. However, cNEN usually belong to the NET category (i.e. G1 and G2 tumors), i.e. tumors with maximally low-grade malignant behavior, and are biologically less aggressive than solid NET [16].

These considerations imply that a careful histological characterization and subtyping, aided by the use of routine ancillary methods such as immunohistochemistry, can assist in further stratification and – possibly – better clinical management of cystic pancreatic lesions. Moreover, the identification of additional molecular markers, e.g. through deep-sequencing-based analyses of tumor subtypes for the prediction of high-risk biological behavior, might help in refining the current strategies of management of these lesions in the future.

Hackert: The practical performance of surveillance, if indicated, is certainly depending on the experience of the respective center. Besides investigation of the patient and the clinical examination, a blood test for the routine parameters including pancreas and liver parameters as well as the tumor markers carcinoembryonic antigen (CEA) and especially CA 19-9 is recommendable. For surveillance imaging, endoscopic ultrasound (EUS) and MRI seem to be the methods of choice to avoid recurrent X-ray exposition by CT scans. EUS and MRI seem to be equally effective if the examiner-dependent experience level is sufficiently high in a center. Especially for EUS, this is crucial to allow a precise evaluation of the cystic lesion and of the changes in the surveillance course. For MRI surveillance, technical conditions should allow a thin-slice imaging and an inclusion of an MRCP (magnetic resonance cholangiopancreatography) sequence, e.g. in an 'all-in-one' protocol. If both modalities are present with similar expertise in a center and there are no patient-related contraindications to one of them, the modality should be chosen in agreement with the patient, who may prefer one or the other. Intervals of screening are practically chosen between 3 and 12 months according to the 'surveillance state' of the cystic lesion. This implies that after initial diagnosis and decision for surveillance a short interval of 3 months is advisable to characterize growth behavior. In case of unchanged features of the lesion, 6 months can be chosen for the next follow-up period if no worrisome features are present. In the long-term surveillance, which is only advisable for cystic lesions without any worrisome features anyway, annual examinations seem to be sufficient.

Mayerle: The decision to follow an IPMN is a matter of clinical judgment based on patient age, family history, symptoms, comorbidities, perceived pancreatic cancer risk, and patient preference. We have to keep in mind that the prevalence of cystic pancreatic lesions is 10% in patients above the age of 80 years and that those occur at multiple sites as a field defect in 10–15%. Furthermore, in this cohort only a minority will die from pancreatic cancer if all-cause mortality is considered. At baseline, history/physical examination and MRI/MRCP or EUS should be performed. MRCP has a sensitivity of 91.4–100.0% and a specificity of 89.7% to detect a duct connection of the cystic lesion while EUS is the most sensitive method for detecting the presence of mural nodules [17]. For surveillance, patients without 'high-risk stigmata' should undergo short-interval (3–6 months) pancreatic MRI/MRCP or EUS to establish the static behavior of the cystic lesion, if prior imaging is not available. Subsequently, surveillance should be stratified with regard to the size of the lesion. The precise algorithm can be found in the Fukuoka guidelines [18]. There is no evidence that patients are endangered when following those guidelines. Surgically fit patients with 'high-risk stigmata' detected on surveillance should undergo resection. Shorter surveillance intervals (3–9 months) should be considered in patients whose IPMN progresses toward these in-

dicators or patients who already have 'high-risk stigmata' and, for reasons of operative risk or personal preference, have chosen surveillance over resection. The issue of whether a rapid growth rate is correlated with an increased risk of malignancy remains unclear; however, shorter surveillance intervals are recommended in such patients [11].

Grenacher: I completely agree with the answer of Professor Mayerle. For follow-up surveillance with the proviso for patient comfort, I would prefer the non-invasive method of MRI including MRCP prior to EUS.

Question 5: Which impact does EUS-guided or percutaneous biopsy have on decision making?

Esposito: As discussed above, histological analysis and routine immunohistochemical characterization (e.g. MUC1, MUC2, MUC5A for IPMN; synaptophysin and Ki-67 for cNEN; beta-catenin for solid pseudopapillary neoplasms (SPN); MUC6 and inhibin for SCN) as well as molecular tests (*GNAS* for IPMN, *CTNNB1* for SPN) can provide important information concerning diagnosis and, partly, risk stratification [19]. However, technical issues as well as the experience of both the clinician performing the fine needle aspiration and the pathologist evaluating the specimens are critical factors for achieving higher sensitivity and specificity rates. In the hands of experts, this technique has an important impact on the decision making process. The development of molecular tests is going to further improve the diagnostic accuracy in the near future [20].

Hackert: The performance of any cyst fluid, cytology, or biopsy analysis – either EUS-guided or percutaneously – is not routinely recommendable. CEA in cyst fluids has not proven to be a useful marker for the differentiation between benign and malignant lesions, and neither have any other fluid markers yet. Cytology or biopsy may be useful in highly selected patients as well as in centers with great experience in the pathological work-up of these samples. Besides a maximum accuracy of about 80% for malignancy prediction, the potential danger of spilling cyst content with the consequence of dissemination of tumor cells needs to be considered. Therefore, especially the puncturing of cysts with worrisome features seems to be critical and should be avoided.

Mayerle: Elevated CEA in the cyst aspirate is a marker that distinguishes mucinous, premalignant from non-mucinous, benign lesions, but not benign from malignant cysts. A cut-off of 400 ng/ml improves the specificity at the expense of the sensitivity. A low CEA level does not exclude a mucinous cyst. Cyst fluid lipase is not uniformly elevated in IPMN, and MCN may also exhibit elevated lipase levels. Serous cysts typically have low levels of both CEA and lipase. Cytology can be diagnostic, although the sensitivity is limited by the scant cellularity. In summary, interpreting the results of biochemical markers in cyst fluid is a complex exercise in pattern recognition and should be reserved for patients in whom additional information will have an impact on the surgical decision making [21].

Question 6: Should surveillance, treatment, and follow-up of precancerous lesions of the pancreas be further centralized in Germany?

Esposito: Yes, for the reasons outlined above.

Grenacher: Yes, for the reasons given in this discussion.

Hackert: Probably more important than more centralization is the aim of creating the required expertise in additional places. As the number of patients with cystic lesions kept under surveillance, treated, and followed-up is likely to increase, center experience is increasingly required. This does not imply keeping or reducing the number of centers with the aim of more patients in less centers, but the creation of high-quality centers in more places to facilitate access to the centers for the respective patients and cooperating practitioners.

Mayerle: As outlined above, diagnosis and surveillance of cystic pancreatic lesions is a complex exercise in pattern recognition and thus should be in the hands of experts.

Participants

Univ.-Prof. Dr. Irene Esposito
Institut für Pathologie
Medizinische Universität Innsbruck
Müllerstraße 44, 6020 Innsbruck, Austria
irene.esposito@i-med.ac.at

Prof. Dr. med. Lars Grenacher
Abteilung Diagnostische und Interventionelle Radiologie
Radiologische Klinik
Universität Heidelberg
Im Neuenheimer Feld 110, 69120 Heidelberg, Germany
lars.grenacher@med.uni-heidelberg.de

Prof. Dr. Thilo Hackert
Klinik für Allgemein-, Viszeral- und Transplantationschirurgie
Universitätsklinikum Heidelberg
Im Neuenheimer Feld 110, 69120 Heidelberg, Germany
thilo_hackert@med.uni-heidelberg.de

Prof. Dr. med. Julia Mayerle
Klinik für Innere Medizin A
Ernst-Moritz-Arndt-Universität Greifswald
Ferdinand-Sauerbruch-Straße, 17475 Greifswald, Germany
mayerle@uni-greifswald.de

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